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This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on **Hepatitis B vaccination: a completed schedule…. enough to control HBV life-long?** - Milan, Italy.
November 17-18, 2011.

Editorial

This issue of *Viral Hepatitis* reviews topics covered at the VHPB's autumn meeting held on November 17-18, 2011 in Milan, Italy.

This meeting provided the opportunity to review long-term immunogenicity and efficacy of a complete course of hepatitis B (HepB) vaccine and field effectiveness of the implemented HepB immunization programmes. Recent data on immune memory induced by HepB vaccine and on the anamnestic response after a booster dose were presented. The impact of breakthrough infections was discussed, as well as the potential impact of hepatitis B virus (HBV) mutants. An evaluation of the current HepB booster vaccination recommendations was made and further discussions covered currently used definitions, standards and terminology.

Data presented at the meeting confirmed that HepB vaccination has proven to be a safe and effective way of protecting populations from developing clinical acute or chronic HBV infection. Global routine infant immunization programmes have succeeded in the interruption of perinatal transmission of HBV and resulted in a decrease in the prevalence of hepatocellular carcinoma (HCC).

Many studies confirm that HepB vaccine-induced anti-HBs antibody levels decline over time. The higher the titre after a primary vaccination course, the longer the antibody persists and the more likely an anamnestic response occurs after a booster dose. Novel vaccine adjuvants have a significant effect on early immune response, but their impact on long-term immunity needs further research. An anti-HBs titre of ≥10mIU/mL, measured one to three months after a completed primary course, has been considered as protective for evaluation of primary vaccination (the so-called "way up"), but it was questioned whether this threshold should be used for evaluation of long-term protection, as a decrease of the antibody level below this cut-off does not mean an absence of protection (the so-called "way down"). Consequently, monitoring antibody response alone does not determine long-term immunity and, additionally, the focus should be on surveillance and long-term follow up of vaccinated cohorts.

Data from several studies show that residual B and T cell immune memory persists beyond the loss of circulating antibody. However, it is not known how long protection lasts or how factors such as exposure to the HBV virus, known as "natural boosting" (exposure to HBV), contributes to protection on an individual level or for the population as a whole.

With the exception of non-responders and some other "at risk" groups (e.g., health care workers and immune-compromised persons), to date, a booster dose is not regarded as necessary in routine immunization programmes.

Most vaccinated individuals have good immune memory and show a strong anamnestic response following a booster dose up to 25 years later. An increased number of failures to develop a response following a booster dose (so-called "boostability") has been reported recently and requires further investigation; this finding does not mean that these persons become unprotected or are at risk of developing HBV.

Even 25 years following the introduction of national universal immunization policies in different regions of the world, vaccination failures and escape mutants are rare events; where they occur, they do not result in new, transmittable cases of HBV amongst the vaccinated population, hence they are not considered as a public health problem. However, continued surveillance is necessary.

Meeting discussions identified the need to clarify and standardize a number of terms, such as "primary course", "vaccine failure", "protective level", "seroprotection", "booster", "anamnestic response", "breakthrough infection" and "immune memory". The VHPB will be organizing a workshop in order to address these disparities.

Steven Wiersma and Alessandro Zanetti, on behalf of the Viral Hepatitis Prevention Board

Hepatitis B vaccination: a completed schedule…. enough to control HBV lifelong? Milan, Italy, November 17-18, 2011

Long-term immunogenicity and efficacy of hepatitis B vaccine

To date, 179 countries have a universal infant HBV vaccination programme. Although these programmes have now been running for up to 25 years and are very successful, the adoption of universal vaccination policies raises a number of questions, for example:

- whether newborns will maintain immunity until adolescence and adulthood, when the risk to develop chronic or acute clinical HBV infection is lower; and
- whether long-term immunity is affected by the age at which individuals are vaccinated (infancy, adolescence, adulthood) or by the schedule of primary vaccination (number of doses, the amount of antigen in the vaccine [paediatric or adult dose], vaccine with or without Hepatitis B Immune Globulin [HBIG]); and whether a booster is needed to maintain immunity.

Long-term immunogenicity and efficacy after primary vaccination

Specific antibodies induced by HBV vaccine protect against HBV infection. In a typical antibody response to primary HBV vaccination, the third vaccine dose acts as a booster dose, eliciting a dramatic response leading to a peak antibody level and then a decrease. The decrease follows similar kinetics regardless of the magnitude of the peak antibody level [1]. Generally, within 14-16 months the remaining antibody level is around 10% of the peak anti-HBs level. It continues to decrease with a half-life increasing with the time after primary vaccination [2]. Persistence of antibody depends on and can be assessed by the peak anti-HBs level after the last (third or fourth) dose of the primary immunization series. Therefore in individuals that start with a high peak antibody level, the titre may never decrease to below 10mIU/mL anti-HBs, considered to be the limit of protection against infection. In immune-competent individuals the peak anti-HBs level depends mainly on age at vaccination, vaccine dosage, and host genetic factors. However, apart from specific antibodies, cellular immune mechanisms following primary vaccination appear to have an important role in protection against HBV disease (see studies described below).

High endemic region

In **Thailand**, HBV is a significant health problem. In 2004, liver cancer accounted for 60 per 100,000 deaths in males and 30 per 100,000 deaths in females. Between 1986 and 1989, 1600 pregnant women were screened for HBV and it was found that 6% were carriers of which 40% were HBeAg positive. Newborns were vaccinated against HBV within 12 hours of birth.

A number of studies conducted between 1986 and 1989 evaluated protective efficacy in children up to one year of age. As shown by the results in the Table below, the overall vaccine protection at one year of age was 96.2%. Vaccination with or without HBIG failed to protect only 2.5% of newborns and it is possible to conclude that protective efficacy against the chronic carrier state is high [3].

Long-term follow-up of the newborns in these trials shows that 17 years post-vaccination there have been no HBV cases with evolving chronicity, although transient presence of HBsAg or transient and/or long-term presence of anti-HBc antibody indicate that there has been exposure to HBV, but none of these subjects had clinical symptoms. These findings show that primary infant vaccination with a recombinant HBV vaccine confers long-term protection against clinical disease and against HBV infections that evolve towards chronicity [4].

Protective efficacy at one year of age against chronic carriage in infants born to HBeAg positive mothers [5]

Trial period	Mother cohort	Vaccination schedule		Protective efficacy	Chronic HBV carriage among newborns
	N	Status			
1986-1987	59	HBsAg+/HBeAg+	0, 1, 2, 12 months No HBIG	94.8%	2/59 carriers from HBeAg+ mothers
1987-1988	65	HBsAg+/HBeAg+	0, 1, 2, 12 months With HBIG	97.6%	1/65 chronic carriers
1988-1989	60	HBsAg+/HBeAg+	0,1,6 months With HBIG	100%	0/60 chronic carriers
	59	HBsAg+/HBeAg+	0,1,6 months No HBIG	92.2%	3/59 chronic carriers
Total				**96.2%**	**6/243 (2.5%)**

In another Thai study, 87 high-risk adolescents who had received a complete primary vaccination course of recombinant HBV vaccine 18-20 years earlier were investigated for their HBV humoral and cellular immunity. Overall, 58.6% of adolescents were still positive for humoral immunity (anti-HBs ≥ 10mIU/mL), and 50.6% were positive for cellular immunity (as measured by enzyme-linked immunospot assay [ELISpot]). There was no correlation between the level of anti-HBs and positive ELISpot results. It was concluded that additional studies are required to determine if a booster dose should be considered for high-risk groups [6].

Two other studies conducted in Thailand demonstrated long-term anti-HBs persistence up to 7 or 10 years, induced by primary vaccination in children with the combined diphtheria, tetanus, pertussis and HBV (DTPw-HBV) vaccine given at 2, 4, 6 months and a 4th dose at 18 months [7]. The proportion of subjects with anti-HBs concentrations ≥10mIU/mL was 90.9% at the end of the 7-year study (subjects receiving DTPw-HBV vaccine with 10µg HBsAg, following a birth dose of HBV) and at least 60.9% at the end of the 10-year follow-up study (subjects receiving different formulations of DTPw-HBV vaccine).

In **The Gambia**, HBV vaccination was introduced gradually between 1986 and 1990, in the first phase of the Gambia Hepatitis Intervention Scheme (GHIS) programme (see Chapter on Effectiveness of universal hepatitis B vaccination). Countrywide coverage of HBV vaccination was achieved 4 years after the start of its introduction. Studies conducted in 2008 in The Gambia, with a vaccination coverage rate of 92% for the first as well as for the third dose, have shown a decrease in anti-HBs antibody titres over time and according to peak antibody response. As of 10-14 years after primary vaccination a steady-state level was reached that was independent of the peak titre.

In 2008, data obtained from villages of the Keneba and Manduar regions in The Gambia showed that vaccine efficacy against HBsAg carriage was around 95% (irrespective of age). Prior to vaccination, carrier rates in children had been around 10% (with a peak rate up to 40% in children under 10 years of age in one village). Vaccine protection against infection decreased with increasing age of vaccinated individuals (from 84% at 4 years of age to 51% the age of 20), whereas vaccine efficacy against chronic carriage remained quite constant at ages 4 to 20 years (94% to 97%).

A gradual waning of anti-HBs over time was also observed among vaccinated individuals in **Taiwan**. The anti-HBs seropositivity rate decreased from 99% at 1 year to 83% at 5 years, 71.1% at 7 years, 37.4% at 12 years, and 37% at 15-17 years. At the same time, the prevalence of HBV infection markers (HBsAg, anti-HBc) decreased [8].

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Low/intermediate endemic region

A randomized, controlled multicentre study was conducted in **Italy** to assess the duration of immunity and the need for a booster dose in healthy children (born to HBsAg negative mothers) primed 5 years previously with 3 doses of Hexavac or Infanrix Hexa during their first year of life (at 3, 5 and 11 months of age) [1]. Five years after the initial vaccination, the children were tested for anti-HBc and anti-HBs antibodies. Of the 1543 children enrolled, 3 were excluded because they were anti-HBc positive (2 primed with Hexavac and 1 with Infanrix Hexa). Of the 1540 children remaining in the study, 909 had an anti-HBs titre ≥10mIU/mL (57.2% 10-100mIU/mL, 38.9% 100-1000mIU/mL, 3.9% >1000mIU/mL) 5 years after primary vaccination and did not receive a booster dose as they were considered immune. Of these 909 children, the proportion of children with protective levels of anti-HBs were significantly higher in those vaccinated with Infanrix Hexa (83.2%) compared to those vaccinated with Hexavac (38.4%), which was suspended in 2005 by the European Medical Agency because of concerns over the immunogenicity of the HBsAg component contained in this vaccine. However, 508 out of 549 (92.5%) children who were given a monovalent booster dose (Engerix B or HBVaxPro) 5 years after primary vaccination because their level of anti-HBs was <10mIU/mL, had an anamnestic response regardless of which hexavalent vaccine they had been primed with.

Immune memory does persist in children with anti-HBs <10mIU/mL confirming that immunological memory for HBsAg can outlast the presence of antibodies. Responses to a booster dose of monovalent HBV vaccine are consistent with the induction of immune memory against future HBV infection, and were observed regardless of the pre-booster anti-HBs concentration. At a five year follow-up there is no evidence that a booster dose is needed to sustain immunity in children vaccinated in infancy with hexavalent vaccines. Follow-up beyond 5 years is necessary to see if immune memory persists into adulthood when the risk for HBV infection is higher. To this end, 2 important cohorts vaccinated with monovalent vaccines are being followed in Italy: those vaccinated in the first year of life; and those vaccinated at 12 years of age. Ten years after vaccination, anti-HBc prevalence is 1-2% in young adults who were vaccinated as adolescents whereas it is not found in those vaccinated as infants, mainly because the risk of infection in young adults is much higher than in infancy.

Prior to 1984, **Alaska** was an area with high HBV endemicity. However, due to the introduction of universal newborn HBV vaccination in 1984 and a catch-up vaccination programme for older children and adults (1984-1988), the region was re-classified after 2000 as intermediate endemic.

The collaborative Vax Demo 30 study of Alaska Natives is investigating long-term immunogenicity and efficacy in children and adults. Of 3000 Alaska Natives screened in an initially endemic area (8% HBsAg positive), 1630 seronegative people over the age of 6 months (the majority was >1 year) from 15 different Yukon-Kuskokwim Delta villages were identified. Between October 1981 and May 1982, this study cohort had received plasma-derived vaccine (at 0, 1 and 6 months) and 6 months after the 3rd dose 94% had achieved an anti-HBs titre ≥10mIU/mL. Individuals that were younger than 20 years old at the time of vaccination developed the highest antibody concentrations (99% ≥10mIU/mL), while only 70% of those above the age of 50 had anti-HBs ≥10mIU/mL.

In the Alaska HBV Vaccine Demonstration Project, 1530 children and adults that were vaccinated in 1981 were followed up yearly for 11 years and at year 15 post-vaccination. At 5 years, 81% had anti-HBs levels ≥10mIU/mL [2]; at 7 years 74% had anti-HBs levels ≥10mIU/mL [3]; and at 15 years 66% had anti-HBs levels ≥10mIU/mL [4]. After the full study period, anti-HBs geometric mean titre (GMT) decreased from a mean concentration of 822mIU/mL to 27mIU/mL. During the 15 years of the study, no chronic carriers or acute symptomatic HBV were identified, suggesting that cellular immunity lasts much longer than humoral immunity. There were 23 breakthrough infections (defined by the presence of anti-HBc), which occurred more frequently in non-responders, than in responders [4]. Six out of the 23 cases were transiently HBV DNA positive, 4 of these had HBV surface mutants and 1 transiently had the 145R escape mutant. None of these cases are currently HBV DNA positive, although one person did remain HBV DNA positive for 3-5 years, but the concentration was less than 3 logs and was considered unlikely to be infectious.

Further follow-up of the residents of 7 of 15 villages, 22 years after initial vaccination, showed that 59% still had anti-HBs levels ≥10mIU/mL [5]. A booster dose of Recombivax was given to 155 people who had antibody levels <10mIU/mL and, of these, 81% developed an anamnestic response (defined as 4 fold increase or increase above 10mIU/mL) by 30-60 days after the booster dose. The protective efficacy of the vaccine (defined as having anti-HBs ≥10mIU/mL after primary vaccination + an anamnestic response after the booster) was 94%.

