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## Editorial

This issue of *Viral Hepatitis* reviews topics covered at the VHPB's spring meeting held on March 11-12, 2004, in Sevilla, Spain. Recent data on long-term persistence of vaccine-induced hepatitis B antibodies and immune memory; and the potential role of hepatitis B virus (HBV) mutants in hepatitis B vaccination programmes were the main topics that were discussed among the participants. The meeting concluded with an overview of current hepatitis B booster recommendations from the World Health Organization, the European Consensus Group on Hepatitis B Immunity, and the Centers for Disease Control and Prevention, which are still valid.

### Hepatitis B vaccination programmes - achievements and challenges

In countries where hepatitis B vaccination programmes are being implemented, substantial progress has been made toward eliminating HBV infection as well as hepatitis A, hepatitis C and hepatitis D (Delta) virus infections. Recent data derived from universal hepatitis B vaccination programmes in Alaska, Canada, Italy, Spain, Gambia, Saudi Arabia, Taiwan, and Singapore have all demonstrated significant declines in HBV incidence and prevalence in areas where high hepatitis B vaccination coverage levels (ca. 90%) have been attained.

Hepatitis B vaccines - whether they are plasma-derived or based on recombinant DNA technology - provide the best protection against HBV infection and hepatocellular carcinoma (HCC). HCC is one of the ten most common malignant tumors worldwide and the majority of cases are related to chronic infection with hepatitis viruses, particularly among children infected with HBV. Since currently available therapies for chronic HBV infections, cirrhosis, and HCC cannot effectively prevent HBV-related complications, strict compliance with immunisation programmes that include the hepatitis B vaccine must be achieved. In developing countries with high endemicity, scarce human and financial resources remain potential threats to vaccination programmes. Poor compliance may also be evident in areas with low prevalence where, in the absence of disease, vaccination may not be considered necessary.

Long-term studies that have been carried out worldwide among infants, children, and adults have shown that although there may be a decline in hepatitis B antibody levels over time, long-term memory persists for at least fifteen years among individuals who have responded to a complete hepatitis B primary vaccination series. Currently, there are no data that support the use of booster doses of hepatitis B vaccine among immunocompetent individuals who have responded to a complete primary vaccination series.

Various mutations occur in nearly every part of the HBV genome. It is known that HBsAg mutants may cause persistent infections and may be associated with chronic hepatitis. Although there are a number of areas needing further study (e.g., how mutations evolve and how to develop easier methods to detect mutations and to test transmission risk in susceptible persons), currently there is no clear evidence that HBV mutants can infect persons who have been successfully immunised against HBV, except in post-exposure situations, nor is there any convincing evidence to date that hepatitis B vaccine formulations will need to be changed in the near future.

The VHPB recognises the need for further investigations to be carried out that address questions relating to determinants of duration of protection, the role of HBV mutants, breakthrough infections, and immunological memory in persons whose antibody responses, although present initially, have fallen to undetectable levels.

The VHPB continues to advocate for universal infant immunisation as a priority in vaccination strategy to eliminate HBV infections.

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## Hepatitis B vaccine: long-term efficacy, booster policy, and impact of HBV mutants on hepatitis B vaccination programmes - a VHPB Symposium Report - Sevilla, Spain, March 11-12, 2004

### Hepatitis B: efficacy of vaccines and effectiveness of vaccination programmes

## Hepatitis B vaccine studies in Alaska

### Evolution and impact of hepatitis B control and prevention measures

Universal hepatitis B vaccination for all infants has been in place in Alaska since 1984. Additional hepatitis B prevention measures have played an important role in Alaskan public health, such as screening pregnant women (introduced in 1980) in two Alaskan hospitals and hepatitis B immunoglobulin (HBIG) given to infants born to hepatitis B surface antigen (HBsAg-) positive mothers.

Other important milestones in Alaska's hepatitis B programmes include:

- 1981-1982: a hepatitis B vaccine demonstration project carried out in southwest Alaska, described in more detail below;
- 1983-1987: screening 53,000 (75%) Alaskan natives and vaccinating 40,000 who were considered susceptible;
- 1987: an estimated 90% of susceptible persons in endemic areas immunised.

As a result of Alaska's ongoing hepatitis B immunisation programme, the incidence of acute hepatitis B virus (HBV) infection has been declining. There is now a generation of children who are free of chronic HBV carriage. There has also been decreasing incidence of hepatocellular carcinoma (HCC) in persons under thirty years of age.

### Hepatitis B Vaccine Demonstration Program (Vax Demo Study)

A number of long-term hepatitis B vaccine and booster studies have been carried out among Alaskan natives. One of the longest such studies was the Hepatitis B Vaccine Demonstration Program ('Vax Demo'), initiated in southwest Alaska in 1981 to demonstrate that, under field conditions, the (plasma-derived) vaccine was safe, immunogenic, and efficacious [1]. The study population comprised 1,630 seronegative Yupik persons from seventeen villages, aged six months and older, who were vaccinated with plasma-derived hepatitis B vaccine at 0, 1, and 6 months. Follow-up serology testing was conducted yearly for the first eleven years and then again at age fifteen. HBV DNA was tested on all persons who acquired anti-HBc during the study period. Reports of the interim analyses were published at five, seven and ten years, with fifteen year results submitted [2-5].

The initial results of the Vax Demo study showed that 94% of the subjects had developed protective antibody levels. Persons under twenty years of age had the highest response rate (99%) and the highest antibody levels. Persons older than fifty years had lower response rates (70%).

In the ten-year follow-up study, 76% of the study participants still had anti-HBs levels above 10 mIU/ml, 0.09% contracted HBV infection (anti-HBc positive), and none developed clinical hepatitis or became a carrier.

In the fifteen-year follow-up, 66% still had anti-HBs levels above 10 mIU/ml and none developed clinical hepatitis or became a carrier.

In 2003-2004, the study continued with a twenty-two year follow-up that involved contacting 1,030 of the original participants from seven villages who were tested for HBV markers. If a subject had less than 10 mIU/ml anti-HBs, then a booster dose of vaccine was given, and re-testing was done at the following intervals: (a) 10-14 days; (b) 1 month; and (c) 1 year.

*Conclusions of the Vax Demo Study*

Based on long-term follow-up of participants, the following conclusions were drawn:

- Long-term protection in children and adults lasts at least fifteen years after hepatitis B vaccination.
- Booster doses in these groups are not needed for at least fifteen years.

**Other long-term follow-up studies on infant hepatitis B vaccination**

Most of the studies on infant hepatitis B vaccination and its long-term protective value have been carried out among infants born to HBsAg-positive / HBeAg-positive mothers.

The vaccine schedules and number of doses vary considerably:

- (1) immunisation beginning at birth versus at 2-3 months of age;
- (2) administration of the last vaccine dose at 6 months versus 12 months of age;
- (3) administration of 3 versus 4 doses.

Some of these studies concluded that:

- 51% - 85% of children of HBsAg-positive / HBeAg-positive mothers vaccinated in infancy had anti-HBs levels  $\geq 10$  mIU/ml at 10 years.
- In a Hawaiian study of low-risk infants given 2.5  $\mu$ g hepatitis B recombinant vaccine at birth, only 19% had anti-HBs levels  $> 10$  mIU/ml at 6 years, but all responded to a booster dose.
- The results of a study on long-term protection of infant hepatitis B vaccination in Alaska suggest that anti-HBs levels decline more rapidly in children of HBsAg-positive / HBeAg-negative or HBsAg-negative mothers.

**Long-term child booster studies**

The objective of the hepatitis B child booster studies was to determine the response to a booster dose in children who had received their primary hepatitis B vaccination during infancy. The studies were carried out among the following cohorts:

- children whose initial response to hepatitis B vaccine was unknown;
- children who had documented anti-HBs levels  $\geq 10$  mIU/ml after primary vaccination.

Among the first cohort of 310 children who were immunised on schedule at birth but whose response to the vaccination was unknown, 208 were tested at age five. Children with anti-HBs less than 10 mIU/ml were given a hepatitis B vaccine booster dose. The other group, comprising 102 children, deferred testing until age nine and was also given a booster dose if anti-HBs was less than 10 mIU/ml [6].

Number of children	Vaccine type	Maternal HBsAg	Mean age	% anti-HBs $\geq 10$ mIU/ml*	Booster response
102	Plasma	Negative	8.9 years	41%	33/54 (61%)
208	Recombinant	Negative	5.1 years	12%	120/134 (90%)

\*at time of booster dose

Number of children	Vaccine type	Maternal HBsAg	Mean age	% anti-HBs $\geq 10$ mIU/ml*	Booster response
17	Plasma	Negative	12.6 years	4/17 (24%)	8/12 (67%)
36	Recombinant	Negative	7.5 years	0/36 (0%)	32/35 (91%)
16	Plasma	Negative	12.1 years	5/16 (31%)	9/10 (90%)

\*at time of booster dose

*Conclusions of long-term infancy studies (see tables above)*

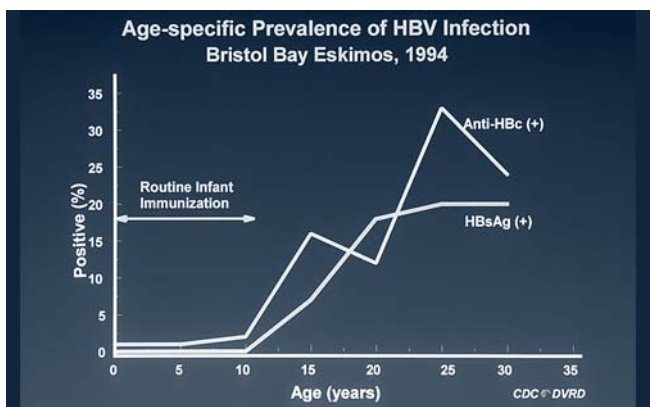
- Among children who are vaccinated against hepatitis B in infancy, anti-HBs levels decline rapidly; among those vaccinated with a recombinant vaccine, anti-HBs levels decline the fastest.
- There is a good (90%) response to a booster dose of vaccine given at five or seven years of age.
- Some children at ages nine and twelve failed to respond to a booster dose, including 10% to 30% of children who were known to respond to the initial series of immunisation.