The Vax Demo 30 study is ongoing and is currently focused on reaching the 15 villages to give boosters to people with anti-HBS <10mIU/mL, who did not receive a booster dose 22 years after primary vaccination, and to follow them up 4 weeks later. Preliminary results from 6 villages show that among 130 persons vaccinated 30 years ago, 56% still had anti-HBs levels ≥10mIU/mL, even though they never received a booster dose, with slightly higher percentages in the older age groups (>40 years). Individuals that had anti-HBs <10mIU/mL (2-10mIU/mL) at 22 years post-vaccination and were given a booster dose, demonstrated an anamnestic response; while those with anti-HBs titres below 2mIU/mL were less likely to develop an anamnestic response. Follow-up of 35 people who were boosted at 22 years, showed that 50% of those <40 years of age and 31% of those 40-60 years of age had anti-HBs ≥10mIU/mL at year 30, but no one over the age of 60 had still anti-HBS ≥10mIU/mL.

From these data from Alaska it is possible to conclude that HBV vaccine is highly efficacious and confers a high level of humoral protection against acute symptomatic and chronic HBV, for at least 22 years, when administered in children ≥1 year, and adults under the age of 50. Those under 50 years of age (and especially those below 20 years) at the time of vaccination were more likely to maintain antibodies.

Defining long-term protection

Generally, the cut-off of 10mIU/mL of antibody is considered seroprotective for evaluation of primary vaccination. This threshold orig-

inates from animal experiments, and was defined at the time when only less sensitive radio-immunoassays were available. The long-term data presented at the meeting challenge the use of this threshold for evaluation of antibody persistence, because they show that protection lasts longer than detectable antibody. It was questioned during the meeting whether anti-HBs ≥10mIU/mL is a correct threshold for protection: it could be a cut-off for development of the antibody response after primary vaccination (the so called "way up"), but the threshold may not be applicable during the phase when the amount of antibodies starts to wane. Conversely, the level of 10mIU/mL may not be protective if a person become immunocompromised, however the financial cost of keeping the general public at a higher level (e.g., 100mIU/mL) would be prohibitive. For legal reasons, in the UK the level of 100mIU/mL of antibody is taken as the protective level for health care workers (HCW).

From a public health perspective, it is significant that none of the presented follow-up studies in areas of low/intermediate HBV prevalence or high endemic areas have shown acute HBV, clinical disease or development of the carrier state after primary vaccination. Although breakthrough infections do occur in vaccinated populations, there is no disease or carriage, suggesting that protection lasts longer than detectable antibodies (humoral immunity).

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and related meeting discussions.

Factors influencing long-term protection

When estimating how long protection is needed, it is important to consider the periods with a high risk of exposure to HBV and increased chances for chronic evolution of an acute infection. Following the neonatal period, childhood is the next high risk period, i.e., when horizontal transmission can occur. Infection during childhood is not innocuous because it more likely evolves towards chronicity than infections later in life. The next high risk periods are adolescence and adulthood, in which the onset of sexual activity is increasing the risk of sexual transmission. People may also be at risk during their working life through occupational exposure (e.g., HCW) and also through sexual activity or medical interventions in risky settings (e.g., when travelling to high endemic areas).

Response to vaccination: factors related to the vaccine

Collective studies from Alaska have shown that anti-HBs persists longer in individuals vaccinated with plasma-derived vaccine than in those vaccinated with recombinant vaccine, but the response to a recombinant booster dose is better in those primed with recombinant vaccine than in those primed with plasma-derived vaccine.

In Alaska, 200 vaccinated HCW were divided into 2 groups: those with anti-HBs <10mIU/mL and those with anti-HBs of 10-50mIU/mL 3 to 12 years after primary vaccination. These subjects were then randomised to receive either a paediatric or an adult strength of booster dose. Regardless of the dose strength, they all showed a booster response (>10mIU/mL anti-HBs). However, the level of anti-HBs was higher if they received the adult dose and if they had a pre-booster anti-HBs titre of 10-50mIU/mL.

It is important to consider the number of HBV vaccine doses that are necessary to confer protection because providing HBV vaccination by means of a (hexavalent) combination vaccination is becoming more common and many European countries are moving towards giving a primary series of 2 doses often with a booster in the second year of life (rather than 3 doses and a booster). Immunological

The following factors can affect the response to vaccination:

Factors related to the vaccine or vaccination schedule:

- type of vaccine (plasma-derived versus recombinant, monovalent versus penta- or hexavalent combination vaccine);
- route of administration of vaccine;
- vaccine composition (antigen concentration – 20, 10, 5 or 2.5µg);
- number of doses;
- vaccination schedule (higher response if 1st dose is given at >2 months of age than at birth and higher if last dose given at 12 rather than at 6 months of age);
- interaction with other vaccines;
- adjuvants.

Factors related to the individual:

- age (older age resulting in poorer response);
- gender (females responding better than males);
- BMI (high BMI resulting in poorer response);
- exposure to HBV (natural booster);
- immunocompetence (poorer response in immunocompromised);
- smoking (poorer response in smokers);
- genetics (vaccines may be less effective for some genotypes, see Chapter on Breakthrough infections);
- co-infections.

Comparison of vaccine efficacy in The Gambia in children vaccinated with different numbers of HBV vaccine doses

Timing/number of doses	Infected (anti-HBc+)	% VE against infection	Chronic infection (HBsAg+)	% VE against chronic infection	Peak anti-HBs GMT) mIU/mL)	Median age at follow-up (years)
Pre-vaccination	61%	n/a	20%	n/a	n/a	n/a
1 dose	19%	69%	0%	-	-	-
2 dose	8%	86%	1.6%	92%	158	7.0
3 dose	7%	88%	1.7%	92%	491	4.3
4 dose	9%	85%	0.9%	86%	-	-

VE = vaccine efficacy; - = not presented; n/a = not applicable

theory and mathematical modelling suggest that 2 doses (or even 1 dose) could offer protection similar to that achieved with 3 doses. Reducing the number of doses could have important implications for resource-poor countries. Several studies in adults and adolescents have shown similar long-term protection after 2 (or 1 dose) as with 3 doses. An observational study of children in the Gambia receiving 2 or 3 vaccine doses showed that, although peak antibody titres after 11 months were initially higher in the group that received 3 doses, there was no difference in the level of protection and the incidence of infection between the two groups at follow-up at 5-7 years (see Table below). Surveillance data on vaccine effectiveness are essential when deciding whether additional vaccine doses are necessary, or if the current dosing schedule is optimal, or whether fewer doses could be sufficient (3-dose versus 2-dose schedule) [1].

The interval between vaccine doses may also affect the magnitude of the antibody response. In a group of 620 newborns born to HBsAg positive mothers in the Czech Republic, the number of children with a protective anti-HBs level was statistically higher after immunization with the long schedule of 0, 1, 6 months combined with passive immunization (HBIG) (93.1%) than after the short schedule of 0, 1, 2 months with HBIG (N=29, 82.1%).

Adjuvants increase the inflammatory response at the injection site, thus increasing the recruitment and activation status of inflammatory cells and antigen presenting cells that support the early phase of immune response (see chapter on Principles of immune memory). Compared to non-adjuvanted vaccines (e.g., influenza) or alum-adjuvanted vaccines (e.g., against HBV, human papilloma virus (HPV)), vaccines with novel adjuvants have a potent effect on the quality and magnitude of the humoral immune response (e.g., the AS03-adjuvanted H5N1 influenza vaccine, the AS04-adjuvanted HPV or HBV vaccines). Adjuvants induce a more rapid rise of antibody levels as well as higher peak GMT levels. Addition of adjuvants (oil-in-water emulsions such as MF-59 or AS03, or TLR-agonists such as MPL (AS-04)) to e.g., influenza or HPV vaccines induces more cross-reactive antibodies. These are antibodies that not only interact with the vaccine strains (homologous) but also with virus strains that are not included in the vaccine (heterologous). Since adjuvanted vaccines generally induce higher peak GMT antibody levels it can be expected that these immune responses are more persistent than those induced by non-adjuvanted vaccines. However, further research is needed on the effects of adjuvants on long-term protection and in particular on T and B cell memory.

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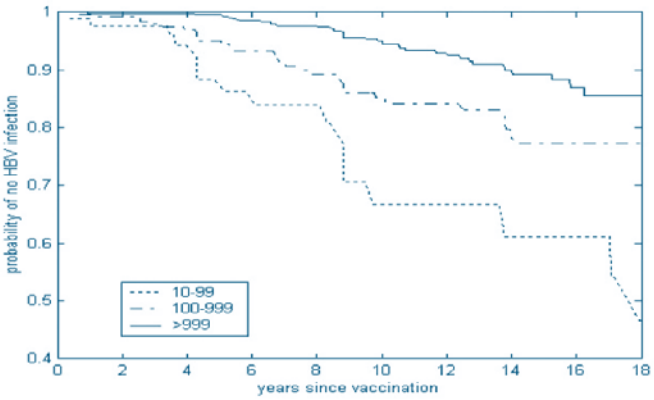
Response to vaccination: factors related to the individual

Multiple studies from Alaska have shown that anti-HBs levels decline faster in those who received a first vaccine dose at birth, than in those vaccinated as children at older age or as adults. When vaccination was started at birth, less than 5% of children given recombinant vaccine and less than 15% of children that received plasma vaccine still had anti-HBs >10mIU/mL at 10 years of age, and only about 50% are able to develop a booster response at adolescence. In this cohort of responders vaccinated at birth, 6 children were found to have breakthrough HBV infection, 2 of these had transient HBV DNA, but none of these children were symptomatic or became HBsAg positive [1].

However, post-vaccination titre may be a stronger predictor of antibody persistence than age at vaccination as shown by Alaskan follow-up data: those with a high titre after vaccination were more likely to still have detectable antibody levels 22 years later.

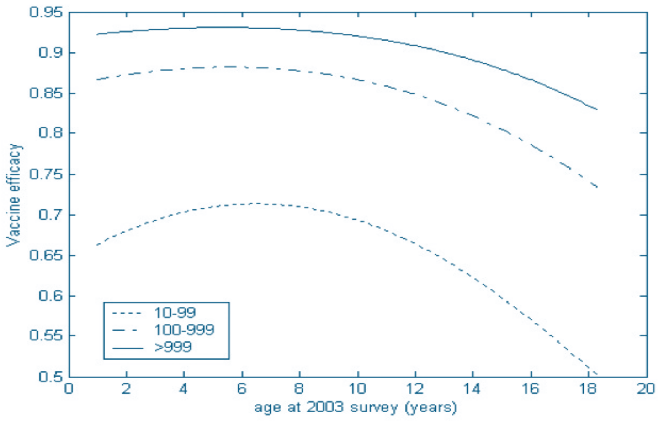
Follow-up data from The Gambia (Keneba-Manduar region) after primary HBV vaccination confirm that peak level of antibody and the time since the last dose of vaccine are related to the risk of infection. There is exponential decline of anti-HBs titres over time (between one third and two thirds no longer had detectable anti-HBs after 15-20 yrs), however the probability that individuals with a very high primary response (>1000mIU/mL anti-HBs) become infected after 18 years is less than in those with a level 10-100mIU/mL (15% compared to 50% risk of becoming infected, see Figure on next page).

Probability of vaccinated individuals remaining uninfected (anti-HBc negative) based on time since vaccination and peak anti-HBs response [2]



This is also reflected in vaccine efficacy over time (see Figure below): in primary responders with a lower titre (10-99mIU/mL) vaccine efficacy declined to 50% after 18 years while in primary responders with a high titre (>999mIU/mL) vaccine efficacy was still about 85% 18 years later.

Vaccine efficacy against HBV infection (anti-HBc positivity) over time after vaccination, by primary peak anti-HBs response [2]



Response to primary vaccination is a determinant of whether immune memory will persist. Primary responders are twice as likely to have an anamnestic response following a booster dose and the response is generally higher than in primary non-responders. In many areas, a natural booster response may contribute to maintaining measurable levels of anti-HBs, but currently it is not known to what extent long-term protection depends on ongoing natural exposure.

Genetic hypo-responsiveness can also cause low responsiveness to the HBV vaccine. Human Leukocyte Antigen (HLA) analysis of 23 low responders (anti-HBs <10mIU/mL or 10-20mIU/mL after 6 vaccine doses) in Taiwan, showed that 9 were positive for DR14 and DR52, suggesting that these HLA-types may be involved in the low immune responsiveness to HBV vaccination [3].

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Based on presentations by
B. McMahon, Alaska Native Medical Center, Alaska and Centers for Disease Control and Prevention (CDC), Atlanta, USA;
M. van der Sande, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands and Utrecht Medical University Centre, The Netherlands;
Y-H. Ni, Children's Hospital and College of Medicine, Taipei, Taiwan.

The potential of mathematical modelling to assist in the development of vaccine schedules

There are different measures of vaccine effectiveness and it is often assumed that immunogenicity in terms of antibody response to vaccine is directly related to vaccine efficacy (reduction in incidence of infection). It is difficult to determine the optimum vaccine schedule and mathematical modelling could prove helpful in providing guidance. A mathematical model is based on assumptions about interactions and rates and allows:

- quantitative description of a system;
- comparison with observed data;
- predictions to be made of untested scenarios (e.g., number of doses).

A mathematical model was presented at the meeting, evaluating the antibody response to HBV vaccines following different vaccination schedules. The model parameters are estimated from a dataset of 10,815 post-vaccination antibody titres obtained from 1923 adults included in different clinical HBV vaccination trials. Model simulations indicated that a single vaccine dose could cause priming of immune memory, as evidenced by the similar absolute increase in anti-HBs after 6 months in 0, 6 and 0, 1, 6 schedules. Both schedules generate comparable anti-HBs GMT's, suggesting that 3 doses may not be needed and a 2 dose schedule may be adequate. The model also indicated that some individuals with anti-HBs <10mIU/mL are still immune after being primed without booster dose or after antibody decay post-booster. However, the fact that the model defined memory as the ability to produce a particular antibody titre was challenged. Also, for most immunologists the ability of one dose of an antigen to produce adequate immune memory, with high affinity antibodies, would be questionable.

Several studies presented at the meeting indicate that age at vaccination could be an important predictor of antibody kinetics. However, in the model presented, age-specific response was not reflected. The model provides information on adults, but does not provide data on children.

Based on a presentation by
J. Wilson, Warwick University, Warwick, UK,
and related meeting discussions.