**Youth hepatitis (Yo-Hep) booster study in Alaskan natives**

The effectiveness of a hepatitis B booster dose in children who were vaccinated with a recombinant hepatitis B vaccine at birth is under investigation. This study is based on two cohorts: (a) 200 children aged four to five years; and (b) 200 children aged ten to thirteen years. Follow-up anti-HBs testing takes place at ten to fourteen days and one month following the booster dose. The results of this study are expected in autumn 2004.

**Bristol Bay Hepatitis Survey**

A serosurvey [7] was carried out in Alaska in 1994 among 603 Bristol Bay Eskimos approximately thirty years of age, ten years after initiation of universal hepatitis B immunisation. The purpose was to evaluate the effectiveness of a hepatitis B immunisation programme in eliminating HBV transmission among Alaskan natives in a region in which HBV infection is endemic. In 1984 the prevalence of HBsAg was 13%. Ten years later the HBsAg prevalence was 0% (ages 0-10), 8% (ages 11-15), 18% (ages 16-20), and 21% (ages 21-30), respectively, as shown in the figure below.



**Chronic hepatitis B in Alaskan natives**

All Alaskan natives are offered testing every six months for liver enzymes and for alpha-fetoprotein (AFP). Participants who are also at baseline are tested for HBV genotype, HBV DNA levels, and viral mutations that may be associated with liver disease:

- Pre-core mutant: development of cirrhosis
- Core-promoter mutation: development of liver cancer

### Questions regarding HBV immunisation

Questions still under discussion regarding hepatitis B booster immunisation are whether to wait for symptomatic hepatitis to occur in vaccinated individuals, or to vaccinate at a time when an anamnestic response can no longer be demonstrated.

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*Based on a presentation by Dr Brian McMahon, Viral Hepatitis Program, Alaska Native Medical Center, CDC, Anchorage, Alaska, USA.*

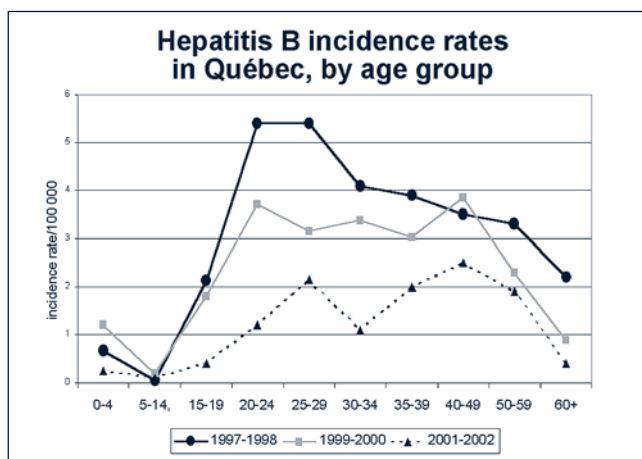
## Follow-up of hepatitis B vaccination programmes in Canada

Hepatitis B endemicity is low in Canada: 0.5% of the population are HBsAg-positive and 5% have serological HBV markers. Peak incidence of HBV infection occurs among persons between fifteen and forty years of age. Currently there are three licensed hepatitis B vaccines in Canada, produced by two vaccine manufacturers.

### Routine hepatitis B immunisation in Canada

Canada began implementing its school-based hepatitis B immunisation programme in 1992, which varies from province to province. Hepatitis B vaccination coverage is targeted to pre-adolescents, i.e., grades 4-7 children usually aged 9-10 years [1] to whom the vaccine is available free of charge, but conditional upon written parental consent. The three-dose schedule is 0, 1, and 6 months, and coverage is 90%.

In the Province of Québec, hepatitis B incidence rates fell dramatically between 1997 and 2002, as shown in the figure below. Peak incidence (approximately 5 / 100,000) occurred in 1997-1998 among the twenty to twenty-four year age group and dropped to about 1 / 100,000 in 2001-2002. The lowest incidence for the 1997-2002 period was among children and adolescents five to fourteen years of age.



### Québec long-term hepatitis B study

A fifteen-year cohort study began in 1996 [1]. The goals were to measure the proportion of children who would still be protected

against hepatitis B virus infection at age twenty-five, to examine the need for a booster dose, and, if needed, to determine the appropriate age for a booster dose. Yearly contacts were maintained with the subjects through a newsletter.

The general objectives of the study were as follows:

### Primary objectives

- to evaluate the persistence of antibodies to two hepatitis B vaccines – Engerix-B (EB) and Recombivax-HB (RB) – in all subjects at age 25; and
- to compare the levels obtained in those given a booster injection at age 15 or age 20 with those not given a booster injection

### Secondary objectives

- to determine the antibody levels at ages 15 and 20, five to ten years after primary vaccination;
- to determine the effect on antibody levels of a booster injection at ages 15, 20, and 25 years; and
- to evaluate the reactogenicity of the booster dose

The general study design took into account baseline antibody measurement and randomisation of the cohort in three groups. For each group, after five (A), ten (B), or fifteen (C) years, respectively, the following are carried out:

- taking a pre-booster blood sample
- giving a hepatitis B vaccine booster dose
- taking blood samples one month and one year after giving booster dose

The chronology of the general study method is shown below:

### year 0

- 2,255 subjects vaccinated in 1995-1997;
- vaccines that were used: EB 10 µg (0, 1, 6) or RB 2.5 µg (0, 1, 6)

### year 5

- 1,962 remaining subjects were randomised in 3 groups (A, B, C); group A received a vaccine booster dose of either EB 10 µg or RB 5 µg

For all groups, testing is carried out for anti-HBs, anti-HBc, and

HBsAg, after primary vaccination and before the booster dose. At year 15 of the study, anti-HBs, anti-HBc, and HBsAg levels are tested. Anti-HBs levels are tested at one month and one year after the booster dose. A summary of the currently available results is shown below.

**Persistence of antibodies, five years after the primary immunisation:**

- 5.1% had no detectable anti-HBs
- 15.4% had a titre inferior to the seroprotective level
- No subject became anti-HBc-positive.
- No subject had an increased anti-HBs titre.

**Persistence of protection, one year after the booster dose:**

- 2 subjects (0.36%) had no detectable anti-HBs titres
- 9 subjects (1.6%) had an anti-HBs titre between 1-9 mIU/ml
- For these 11 subjects:
  - All had an anti-HBs titre between 10 and 99 mIU/ml after primary vaccination.
  - All had an anti-HBs titre between 0 and 9 mIU/ml before the booster.

**Geometric mean titres (GMTs) of anti-HBs:**

- GMTs were higher in the EB than in the RB group at each point
- 5 years after primary vaccination: 29-fold decrease in EB group and 56-fold decrease in RB group
- 1 month after the booster: 449-fold rise in EB group and 252-fold rise in RB group
- strong correlations between initial, 5-year pre-booster, 1 month and 1-year post-booster dose anti-HBs titres

Five out of eleven (45%) of the subjects with anti-HBs levels of 10-99 mIU/ml after primary vaccination remained under 10 mIU/ml after the five-year booster. This may suggest that this titre is not an adequate predictor of long-term protection in this population.

The results of the study show that 1.96% of all subjects with over 10 mIU/ml anti-HBs after primary immunisation had titres below 10 mIU/ml after the five-year booster, which may suggest that there was no immune memory.

**Conclusions**

This study showed that both EB (10 µg) and RB (2.5 µg) are highly immunogenic in 9- to 10-year olds and that they provide protection for at least five years in 99% of vaccinees with a titre  $\geq$  10 mIU/ml after primary vaccination.

A titre of < 100 mIU/ml of anti-HBs after primary hepatitis B vaccination in pre-adolescents may not be sufficient for long-term protection against HBV infection.

A booster dose is not required after five years. However, longer follow-up is necessary in order to take a decision about booster doses in pre-adolescents who are vaccinated with paediatric doses of hepatitis B vaccine.

Further investigation will also be required to determine the proportion of seroprotected young adults and the proportion of responders to a challenge with booster doses given ten and fifteen years after the vaccination.

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*Based on a presentation by Dr Bernard Duval, Groupe Scientifique en Immunisation, Institut National de Santé Publique du Québec, Québec, Canada.*

## Follow-up of hepatitis B vaccination programmes in Gambia

In 1980, a cross-sectional survey was carried out in two Gambian villages – Keneba and Manduar – to identify children and their mothers with HBV markers. These two villages were selected as pilot villages for national introduction of hepatitis B vaccination. Beginning in 1984, all infants and non-immune children under five years of age in Keneba and Manduar were immunised against hepatitis B virus. These immunisations were based on a 2, 3, and 4 month schedule. Testing for HBV antibodies was carried out among these children at one year of age.

Since then, a number of longitudinal and repeated cross-sectional studies have been carried out to assess long-term hepatitis B vaccine efficacy among subjects less than twenty years of age in an HBV-endemic country. These studies took place in 1989, 1993, 1998, and 2003 [1-4].

The Keneba and Manduar survey was designed to determine the duration of protection against HBV infection following hepatitis B vaccination in infancy and early childhood. Results from the 1998 survey showed that the vaccine efficacy against chronic HBV carriage was 94% and did not vary significantly among the various age groups. Efficacy against infection was 80%, and significantly lower (65%) in the fifteen- to nineteen-year old age group. The effect of vaccination against hepatitis B infection on prevalence of hepatitis B virus surface antigen and hepatitis B virus core antibody in 1998 is shown in the table below [4].

**Effect of hepatitis B vaccination on HBsAg and anti-HBc prevalence in two Gambian villages (1998)**

Age (years)	Keneba		Manduar	
	HBsAg	anti-HBc	HBsAg	anti-HBc
1-4	2/175	4/175	1/65	5/65
5-9	0/167	5/167	0/58	4/58
10-14	1/172	20/172	1/73	14/73
15-19	1/119	40/119	2/27	10/27

**Risk factors for breakthrough infection**

Independent risk factors associated with breakthrough infection were gender, village, length of time since vaccination, and peak antibody response. Boys and young men had a higher risk, as did people living in Manduar, which, before vaccination, had a remarkably high rate of infection (71%) among young children over a four-year period. In participants in some of the study groups, who were given different doses by different routes, time since vaccination seemed to be a major risk factor.

Breakthrough infections and chronic carriage were clearly and strongly related to peak antibody concentrations. Thus half of the children who failed to produce detectable concentrations of antibody

became infected, most within the first five years after vaccination, and of those infected, nearly half became chronic carriers. However, as the numbers were small and as the vaccines, doses, and routes of administration varied, the investigators were not able to assess formally which of these factors were the most important determinants of breakthrough infections resulting in chronic carriage of hepatitis B virus [4].

#### Conclusions of the Keneba and Manduar studies

The authors involved in recent stages of the Keneba and Manduar research concluded that the long-term study of hepatitis B vaccination in infancy in a country where the infection is endemic showed that vaccine efficacy against infection waned with time. Efficacy against chronic infection, however, remained high over a fourteen-year period [4]. Nevertheless, the numbers involved in these studies were relatively small and a larger study of efficacy during adolescence is necessary before it can be concluded that a booster dose is not needed before the onset of sexual activity. In Africa and elsewhere, the risks of HBV infection and chronic carriage might be increased by the presence of other sexually transmitted infections, as is the case for HIV-1 [4]. Based on the findings of the Keneba and Manduar studies, Gambia did not change its current immunisation policy (i.e., 0, 1, 6 months schedule and no booster).

#### Gambia Hepatitis Intervention Study

The Gambia Hepatitis Intervention Study (GHIS), initiated in 1986, is a collaborative project comprising the International Agency for Research on Cancer, the government of the Republic of The Gambia, and the Medical Research Council in the United Kingdom [5,6].

The aims of the GHIS project were:

- to assess the level of protection provided by hepatitis B vaccination during the first year of life against subsequent HBV infection, chronic carrier status, and primary liver cancer; and
- to demonstrate the feasibility and effectiveness of integrating hepatitis B vaccination into the national Expanded Programme on Immunization (EPI).

The design of the GHIS included a stepped-wedge introduction of a plasma-derived hepatitis B vaccine, administered at 0, 2, 4, and 9 months of age. Cross-sectional surveys were carried out to estimate vaccine efficacy at four and nine years of age, involving 1000 vaccinated children who were followed up on a yearly basis. Vaccination was gradually introduced, beginning in July 1986 until February 1990 when full national coverage had been reached.

The subjects comprised two cohorts of approximately 60,000 children each, with one group receiving the routine EPI vaccines (BCG, OPV, DPT, measles, and yellow fever), and the second group receiving all of the routine EPI vaccines plus the hepatitis B vaccine.

From September 1995 to September 1996, a cross-sectional survey was conducted of unvaccinated children in order to determine vaccine efficacy against HBV carriage and infection. These children were selected from areas of the country that matched those children who had been recruited for the vaccinated cohort, but where the

hepatitis B vaccine was not being given during the first year of life. Only children who were identified in the GHIS vaccination database as being unvaccinated were included in the study. Following informed consent, a blood test of the child was carried out, and those children who were found to be HBsAg-positive were re-tested one year later.

Definitions regarding infection and carrier status were as follows:

UNINFECTED	Tested negative for HBsAg and anti-HBc
CHRONIC CARRIER	Tested HBsAg-positive twice, one year apart
BREAKTHROUGH INFECTION	Anti-HBc positivity in a vaccinated child, irrespective of the number of vaccine doses or antibody response

The results of the study show that protection against HBV chronic carriage, following infant vaccination, is over 90% at 9 years of age. Even if the loss during follow-up of some known carriers is taken into account, the estimate remains at 90%. Protection against infection is more difficult to interpret because of the reversion from positive to negative of anti-HBc in a proportion of vaccinees who are infected. These findings suggest that a booster dose of vaccine will not be required in the medium-term future. However, some caution and further evaluation of vaccine efficacy are recommended [5].

#### Conclusions

The results of these studies show the high level of protection that infant hepatitis B vaccination provides against HBV infection and chronic carrier status, and that no booster dose of hepatitis B vaccine is needed during the first ten years of a child's life.

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*Based on a presentation by Dr Andrew Hall, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom.*

## Update of the universal vaccination programme in Italy

Italy's hepatitis B vaccination programme has resulted in considerable progress towards prevention and control of hepatitis B virus (HBV) infection [1]. Selective immunisation against hepatitis B was first implemented in Italy in 1983 and targeted to risk groups. In 1991, Italy began a mandatory universal vaccination

programme for infants and twelve-year old adolescents, together with mandatory HBsAg screening of pregnant women.

Italy's overall hepatitis B vaccination coverage rate is approximately 95%. However, there are regional differences: for example, coverage

among adolescents is about 80% in southern Italy, where acceptance is somewhat lower, compared with the northern regions where coverage has reached 100%.

The hepatitis B vaccination coverage rate among health-care workers and household contacts of carriers is still insufficient, however, and also reflects regional differences between North and South.

#### Decline in hepatitis B incidence

Hepatitis B incidence in Italy has dropped dramatically since implementation of universal infant vaccination. Between 1991 and 2003, the overall number of new cases of hepatitis B dropped by 80% compared with data for 1985 to 1990. Particularly striking is the reduction in incidence among individuals in the fifteen to twenty-four year age group. No clinically overt hepatitis B cases have been reported thus far in any of the vaccine recipients.

#### HBsAg mutants and breakthrough infections

Occasional breakthrough infections occur due to the G145R mutant or to less frequent S-gene mutants (P120S, B127S) among liver transplant recipients and in children born to HBsAg carrier mothers. However, there is no evidence, at present, that S-gene mutants pose a threat to Italy's established hepatitis B vaccination programme.

#### Changing patterns of hepatitis B infection in Italy

Since Italy's implementation of universal hepatitis B vaccination, levels of HBV markers have dropped to near zero among children and adolescents during the last decade. In parallel with the decline in HBV infection, hepatitis D (Delta) virus infection has also declined significantly in Italy.

During the last twenty years, Italy has seen a progressive decline in hepatitis B as a result of:

- social, behavioural, and demographic changes
- general improvements in Italy's standards of living and hygiene
- introduction of public health measures such as refinement in blood screening, use of universal precautions in medical settings, and implementation of vaccination programmes.

Italy's priorities for future prevention and control of HBV infection will focus on:

- maintaining mandatory vaccination of infants and HBsAg testing of pregnant women
- catch-up immunisation of unvaccinated adolescents
- increasing hepatitis B vaccination coverage in high-risk groups
- examining the potential need for vaccine booster doses.

#### HBV vaccination and immunological memory

Preliminary data from Italian studies [2] provide evidence that a strong immunological memory may persist eleven years after immunisation of healthy infants and children who have completed a primary course of hepatitis B vaccination.

Reaching a consensus on this last key point is an urgent need in Italy, since at the end of the year 2003, the first infant cohort vaccinated in 1991 reached the age at which adolescent vaccination takes place (12 years). Hence, vaccination of 12-year old adolescents was stopped at the beginning of 2004.

A large study is now in progress evaluating the anamnestic response to a booster injection of hepatitis B vaccine in cohorts of children vaccinated as infants, and young adults vaccinated as adolescents who lost protective levels of anti-HBs (< 10 mIU/ml) twelve years after the primary course. Preliminary data indicate that almost all vaccinees who had lost anti-HBs showed a rapid and vigorous anamnestic response when boosted.

In conclusion, based on the currently available evidence, booster doses of hepatitis B vaccine do not appear to be necessary to maintain life-long immunity.

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*Based on a presentation by Dr Alessandro Zanetti, Institute of Virology, Faculty of Medicine, University of Milan, Milan, Italy.*

## Follow-up of hepatitis B vaccination: studies in Spain

Spain's earliest hepatitis B immunisation programme dates back to the 1980s when selective immunisation targeted to risk groups was first implemented. However, this risk-group immunisation strategy was found to be inadequate in reducing hepatitis B incidence and prevalence. In October 1991, a universal hepatitis B vaccination programme targeted to 12-year olds was implemented in Catalonia. A few months later, in 1992, the National Council of Health recommended that all seventeen autonomous regions adopt a school-based hepatitis B adolescent immunisation programme.

By 1996, Spain's overall hepatitis B vaccination coverage rate was 83%, with marked regional differences ranging from low coverage in Cantabria (25%) and the Canary Islands (47%) to 99% coverage in the regions of Navarra and Rioja. Since 1998, all autonomous regions have had adolescent hepatitis B immunisation programmes in place.

Data for the period 1998-2000 show that the annual incidence of new hepatitis B cases in Spain was 100-150 per 100,000 inhabitants. This corresponds to approximately 60,000 new cases per year and 12,000 cases per year of symptomatic acute hepatitis B.

Because risk-group and adolescent immunisation programmes alone are not adequate to control hepatitis B virus infection, by 2000 Spain had also implemented a universal infant hepatitis B immunisation programme in all seventeen autonomous regions, with the result that 98% of infants received 3 doses of the hepatitis B vaccine [1]. The new vaccination calendar, approved by the National Council of Health on November 19, 2003, has been operational since March 1, 2004 [2].

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*Based on a presentation by Dr Vicente Carreño, Fundación para el Estudio de las Hepatitis Virales, Madrid, Spain.*

## Evaluation of the school-based hepatitis B vaccination programme in Catalonia (Spain)

Catalonia's earliest hepatitis B vaccination programmes, which had begun in 1984, were targeted to high-risk groups and to newborns of HBsAg-positive mothers. This strategy, however, had little impact on reducing incidence of the disease and its long-term consequences.

### The need for universal hepatitis B vaccination in Catalonia

By 1990, it had become clear that universal vaccination would be needed for effective hepatitis B prevention, and three options for mass vaccination were considered: (a) infants; (b) pre-adolescents; and (c) infants and pre-adolescents. Catalonia's choice was for a school-based pre-adolescent vaccination programme. The rationale for such a strategy was based on a number of factors, such as the high risk of HBV infection and disease during adolescence and early adulthood, and lower risk in infants and younger children. The rapid impact of vaccination on hepatitis B disease incidence rates and the high presumed vaccination coverage in schools were also taken into account. And precedents had already been set for achieving high coverage in other school-based vaccination programmes, such as measles-mumps-rubella (MMR) at eleven years of age, and tetanus-diphtheria (Td) at fourteen years of age.