Immune response and effect of (natural) booster

Principles of immune memory

Adaptive immune system

In addition to the immediate, non-specific, response to an infection, immune memory is the principal feature of the adaptive immune system.

Immune memory is the ability to:

- maintain a protective level of specific antibody due to long-lived plasma cells;
- produce an accelerated immune response when re-exposed to the same pathogen, due to the generation of memory B cells and memory T cells which are able to migrate to sites of inflammation.

Within hours of exposure to an antigen, dendritic cells, resting B cells and short-lived plasma cells, neutrophils, granulocytes and monocytes are recruited to the site of the infection. Resting B cells and short-lived plasma cells are responsible for rapid production of low affinity antibody during this early phase. Dendritic cells present the antigen to the naïve T cells in the T cell zone of the secondary lymphoid organs (particularly in the lymph nodes). Naïve T cells are activated by the interaction with antigen-presenting dendritic cells, clonally expand and become effector memory CD4+ or CD8+ cells, the latter differentiating into T cells, which mediate lysis of infected host cells. Naïve T cells can also become central memory cells, which persist in the peripheral blood and may last a lifetime. Central memory cells are pivotal, because in the presence of high levels of antigen they can turn into effector memory cells and terminally differentiated T cells (capable of killing infected cells). Following re-exposure to the same antigen (e.g., by booster vaccination or re-infection) the immune response starts from long-lived central memory cell stage and therefore develops much faster and more vigorously.

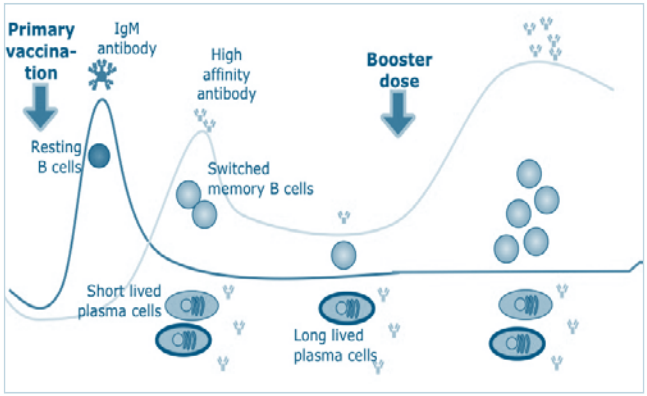
The ability to generate short-lived plasma cells differs among individuals. Short-lived plasma cells continue to produce low affinity antibody at a high level, but die within days. Long-lived plasma cells migrate to the bone marrow and are responsible for persistence of antibody. Switched memory B cells, which have a high affinity for antigen, are able to recognize and protect against future antigen exposure.

Based on presentations by
G. Leroux-Roels, Center for Vaccinology (CEVAC), Ghent, Belgium;
R. Carsetti, Research Center Ospedale Bambino Gesu, Roma, Italy;
M. Clerici, Immunology, University of Milano, and Fondazione Don Carlo Gnocchi, Italy.

Memory B cell response

The prototypic B cell immune response following vaccination and a booster dose (or natural booster) is shown below. Resting B cells and short-lived plasma cells that die quickly are responsible for the initial rapid production of low affinity antibodies, mainly of IgM isotype. Although long-lived plasma cells produce high affinity antibodies, they express no antigen receptor at the cell surface. Protection against future antigen exposure relies upon switched memory B cells which have a high affinity for antigen, are able to recognize infection, and respond by producing selected high-affinity antibodies.

Immune response after primary vaccination and memory activation after booster



It has been shown that in adults, 50% of B cells in the blood are memory B cells [1]. Two types of memory B cell have been identified: IgM-producing B cells (low affinity antibodies for first line defence) and switched memory B cells (important for immune memory).

In a study of Italian children vaccinated with either Hexavac or Infanrix Hexa, most of those vaccinated with Infanrix Hexa still had high levels of antibody 5 years after vaccination, whereas those vaccinated with Hexavac had lower levels of antibody. However, the levels of B cells and frequency of memory B cells, as measured by an ELISpot assay, were comparable between the Hexavac and the Infanrix Hexa group. In this study, there was no correlation between serum antibody level and memory B cell frequency. This suggests that the lower antibody persistence in those vaccinated with Hexavac could be due to lower levels of long-lived plasma cells in the bone marrow.

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Based on a presentation by
R. Carsetti, Research Center Ospedale Bambino Gesu, Roma, Italy.

Memory T cell response

T cell memory is complex and exploring T cell responses in humans is technically difficult. It is not clear how long memory T cells remain in the body. They have been detected up to 12-15 years after vaccination, but it is likely that even when numbers of T cells fall below a detectable level, following a booster dose or re-infection the numbers would rise again.

A multi centre study of 105 Italian children who were given a booster dose 5 years after primary HBV vaccination (65 with Hexavac and 40 with Infanrix Hexa) [1] investigated whether decline in antibody titres below 10mIU/mL translates into a loss of immune memory and whether T cell memory persists when serum antibodies have declined. HBV specific memory T cells could be detected, directly in peripheral blood or after in vitro restimulation of purified peripheral blood lymphocytes with HBV antigen, up to at least 5 years after vaccination and regardless of the vaccine used. In this study, Hexavac appeared to be less efficient than Infanrix Hexa in inducing naïve CD8+ T cells to transform into central memory cells, effector memory or terminally differentiated T cells. This was also reflected by a significantly lower production of interferon-gamma (IFN-γ) by HBV-specific effector cells in children vaccinated with Hexavac. Vaccinated individuals who had antibody titres <10mIU/mL at year 5 (so called "non-responders"), regardless of which vaccine they received, had high quantities of naïve CD8+ T cells but lower quantities of central memory cells, effector cells, terminally differentiated cells and IFN-γ, than "responders" (titres above 10mIU/mL at year 5). In terms of the vaccine-induced CD4+ cell response, no difference was noted between the two hexavalent vaccines or between responders and non-responders. This study suggests that the alterations to the different subsets of memory T cells can be used to evaluate the efficacy of a vaccine and to assess the quality of an immune response. However, the relevance of CD4+ and CD8+ T cell response assessments was questioned during the meeting discussions. In particular, the difference in CD8+ T cell response between the two hexavalent vaccines was challenged, because other research has indicated that regular alum-adjuvanted HBV vaccines might be unable to induce (measurable) CD8+ T cell responses.

Furthermore, the antigen specificity of the ELISpot assay to measure antigen-specific CD4+ T helper cells was questioned, because of the important frequency of non-specific bystander cells (such as natural killer cells), that also produce spots.

Further research is needed to fully understand the complexities of the cellular immune response to HBV. Studies presented at this meeting show that such responses contribute to protection, integrating and possibly improving humoral-mediated immunity. It would be useful to characterize the cellular immune response in people vaccinated at an early age and in those vaccinated at an older age, so that these data could be compared to age groups that respond particularly well and have long persistence of antibody. Also, it would be worth studying cellular immune responses in relation to other influencing factors.

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Based on a presentation by
M. Clerici, Immunology, University of Milano, and Fondazione Don Carlo Gnocchi, Italy, and related meeting discussions.

The role of immune memory in responses to booster HBV vaccination and exposure to HBV (natural booster)

Immune memory following HBV vaccination can be demonstrated by:

- the prevention of reinfection or disease (epidemiology)
- persistence of specific antibodies in the protective range
- an anamnestic response following a booster dose or natural booster
- the demonstration of memory T and/or B cells.

Following primary HBV vaccination, immune memory, which even can outlast the presence of anti-HBs antibodies, is responsible for the ability to respond to a booster dose or exposure to HBV (natural booster). In the numerous studies investigating booster response, different criteria are used to define the response, such as a 2-fold increase or 4-fold increase of anti-HBs antibody concentration in comparison with the pre-booster concentration, or any increase from a negative level of anti-HBs antibody. Standardization of the criteria to define a response following a booster dose or a natural booster would facilitate the interpretation and comparison of these studies.

Antibody response to natural booster

In a vaccinated population two responses can occur after infection with HBV: either breakthrough infection or natural booster response. A natural booster response can be defined as an increase in anti-HBs level without revaccination and no appearance of anti-HBc. Natural booster response can contribute to the persistence of anti-HBs antibodies, particularly in areas of high HBV prevalence.

The Vax Demo 30 study in Alaska, a region with intermediate endemicity, provides follow-up data up to 30 years post-primary vaccination. It was found that in 1530 individuals followed for the first 10 years after immunization, 8.2% showed evidence of a natural booster effect (defined as a 4-fold rise in anti-HBs without anti-HBc) [1]. The number of anti-HBc breakthrough infections in this group had declined over time (25 in first 15 years, 0 between 15 and 22 years). The prevalence of natural booster is likely to have decreased over time due to the decline in the prevalence of infection in the population. The infectivity in the population is mainly affected by the predominant HBV genotype circulating in the community. As shown in Alaska during a 21 year follow-up study, 50% of individuals infected with HBV genotypes A2, B6, D and F1 were already HBeAg negative when they were under the age of 20 (median age range 16.1-19.8 years), whereas the median age for 50% seroconversion to HBeAg negative status was 47.8 years in patients with genotype C2 [2].

The Czech Republic is a low endemic country with 0.56% HBsAg prevalence, where there has been screening of pregnant women and vaccination of newborns of HBsAg positive mothers since 1988. In a study of children (1-18 yrs old) born to HBsAg positive mothers, a natural booster response was found in 38 (6%) children (booster response was defined as a 2-fold increase if first anti-HBs ≥100 mIU/mL, a 4-fold increase if first anti-HBs <100mIU/mL, or at least 40mIU/mL, if first anti-HBs <10mIU/mL).

In Thailand, a country with high endemicity, isolated natural booster responses occurred between 10 and 20 years after the start of pri-

mary vaccination, at the same frequency in HBeAg positive mothers, and in HBeAg negative /or HBsAg negative mothers.

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Antibody response to booster vaccination

Opinions over when to measure antibody response to a booster dose seem to be divided. Data described below (see page 11) from a booster dose study in college students in Taiwan suggest that anti-HBs responses could be induced as early as 1 week following a booster and that these responders are likely to have protective titres after a single dose and may not need further booster doses. However, data from Alaska show that 2 weeks after a booster dose may be the optimal time to measure the anti-HBs response, which corresponds to the time needed to develop an adaptive immune response with high affinity antibodies (i.e., 14 days).

In the majority of individuals who received a complete primary HBV vaccination schedule, the ability to develop an anamnestic response to a booster seems to persist up to at least 10 years. In the Czech Republic, vaccination of newborns of HBsAg positive mothers started in 1988. These newborns were tested for anti-HBs biennially, and (up to 2002, age 0-14 years) they received a booster dose within 3 months after detection of anti-HBs <10 mIU/mL. Following the booster dose given to 159 anti-HBs negative children born to HBsAg positive mothers, an anamnestic response with anti-HBs titres ≥40mIU/mL was found in 151 cases (95.0%), a lower increase (10-39mIU/mL) was found in 5 cases (3.1%), 2 children required 2 booster doses, and 1 child required 3 booster doses to achieve at least 10mIU/mL anti-HBs.

However, the ability to respond to a booster declines over time and can be lost. If booster doses are given they should be given while immune memory persists, i.e., within 10-15 years after infant vaccination, and before entering young adulthood when the risk of sexual transmission is high. Waning of the ability to respond to a booster dose seems to be more frequent in individuals vaccinated at birth and/or with low doses of vaccine and especially in individuals with low initial anti-HBs levels. For instance, a study in Micronesian adolescents vaccinated at birth showed that after 15-24 years, 57% had lost the ability to respond to a booster dose [1]. Pre-boost presence of anti-HBs is a predictor of a booster response of anti-HBs >10mIU/mL: individuals who were anti-HBs positive at 5 years of age after infant vaccination starting at birth were more likely to respond to a booster dose than those who had become anti-HBs negative after they were 5 years old [2].

Data from Alaska show that by 22 years post- primary vaccination, 7% of individuals vaccinated as children or adults failed to respond to a booster dose; and among those vaccinated as infants up to 40% had lost the ability to respond 15 years later.

Collective data of booster dose studies conducted in Alaskan children who received primary vaccination with either recombinant HBV vaccine or plasma-derived vaccine starting at birth are shown

Alaska booster dose studies in children given recombinant HBV vaccine starting at birth

Age at booster dose	% anti-HBs >10	Number given a booster	% booster response
HBV negative mother			
5 years [3]	12.5%	134	90%
5-7 years [2]	29%	158	99%
7.5 years [3]	0%	35	91%
10-15 years [2]	5%	138	88%
15 years [4]	0%	35	51%

Alaska booster dose studies in children given plasma-derived HBV vaccine starting at birth

Age at booster dose	% anti-HBs >10	Number given booster	% booster response
HBV negative mother			
9 years	41%	54	67%
13 years	24%	12	67%
12-15 years	21%	74	71%
HBV positive mother			
12 years	31%	10	90%

in the Tables on page 10. These studies illustrate that the ability to respond to a booster dose reduces as the length of time since primary vaccination increases.

In the Yo-Hep booster dose study 378 children in Alaska who received primary vaccination starting at birth were boosted, either at 5-7 years after primary vaccination with recombinant vaccine (N=166), or at adolescent age of 10-14 years after primary vaccination with recombinant vaccine (N=138), or after primary vaccination with serum-derived vaccine (N=74). The ability to respond to the booster dose decreased with increasing age. At 13 and 14 years of age only about 50% were able to respond to a booster dose.

A continued follow up of the Yo-Hep booster dose study, including 107 individuals who all responded to the booster dose, showed that 6-9 years after the booster dose, 60% had anti-HBs below 10mIU/mL and the levels were almost as low as those pre-boost. Factors that were significant for still having anti-HBs titres >10 mIU/mL at 6-9 years after the booster dose, were pre-boost anti-HBs level and the level of booster response at 2 and 4 weeks.