In 1991, Catalonia became the first autonomous region of Spain to introduce a programme of universal hepatitis B immunisation for twelve-year olds. This school-based hepatitis B vaccination strategy proved to be highly successful in reducing incidence and prevalence of HBV. Today, the school-based pre-adolescent hepatitis immunisation programme is being implemented in all of the seventeen autonomous regions, and is Spain's main strategy in hepatitis B prevention.

The results of a cost-effectiveness analysis of the pre-adolescent-based programme, compared with programmes targeted to other age groups, are shown in the following table:

Vaccination strategy	Cost per infection avoided (in 1991 pesetas)
Vaccination of infants	254,000
Vaccination of infants & pre-adolescents	182,000
Vaccination of pre-adolescents	129,000

Source: [1]

The annual cost of the pre-adolescent immunisation programme was 3.1 million euro based on 1991 prices.

### Evaluation of operational and health targets of the programme

The *operational target* was to achieve high coverage of more than 90% in school children by the year 2000. The number of vaccine doses administered provided administrative data for evaluation of the programme. Serological data were also taken into account based on the prevalence of vaccine-induced immunity (anti-HBs positive and anti-HBc negative) in adolescents fourteen years of age.

The *health target* was aimed at 90% reduction in prevalence of hepatitis B virus infection in the 15 to 24-year age group, with < 1 case per 100 persons. Serological data were taken into account to determine the prevalence of anti-HBc-positive cases within that age group.

### Results of the programme

By 1996, the overall prevalence of markers of past and present HBV infections had already diminished from 16.9% to 9.1%, a reduction of 46% (comparison between 1989 and 1996) [2].

At present, Catalonia's pre-adolescent vaccination programme is well established and its overall success is evident when evaluating the results for the period 1990 to 2001:

- 94% hepatitis B vaccination coverage
- 90% reduction in the prevalence of markers within the 15 to 24-year age group
- 80% reduction in the incidence of hepatitis B disease in the 10 to 19-year age group.

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Based on a presentation by Lluís Salleras, Department of Public Health, School of Medicine, University of Barcelona, Barcelona, Spain.

## The decline of hepatitis B virus infection in the Kingdom of Saudi Arabia

### Epidemiology of hepatitis B virus (HBV) infection in Saudi Arabia

HBV infection is endemic in Saudi Arabia. Between 7% and 8% of apparently healthy adults in the Saudi population are HBsAg carriers, and at least one hepatitis B marker is positive in 60% to 70% of the population. Hepatitis B virus transmission occurs mainly horizontally and early in life within the Saudi population.

Based on pooled data from surveys up to 1988 [1], the prevalence of HBsAg was marked by regional and gender differences, as shown in the following table:

PROVINCE	NUMBER OF MALES TESTED	% POSITIVE	NUMBER OF FEMALES TESTED	% POSITIVE
Central	2155	6.9	4494	4.1
Southwest	1593	13.8	5642	3.9
Eastern	7838	11	462	8.2

### Integration of hepatitis B vaccination in Saudi Arabia's EPI

With the aim of reducing the HBV reservoir, and the incidence and prevalence of HBV-related diseases, Saudi Arabia integrated



universal hepatitis B vaccination into its Expanded Programme on Immunization (EPI) in 1989. Since then, there has been a major reduction in HBV infection. A chronology of hepatitis B programmes in Saudi Arabia is shown in the following table:

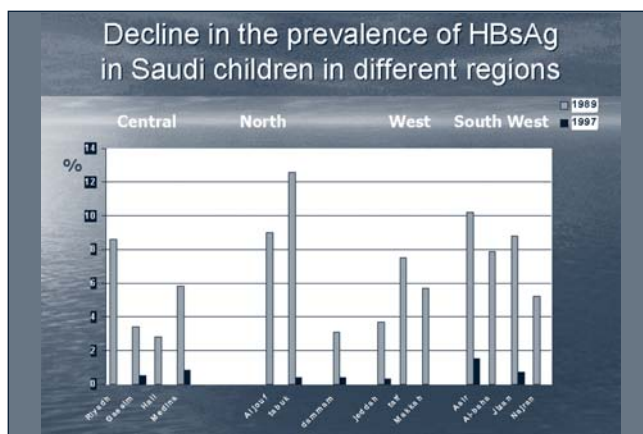
PROGRAMME TYPE	YEAR OF IMPLEMENTATION
<b>Mandatory</b>	
All newborns (0-1 year)	1989
Children at school entry (6-7 years)	1990
<b>Voluntary</b>	
Pre-school children (1-5 years)	1990 / 1991
Health personnel (adults)	1990
Others	1989

According to these programmes, all Saudi citizens under the age of eighteen years should have been vaccinated by the year 2000.

#### Evaluation and impact of the hepatitis B vaccination programme

Following the introduction of universal hepatitis B vaccination in Saudi Arabia, first-dose coverage increased from 90% in the first year of implementation to 95% in the second year, and third-dose coverage increased from 73% in the first year to 90% in the second year [2].

In 1997, a national survey was carried out to determine whether HBV prevalence had declined among Saudi children eight years after the integration of the hepatitis B vaccine into the national EPI. Comparative data for the years 1989 and 1997 show that HBsAg prevalence in Saudi children declined in all areas of the country [3,4].



The prevalence of other viruses, such as hepatitis A and hepatitis C virus, also declined dramatically during this eight-year period.

The success of hepatitis B vaccination in Saudi Arabia is attributed to a strong national health policy, funding, an effective EPI system, and external monitoring and auditing of vaccination programmes.

#### Changing epidemiology of hepatitis B in unvaccinated Saudis

There has also been a significant decline of HBV markers among

unvaccinated Saudi adults. Cross-sectional studies carried out in Gizan (South-western region) in 1985 and 1986 show that 12% to 32% of 'healthy' persons were HBsAg positive. Community-based follow-up studies, with a larger number of subjects, were conducted in 1992 and 1997 and showed a clear trend in declining HBsAg prevalence in asymptomatic adults in this area among both males and females, as shown in the table below:

Declining HBsAg prevalence in asymptomatic adults in Gizan (%)			
	1985	1992	1997
<b>Males</b>	19.9	9.4	5.8
<b>Females</b>	9.3	6.1	4.2
<b>Total</b>	13.9	7.7	5.1

Further studies [5] carried out in four groups of subjects in Gizan between 1995 and 1998 showed significantly lowered HBsAg prevalence, compared to the prevalence rates measured in 1985 and 1986. The results were as follows:

- 5.4% prevalence in male blood donors (n = 14,883) tested between June 1995 and June 1997;
- 5.1% prevalence in male and female volunteers (n = 1,172) recruited from the community in 1997;
- 9.4% prevalence in patients (n = 4,692) hospitalised from June 1995 to June 1996;
- 0.9% prevalence in children (n = 229) under 10 years of age in 1997 / 1998, of whom only two were HBsAg-positive.

Similarly, declining trends were also evident in other regions of the country, and may be directly attributed to hepatitis B vaccination and complementary control measures, and indirectly to other factors such as health education and socio-economic progress.

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Based on a presentation by Dr Ephraim Ayobanji Ayoola, Department of Gastroenterology, King Fahd Hospital, Gizan, Saudi Arabia.

## Follow-up of hepatitis B vaccination programmes in Taiwan and Singapore

#### Taiwan's success in reducing hepatocellular carcinoma through hepatitis B immunisation

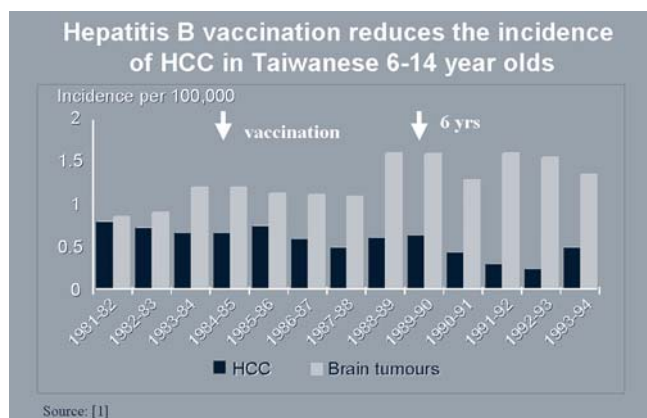
HCC or primary liver cancer is one of the ten most common malignancies worldwide, with approximately 75% to 80% of cases related to chronic infection with hepatitis B and C viruses. The hepatitis B virus (HBV) accounts for approximately half of all cases of HCC worldwide. While HCC can occur in people of all ages, it can develop in childhood or adolescence after perinatal HBV

transmission, which is the main route of HBV transmission in Asia. The most effective preventive measure against HBV infection and HCC is hepatitis B vaccination.

Taiwan was the first country in the world to launch a population-based hepatitis B vaccination programme. The initial phase of this programme, which was implemented in 1984, was targeted to hepatitis B vaccination for infants born to HBsAg-positive mothers.

In 1986, the programme was extended to all newborns, with coverage rates ranging from 84% to 94%. The hepatitis B vaccination programme was gradually extended to all pre-school and school-age children and, finally, to adults.

Since the implementation of Taiwan's universal hepatitis B vaccination programme, the incidence of HCC among children has declined.



The peak age of hepatocellular carcinoma is in adults between forty and sixty years of age. Thus, the main reduction in peak incidence of HCC in Taiwan will only be seen thirty to forty years following the launch of the universal hepatitis B vaccination programme – i.e., in the year 2024.