A study in Taiwan among college students indicated that a notable proportion of fully vaccinated infants may have lost immune memory (conferred by HBV vaccine and measured through an anamnestic response after booster) by the time they reach adolescence. It was estimated that an anamnestic anti-HBs response was absent in approximately 10% of Taiwanese 15–18-year-olds who may be potentially vulnerable to HBV infection [5]. This appears to be coupled with a lack of memory T cell cytokine responses, since 27% of those who received a booster dose in the study remained negative for HBsAg-specific IFN-γ or interleukin (IL)-5-secreting peripheral blood mononuclear cells (PBMCs; as measured by ELISpot) [5]. To address the issue of long-term protection after infant primary HBV vaccination, the kinetics of the humoral immune response to 3 booster doses (0, 1 and 6 months) was studied in 127 HBsAg negative, anti-HBc negative, anti-HBs negative college students who had completed HBV vaccination as newborns [6]. No significant differences in post-booster anti-HBs titres were found during the 7-month follow-up period with respect to age, family history of HBV carriage, blood type, or body mass index or gender. However, there may be a link between blood type and response to a booster dose, because none of the 8 students with blood type AB had an early booster response (at 1 week post-booster). One month after the first booster dose, 24.4% of students had anti-HBs titres <10mIU/mL. Only 20.5% had an early booster response with titres ≥10mIU/mL at 7-10 days. These early responders eventually had titres up to 20 times higher than those who could not mount an early response (<10mIU/mL at 7-10 days post booster) and this difference persisted to 6 months, but was no longer seen at 7 months. The seroconversion rate after a second booster dose was as high as 94.5% and after 3 booster doses, all but one had seroconverted. Some of those who had a slow or no response to the booster doses might be non-responders but they were few (less than 10%), which is in line with previous studies that estimated non-responding rates to HBV vaccines to be low [5, 7]. In terms of the kinetics of anti-HBs titres in the present study, 13.4% did not sustain an anti-HBs response between booster doses.

Following a booster dose, anti-HBs rapidly falls. The Vax Demo 22 study in Alaska showed that only 41% of individuals still had anti-HBs titres >10mIU/mL at 1 year following the booster dose. The GMT fell from 87mIU/mL at 2 weeks after the booster dose to 8mIU/mL at 1 year. These findings were supported by another study of booster dose response in HCW, which showed a rapid fall of GMT in the first year following the booster.

Despite the waning antibody response to a booster dose, individuals that are not able to achieve an anamnestic response may still mount a protective response to infection. Indeed, memory B and T cells are likely to persist beyond measurable anti-HBs and they are thought to continue protecting against acute and chronic disease. This suggests that investigating the antibody response to a booster dose may not be enough to determine long-term immunity and protection.

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Effectiveness of universal hepatitis B vaccination

High endemic region

The Gambia

In the 1980s, HBsAg carriage in The Gambia was 10% in children and 15% in adults and the most common route of infection was via horizontal transmission. The annual incidence of hepatocellular carcinoma (HCC) was high: 23/100,000 population.

The Gambia Hepatitis Intervention Scheme (GHIS) is a partnership between the International Agency for Research on Cancer, the Medical Research Council in the UK, and the Gambian Government. During phase 1 of the GHIS programme, newborn HBV vaccination was gradually introduced between 1986 and 1990. During this phase, about 60,000 newborns received the vaccine and 60,000 non-vaccinated newborns acted as controls. In phase 2 (1990-2010) of the GHIS programme, a national cancer registry was established and vaccine efficacy studies were carried out. Phase 3 (2010-2035) will involve intensive surveillance for HCC.

Plasma-derived HBV vaccine is administered following a 4 dose schedule, with the first 3 doses given within the first 4 months of the child's life. Due to logistics, the median time before a newborn receives the birth dose is 22 days. By 2008, it was estimated that between 85-90% vaccine coverage was achieved for the first 3 doses. Nationwide vaccination has been very successful at reducing HBsAg carriage. Of 4500 children under the age of 18 years tested for HBsAg in 2009, the highest rate (1.8%) was in the 15-17.5 year age group, however before vaccination the rates were up to 10-12% in some age groups. In 2008, 127 breakthrough infections were detected in 1251 fully vaccinated subjects in two villages (Keneba and Manduar), but these infections were not persistent infections as in none of the 100 HBsAg-negative/anti-HBc positive subjects tested, could HBV DNA be detected. In The Gambia, HCC is mainly attributable to HBV, especially in patients below 50 years of age [1]. Based on age-specific incidence rates of common cancers in The Gambia between 1987 and 2002, the preliminary GHIS results indicate that HBV vaccination is efficient in preventing HCC [2]. Assuming an attributable risk of 70%, the estimated protective effectiveness of HBV vaccination against HCC was 68% [2].

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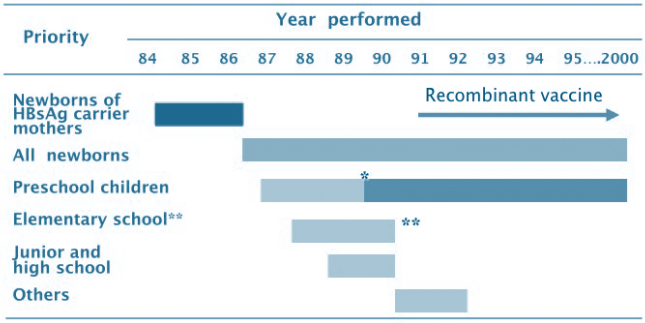
Based on a presentation by
H. Whittle, London School of Hygiene and Tropical Medicine, London, UK.

Taiwan

Prior to universal vaccination, Taiwan used to be a high endemic area of HBV infection, around 90% of the population aged 40 years and above were estimated to have been infected with HBV. About 2.5 million people (15%-20% of the adult population) were estimated to be HBV carriers. In addition to being sources of transmission, carriers are likely to develop chronic hepatitis, liver cirrhosis and HCC. Chronic HBV infection is responsible for about 80% of the current cases of liver cirrhosis and HCC, which are among the leading causes of mortality in Taiwan. HCC is the leading cause of cancer death in males in Taiwan.

Between 1984 and 1986, Taiwan launched the first HBV universal infant vaccination programme in the world. The progression of the HBV vaccination programme since 1984 in Taiwan is shown in the Figure below. Initially, the main focus was newborns born to HBsAg positive mothers. Since 1986, all neonates have been vaccinated and between 1987 and 1992 there has been a catch-up programme of vaccination for individuals born before the start of universal newborn vaccination. Proof of HBV vaccination is a requirement before entry into elementary school.

HBV vaccination policy in Taiwan, from 1984



* *July 1987 ~ Sep. 1990: Vaccinate preschool on voluntary base with payment. After Oct. 1990: Catch-up vaccination without charge for children up to 1st graders*

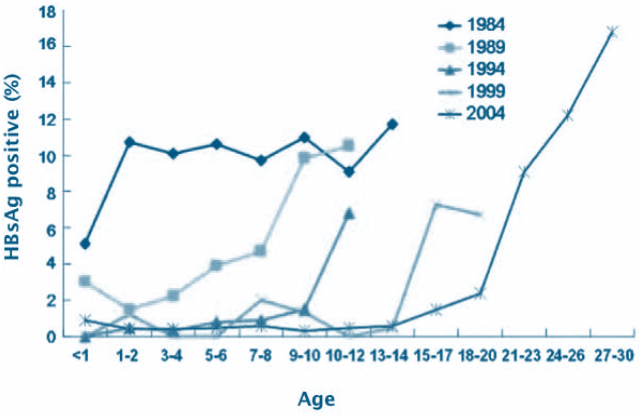
** *After July 1991, all first graders were checked for their vaccination record. Non- or incompletely vaccinated pupils needed to be vaccinated.*

The primary goal of universal infant HBV vaccination was to control chronic HBV infection in early infancy. If a newborn becomes infected with HBV, there is a >90% chance of them becoming a chronic carrier, whereas acquisition in later childhood leads to a 20% chance of becoming a chronic carrier. This risk of becoming a chronic carrier continues to decrease with age and is low when infection is acquired in adulthood. Studies of perinatal transmission from HBsAg positive mothers have shown that 90% of infants will be chronic carriers if the mother is HBeAg positive, whilst less than 5% of children will become carrier if they are born to HBeAg negative mothers (most will have acute, fulminant HBV, or remain uninfected). In Taiwan, pregnant women are screened for both HBsAg, all positives are further tested for HBeAg. Newborns of HBsAg negative mothers and newborns of HBsAg positive/HBeAg negative mothers receive vaccine (3 doses at 0, 1, 6 months) but no HBIG while only newborns of HBsAg positive/HBeAg positive mothers receive HBIG (within 24hrs after birth) and 3 doses of vaccine (at 0, 1, 6 months) in order to save costs.

Data from the Taiwan Centers for Disease Control (Taiwan CDC) show that the overall vaccine coverage rates from July 1984 to December 2002 were 97%, 95%, and 93% for the 1st, 2nd, and 3rd doses, respectively, and have remained quite stable over the years (not falling below 85% for 3 doses) [1]. A coverage rate of over 95% for completion of three doses was shown since 2000.

Over the 25 years of the universal infant vaccination programme, the effectiveness of this strategy has been proven. A series of prevalence surveys on children born before and after the start of the national vaccination programme, show a steady decrease in HBsAg seroprevalence in Taiwan after the national vaccination programme was launched, with 78% to 87% vaccine effectiveness. In Taipei the HBsAg rate declined from 9.8% to 0.6% in 20 years (1984-2004) [2, 3]. A graphical presentation of the decline between 1984 and 2004 [4] is presented in the Figure below.

HBsAg prevalence in children and young adults in Taipei city (1984-2004) [4]



Studies of liver disease have documented a 68% decline in mortality from fulminant hepatitis in infants and a 75% decrease in the incidence of HCC in children 6–9 years of age after the national vaccination programme began.

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Thailand

Following 2 test projects involving 12 provinces, universal newborn HBV vaccination was included in the expanded programme of immunization (EPI) for Thailand in 1992 (3 doses at 0, 2, 6 months). Universal HBV vaccination has reduced the number of acute HBV cases and the number of HBV carriers. In 1988, before implementation of HBV vaccination, 5-6% of children were HBsAg carriers. In 2004, in children younger than 15 years of age (born after HBV vaccine was included in the EPI programme), the HBsAg carrier rate had reduced to 0.7% and in those above 18 years of age (born before HBV vaccine was included in the EPI programme) the HBsAg carrier rate was 3% [1]. The reduction in carriers is expected to lead to a reduced incidence of chronic liver disease (cirrhosis and HCC) in the future.

A field trial involving 29,000 children in the Chiang Rai province comparing the use of combined diphtheria, tetanus, pertussis and HBV vaccine (DTPw-HBV; 25,000 children) with separate administration of DTPw and monovalent HBV vaccines (4000 children), showed that vaccination with the combined DTPw-HBV vaccine resulted in a decrease in infection rate and a reduced carrier rate of around 0.2% after receiving the combined vaccine and 1.15% when the HBV vaccine was administered separately [2]. The long-term antibody persistence in children that have received this combined vaccine has been shown [3]. Additional benefits of the combined vaccination approach include high compliance and coverage; fast implementation; and economic savings (logistical cost-savings, demonstration of cost-effectiveness of DTPw vaccine). Due to these benefits, the combined DPTw-HBV vaccine was added to the EPI in Thailand.

HBV monovalent vaccine is given at birth and the combined DPTw-HBV vaccine is given at 2, 4 and 6 months of age. If the mother is HBsAg positive, giving an extra dose of HBV monovalent vaccine at 1 month reduces the risk of the child becoming infected by two thirds [4]. Although 5 vaccine doses are recommended for infants born to HBsAg positive mothers, there is no universal screening of pregnant women in Thailand. The drawback of screening is that it produces a situation where the need for immunization is identified, but the resources may not be available (e.g., HBIG is often not available outside large cities). An additional vaccine dose at one month (outside the EPI schedule) for newborns of HBsAg positive mothers would prevent vertical transmission as efficiently as providing HBIG.

Attention should be focused on the significant population of HBsAg positive migrant workers in Thailand. A study has shown that the percentage of migrants from Laos, Cambodia and Myanmar who are HBV DNA positive are 6.9%, 10.8% and 9.7%, respectively; compared to 3.9% for the Thai population [5].

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Based on a presentation by
Y. Poovorawan, Center of Excellence in Clinical Virology, Bangkok, Thailand.

Low/medium endemic region

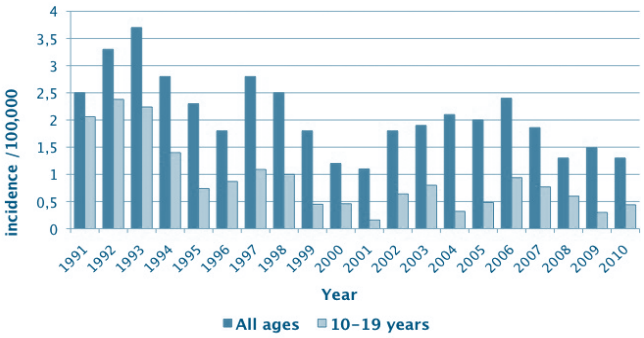
Spain

Before vaccination, HBV infection in Catalonia, a region of Spain with 7.5 million inhabitants, was a significant health problem. Although there were no accurate data, it was estimated that the annual HBV incidence was 20-30/100,000. Vaccination of newborns of HBsAg positive mothers and other risk groups was started in 1984. At the end of the 1980s, there were no reliable data on the incidence of HBV, because all cases of viral hepatitis were reported aggregated. However, estimates indicate that in Catalonia, 1% of the population were chronic HBsAg carriers (intermediate endemicity), which was similar to the carrier rate in other European countries. In a sample of the population in 1989, the prevalence of HBsAg in children (<15 years of age) was 0.5% and in adults (≥15 years of age) was 1.7%; the anti-HBs prevalence was 1.6% and 18%, respectively [1].

The selective vaccination of risk groups had limited impact and clinical cases were being detected mainly in adolescents (none were detected in children). Therefore, it was hoped that universal vaccination of pre-adolescents with 3 doses of vaccine, which was included in well-established school vaccination programmes from 1991, had the potential to eliminate the disease in a safe, cheap and effective way. The prevalence of HBsAg carriers was very low (0.1%) in 1996, five times lower than the figure obtained in this age group in 1989 (0.5%). This suggests that the carrier detection programme among pregnant women and the passive-active immunization of newborn babies from HBsAg positive mothers introduced in 1984 was working adequately. It also confirms that horizontal transmission during infancy was negligible in Catalonia and that the decision taken in 1990 not to vaccinate all newborns and to concentrate efforts on mass vaccination of pre-adolescents was right [2]. Between 1992 and 2010, vaccine coverage has been around 80-90%, but the results of the vaccine-induced immunity (anti-HBs positive/anti-HBc negative) studies in adolescents suggest that coverage is under-reported [3]. In 2002, universal HBV vaccination of infants (2 months of age) was included in the programme.