#### Long-term immunogenicity and efficacy of HBV vaccination in Taiwan

There have been few large-scale prospective studies carried out in community-based populations to assess long-term immunogenicity of hepatitis B vaccine. One such study [2] was carried out in Taiwan comprising 1,200 school children seven years of age who were recruited into the study ten years following the launch of universal HBV vaccination in 1986. Serological testing was carried out for HBsAg, anti-HBs and anti-HBc. Booster vaccinations were given to 200 of the 504 vaccinated non-carrier children with undetectable or low anti-HBs. Summary results of this study show that:

- The HBsAg-positive rate was 0.7%.
- The percentage of protective anti-HBs levels in 951 children without booster vaccination gradually decreased from 71.1% at age 7 years to 37.4% at age 12 years.
- Eleven children had new HBV infections with anti-HBc positivity as the only marker. Nine of the eleven children were at least anti-HBc positive twice one year apart (see table below).
- None of the children became positive for HBsAg or had detectable HBV DNA measured by polymerase chain reaction methods.
- Only 1 of the 200 children in the booster group and 2 of the 258 children in the non-booster group developed new anti-HBc positivity.

#### New annual anti-HBc seropositivity rate\* [2]

AGE	NUMBER OF NEW CASES	PERCENTAGE
8	3/1108	0.3
9	1/1020	0.1
10	1/1958	0.1
11	0/925	0.0
12	1/914	0.1
13	3/769	0.4

\* at least anti-HBc positive twice one year apart

The results of this study suggest that routine booster vaccination

may not be required to provide protection against chronic HBV infection before the age of fifteen years.

#### Prevention and control of HBV infection in Singapore

Singapore launched a mass hepatitis B vaccination programme in October 1985 targeted to infants born to HBsAg-positive mothers. In September 1987, the programme was extended to all newborns, and in February 2001 to adolescents and young adults fifteen to twenty-four years old.

#### Hepatitis B carrier status after vaccination

Hepatitis B vaccination coverage rates in Singapore increased from 85% in 1993, to 91% in 1994 and to 94% in 1995.

- For vaccinated babies born to carrier mothers, perinatal transmission was reduced by 80% to 100%, with no carriers detected among newborns of HBsAg-negative mothers.
- In primary school children, HBsAg prevalence dropped from 4% in 1987 to 0% in 1996.
- In secondary school children, the HBsAg prevalence rate was less than 1% in 2001.
- Serological surveys in 1993 and 1998 showed that none of the persons who were vaccinated were HBsAg positive, whereas the antigen was detected in 4% to 5% of unvaccinated persons.

#### Decrease in HBsAg carrier rates and HCC incidence in a non-vaccinated population

HBsAg carrier rates also decreased among non-vaccinated persons. Among national servicemen in Singapore, the HBsAg-positivity rate declined from 8.1% in 1984 to 4.4% in 1998.

For antenatal women, the overall HBsAg prevalence rates dropped dramatically over a twenty-year period, as shown below:

- 1980-1981 ..... 4.4%
- 1983-1985 ..... 4.1%
- 1996 ..... 2.9%
- 2000 ..... 2.3%

The age-standardised incidence rate of HCC among males in Singapore also dropped from 27.8/10<sup>5</sup> per year during 1978 to 1982 to 19.0/10<sup>5</sup> per year during 1988 to 1992.

#### General challenges in preventing hepatocellular carcinoma

In hepatitis B high-endemic areas such as Asia and Africa where human and financial resources may be scarce, vaccination programmes will be limited in what they can achieve in terms of acceptance and coverage. Compliance is particularly poor in areas where vaccine costs are not covered by the government and where the population may lack knowledge regarding the health benefits of vaccination. Compliance may also be poor in areas with low prevalence where, in the absence of disease, vaccination may no longer be considered necessary.

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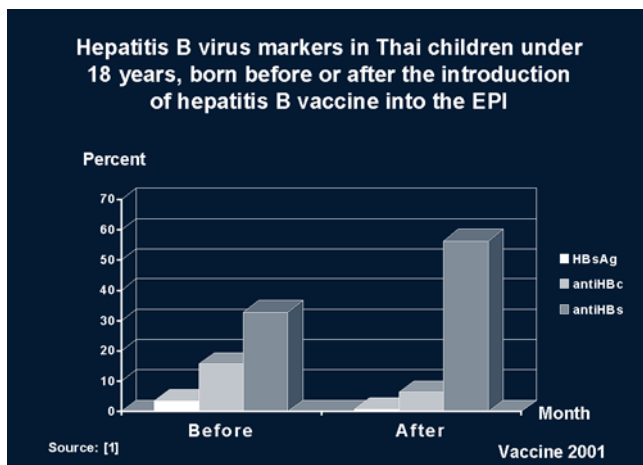
*Based on a presentation by Dr Sheng-Nan Lu, Department of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang-Gung Memorial Hospital, Kaohsiung, Taiwan.*

## Follow-up of hepatitis B vaccination: studies in Thailand

Thailand's Expanded Programme on Immunization (EPI) has achieved considerable success in increasing vaccination coverage and reducing the burden of vaccine-preventable diseases among children. Since the introduction of a hepatitis B three-dose schedule (0, 2, and 6 months) in 1992, as an integral part of the EPI in Thailand, hepatitis B vaccination coverage has increased from approximately 30% to approximately 80%.

### Impact of hepatitis B vaccination in Thailand

Based on data [1] from five representative Thai provinces, an evaluation was carried out on the impact of hepatitis B vaccination on country-wide prevalence of HBV infection and carrier rate. The study population comprised 400-488 healthy, immunocompetent subjects per geographical area, whose ages ranged from six months to eighteen years, and whose sera were examined for HBV markers. Comparative data, obtained from two groups of children (those born before and those born after the integration of hepatitis B vaccine into the EPI) are shown below.



The study concluded that since 1992, the hepatitis B vaccination coverage rates in these five areas were between 71.2% and 94.3%. The HBV carrier rate decreased from 3.4% to 0.7% following implementation of the EPI strategy.

To illustrate the success of the Thai universal hepatitis B vaccination programme, a comparison with the equally successful Taiwanese programme is shown in the table below.

Impact of universal hepatitis B immunisation on subjects born before or after the start of the programme: situation in 1999			
	Born before start	Born after start	
<b>Taiwan (start in 1984)</b>			
Age group	15-20 year	< 15 year	
HBsAg carrier rate	7 %	0.7 %	
<b>Thailand (start in 1989-1992)</b>			
Age group	10-18 year	< 10 year	
HBsAg carrier rate	3.4 %	0.7 %	

Sources: [1,3]

### Hepatitis B boosters?

Another serological study [2] carried out in five geographical areas

of Thailand sought to examine the impact of the three-dose hepatitis B vaccination schedule and the resulting long-term protection. The subjects were aged one to ten years and had received the full hepatitis B vaccine course. Using ELISA testing for HBsAg, anti-HBs, and anti-HBc, prevalence for all age groups was as follows:

- HBsAg ..... 0.7%
- anti-HBs ..... 71.4%
- anti-HBc ..... 5.5%

Although the prevalence of anti-HBs decreased with age, it remained at 56%-65% among those aged six to ten years.

This study concluded that an additional vaccine booster dose does not appear to be needed to prevent HBV infection, and that using the current three-dose schedule could permit the eventual eradication of chronic carriage in Thailand.

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Based on a presentation by Dr Michel Stoffel, Clinical Development, GlaxoSmithKline Biologicals, Rixensart, Belgium, prepared by Dr Yong Poovorawan, Department of Pediatrics, Chulalongkorn University and Hospital, Bangkok, Thailand.

### NEW – Response by the World Health Organization's GACVS to the paper by MA Hernán et al.: 'Recombinant hepatitis B vaccine and the risk of multiple sclerosis'

The Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organization has given careful consideration to the article published by MA Hernán and others in the 14 September 2004 issue of *Neurology* (2004; 63:838-42) on the risk of multiple sclerosis (MS) associated with recombinant hepatitis B vaccine. The findings are based on a case control study conducted within the General Practice Research Database (GPRD) in the United Kingdom. ... On the basis of the data and argument given by Hernán et al. in their article, the GACVS does not believe that the findings provide convincing support for the hypothesis that immunisation with recombinant hepatitis B vaccine is associated with an increased risk of multiple sclerosis.

The GACVS has noted that the findings and conclusions of the Hernán paper are at variance with those of a number of others; namely Ascherio (2001), De Stefano (2003), Touze (2002), Sturkenboom (1999), Confraveux (2001), Zipp (1999), Sadovnick (2000). ... For the time being, the GACVS has advised the WHO that the evidence and argument submitted by Hernán et al. are insufficient to support the hypothesis of a link between hepatitis B vaccination and MS, and do not justify discontinuation or modification of immunisation programmes with HBV. The latter have had a demonstrated profound beneficial public health benefit worldwide.

Source: [http://www.who.int/vaccine\\_safety/topics/hepatitisb/multiple\\_sclerosis/sep\\_04/en/](http://www.who.int/vaccine_safety/topics/hepatitisb/multiple_sclerosis/sep_04/en/)

## Long-term persistence of vaccine-induced hepatitis B antibodies and immune memory

### Kinetics of hepatitis B surface antigen specific immune responses in acute and chronic hepatitis B

In hepatitis B virus (HBV) infection, strong and multi-specific Th-cell and cytotoxic T-cell (CTL) responses are associated with spontaneous recovery, while patients with chronic courses of the disease have weak and oligospecific T-cell responses. All components of the immune response add to virus control:

- antibodies against surface proteins limit viral spread
- CTL control virus replication in infected target cells by cytolytic and non-cytolytic mechanisms, and
- Th cells add to non-cytolytic virus control and provide help to CTL and B cells.

It is known from active or passive vaccination studies that anti-HBs antibodies developing after acute infection provide protection against *de novo* infection [1,2]. In the past, it was believed that chronic HBV carriers were unable to mount such an antibody response, since only approximately 5% and 15% of chronic HBV carriers are seropositive for anti-HBs and anti-preS antibodies in the presence of HBsAg, respectively [3-5]. This is due to super- or co-infection of patients with different HBV subtypes or mutants [4]. However, more recent studies have proven the existence of anti-envelope antibodies in the majority of patients with chronic hepatitis B, correlating to the inflammatory activity of the hepatitis [6]. These antibodies are, however, undetectable with standard means, due to their capture in immune complexes with HBsAg. Moreover, on the single-cell level, HBsAg-specific B-cell frequencies are not different from those of donors with resolved hepatitis B, but widely reduced compared to patients with acute symptomatic infection [7]. Thus, there is no clear evidence for an anti-HBs-defect in chronic hepatitis B.