The reported incidence of HBV in Catalonia from 1991 to 2010 is shown in the Figure below.

Reported incidence of HBV in Catalonia, 1991-2010



The reported incidence of acute HBV has fallen by 48% in the population as a whole since the introduction of universal vaccination of pre-adolescents 19 years ago. The decrease was greatest (61%) between 1991 and 2001. In the 10-19 years age group, which includes vaccinated cohorts, the reduction in incidence was 81%, and the greatest reduction was observed between 1991 and 2001 (100% in males and 74.2% in females). Despite this fall in the reported incidence of acute HBV, no reduction has been observed since 2001 in the 10-19 years age group or in the population as a whole. Between 2002 and 2010, the percentage of migrants has increased by 171% in the whole population in Catalonia, and by 161% in the 10-19 years age group. However, whether the sub-optimal response of pre-adolescents to universal HBV vaccination in Spain is due to the higher proportion of unimmunized pre-adolescent migrants is yet to be proven. For instance, over the last decade in the UK, where there is no universal immunization programme, immigration has also rapidly increased. Although chronic HBV has increased, acute HBV is at an all-time low in the UK, which suggests that immigration does not necessarily lead to an increase in acute HBV. New studies to understand the factors associated with the stabilization of reported HBV incidence rates in Catalonia in recent years should be carried out. Specific activities targeting the vaccination of migrants were proposed in order to improve the impact of HBV vaccination in Catalonia. Special efforts should be directed at migrants coming from countries without universal vaccination or where vaccine coverage is low.

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Based on a presentation by
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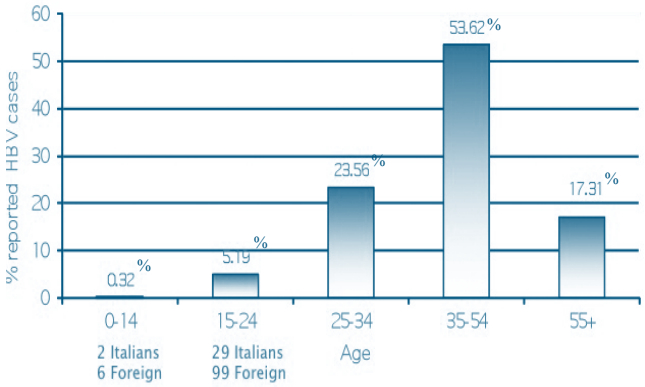
Italy

Before HBV vaccination, the main modes of HBV transmission in Italy were perinatal and horizontal, sexual, and via re-used syringes and needles. Vaccination of high risk groups started in 1983 and in 1991 universal vaccination of infants and adolescents was implemented.

SEIEVA, the Italian national surveillance system of the National Institute of Health started in the 1980s to collect data on clinical hepatitis cases. The incidence of HBV infection in Italy has dramatically declined over the last 20 years. HBsAg prevalence rates of 2.1% to 3.4% were observed in the early 1980s, and these decreased to 0.8%-1.6% in the late 1980s [1, 2]. At the end of the 1980s, Italy was a country of intermediate HBV endemicity, with about 2 million chronic carriers. Due to universal vaccination of infants and adolescents, combined with improved social and economic conditions, the incidence of HBV infections in Italy declined remarkably from 12 cases/100,000 in 1985 to 0.9 cases /100,000 in 2010. The number of chronic carriers has also declined to about 500,000. Currently, there are approximately 100,000 cases of HBV-related cirrhosis annually and 1500 deaths per year related to HBV.

Distribution of notified HBV cases by age, SEIEVA 2006-2010



HBV cases notified to the SEIEVA surveillance system in 2006-2010, mainly occurred in adults 35-50 years of age (see Figure below, left). In this period, 16% of notified HBV cases were migrants, mainly from Eastern Europe, Africa and Asia.

Furthermore, data collected by SEIEVA reveal that the majority of newly reported cases of acute HBV occur in unvaccinated adults. The most important risk factors for newly acquired infection are: sexual contact with infected individuals; beauty treatments (i.e., pedicures, tattoos); iatrogenic exposure; and intravenous drug use.

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Based on a presentation by
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Bulgaria

Bulgaria is a country of intermediate endemicity, with 3-5% HBV carrier prevalence and more than 30% of the population with serological evidence of HBV infection. Since 1983, notification of all acute cases of HBV infection has been mandatory, as well as all positive laboratory cases. Between 1988 and 1991, there was selective vaccination of newborns born to HBsAg positive mothers. Newborn vaccination was started in 1991 and became routine by 1992.

Before the introduction of vaccination, HBV incidence in newborns and children 1-3 years of age was 31.1 and 31.6 per 100,000, respectively. HBV incidence was highest in persons 4-7, 15-19 and 20-29 years of age: 55.9; 52.0 and 50.2 per 100,000, respectively. During 1988-1991, the period of selective vaccination, HBV incidence declined only in infants (by 40.9%).

In addition to other public health measures, the adoption of the universal newborn vaccination strategy has led to a significant decrease in HBV infection. The annual incidence of reported acute HBV cases among children 0-14 years of age has decreased by 97.6% and among adolescents 15-19 years of age by 88.4%. This decline corresponded to the cumulative number of vaccinated newborn cohorts.

A model-based economic assessment of introduction of universal newborn HBV vaccination in Bulgaria was made by using cost-benefit analysis and comparing two vaccination strategies: "without vaccination" and "universal vaccination of all newborns". The capital costs (equipment, building, ...) as well as the indirect costs were not taken into account in the model. Nevertheless, this cost-benefit assessment confirmed the high effectiveness of the HBV vaccination programme introduced in 1991 and showed that universal vaccination of all newborns would significantly reduce the expected number of HBV cases and deaths and total medical costs related to infection, and that vaccination would be both medically and economically beneficial. The economic effect of the vaccination was expected to be realized 19 years after introduction of the programme when the benefits should exceed its costs.

The full effect of the immunization programme was expected to be achieved in 2011, when all adolescents up to 19 years of age would be protected by the vaccination they received as newborns. At present, the annual incidence of reported acute HBV cases is highest among young adults 20-24 years of age. A decline of HBV incidence in this age group is expected during the next 5 years.

Based on a presentation by
M. Kojouharova, National Centre of Infectious and Parasitic Diseases, Sofia, Bulgaria.

USA

In the US, recommendations for HBV vaccination of several high risk groups have been implemented between 1982 and 2011, as detailed in the Table below. Surveys have reported sub-optimal vaccine coverage in non-high risk healthcare personnel [1]; high risk adults [2]; and chronic haemodialysis patients [3, 4].

Advisory Committee on Immunization Practices (ACIP) recommendations for HBV vaccination for high risk groups in the US

Year	Recommendation
1982	Groups at high-risk for HBV infection: health-care providers, MSM, IDUs, haemodialysis patients, household and sexual partners of chronic HBV, inmates of long-term correctional facilities, others [5]
1984	Infants born to women with chronic HBV
1985	Heterosexual persons with multiple sex partners, international travellers to HBV-endemic areas
1990	Public safety workers exposed to blood, family contacts of adoptees from HBV-endemic areas
2011	Adults with diabetes mellitus <60 years of age should be vaccinated; ≥60 years of age may be vaccinated at the discretion of the treating clinician.

The recommendations for universal HBV vaccination in the US are shown in the Table below [5].

ACIP recommendations for universal HBV vaccination in the US

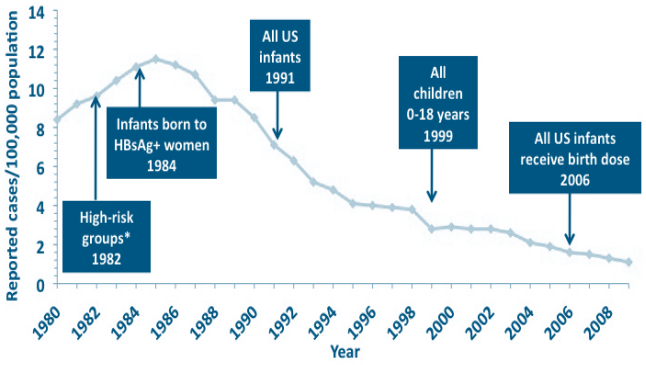
Year	Recommendation
1991	All US infants (at birth or 1 month of age)
1995	Catch-up vaccination. All unvaccinated children 11-12 years of age
1999	Catch-up vaccination. All unvaccinated children 0-18 years of age
2002	Preference for vaccination starting at birth
2006	First dose hepatitis B vaccine recommended at "birth" (before hospital discharge)

Vaccine coverage for infants (19-35 months) is currently greater than 90%, which meets the 2020 projected target [6]. In 1998, universal vaccination coverage for the birth dose (usually by 3 days of age) was 56%. However, in 1999, after a temporary recommendation to postpone the birth dose (due to a thimerosal safety concern) coverage fell to 32%. In 2010 birth dose coverage was still less than 65%, while the objective is 85% coverage by 2020 [7]. In 2010, the vaccination coverage for adolescents (13-17 years of age) was above 90% [8]. It is becoming more common that schools in the US require children and adolescents to be vaccinated against HBV prior to entry.

The national notifiable disease surveillance system (NNDSS) in the US relies on weekly voluntary reporting by state and territorial health departments [9]. Recording has been more consistent since reporting transitioned to electronic systems starting in 1990. NNDSS is designed for acute (symptomatic) infectious disease reporting. There is no reliable way of reporting chronic HBV cases. A limitation of the NNDSS is missing information (such as risk exposure, vaccination history) in up to 50% of the cases reported. Among cases with risk information, only 20% of 2009 cases had a risk identified. Alternatively, when multiple risks are identified, it is also not possible to confirm the source of HBV infection. However, the biggest limitation of the system is under-reporting. Modelling indicates that 10 cases of new HBV infection occur for every case that is reported.

The incidence of acute HBV cases reported to the system between 1980 and 2009 is shown in the Figure below [9]. Since 1990, there has been an 84% overall decrease in acute cases reported.

Incidence of reported acute HBV cases in the US between 1980–2009 [9]



*Health-care providers, MSM, IDUs, hemodialysis patients, household & sexual partners of persons with chronic HBV, inmates of long-term correctional facilities

The greatest declines in incidence were among infants and children 0-19 years of age, but there were also significant declines in the age groups 20-29 years and 30-39 years. Smaller declines were seen among adults ≥50 years. In 2009, the highest incidence was in the age group 30-39 years. There have been marked declines in HBV incidence in all ethnic groups; the highest rates of HBV incidence remain among Black, non-Hispanic individuals.

Between 1996 and 2010, 29 outbreaks of HBV infection in institutional care facilities (involving one or more nursing homes or assisted living facilities) were reported to the US Centers for Disease Control (CDC) among adults with diabetes receiving assisted blood glucose monitoring or other diabetes care procedures. These outbreaks raised a question of possible increased risk for HBV infection among unvaccinated adults with diabetes. Examination of the CDC's National Health and Nutrition Examination Survey (NHANES), a nationally representative survey of non-institutionalized adults, found an overall 60% increase in the seroprevalence of anti-HBc ($p<0.001$) among adults with diabetes compared to adults without diabetes. In the age group 18-59 years, the increase was highest (70%, $p<0.001$) and in the age group ≥60 years the increase was 30% ($p=0.032$). However, in this survey, the sample size was not large enough to evaluate the seroprevalence of HBV infection among adults with diabetes after controlling for known HBV infection risk factors. Therefore, a retrospective study was conducted to examine the risk among 865 adults with acute HBV infection, of which 11% had diabetes. In the age group <60 years, there was 2 times higher odds of HBV infection, and in the age group ≥60 years, there was 1.5 times higher odds of HBV infection, after stratifying for adults with diabetes who had no known HBV risk behaviour [10]. The population of diabetes patients is relatively important in the US, and therefore adults with diabetes represent a high number of HBV cases.

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Based on a presentation by
T.V. Murphy, Centers for Disease Control and Prevention (CDC), Atlanta, USA.

Alaska

Universal newborn HBV vaccination started in Alaska in 1984, and catch-up vaccination for children and adults was introduced between 1984 and 1988 (40,000 vaccinated). This has led to a shift from a high endemic status prior to 1984 to an intermediate status since 2000.

The incidence of symptomatic HBV infection in the Alaska Native population has dramatically declined.

Over this time, infectivity of chronic carriers has reduced. Acute HBV and HCC in children were eliminated [1]. In 2011, no HBsAg carriers were reported in children and adolescents under the age of 20. The prevalence of HBeAg in HBsAg positive adults and children has fallen from 40% to around 1%.

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Based on a presentation by
B. McMahon, Alaska Native Medical Center, Alaska and Centers for Disease Control and Prevention (CDC), Atlanta, USA.

Breakthrough infections

During the meeting it became evident that there is no clear, standardized definition of the term “breakthrough infection”. However, it can be defined as an infection in an appropriately vaccinated individual (number of doses, spacing between doses) that is confirmed by a positive serological test for HBV and/or clinical disease. Breakthrough infections may have a booster effect on the anti-HBs antibody titre. The majority of breakthrough infections are clinically mild infections with only anti-HBc seroconversion in the absence of HBsAg positivity. However, breakthrough infections can also result in a significant, acute clinical infection; or, in case HBsAg is present, can imply a risk of becoming a chronic carrier.
Interpreting data from studies of breakthrough infection is hampered by discrepancies in how the infection is defined (1 positive result or 2; use of the definition “transient” (isolated) positive results of anti-HBc antibody, HBsAg and/or a transient raise in ALT).

Three different situations of breakthrough infections were considered during the meeting:

- vaccine failure;
- infected infants born to a HBsAg positive mother;
- emerging mutants.

Vaccine failure

Breakthrough infections can occur in fully vaccinated individuals due to the known/unknown failure of the vaccine (e.g., deteriorated vaccine) or due to inadequate vaccination. Vaccine failure is either an event that has no consequence (anti-HBc is present but no acute infection or chronic disease develops), or is an event that leads to acute infection and/or chronic disease.

Although the number of vaccinated people in Italy has increased, the percentage of acute hepatitis cases among vaccinated people between 2001 and 2010 has remained stable. Before cases of clinical HBV are reported to the Italian national surveillance system SEIEVA, clinicians exclude chronic infection based on the history of clinical illness, previous test results, and presence of IgM anti-HBc.