Although all major HBV-derived antigens raise significant CTL responses in acute and chronic infection [8], on a Th-cell level, responses to the core antigen are immunodominant, whereas HBsAg- and preS-specific proliferative responses are weak, even in the acute inflammatory phase of the disease, when Th-cell and CTL responses of other specificities are peaking [9]. This results in equivalent low envelope-specific Th-cell reactivities in patients with acute or chronic hepatitis B [10]. However, for control of viral replication, core-specific Th cells seem to be crucial, as demonstrated by their timely association with HBsAg seroconversion [9] and by HBsAg seroconversion of chronic HBV carriers after adoptive transfer of bone marrow from donors with resolved HBV infection but not from HBsAg-vaccinated donors [11].

#### Conclusions

HBV-envelope antigens do represent strong B-cell antigens in acute and chronic HBV infection leading to complete or partial virus neutralisation, aiming to limit viral spread and to provide protective immunity. Envelope-specific Th cells and CTL are weak, however, in any stage of acute or chronic infection and, therefore, appear to be of minor significance for virus control and HBsAg clearance, where core and polymerase-specific T cells seem to be crucial. Thus, HBV-envelope antigens represent suitable protective vaccines and might play a role as 'adjuvants' for a core antigen-directed therapeutic vaccination [12-14].

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Based on a presentation by Dr Wulf Otto Böcher, I. Medizinische Klinik und Poliklinik der Universität, Johannes-Gutenberg University, Mainz, Germany.

## Immune memory after hepatitis B vaccination

A key feature of the adaptive immune system is its ability to respond to a pathogen or an antigen it has previously encountered either through exposure to the disease itself or through vaccination. The ability to respond again, with a more rapid, larger, and qualitatively different response is known as anamnestic response.

### Long-term efficacy of hepatitis B immunisation

Almost all individuals adequately vaccinated against hepatitis B have shown evidence of immunity in the form of persisting anti-HBs (the protective antibody that develops following recovery from hepatitis B virus infection or after vaccination) and / or *in vitro* B-cell stimulation or an anamnestic response to a vaccine challenge [1]. Protection against HBV infection is bound to anti-HBs concentrations of  $\geq 10$  IU/l (measured 1 to 3 months after administration of the last dose of the primary schedule) and antibody persistence depends on the initial (peak) anti-HBs concentration.

### Kinetics of anti-HBs after hepatitis B vaccination

The kinetics of anti-HBs after hepatitis B vaccination is very similar in every vaccinated individual, irrespective of the peak antibody level after the third vaccination. The half-life of anti-HBs is a function of time - i.e., very short initially and becoming longer with time after the last vaccination. Disturbances to the immune system, such as specific disorders and certain drugs (e.g., anti-epileptics) also influence anti-HBs kinetics [2-5].

Results based on long-term follow-up studies that have been carried out in various populations in North America, Europe, and Asia, show that in 10% to 50% of all successfully vaccinated individuals, the anti-HBs concentration decreases below 10 IU/l within ten years.

#### Persistence of anti-HBs after hepatitis B vaccination

Population	Time after first vaccination	Anti-HBs $\geq 10$ IU/l (%)
Alaskan natives (n = 959) [6]	10 years	76
Taiwanese children (n = 539) [7]	10 years	85
Italian children (n = 223) [8]	11-14 years	75
Chinese children (n = 52) [9]	15 years	50

### Breakthrough infections after successful hepatitis B vaccination

Breakthrough infections [10] have occurred in successfully vaccinated individuals. Data published so far showed that:

- The risk of hepatitis B infection is inversely related to the maximal antibody response to vaccine.
- The risk of infection increases with declining anti-HBs.
- The vast majority of infections in successfully vaccinated individuals are clinically silent.
- Protection against clinically important disease outlasts the presence of detectable antibodies.

However, there is still a need for long-term follow-up studies to identify breakthrough infections and for further research into the humoral and cell-mediated immune basis of memory. Additional

data are needed to distinguish between sub-clinical and breakthrough infection [10].

### Conclusions

Some of the difficulties in determining the length of protection after hepatitis B immunisation are summarised below:

- Follow-up studies with an observation time much longer than 10 years are still rare.
- The number of vaccinees available for follow-up decreases with time and the data become less significant.
- In countries with low endemicity, the risk of hepatitis B infection is very low so that challenge will be rare.
- Immunological memory, thus far, has been demonstrated mainly by anamnestic response to re-vaccination while reliable and sensitive cellular tests are seldom used.

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## Impact of HBV mutants on vaccination programmes

### Vaccine-escape HBV mutants

Among the hepatitis viruses affecting humans, hepatitis B virus (HBV) is the only DNA virus. The HBV genome consists of a small, circular, partially double-stranded DNA molecule that is approximately 3200 nucleotides in length [1,2].

Before genome replication of the virus can occur, an RNA intermediate or pregenome is produced [3]. The HBV DNA genome is subsequently generated by reverse transcription of the pregenome; HBV thus displays the features of a retrovirus [4]. The genomic RNAs contain the complete genetic information of the virus.

#### HBV replication and mutation

Replication of the virus occurs only in the liver. Hepatitis B virus has four overlapping open reading frames (ORFs), which allow the virus to produce an extended class of diverse proteins [5]. The ORFs are S (surface), C (core), P (polymerase) and X [6]. The overlapping ORFs restrict the mutation rate of HBV, which is approximately one nucleotide per 10,000 bases / infection per year, ten-fold higher than other DNA viruses. Thus,  $10^{10}$  mutations enter the virus pool daily.

Various mutations have been observed in almost every part of the HBV genome. Some common features are that:

- Their frequency increases with the progression of the infection.
- They are selected during the time of environmental pressure.
- They make overlapping changes for both overlapping ORFs.

The HBV mutations that have been most studied are:

- immune escape and vaccine-escape mutations of HBsAg
- precore and core promoter mutations, which prevent HBeAg secretion
- mutations leading to resistance to lamivudine (a potent inhibitor of RNA-dependent DNA polymerase of HBV), i.e., treatment-escape mutations
- mutations associated with HCC.

#### Vaccine-escape mutations

Hepatitis B vaccines currently in use contain subviral particles that are composed of HBsAg. During intramuscular injection, they induce production of antibodies against HBsAg (anti-HBs) and proliferation of HBsAg-specific cytotoxic T lymphocytes.

The excellent qualities of hepatitis B vaccine have been proved over and over again and the vaccine's capacity to effectively protect people against HBV infection is unquestionable. However, in a limited number of reports, cases were described of children who were infected with HBV after having completed a full vaccination course. These cases were attributed to certain HBV strains carrying mutations on the antigenic *a* determinant of HBsAg. The *a* determinant is the dominant epitope cluster of HBV that confers protection, and binds most of the anti-HBs present in hyperimmune serum. Several studies have demonstrated that *a* determinant mutations can bind anti-HBs weakly [7,8].

Future vaccines could include preS1- and pre-S2 antigens. However, there is no convincing evidence to date that vaccine formulations need to be changed in the near future. Nevertheless,

data are still needed from well-designed studies to examine various options for adding mutant antigens in newly formulated hepatitis B vaccines.

#### HBV serotypes associated with mutants

The common *a* determinant of HBsAg can occur with other mutually exclusive subdeterminants, *d* or *y*, and *w* or *r*, resulting in four serotypes *adw*, *ayw*, *adr* and *ayr* [9], each with a geographical distribution, and proving valuable as an epidemiological marker. The *adw* and *adr* serotypes appear to be more likely associated with mutants than *ayw* and *ayr* serotypes.

#### Escape mutants

Surface gene mutations have been detected in:

- infants born to HBe-Ag-positive mothers who developed breakthrough infections despite having undergone full passive-active immunoprophylaxis
- transplant recipients during HBIg prophylaxis to prevent infection of liver homograft in immunosuppressed patients
- HBsAg-negative chronic HBV infections
- patients with HCC
- asymptomatic HBV carriers.

HBsAg mutants may cause persistent infection. Results from a study [10] carried out among children in Singapore showed that:

- Mutations persisted over at least 13 years.
- HBsAg and anti-HBs co-existed in the children.
- Mutants and wild-type viruses co-existed as well.
- During the course of the infection, HBV DNA reduced under the detection limit of hybridisation assays in most of the children, although the children were PCR-positive.
- HBV DNA tended to remain higher in patients having HBsAg mutants with altered first loop of the *a* determinant compared to those with an altered second loop.
- Mutants were detected in some of the mothers.

#### Vaccine-escape mutants in post-exposure prophylaxis of newborns

Almost 4% of babies born to HBsAg-positive mothers are perinatally infected with HBV, despite having had active and passive immunisation. If the babies are born to mothers with a replicative (HBeAg-positive) infection, more than 10% of babies are infected, despite immunisation. In 25% to 50% of these infections, HBsAg *a* determinant mutants could be detected. Some of the infected babies developed chronic hepatitis, which was evident during follow-up examination.

There are still a number of areas needing further study, such as how mutations evolve, how mutants persist while binding to anti-HBs, and why the wild-type virus co-exists with mutants when the only mechanism is selection under immune pressure.

Further study is also needed in developing easy methods to detect mutations. There is also a need for epidemiological and clinical studies to monitor the occurrence and distribution of mutants, to test the risk of transmission in susceptible and immunised persons, and to detect their pathogenicity.

**Conclusions**

- HBsAg mutants may cause persistent infection, and may be associated with chronic hepatitis.
- There is evidence that HBsAg mutants interfere with post-exposure prophylaxis, and may prevent detection of HBsAg in HBV infection.
- While mutants can infect persons who are not vaccinated, there is no clear evidence that they can infect persons who have been successfully immunised against hepatitis B virus, except in post-exposure situations.
- HBsAg mutants are more likely to be present with *adw* and *adr* serotypes.
- While it is difficult to predict the future development of vaccine-escape mutants, further investigation is needed regarding the question of whether they will become prevalent or not.