Between 2001 and 2010, 90.9% of 5252 HBV cases notified to SEIEVA had complete vaccination information. Of these, 144 (3%) were vaccinated individuals who became infected with acute HBV (possible breakthrough infection). Amongst the 144, 30 were co-infected with HCV, hepatitis D (HDV), or both HDV and HCV. From 112 cases of the 144 possible breakthrough infections the

immunization data was available. Only 27 cases of the 112 (24.1%) had received the complete vaccination course according to the correct schedule and before exposure to HBV. Among those correctly vaccinated before infection, the mean age was 24, 21 were male, and 6 were co-infected with HCV, HDV or HCV+HDV. Most common risk factors identified were dental therapy, household contact with HBsAg positive person, and parenteral exposure, followed by IDU and sexual transmission.

By recalculation of 24.1% of the total 144 potential breakthrough infections, there are an estimated 35 true breakthrough cases (correctly vaccinated before exposure) notified over 10 years. If this number of true breakthrough infections in the SEIEVA database over 10 years is extrapolated to the total Italian population, an estimated 5-6 vaccination failures, defined as acute clinical cases in fully vaccinated individuals, would occur in Italy each year. This indicates that breakthrough infection is a rare event.

Molecular characterization of 7 correctly vaccinated cases of breakthrough infection who were HBV DNA positive, showed that 4 cases were attributable to a lack of immune response and 3 to viral mutation able to evade the immune response.

Research from Alaska has shown that breakthrough infection was more likely to occur if a child had failed to respond to vaccination or if they developed a lower anti-HBs GMT. In a few patients anti-HBs had waned and they became anti-HBc positive, then had an increase of anti-HBs. Levels of HBV DNA in these patients that were transiently positive were so low that they are very unlikely to be infective, unless their blood was transfused, and it is uncertain if reactivation would occur if they became immune-suppressed.

Studies from The Gambia have shown that post-vaccination anti-HBs levels decay over time. During 15-20 years follow-up after infant vaccination in The Gambia (GHIS cohort), transient breakthrough infection, defined by the presence of anti-HBc, had occurred in 5-20% of vaccinees. Unless these infections occur in early childhood, they are unlikely to evolve into chronic infection. Although chronic carrier status after vaccination has not been shown in other follow-up studies presented during the meeting, a small number of children (<1%) in this Gambian cohort did become chronic carriers after 15-20 years. It is however not clear whether these children had been non-responders to primary vaccination. In responders to vaccination in other Gambian studies it was demonstrated that the risk of breakthrough infection is higher when the peak anti-HBs titre is lower (10% breakthrough infections when anti-HBs >1000mIU/mL versus 26% when anti-HBs <10mIU/mL). Breakthrough infections occur more commonly in males and their frequency increases with increasing age (from 6% in 1-4 year olds to 37% in 25-29 year olds). HBV DNA could not be detected in any of the HBsAg negative/anti-HBc positive breakthrough cases, suggesting that there is no persistent infection and no vaccine escape mutants have been identified.

In Taiwan, despite the effectiveness of HBV vaccination, breakthrough infections have been detected by the presence of anti-HBc in 4.0-5.7% of vaccine recipients in many studies [1, 2]. The causes of vaccine failure may be lower vaccination coverage and incomplete HBV vaccination in the early era of the nationwide HBV vaccination programme. During 20 years of follow-up of vaccination studies in Thailand, a country with high endemicity, breakthrough infections were seen more often in the second decade of life, suggesting an increase in exposure to HBV with age. Occult infections without any clinical symptoms were found in 25% of HBeAg positive mothers, compared to 7.5% of HBeAg negative mothers. Although breakthrough infections and occult infections were reported, no HBV cases with evolving chronicity were documented.

In addition to antibody titres declining over time in vaccinated people, it is possible that antibody quality also declines over time and may influence breakthrough infections. It would be interesting to know whether antibody affinity and neutralizing capabilities are reduced in individuals that experience breakthrough infections despite having an anti-HBs level >10mIU/mL after full 3-dose vaccination. Unfortunately, there are no commercially available kits to assess the affinity of sero-antibodies.

The role of HBV genotype in breakthrough infections should be further investigated. Two genotypes (E and F) have different “a” determinants and vaccines may be less effective for these 2 genotypes. Although a few breakthrough infection cases with HBV genotype E were reported in Egypt and with genotype F in Italy, in The Gambia (predominant genotype E) and in Alaska (predominant genotype F), there has not been any evidence that vaccination has been less effective. In Taiwan, HBV genotype C became more prevalent in HBsAg positive carriers since universal vaccination was implemented.

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Based on presentations by
M.E. Tosti, Instituto Superiore di Sanita, Rome, Italy;
B. McMahon, Alaska Native Medical Center, Alaska and Centers for Disease Control and Prevention (CDC), Atlanta, USA;
M. van der Sande, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands and Utrecht Medical University Centre, The Netherlands;
H. Whittle, London School Hygiene and Tropical Medicine, London, UK;
C-F. Jan, National Taiwan University Hospital, Taipei, Taiwan;
Y. Poovorawan, Center of Excellence in Clinical Virology, Bangkok, Thailand.

Infected infants born to HBsAg positive mothers

The Netherlands

HBV vaccination in the Netherlands has been implemented over the years as follows:

1983	At-risk occupations and patient groups
1989	Universal antenatal screening + vaccination of infants born to HBsAg positive mothers
2002	Behavioural high-risk groups - injecting drug users (IDU) - men who have sex with men (MSM) - commercial sex workers (CSW) - heterosexuals with high rate of partner change (stopped in 2007)
2003	Children of migrants from endemic countries
2011	Universal infant vaccination

The current vaccination schedule in the Netherlands for infants born to HBsAg positive mothers is HBIG at birth and HBV vaccine at 0, 2, 3, 4, and 11 months. An evaluation of the effectiveness of vaccination of infants born to HBsAg positive mothers between 2003 and 2007 showed that vaccine coverage was high: of 2657 infants born to HBsAg positive mothers registered in the national database, 2416 (91%) received HBIG at birth and ≥3 doses of vaccine. An HBV test result was available for 2121 infants and, of these, 13 were HBsAg positive (0.6%, 2 from the same mother). All HBsAg positive children except one had high anti-HBc levels, while 3 HBsAg negative infants also had a persistent high anti-HBc titre. Of the 12 mothers of these infants, 10 were HBeAg positive and 2 were HBeAg negative. These findings show that the rate of perinatal infection in this particular population with high coverage of HBV vaccine and HBIG is very low (0.6%) and that, in most cases, the vaccine is effective in protecting the infants born to HBsAg positive mothers. No difference in the rate of perinatal infection was found between different vaccination schedules.

Research from the Netherlands has shown that children of Chinese mothers are at nine times higher risk of perinatal infection despite vaccination [1]. The higher prevalence of HBV genotype C within the Chinese community in the Netherlands may be a significant factor in the increased risk of perinatal infection in their children, but genotype data were not available in this study. To avoid transmission, antiviral treatment should be considered for all HBsAg positive pregnant women of Chinese descent.

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Based on a presentation by M. van der Sande (on behalf of Susan Hahné), National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands.

Taiwan

A seroepidemiologic survey conducted in 2004 in Taipei, Taiwan, identified 40 out of 7234 children (0.5%) who were chronic carriers [1]. The 40 children had all received over 3 doses of vaccine, 30 were born to HBsAg positive mothers; 2 were born to HBsAg negative mothers but their main caregivers were HBsAg positive; and for 8 children the status of the mother was unknown. Although the serological status before vaccination was unknown, these results indicate that, after newborn vaccination, maternal HBsAg status is probably an important factor in determining whether or not a child can become infected and develop chronicity.

In another study of HBV perinatal infection in neonates born to high-risk mothers (HBeAg and HBsAg positive) from 1984-1993 in Taiwan, 2.4% newborns (16/665) were HBsAg seropositive and all became chronic carriers [2].

In a prospective study in Taiwan of 1598 infants born to HBsAg positive mothers between 2009 and 2011, 302 born to HBeAg positive mothers received HBIG and HBV vaccine and 9.3% became HBsAg positive. Among those born to HBeAg negative mothers who received HBIG and HBV vaccine (1133 infants) or only vaccine and no HBIG (163 infants), none became HBsAg positive. This study shows that breakthrough infections not only occurred in newborns born to HBeAg positive mothers who were vaccinated without HBIG, but also in newborns who did receive HBIG, indicating that the HBeAg positive status of the mother has an important role in breakthrough infections. In the past, it has been considered that there exists a direct correlation between HBeAg positivity and viral load. The presence of HBeAg is normally a marker for high replication, however being HBeAg positive does not imply that viraemia (high viral load) will be present. Results presented in the table overleaf show that children born to HBeAg positive mothers with high viraemia (>106 copies/ml HBV DNA) were more likely to be HBsAg positive (5/55), while none of the children born to HBeAg negative mothers with high viraemia became HBsAg positive.

Although the number of cases was small, the data from Taiwan show that there might be a dichotomy, where HBeAg positivity is one risk factor and high viral load is another. Possibly there are additional factors with an impact on breakthrough infections.

Research is needed into the use of antiviral therapy (e.g., Tenofovir) for high-risk pregnant women during the last trimester, in order to reduce their viral load and attempt to prevent intrauterine and perinatal transmission to infants.

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Based on a presentation by Y-H. Ni, Children's Hospital and College of Medicine, Taipei, Taiwan.

HBsAg status in vaccinated infants born to HBsAg positive mothers in Taiwan, according to maternal viral load and HBeAg status

Maternal HBV DNA (copies/mL)	Maternal HBeAg (+)	Children HBsAg (+) (rate %)	Maternal HBeAg (-)	Children HBsAg (+) (rate %)
$\geq 10^8$	31	4 (12.9%)	2	0 (0%)
10^7	20	0 (0%)	1	0 (0%)
10^6	4	1 (25%)	3	0 (0%)
10^4~10^5	8	0 (0%)	26	0 (0%)
$<10^4$	20	0 (0%)	191	0 (0%)
Total	83	5 (6.02%)*	223	0

**95% confidence interval [2.3%-13.7%]*

Czech Republic

When identifying breakthrough infections in children, it is important to consider passive transfer of HBsAg and anti-HBc from mother to child to be able to identify age-dependent false positive results. Research from the Czech Republic showed that umbilical blood and the venous blood of children up to 1 month of age is often positive for HBsAg, but after 1 month it is relatively rare. Anti-HBc was found in venous and umbilical blood of children born to HBsAg positive mothers and until the age of 6 months, but after 2-3 years anti-HBc prevalence is low.

In a study in the Czech Republic the following different definitions of breakthrough infection were considered:

- HBsAg carrier status (at least 2 positive results in a child older than 1 month);
- isolated HBsAg positive result (one positive result in a child older than 1 month);
- anti-HBc seroconversion (at least 2 anti-HBc positive results in a child aged 3 years or older with previous waning of anti-HBc);
- long-term persistence of anti-HBc (at least 2 anti-HBc positive results in a child aged 3 years or older without previous waning of anti-HBc);
- isolated anti-HBc positive result (one positive result in a child aged 3 years or older).

HBsAg carrier status obtained through vertical transmission was found in 2 children (0.3%) before they were 12 months old. One of the two children had an escape mutant. Isolated (single) HBsAg positive results were detected in another 3 children, however subsequent investigations excluded HBV infection [1].

In this study, 5 (0.8%) children with waning maternal anti-HBc had an anti-HBc seroconversion, i.e., *de novo* development of own anti-HBc after contact with the virus. Long-term persistence of anti-HBc was found in 5 children (0.8%). Isolated (single) anti-HBc positive results were detected in 11 children from 3 to 14 years of age, but appeared to be false positive.

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Based on a presentation by

L. Roznovsky, Department of Infectious Diseases, Ostrava, Czech Republic.

Emerging mutants and the use of antiviral agents

HBsAg is a complex protein and both vaccine and antiviral drugs select for mutations which may impact on its surface antigenicity. This raises a concern over the consequence of HBsAg mutants emerging in an era of increased levels of immunization and use of antivirals. It is important to understand how common these HBsAg mutations are in HBV infected populations and whether the mutant variants are being transmitted (particularly to vaccinated individuals) and can lead to the development of acute or chronic hepatitis. However, studies of the prevalence of HBsAg mutants are limited because viral sequencing is both laborious and expensive. The results of direct viral sequencing alone may not accurately reflect changes in antigenicity.

In Taiwan, seroepidemiologic surveys have been carried out every 5 years since 1984 for a group that includes vaccinated individuals in endemic areas (before and after universal infant vaccination programme), blood donors, children of HBsAg carrier mothers and high-risk groups. HBV universal vaccination has increased the prevalence of HBV surface gene mutants, especially sG145R and sT126A/S (48%) among vaccinated individuals with HBV infection. Although HBV vaccination seems to have increased the rate of surface gene mutants, currently the prevalence of these mutants is stable and in the total vaccinated population it has not increased. HBV surface gene mutants do not necessarily lead to a more severe disease course, because they are less competent at replicating compared to the wild type. However, the outcome of infection with such surface mutants may be worse in transplanted patients. In a study of 9 vaccinated pediatric patients who received liver transplants for reasons other than HBV, transplanted patients contracted HBV from the donor liver and became HBsAg positive. This study showed that only 3 had wild-type infection and the other 6 were infected by surface gene mutants due to selection pressure by the vaccination in the recipient [1]. Preliminary data from this ongoing study indicate that, unlike 2 individuals with de novo wild-type HBV infection who tended to seroconvert and fully recovered, all 4 patients with persisting HBsAg positivity were infected with surface antigen mutants.

The Luminex assay for HBsAg epitope mapping that allows ex vivo phenotyping of HBsAg directly from patients' sera, is a rapid, highly sensitive and efficient tool that uses a panel of monoclonal antibodies recognising discrete and overlapping epitopes on the HBV envelope. The Luminex assay allows large population based studies to be undertaken, which can provide information on the prevalence of these mutants.

In the UK a selective HBV vaccination programme is in place; only newborns born to HBV infected mothers receive prophylaxis. If the mother is HBeAg seropositive, infants receive vaccine and HBIG. If the mother is HBeAg seronegative, vaccine only is administered, unless the mother's viral load is greater than 10^6IU/ml, in which case vaccine and HBIG are given. To prevent transmission, the UK is also considering the use of Tenofovir in the last trimester for infected pregnant women with very high viral loads. Follow-up of babies born to HBeAg positive mothers at 1 year of age, shows that vaccination is effective in preventing transmission in the majority of cases. However, a small number of babies are HBsAg positive and HBV DNA positive at 1 year. Viral sequencing of samples from 52 such newborns revealed that 21 had mutations in the major antigenic region for HBsAg. Epitope mapping using Luminex showed that 13 had an altered surface antigenicity.