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## Current booster recommendations

### WHO hepatitis B booster recommendations

From a WHO (World Health Organization) perspective, hepatitis B vaccine should be included in universal childhood immunisation schedules for all children in all countries. Some industrialised countries administer the vaccine to adolescents as their primary immunisation strategy [1], sometimes in addition to their universal infant immunisation programme.

WHO has set the following priorities, in order of importance, for a hepatitis B immunisation strategy:

- universal infant vaccination
- prevention of perinatal HBV transmission (from mother to neonate)
- catch-up vaccination for older age groups

**HBV vaccine boosters**

WHO does not recommend hepatitis B vaccine booster doses, based on the following:

- Many studies have shown that infants, children, and adults who have responded to a complete hepatitis B immunisation series are protected from the disease for as long as 15 years, even if they lose protective antibodies over time.
- Long-term protection relies on immunological memory, which allows a protective anamnestic antibody response after exposure to the hepatitis B virus.

**Additional studies needed**

Additional information is still needed, however, to establish if booster injections are needed for adults beyond fifteen years after hepatitis B vaccination.

Further data are also needed for children who are immunised at birth in order to determine if immunological memory persists into adolescence and advanced adulthood, age groups at higher risk of infection either by lifestyle or by professional exposure to HBV (especially in industrialised countries).

To address these issues, cohort studies of immunised subjects are, therefore, warranted.

**Conclusions**

There are no data as yet that support the need for booster doses of hepatitis B vaccine in immunocompetent individuals. Almost all adequately vaccinated individuals have shown evidence of immunity in the form of persisting anti-HBs antibodies and / or *in vitro* B-cell stimulation, or an anamnestic response to a vaccine challenge.

Some countries, however, consider the administration of booster doses of hepatitis B vaccine as an option to provide reassurance of protective immunity against benign breakthrough infection.

Appropriate monitoring of vaccine-escape / treatment-escape mutants will require setting up an independent global network for this purpose.

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*Based on a presentation by Dr Daniel Lavanchy, Global Alert and Response, Department of Communicable Disease Surveillance and Response, World Health Organization, Geneva, Switzerland.*

## European Consensus Group on Hepatitis B Immunity – Are boosters needed for lifelong hepatitis B immunity?

Following a meeting in Florence, Italy in October 1998, the European Consensus Group on Hepatitis B Immunity concluded that there were no data to support the need for booster doses of hepatitis B vaccine in infants, children, and adolescents, and in immunocompetent individuals who have responded to a complete primary course [1]. The recommendation was based on evidence that routine boosters are not needed in most vaccinees due to the following:

- the good *in vivo* anamnestic antibody responses that result from exposure to the hepatitis B virus or to hepatitis B immunisation
- the protective, particularly B-cell-mediated immunity that persists with waning or absent antibody responses

In March 2004, nearly six years following the 1998 European Consensus Group recommendation, it is appropriate to question whether there is further evidence to support or to exercise caution regarding this point of view.

A *clinically significant HBV infection* is viewed as one resulting in a positive serum test for HBsAg, the rationale being that such an infection renders the individual infective to others and could lead to chronic carriage of HBV. An exposure to HBV that does not lead to infection may simply boost the titre of anti-HBs. Seroconversion for anti-HBc in the absence of HBsAg can generally be viewed as evidence of *clinically benign breakthrough infection* [2].

The crucial question is: Do breakthrough infections in immunocompetent vaccinees occur among those who have responded satisfactorily to a primary hepatitis B vaccination course?

### Mechanism of immune memory

Immune memory is made up of a complex interplay among memory B cells, memory T helper cells, memory cytotoxic lymphocytes (CTL), and antigen / antibody complexes.

*In vitro* studies have shown that if the hepatitis B vaccine administered in a primary series initially induces an anti-HBs titre greater than or equal to 10 mIU/ml, then memory B- and T-helper cells retain the capacity to generate antibodies following re-exposure to HBsAg, even if the anti-HBs titre falls to less than 10 mIU/ml later on [3,4].

Results from follow-up studies carried out in endemic and non-endemic countries among persons vaccinated with hepatitis B vaccine are shown below:

Countries	No of subjects	Time since vaccination	≥ 10mIU/ml (%)	Anti-HBc	HBsAg	Clinical
USA (carrier mothers)	70	4-9	83	3	0	N/A
Belgian adults	40	8	93	0	0	0
NZ children	125	9	95	11	0	N/A
Italian infants	587	5	33-91	0.2	N/A	0
US HCW	985	6	85	N/A	N/A	N/A
Spanish children	462	6.5	85	9	0	0
TOTAL	2,269	4-9	33-95	24	0	0

Source: [5]

Countries	No of Subjects	Time since vaccination	≥ 10mIU/ml	Anti-HBc	HBsAg	Clinical	Comments
Alaska (adults and children)	1017-1497	7	74	8	0	0	3 of 8 initial response ≥ 10mIU/ml
Hong Kong (children)	63-101	5	87	0	0	0	
India (adults)	63-101	5	84	0	0	0	
India (adults)	34	8-10	84	0	0	0	
Senegal (infants)	92	9-12	88	18	2	N/A	No difference in HBsAg between boosted & non-boosted. Increase antiHBc with time
Taiwan (measles)	1357	7	77	25 (1.9%)	9 (0.6%)	N/A	
New Caledonia	527	10	84	49 (8.3%)	8 (1.3%)	N/A	
Gambia	~990	~14	63-100	25%	10	N/A	Different schedules include 1D, 1D+1M & 1M & 1M only 7 of 10 HBsAg positive were ≥ 10mIU/l post vaccination

Sources: [5-9]

In the absence of HBsAg, anti-HBc is a marker of past HBV infection. Further studies are needed to evaluate the significance of core antibodies in terms of (a) whether the apparently transient infection of hepatocytes could result in long-term chronic liver disease, and (b) whether reactivation of HBV infection could occur in immuno-compromised patients (e.g., HIV/AIDS patients).

In interpreting the data from reports obtained from hepatitis B vaccination studies in developing countries, the following factors need to be taken into consideration:

- maternal HBV status for infant immunisation
- dose of hepatitis B vaccine and route of administration
- immediate post-vaccination response (usually not documented)
- other infections, particularly HIV infection
- nutritional status

Other long-term follow-up studies should be carried out to assess:

- the level of protection (including immunological memory) in adolescents and older age groups, following vaccination in infancy
- the burden of disease from breakthrough infections, particularly in long-term follow-up studies following hepatitis B vaccination
- the burden of disease on a long-term follow-up basis from breakthrough infections occurring among vaccinees who were on a 2-dose schedule (a schedule that is registered in some countries for adolescents)
- the role of HBV escape mutants

### To boost or not to boost

Further studies in hepatitis-B-endemic countries will determine whether susceptibility to persistent carriage of HBV in vaccinated persons increases with time. While such studies in the above-mentioned areas are still needed, there are currently no data to support the need for booster doses of hepatitis B vaccine in infants, children, and adolescents, and in immunocompetent adults who responded to a complete primary course.

The European Consensus Group on Hepatitis B Immunity believes that investigations must be carried out not only to ensure that the vaccinees who participate in long-term follow-up studies respond adequately, but that attention is also focused on assessing immunological memory in persons whose antibody responses were initially present but subsequently declined to undetectable levels.



Monitoring of anti-HBs titres is recommended for vaccinated persons considered at risk of HBV infection, if immunocompromised (e.g., haemodialysis patients). Adult vaccinees with  $\leq 10$  mIU/ml anti-HBs after a full hepatitis B vaccination course, measured 1 to 3 months following vaccination, should be considered for re-vaccination.

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## Are booster doses of hepatitis B vaccine necessary? Current CDC recommendations and gaps in knowledge

The Centers for Disease Control and Prevention (CDC) does not currently recommend booster doses of vaccine for routine infant, childhood, adolescent, or adult hepatitis B vaccination programmes. This recommendation is based on long-term efficacy studies and booster-dose studies that have been published to date, as well as United States surveillance data that suggest no cases of acute hepatitis B are occurring among vaccinated children and adolescents.

#### Impact of hepatitis B vaccination programmes in the United States

Hepatitis B vaccination programmes began in the United States in 1982 with selective vaccination of persons at increased risk of hepatitis B virus (HBV) infection. Since then, the programme has expanded to include routine infant, childhood, and adolescent vaccination.

- 1982: selective vaccination of children, adolescents, and adults at increased risk of infection
- 1984: prevention of perinatal transmission through routine screening of pregnant women
- 1991: routine vaccination of infants beginning at birth
- 1995: routine vaccination of adolescents (aged 11-12 years)
- 1999: catch-up vaccination of unvaccinated children and adolescents (through 18 years)

Groups considered at increased risk of HBV infection and for whom hepatitis B vaccination is recommended in the United States include:

- injecting drug users
- sexually active homosexual and bisexual men
- heterosexual men and women with more than one sex partner
- persons recently tested for another sexually transmitted infection (STI)
- household contacts and sex partners of persons with chronic HBV infection
- persons with occupational exposure (e.g., health-care workers)
- recipients of certain blood products (e.g., clotting-factor concentrates)

- clients and staff of institutions for the developmentally disabled
- haemodialysis patients
- international travellers
- inmates of long-term correctional facilities
- adoptees from high HBV-endemic countries

Substantial progress has been made in eliminating HBV transmission in children and reducing the risk for HBV infection in adults. Between 1990 and 2001, acute hepatitis B incidence in the United States declined by 66%, to 2.8 cases per 100,000 population. Among children, incidence declined by 89% and among adolescents by 85%.

Hepatitis B vaccination coverage among children in the United States increased from 8% in 1992, the first year of the routine infant vaccination programme, to 90% in 2002. Although coverage also increased among adolescents, from approximately 10% in 1997 to approximately 67% in 2001, there is still a gap in terms of reaching the target coverage of 90%.