Preliminary results of a study of drug-driven surface antigen mutants, using Luminex, indicate that these mutants do not lead to loss of surface antigenicity as was previously thought [2].

In conclusion, while 179 countries have universal infant HBV vaccination programmes with high levels of coverage reaching 75-80%, breakthrough infections are rare events (e.g., an estimated 5 cases per year in Italy which has an immunized population denominator of 16-17 million) and do not seem to be affecting public health. Even when immune memory wanes and the ability to develop a booster response is no longer present, breakthrough infections remain rare. From the point of view of protecting a population from HBV, it is not vaccine failure but failure to vaccinate that is the current issue. However, there is a need for continued monitoring and surveillance, as well as continued evaluation of current vaccination schedules. HBV viral mutants occur at such a low frequency that their public health importance seems to be minimal compared to the impact of universal HBV vaccination. Presently, HBV does not seem to take advantage of breaking through immune protection. However, due to the long cycle effect, highly infectious viruses (such as influenza) take about 10-20 years to breakout and become a pandemic. It may take HBV much longer (generations) to breakout because it is much slower than influenza in terms of transmission; it seems to be more stable (although new antiviral drugs may affect this stability); in many cases it is self-limiting (acute cases do not become carriers); and many mutants are replication-incompetent. Caution is needed until, in addition to a high prevalence of vaccine-induced immunity, there is evidence that variants are not becoming established and transmitting to vaccinated individuals. With reference to occult HBV infection (undetectable HBsAg but DNA positive), research in Taiwan on previously vaccinated liver transplant recipients has shown that *de novo* transmission of HBV virus mutants from donor livers does occur. Therefore, improved surveillance is important, and should be continued for many years to evaluate the development and transmission of mutants. Especially the immune-suppressed deserve closer attention because in these individuals the virus could reactivate and escape variants could become a problem. It would be significant if vaccinated family members, household contacts or sexual contacts of a person with an escape mutant subsequently become infected and this is likely to be where transmission, if it happens, will be seen first.

Further research is needed into how factors, such as environmental viral load in the community, influence breakthrough infections. In addition, research is needed to determine if booster doses decrease breakthrough infections over time; although this is difficult to evaluate because of the changing dynamics of the virus due to vaccination (fewer infections in the population means less opportunity for transmission). Nevertheless, in 3 study groups in Alaska that received a booster dose, no evidence of breakthrough infections was observed. In Alaska at the time that screening commenced, 40% of the population was HBeAg positive, whereas today less than 1% are HBeAg positive, because the whole population is vaccinated.

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Based on presentations by
Y-H. Ni, Children's Hospital and College of Medicine, Taipei, Taiwan;
S. Ijaz (presented for R. Tedder), Health Protection Agency, London, UK
and related meeting discussions.

To boost or not to boost: current and future HBV vaccination booster policies

Country and regional policies

This section presents how currently available long-term immunogenicity and effectiveness data of HBV vaccination studies and programmes have led to current HBV booster vaccination recommendations in a number of countries.

Italy

In Italy, universal HBV vaccination of infants and adolescents was implemented in 1991. A multicentre study in previously vaccinated individuals was started in 2003 to assess the long-term duration of immunity and the need for booster, after vaccination. This study of 1212 healthy children vaccinated as infants (3 doses of pediatric Engerix B, at 3, 5, 11 months of age) and 446 healthy adult airforce recruits vaccinated as adolescents (3 doses of adult Engerix B, at 0, 1, 6 months) showed that, 10 years after primary vaccination, 64% of the children and 89% of the adults still had anti-HBs levels ≥10mIU/mL. The adults had higher anti-HBs titres than the children. In both groups however, most individuals (96% of children and 97% of

adults) developed an anamnestic response following a booster dose, even if their anti-HBs levels had decreased below10mIU/mL, but in the adult group the post-booster GMT was higher [1]. This indicates that immune memory persists and that the routine use of HBV vaccine booster doses is not required to maintain long-term protection in immunocompetent individuals primed as infants or adolescents 10 years earlier.

A total of 571 children from the study cohort continued to participate in a follow-up study. Of these children, 199 (group A) had anti-HBs titre <10mIU/mL (10 years after primary vaccination) and were given a booster dose in 2003, 372 (group B) had anti-HBs ≥10mIU/mL and did not receive a booster dose. In 2010, when considering all children studied (boosted or not), 72.9% had maintained anti-HBs >10mIU/mL (47.6% 10-100mIU/mL; 21.4% 100-1000mIU/mL; 3.9% >1000mIU/mL). No children showed any markers of past HBV infection (all remained anti-HBc negative). The proportion of children with anti-HBs ≥10mIU/mL in 2010 was 67% of group A (booster in 2003) and 75.8% of group B (no booster) and the GMT was similar in both groups. Assuming that those given a booster dose in 2003 would still be seronegative in 2010 if they had not received the booster, it can be estimated that about 50% of adolescents lost seroprotective antibodies (anti-HBs below 10mIU/mL) 17 years after primary vaccination as a child.

As a second part of this 17 year follow-up in Italy, antibody persistence was studied in 297 teenagers (vaccinated in the first year of life with 3 doses of pediatric Engerix B), and in 409 young adults (blood donors vaccinated as adolescents with 3 doses of adult Engerix B). At 17 years after primary vaccination 48.8% of the teenagers and 87% of the young adults retained protective levels of antibody. Both anti-HBs concentrations and the proportion of individuals with protective antibody levels were higher in young adults than in teenagers. These differences could be attributed to a different response to the primary course of vaccination due to the different age at which vaccination was given; different vaccine dose (pediatric 10 g or adult 20g); and/or differences in the degree of natural booster effect during this period. Among the young adults 8 (2%) had anti-HBc antibodies (HBsAg and HBV DNA negative), a marker of past infection, suggesting that natural booster occurred; while no such markers were found in the group of teenagers.

Preliminary results of an ongoing booster study in 181 teenagers boosted 17 years after infant primary vaccination, showed that immunological memory persisted in teenagers even if their anti-HBs was below 10mIU/mL.

In conclusion, the collective information from these studies suggests that, at this time, booster dose(s) are not needed for immunocompetent individuals in Italy. Further study of the anamnestic response to a booster dose given to adults who were vaccinated as adolescents and who lost anti-HBs antibodies over time, will help to clarify the booster issue in the future.

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Based on a presentation by
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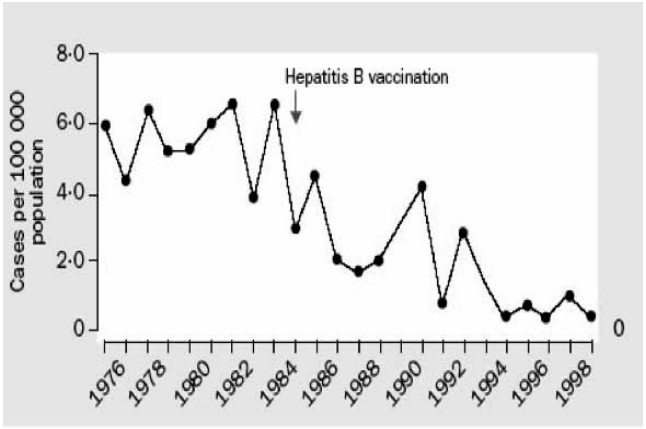
Taiwan

Data from the Department of Health in Taiwan, show that high vaccination coverage (3 doses) in infants is achieved, around 96% in 2005. The Department of Health is working towards 100% vaccine coverage. To achieve this, the focus will be on newborns that are missed by the birth register, i.e., older mothers (>35 years of age) with premature babies that may miss the first vaccine dose, and very young mothers who did not have regular pre-natal care.

The universal infant vaccination policy has been very effective in Taiwan. After 20 years of universal vaccination, the overall HBsAg carrier rate has declined to the present rate of around 0.8%. Over the past 25 years, 6 sero-epidemiological surveys have been carried out in Taipei. The first survey was before the start of universal vaccination and showed that below the age of 1 year, the carrier rate was 5%; around 2 years of age, the carrier rate was 10%; and the rate plateaus between the ages of 2 and 10 years. This suggests that infection between the ages of 0 and 2 years determines progression to chronicity. The carrier rate among babies has reduced since the start of universal vaccination, to around 0.5%. In 2009, the prevalence of HBV carriers in <20 year olds had declined to 0.6%, while before vaccination it had been 9.8% [1, 2]. The carrier rate among pregnant women is 15%, but this is expected to reduce to an estimated 0.6% as women born after implementation of universal vaccination start to have children.

Annual mortality of fulminant HBV in infants in Taiwan (1975—1998) [5, 6]



In children, 100% of HCC cases are due to HBV infection, and maternal transmission accounts for >94% of HBV transmission in children with HCC. Recent childhood HCC data demonstrate that cancer can be prevented by vaccination in particular when universal vaccination will also become effective in pregnant women. Over

18 years (1981-1999), the HCC incidence in children aged 6-14 years has substantially reduced; from 0.54/100,000 in those born before 1984 to 0.15/100,000 in those born after1984 [3, 4]. There has also been important progress in reducing the number of acute HBV cases. In 2010, (20 years after the start of universal vaccination) there were very few acute HBV cases in those under the age of 20 and most of these positive cases were migrants. The incidence of fatal fulminant HBV has also reduced, as shown in the Figure (see previous page) [5, 6].

Long-term follow-up of children up to 10 years after infant HBV vaccination in Taiwan has shown that 50% have levels <10mIU/mL anti-HBs. However, studies of immune memory 10 and 15 years after vaccination show that a booster dose can increase the level to ≥10mIU/mL in 97.4% of vaccinated individuals who were previously seronegative for anti-HBs [7, 8]. In addition, upon in vitro re-stimulation of isolated lymphocytes with HBsAg, HBV specific T cell proliferation could be detected.

In conclusion, universal HBV vaccination of infants in Taiwan provides long-term protection up to 20 years and has led to an important reduction in the number of HBV carriers over time, with no new carriers occurring. Therefore, in Taiwan a universal HBV booster dose is not indicated for primary vaccinated individuals before they reach adulthood [2], nor does a universal booster dose for adults seem necessary because acquisition of HBV in adulthood is in most cases self-limiting and will only progress to chronicity in about 5% of cases.

Therefore, the Government in Taiwan sees no public health rationale for adding a universal booster dose within its HBV immunization programme. Providing a booster dose is an option that health services might consider for workers or a matter for individual choice, but it is not paid for out of the health budget and therefore does not compete with other health programmes that are considered more of a priority.

Upon consideration of whether a booster dose was needed, the Virus Prevention Board in Taiwan issued the following statements [9, 10]:

- The primary goal of HBV immunization is to control chronic HBV infection in early infancy;
- No increase in acute hepatitis B in adolescents vaccinated 20 years ago in early infancy; and
- Preventing acute HBV infection in adolescents will become a higher public health priority, only after chronic HBV infections are successfully controlled.

Booster doses should, however, be considered for immunocompromized hosts. For instance, in a study of children with biliary atresia who undergo liver transplantation and receive an anti-HBc positive liver graft, there is a high chance of them developing *de novo* HBV infection if their anti-HBs titre is not >200mIU/mL [11]. When children who had anti-HBs <10mIU/mL after liver transplantation were given a booster dose, 33% (4/12) remained <10mIU/mL, but did achieve a level above 10mIU/mL after a second booster dose. One year after an immunosuppressive procedure, such as transplantation or chemotherapy, seems an optimal time for a booster dose.

Post-vaccination testing for infants born to HBsAg positive mothers is important and should be performed after completion of the vaccine series, at age 9-18 months. It allows the identification and management of infants that are chronic carriers (HBsAg positive). HBsAg negative infants with anti-HBs levels >10mIU/mL need no further medical management. HBsAg negative infants with anti-HBs levels <10mIU/mL (primary non-responders), according to current policy, should receive a booster dose and be re-tested 1-2 months later.

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Based on a presentation by
Y-H. Ni, Children's Hospital and College of Medicine, Taipei, Taiwan.

Thailand

In Thailand, anti-HBs titres were studied following HBV vaccination (0, 1, 2, 12 month schedule) in a group that received a booster dose at 5 years post-vaccination and compared to a group that were not given a booster [1]. At 20 years post-primary vaccination, 83.9% of the group that received a booster dose at 5 years had anti-HBs ≥10mIU/mL, whereas in the group that did not receive a booster dose only 60.5% had anti-HBs ≥10mIU/mL. When a booster dose was given to both groups 20 years after the primary vaccination, the anti-HBs anamnestic responses were within the same range (95.8%) in both groups. This illustrates that in a highly endemic country like Thailand, immune memory lasts up to 20 years after the original vaccination and that the differences in seroprotection between the two groups at year 5 did not translate into differences in immune memory at year 20. These data indicate that there is no need for booster doses of HBV vaccine in highly endemic countries, which is especially important for resource-limited countries.

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Based on a presentation by
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CDC policy in the US

The CDC/ACIP policy statements (from 1991-2006) regarding a booster dose following routine infant HBV vaccination in the US are detailed below:

- 1991: For children and adults whose immune status is normal, booster doses of vaccine are not recommended, nor is serologic testing to assess antibody levels necessary. The duration of protective efficacy for adolescents who were vaccinated during infancy or childhood must be evaluated; the results will determine future recommendations concerning booster doses [1].
- 2005: Studies are needed to assess long-term protection after vaccination and the possible need for booster doses of vaccine [2].
- 2006: Booster doses are not recommended for persons with normal immune status who were vaccinated as infants, children, adolescents, or adults [3].

Since the statement in 2006, several studies supported by the CDC, including studies in Alaska (detailed in this report), have provided important information about HBV vaccination including:

- Protection persists despite loss of protective antibody; and loss of amnestic response does not indicate susceptibility to HBV infection [4].
- After 22 years post-vaccination, 93% of individuals had evidence of protection and there was no need for a booster dose [5].
- 15 years after vaccination, breakthrough infections remain rare; HBV vaccination prevents infection years after vaccination [6].

The supportive evidence for CDC policy regarding a booster dose following routine HBV vaccination includes the following.