#### Booster dose studies and immune memory


Long-term protection studies [1-15] carried out worldwide among infants, children, and adults from ten to fifteen years after initial hepatitis B vaccination have documented the following (see also the two tables on the following page):

- decline in detectable anti-HBs: levels remained  $\geq 10$  mIU/ml in 48% to 91% of the examined persons
- serological evidence of HBV infection (i.e., anti-HBc) in some vaccinated persons: between < 1% and 14% of the examined individuals were anti-HBc-positive, except in Senegal (27%) and Gambia (31%)
- no symptomatic infections
- development of chronic infections very rare
- despite a decline in anti-HBs, protection presumably persists.

Furthermore, booster dose studies carried out among persons vaccinated as infants and adults show that among those who lose detectable levels of anti-HBs, the majority respond to booster doses

of hepatitis B vaccine, and among the documented responders (i.e., anti-HBs levels  $\geq 10$  mIU/ml after the complete primary series), 97% to 100% respond to boosting. These results suggest that despite the loss of anti-HBs, the immune memory persists.

Long-term protection studies among vaccinated infants					
Country	Years of follow-up	n	Anti-HBs $> 10$ mIU/ml	Anti-HBc positive	HBsAg positive
China	15	52	50%	6%	2%
Alaska	15	119	61%	1%	0
The Gambia	14	175	64%	31%	2.8%
Hong Kong	12	148	74%	1%	0
Taiwan	12	951	37%	2.7%	--
Senegal	9-12	41	68%	27%	2%
Taiwan	10	805	85%	14%	0.4%
Taiwan	10	118	67%	12%	0
Italy	10	53	68%	0	0
Italy	10	474	68%	1%	0
Thailand	8-10	76	62%	9%	0

Sources: [1-11] 

Long-term protection studies among vaccinated adults					
Country (Group)	Years of follow-up	n	Anti-HBs $> 10$ mIU/ml	Anti-HBc Positive	HBsAg Positive
Alaska (20-49 yrs)	15	182	59%	$< 2\%^1$	$< 0.2\%^1$
Italy (HCW)	10	310	85%	0	0
U.S. (MSM)	10	127	91%	4%	0
Alaska <sup>2</sup>	9-10	1194	65-84%	0	1%
U.S. (MSM)	7-9	232	48%	7%	$< 1\%$

<sup>1</sup> Results for all 783 persons in study, not just those vaccinated at age 20-49 years.  
<sup>2</sup> Includes vaccinated children.

Sources: [2,12-15]

### Unanswered questions and gaps in knowledge

Questions still remain as to which determinants of duration of protection are the most important, such as:

- age at vaccination (birth, infancy, childhood, adulthood)
- anti-HBs levels post-primary series
- receipt of hepatitis B immunoglobulins (HBIG)
- vaccine type: plasma-derived or recombinant
- infection pressure: endemicity, maternal HBV status, vaccination coverage
- natural boosting.

The question of natural boosting and HBV infection pressure, and the relationship between the two, is particularly significant in the following contexts:

- high versus low HBV-endemic areas
- areas with catch-up vaccination of older children, adolescents and adults (i.e., Alaska)
- travel from low- to high-endemic areas and the potential for exposure.

The CDC continues to carry out long-term protection and booster-dose studies in high- and low-HBV endemic areas, as summarised below:

- Palau (high endemic)
  - Adolescents (9-10 years) vaccinated at birth with recombinant vaccine
- Alaska (Anchorage, low-endemic)
  - Children (5-7 years) and adolescents (10-13 years) vaccinated

at birth with recombinant vaccine

- Alaska (villages, high endemic)
  - 22-23 year follow-up of infants ( $> 6$  months), children, and adults vaccinated with plasma-derived vaccine.

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Based on a presentation by Dr Susan Goldstein, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

## Conclusions of the meeting

The Viral Hepatitis Prevention Board held its spring meeting, March 11-12, 2004, in Sevilla, Spain. The meeting comprised experts from the World Health Organization, the Centers for Disease Control and Prevention, and other organisations representing the public and private sectors from Europe, North America, the Middle East, and Asia.

The primary objectives of the meeting were to review the most recent data regarding long-term efficacy of hepatitis B vaccine and its long-term effectiveness in universal hepatitis B vaccination programmes. Other topics that were covered during the meeting focused on:

- recent data regarding the potential impact of HBV mutants on hepatitis B vaccination programmes; and
- current hepatitis B booster vaccination recommendations by the World Health Organization, the European Consensus Group on Hepatitis B Immunity, and the Centers for Disease Control and Prevention.

### Long-term efficacy of hepatitis B vaccine

- The hepatitis B vaccine is effective in protecting against clinical HBV infection and chronic carriage for at least fifteen years among infants and children, and among adults who have responded to a complete hepatitis B primary vaccination series.
- *In vitro* studies show that, if the hepatitis B vaccine administered in a primary series induces an anti-HBs titre greater than or equal to 10 mIU/ml, then memory B- and T-helper cells retain the capacity to generate antibodies following re-exposure to HBsAg, even if the anti-HBs titre falls to less than 10 mIU/ml at a later point in time.
- Almost all adequately vaccinated individuals have shown evidence of immunity against HBV infection in the form of:
  - ◆ persisting anti-HBs and / or
  - ◆ *in vitro* B-cell stimulation or anamnestic response to a vaccine challenge.
- Long-term protection studies that have been carried out worldwide among infants, children, and adults from ten to fifteen years following initial hepatitis B vaccination have shown that:
  - ◆ no symptomatic infections occurred
  - ◆ development of chronic infections is very rare
  - ◆ despite a decline in anti-HBs, immune memory persists, providing long-term protection against HBV infection.

### Long-term effectiveness of hepatitis B vaccination programmes

- Long-term surveillance data from countries in Europe, North America, Africa, the Middle East, and Asia point to the success of hepatitis B immunisation programmes, which have contributed to:
  - ◆ decreased incidence of acute hepatitis B virus infection
  - ◆ decreased incidence of hepatocellular carcinoma (HCC) in persons under thirty years of age
  - ◆ a decrease in HBsAg carrier rates providing indirect protection to non-vaccinated persons

### Preventing hepatocellular carcinoma through hepatitis B vaccination

- HBV infection accounts for approximately half of all cases of HCC worldwide. HCC occurs in people of all ages. The main routes of HBV transmission may vary by geographical

area. Studies carried out in Africa show horizontal transmission (sibling to sibling) of HBV as the dominant mode of transmission. In Asia, HCC frequently develops in childhood or adolescence after perinatal HBV transmission from HBeAg-positive mothers to their newborns.

- In Taiwan and Singapore, the incidence of HCC among children has declined since a universal hepatitis B vaccination programme was implemented. As the peak age of HCC is in adults between forty and sixty years of age, a substantial reduction in peak incidence of HCC will be seen thirty to forty years following the launch of this programme.

### Potential impact of HBV mutants on hepatitis B vaccination programmes

- HBsAg mutants may cause persistent infection, and may be associated with chronic hepatitis. Although mutants can infect persons who are not vaccinated, there is still no clear evidence that they can infect persons who have been successfully immunised against hepatitis B virus, except in post-exposure situations.
- HBsAg mutants are more likely to be present with *adw* and *adr* serotypes. However, there is no convincing evidence to date that vaccine formulations need to be changed.
- There is no evidence to date that suggests that HBV mutants present a threat to established hepatitis B vaccination programmes and thus are not viewed as a major public health threat.
- An independent global network should be set up to monitor vaccine-escape / treatment-escape mutants.

### Breakthrough infections

- Breakthrough infections have occurred in successfully vaccinated individuals; the vast majority of these infections are clinically benign (seroconversion for anti-HBc, in the absence of HBsAg).
- In studies that have investigated breakthrough infections and chronic carriage, the number of study participants was small, and vaccine doses and routes of administration varied, so that investigators were not able to assess formally which factors were the most influential. Questions still remain as to which determinants of duration of protection are the most important, such as:
  - ◆ age at vaccination (birth, infancy, childhood, adulthood)
  - ◆ gender
  - ◆ length of time since vaccination and peak antibody response
  - ◆ anti-HBs levels following the primary vaccination series
  - ◆ receipt of hepatitis B immunoglobulins (HBIG)
  - ◆ type of vaccine administered: plasma-derived or recombinant
  - ◆ infection pressure based on: level of hepatitis B endemicity
    - ◇ maternal HBV status
    - ◇ extent of vaccination coverage
  - ◆ nutritional status of vaccinated person
  - ◆ presence of other infections, particularly HIV infection
  - ◆ natural boosting

### Booster doses

- Currently there are no data that support the need for booster doses of hepatitis B vaccine in completely vaccinated infants, children, and adolescents, and in immunocompetent individuals who have responded to a complete primary

vaccination course. This conclusion is based on many long-term efficacy and booster-dose studies that have shown that long-term protection persists for as long as fifteen years and that immunological memory allows a protective anamnestic antibody response after exposure to HBsAg. These data are further supported by surveillance data from many countries around that world where no cases of acute hepatitis B are occurring among children and adolescents who are successfully vaccinated against hepatitis B.

- Some countries, however, have chosen to consider booster doses of hepatitis B vaccine as an option to provide reassurance of protective immunity against benign breakthrough infection.

#### Need for further studies

- Cohort studies of immunised subjects are still needed to determine if booster doses are needed beyond fifteen years after hepatitis B vaccination, and if immunological memory persists into adolescence and adulthood among persons at

higher risk of infection due to their lifestyle or to professional exposure to HBV, especially in industrialised countries.

- In hepatitis-B-endemic countries, further studies need to be carried out to determine whether susceptibility to persistent carriage of HBV increases with time.

In addition, further research is still needed in the following areas:

- long-term studies to identify breakthrough infections
- long-term follow-up studies to determine the burden of disease from breakthrough infections occurring among vaccinees who were on a 2-dose primary schedule
- data to distinguish between sub-clinical and breakthrough infection
- humoral and cell-mediated immune basis of memory
- the significance of core antibodies in terms of:
  - whether the apparently transient infection of hepatocytes could result in long-term liver disease, and whether the reactivation of HBV infection could occur in immunocompromised patients (e.g., HIV/AIDS patients).

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