- Implementation of HBV vaccination programmes in populations with a high endemicity of HBV infection has resulted in virtual elimination of new HBV infections.
- Immunocompetent persons who achieve anti-HBs concentrations of >10mIU/mL after pre-exposure vaccination have nearly complete protection against both acute disease and chronic infection.
- Even when anti-HBs concentrations decline to <10 mIU/mL, nearly all vaccinated persons remain protected against HBV infection.
- Persistence of vaccine-induced immune memory among persons who responded to a primary adult vaccine series with anti-HBs <10mIU/mL has been demonstrated by an anamnestic increase in anti-HBs concentrations.
- Among vaccine recipients, breakthrough infections (detected by the presence of anti-HBc or HBV DNA) are limited, typically transient and asymptomatic, and rarely resulting in chronic HBV infection.

In the US population, individuals vaccinated as children are now reaching adulthood and it is very important that studies of seroprotection and breakthrough infection continue, in order to evaluate whether long-term immunity persists into adulthood.

CDC-supported studies and surveillance that are in progress include:

- A study of long-term immunity in adolescents born to HBsAg negative mothers in Texas (an area of low endemicity) following HBV vaccination (3 doses; with comparison of first dose 7 days after birth versus >4 weeks after birth) and a booster dose.
- An investigation of breakthrough acute HBV infections among individuals <29 years of age.
- A study to evaluate how protection in healthcare students should be measured (whether documented proof of a previous course of vaccination is enough, or whether more doses are necessary for protection now that students who are vaccinated as newborn enter the different HCW programmes). Two training programmes have been investigated [7]; both programmes require documentation of seroprotection (anti-HBs >10mIU/mL) and a booster dose is required for those with a lower titre.

Surveillance activities must continue to collect vaccination information and seroprotection data on all HBV cases among persons <20 years of age. This group is being targeted because they should have been vaccinated as infants and identification of breakthrough infections in this

group will allow revision of the immunization schedule if needed. CDC have been asked by ACIP to review current policy on a HBV booster dose, including a booster dose following routine vaccination.

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Based on a presentation by
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Global Immunization policies

The WHO issues position papers for each vaccine preventable disease, in which the WHO makes clear its policy on the use of the vaccine in the global context, with consideration to vaccination in resource-poor settings, as well as those that are resource-rich. They are designed primarily for use by national public health officials and immunization programme managers. Each position paper is reviewed by experts within and outside the WHO and is published once it has been approved by the Strategic Advisory Group of Experts (SAGE). They are also updated as new information becomes available.

The 2004 WHO Position Paper for HBV [1] states that, "following the primary vaccination schedule, almost all children are protected, probably for life, without the need for booster injections", but also emphasizes that data on the duration of immunity were incomplete. Therefore, the process of updating this Position Paper started in 2008-2009. An adapted GRADE approach (www.gradeworkinggroup.org) is used to assess evidence for interventions. This approach has relied on GHIS data from research in The Gambia, which demonstrates that HBV vaccination in infants confers very good protection against HBsAg carriage up to at least 15 years of age [2]. Since it is the only randomized, controlled trial that is producing regular results, the WHO has also reviewed data from other, observational studies (those with the longest follow-up are shown in the Table below). These studies have provided high quality evidence about the effectiveness of HBV vaccine in preventing infection up to 22 years after infant vaccination.

The quality of the vaccination programmes detailed at this meeting is high, but there exists evidence of large populations where vaccination has been sub-optimal. It is interesting to consider if vaccination discipline will decrease over time and whether quality control measures are necessary to look at sustainability and to ensure the high quality of these programmes. In light of this, the possibility of misreporting of infant vaccination was discussed. For instance, in the Netherlands some misreporting may exist – a comparison of 2 databases where infant vaccinations are recorded in the Netherlands revealed about 10% discrepancy between the databases.

Given that only measuring antibody may not be useful, advice was sought on what other methods should be used to monitor the success of national immunization programmes. The WHO does not feel that the traditional method of monitoring vaccination coverage is sufficient. The WHO Position Statement of 2009 [3] recommends that serologic surveys of HBsAg prevalence serve as the primary tool to measure the impact of immunization and achievement of the control goals, and should be supplemented by acute disease surveillance and mortality data. These surveys can be run relatively inexpensively and have been used in school settings. One such survey of schools in Mongolia showed that the impact of the vaccination programme was sub-optimal.

Observational studies providing evidence of long-term protection after HBV infant vaccination

Country/region	Years of follow-up	n	[Anti-HBs] ≥ 10 mIU/mL (%)	Anti-HBc positive (%)	HBsAg positive (%)
Micronesia	15	105	40	7.6	0
Alaska	15	37	5	0	na
Gambia	15	1099	13.8	10.1	0.7
Saudi Arabia	16-18	1355	38	0	0
Taiwan	20	843	33.6	2.7	1.4
Hong Kong	22	318	76.5/52.4	?	0

Based on its review, the WHO formulated its 2009 Position Paper [3] where it is stated that, "although knowledge about duration of protection against HBV is incomplete, including knowledge on the potential role of natural boosting, there is no compelling evidence for recommending a HBV booster dose in routine immunization programmes".

References

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2 *van der Sande M et al. Long-term protection against HBV chronic carriage of Gambian adolescents vaccinated in infancy and immune response in HBV booster trial in adolescence. PLoS ONE. 2007;2(1):e753.*

3 *World Health Organization. Hepatitis B Vaccines - WHO Position paper. WER 2009, (No. 40);84, 405–420. Available at: http://www.who.int/wer/2009/wer8440.pdf.*

Based on a presentation by
S. Wiersma, World Health Organization (WHO), Geneva, Switzerland; and related meeting discussions.

Conclusions

Italy was the first high-income country to introduce universal HBV vaccination of infants 20 years ago (Bulgaria and Israel started shortly after, then the USA). Today, 179 countries have added HBV vaccination to their routine vaccination programmes. A few northern European countries and Japan have vaccination strategies that are targeted to "at-risk-populations", rather than universal strategies. There has been a rapid take-up of vaccine since 1999-2000 (due to a lower vaccine price and, from 2001 onwards, support from the GAVI Alliance - formerly the Global Alliance for Vaccines and Immunisation - for the poorest countries in the world), with high coverage rates widely reported and maintained.

Long-term immunogenicity and efficacy of HBV vaccine

Due to successful vaccination programmes, the dynamics and epidemiology of HBV disease have been changing. Some universal HBV programmes have been running for up to 25 years and some follow-up research projects for up to 30 years. It is important to know if protection following infant vaccination is maintained into adulthood, when the risk of exposure to HBV is greater, or whether declines in anti-HBs levels over time will translate into an increased risk of disease after exposure.

Many studies confirm that anti-HBs titres decline over time to low or even undetectable levels. The higher the peak titre following primary vaccination, the longer the antibodies persist. Titre and long-term persistence of anti-HBs are related to age at vaccination, type of vaccine, route of administration, number and timing of doses, gender, body mass index, smoking, and possibly host genetics. Novel vaccine adjuvants significantly improve the early immune response, but it is not clear what impact they have on long-term immunity while safety needs further documentation.

Historically, an anti-HBs titre of ≥10mIU/mL measured 1 to 3 months after a completed primary course has been considered protective for evaluation of primary vaccination, but it was questioned whether this threshold should be used for evaluation of persistent protection, as antibody levels decline below this cut off does not mean absence of protection against disease. Conversely, the level of 10mIU/mL may not be protective should a person become immunosuppressed. From a public health perspective, it is significant that none of the presented follow-up studies have reported cases of acute HBV, clinical disease or development of chronic carrier state after successful primary vaccination, even when anti-HBs concentrations decline below 10mIU/mL over time. This indicates that only monitoring antibody response is insufficient to investigate and report on long-term immunity. In terms of public health concerns, the focus should be on the disease and not on a technical cut-off when assessing the effectiveness of HBV vaccine programmes. In addition to serologic surveys, surveillance of acute and chronic disease, and long-term follow-up of vaccinated cohorts are important. It is however recognized that limitations exist; follow-up can be difficult in large cohort studies as often vaccination history is missing.

Immune memory and effect of (natural) booster

Persistence of protection beyond the loss of detectable titres of antibody is due to residual immune memory (B and T cells). Most vaccinated individuals have persisting immune memory for at least 20 years after a complete vaccination course and are able to develop an anamnestic response following a booster dose (so-called "boostability"). However, when a booster dose is given 20-30 years after primary vaccination, antibody titres decline rapidly after the booster dose. Boostability is more likely to be weak or absent if initial antibody titres were low. Recently, there has been increasing evidence of failures to develop an anamnestic response, but this does not seem to imply increased susceptibility to clinically significant HBV disease, since no acute or chronic HBV cases were reported in any of the presented follow-up studies.

A natural booster effect with activation of memory B cells, due to environmental exposure to HBV, can contribute to persistence of anti-HBs antibodies, particularly in areas of high endemicity.

Effectiveness of universal HBV vaccination

Long-term follow-up programmes now extend up to 25-30 years post-vaccination (Alaska, Taiwan, The Gambia and Thailand).

Data from high, intermediate, and low endemic countries worldwide show that there have been several important achievements due to HBV vaccination. Protection against clinical disease and the carrier state has repeatedly been demonstrated among vaccinated individuals even after 20-30 years.

The primary goal of universal newborn HBV vaccination is to control HBV infection in early infancy, due to the high risk of becoming a chronic carrier if HBV is contracted in infancy. Universal newborn HBV vaccination has allowed the interruption of perinatal transmission. A decline has also been found in highly endemic countries, like Thailand, where the HBsAg carrier rate in children <15 years of age reduced from 5-6% to 0.7%. Preliminary results from The Gambia and Taiwan indicate that HBV vaccination can prevent hepatocellular carcinoma leading to a fall in its incidence. In successfully vaccinated subjects, absence of acute and chronic HBV disease has been observed up to 30 years post-vaccination (data from Alaskan study). In low or intermediate endemic countries and regions (such as the USA, Italy, Bulgaria and Catalonia), the incidence of acute HBV has declined significantly since the introduction of universal vaccination. However, higher incidences of acute and chronic HBV in migrants are an issue and studies are needed to determine the epidemiology of HBV infection in these populations, in order to offer targeted vaccination strategies and access to care.

The success of HBV vaccination as a safe and effective public health tool has been clearly demonstrated, although perhaps not always very well communicated. GAVI recognises that the effect of HBV vaccination in reducing the incidence of liver cancer will result in an impact on public health worldwide.

Breakthrough infections

In general, breakthrough infection could be defined as the appearance of anti-HBc with or without clinical disease in successfully vaccinated individuals. Nevertheless, breakthrough infections are rare events (e.g., an estimated 5-6 vaccine failures occur annually in Italy among an immunized population of 16-17 million) and do not seem to be affecting public health, even when immune memory wanes. However, there is a need for continued monitoring and surveillance. In addition, the characteristics of patients with breakthrough infections are often unknown (genotype or host genetic factors may be involved) and require further investigation. So far breakthrough infections haven't become a public health concern; vaccine escape mutants could be a particular risk to immunocompromised individuals, in whom the virus could reactivate. From a public health perspective, at the present time, it is not vaccine failure that is an issue, but failure to vaccinate.

Current and future HBV booster vaccination policies

Currently, decisions to offer a booster dose are mainly based on anti-HBs antibody titre <10mIU/mL after complete vaccination and for HCW in some regions <100mIU/mL is used.

However, decisions about offering an HBV vaccine booster should be based on the appearance of disease in the population, not on numbers measured in studies (e.g., amount of anti-HBs still present). Based on the scientific evidence, HBV booster vaccination for immunocompetent individuals is not recommended for long-term protection. A booster dose could be exceptionally provided to non-responders and some "at-risk" groups, for example, immune-compromised individuals and health-care workers.

Challenges, needs and future steps

A better understanding of the immunological mechanism is needed in terms of long-term protection, response or failure to respond to booster dose, and the reasons for inadequate responses to vaccination. The meaning of cellular and humoral immunity in successfully vaccinated individuals should be further explored, including how this could be translated into public health practice. Studies presented at this meeting show that the cellular immune response to HBV contributes to protection beyond humoral-mediated immunity. Further research is needed to fully understand the complexities of cellular immune response; currently exploring T cell responses in humans is technically difficult and expensive. Standardization of biological reagents, including tests to detect T and B cell immunity, is necessary.

A number of terms need clear, standardized definition, including: immunity and protection, booster, anamnestic response, immune memory, long-term, non-responders, vaccine failure and breakthrough infection. Presently, different use of these terms makes comparison of data difficult and creates confusion among decision makers, health experts and the public. Therefore, there is a need for a working group to standardize definitions. The VHPB planned a workshop to discuss standardization of definitions.

Vaccination programmes, including different vaccination schedules, should be monitored to control the quality and vaccine effectiveness over longer time periods, especially in the changing epidemiological environment. Special efforts are also needed to further increase vaccine coverage up to 100%. Meanwhile, a continued focus should be on the timely delivery of a birth dose of HBV vaccine (ideally within 24 hours of birth), followed by 2 or 3 additional doses. It is important to consider the timing of doses, and the spacing between doses, as these have been shown to influence vaccine effectiveness.

There should be surveillance of immunity in health-care workers and consideration of their need for booster vaccination. Prospective studies are required to define an optimal schedule for booster doses in HCW, and to aid formulation of booster policy, taking into consideration domestic medical-legal issues. Ongoing long-term follow-up studies (such as the Vax Demo 30 study in Alaska) of those vaccinated and given a subsequent booster dose, will provide information relevant to HCW.

The clinical impact of the natural booster effect needs further research. Studies on viral mutants and influence of genotype and phenotype are necessary and should include monitoring, global surveillance networks and continued evaluation of the public health relevance. Vaccination and treatment strategies should take into account the risk of mutant formation.

It remains to be further investigated whether people who have lost detectable antibodies and no longer develop an anamnestic response, are at risk for clinically significant HBV infections (acute disease and chronic carrier state). Currently, follow-up studies in these individuals do not show occurrence of disease or chronic carrier status, but surveillance must continue to better understand the mechanism of protection, if it exists. Despite very good vaccine coverage rates, monitoring coverage is not enough to estimate the impact of vaccination. Sero-surveillance should be conducted for different HBV markers, but also acute disease surveillance, mortality data and long-term follow-up of vaccinated cohorts should be further investigated.

Although knowledge about duration of protection against HBV is incomplete, there is currently no scientific evidence to justify the introduction of an HBV booster dose in routine vaccination programmes.

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