VIRAL HEPATITIS

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CONTENTS

This edition of *Viral Hepatitis* is prepared from material presented at the Viral Hepatitis Prevention Board meeting held 14-16 April 1998 in Lisbon, Portugal.

EDITORIAL

Perinatal transmission from an infected mother to her infant is one of the most serious and effective modes of transmitting hepatitis B virus (HBV) because newborns are at highest risk of becoming HBV carriers and developing subsequent long-term disease such as primary hepatocellular carcinoma (HCC) and cirrhosis. In addition, these carriers form a pool of infected individuals who may infect others in the community.

Babies born to carrier mothers are at risk of infection through exposure to blood and body fluids during delivery. Babies of HBeAg-positive mothers are at particular risk, with 70-90% of these infants becoming infected. These numbers underscore the significant role that perinatal transmission plays in spreading the virus and in maintaining a chronically infected pool of individuals.

Control of perinatal transmission can be achieved by offering vaccine and optionally immune globulin to infants of carrier mothers, or through universal vaccination of newborns starting at birth. Universal screening of pregnant women allows for the advance identification of infants at risk, and makes it possible to offer immunoprophylaxis at birth and later, to follow-up on these infants. In areas where perinatal transmission is high or where screening is not feasible, universal hepatitis B vaccination of newborns at birth can also control perinatal transmission, and has been recommended as the best way to control hepatitis B.

This edition of Viral Hepatitis examines the issue of perinatal transmission of hepatitis B virus, looking at the merits of universal screening programmes for pregnant women and at how vaccine can be used to prevent vertical transmission. An overview of screening programmes in Europe is presented, and the status of hepatitis B prevention programmes is also revisited. Recommendations from the Viral Hepatitis Prevention Board (VHPB) on prevention of vertical transmission are included.

The duration of immunity conferred by hepatitis B vaccine is an issue that has long been debated. This Viral Hepatitis also presents information on whether booster doses are necessary to sustain immunity and looks at the implications this has for a booster vaccination policy. Current studies suggest that healthy vaccinees retain immunologic memory for a number of years and that routine booster vaccination should not be needed to sustain protection. Therefore, it is the view of the VHPB that resources can be better directed to achieving full coverage in universal infant immunization programmes than to administering booster doses of vaccine to individuals who have already been immunized against hepatitis B.

Implementing programmes to control perinatal transmission and answering questions surrounding the issue of booster doses are both important in the fight to control hepatitis B. In particular, controlling perinatal transmission can go a long way towards reducing the overall number of newly infected individuals and in diminishing the pool of chronically infected individuals in the population.

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REPORT ON THE VHPB MEETING IN LISBON, PORTUGAL, 14-16 APRIL, 1998.

UNIVERSAL SCREENING OF PREGNANT WOMEN AND PREVENTION OF PERINATAL TRANSMISSION

Babies born to hepatitis B carrier mothers are at risk of infection through exposure to blood and body fluids during delivery. Neonatal infection is one of the most serious modes of transmitting hepatitis B virus (HBV) because it carries a very high risk of resulting in chronic infection and leading to subsequent long-term disease, such as chronic liver disease and primary liver cancer.

Preventing perinatal transmission is an important element in any nation's strategy for controlling hepatitis B infection in the population, particularly since chronically infected individuals are a reservoir of infection and may infect others in the community.

Universal screening of all mothers during pregnancy will identify carrier mothers and their infants who are at risk of acquiring hepatitis B infection. Various strategies for screening pregnant women have been adopted. These include **selective screening** based on a risk assessment of the mother and **universal screening** of all pregnant women. Another strategy for controlling perinatal transmission is universal immunization of neonates.

Initially, policies of selective screening were adopted, particularly in countries of low endemicity for hepatitis B. Selective screening requires identifying mothers at high risk of infection based on behaviours or ethnicity. Risk factors include: history of intravenous drug use (IVDU); history of blood transfusion; ever rejected as a blood donor; history of sexually transmitted disease; ethnic origin; born or lived abroad; ever institutionalised; occupational exposure; contact of a carrier; or haemodialysis.

Identifying mothers at high risk is a time-consuming process that requires careful history taking. Furthermore, it has been shown that selective screening fails to detect a substantial percentage of carrier mothers. In a comparison of studies listed in the table below between 15% and 60% of carrier mothers were not identified through selective screening.

Proportion of carrier mothers not identified through selective screening

Study location	Overall prevalence	Percent high-risk factors identified	Proportion not recognized
London, UK[1]	38/3,760 (1.0%)	63%	37%
the Netherlands[2]	734/99,706 (0.7%)	52%	48%
Los Angeles, US[3]	23/6,943 (0.3%)	40%	60%
Alberta, Canada[4]	403/122,233 (0.3%)	85%	15%
Nova Scotia, Canada[5]	6/5,754 (0.1%)	50%	50%

source: E. Boxall, Heartland's Hospital, Birmingham, UK

It is now accepted that universal screening is necessary to identify all carrier mothers and most countries in Europe have instituted policies of universal screening (see overview on page 7). Women are screened for HBsAg, and if found positive, counselling and intervention is then offered. Women who have not had antenatal care and who do not present for screening until delivery have been shown to be at much higher risk of being carriers than women who have antenatal care.[2,6]

Once carrier mothers have been identified possible interventions include: management of delivery, which has been shown to have little impact; or more appropriately, administration of hepatitis B vaccine with or without HBIg.

Another strategy for controlling perinatal transmission is universal neonatal immunization. This strategy would be effective in controlling transmission but has some drawbacks. Universal neonatal immunization does not identify carrier mothers and therefore misses the opportunity to offer them counselling and prophylaxis. As yet, there is no consensus on optimum neonatal vaccine schedule, and while coverage rates for the first vaccine dose are high, coverage for the second and third doses is considerably lower.

It is now accepted that universal screening is necessary to identify all carrier mothers and most countries in Europe have instituted universal screening policies.

To be successful, screening programmes must include a number of elements and set certain standards.

First, the screening tests themselves should:

- be simple to perform on large numbers of people;
- have high specificity;
- be relatively cheap to carry out;
- be non-invasive or use a sample which would be collected for other purposes;
- lead to an intervention which is of benefit to both mother and baby.

Second, screening programmes require:

- **an organisational framework** which assigns responsibility for programme coordination and monitoring, training of personnel, communication among healthcare sectors, and record keeping;
- **pre-test standards** that include protocols, training for personnel involved with patients, written and verbal information for women and their partners, and uptake targets;
- **test standards** that require testing with high-quality tests in accredited laboratories;
- **post-test standards** that ensure women have test results explained to them, that verbal and written information is available to women found positive, that 100% of infants at risk receive the first dose of vaccine according to schedule, and that 100% of infants receive the full course of vaccine.

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Based on information presented by Dr Elizabeth Boxall of Heartland's Hospital, Birmingham, UK.

COUNTRY REPORTS: PREVENTION OF VERTICAL TRANSMISSION AND REVIEW OF HB CONTROL PROGRAMMES

B BELGIUM

Screening of pregnant women

Screening of pregnant women is recommended in Belgium, although it is not compulsory. The cost of screening and vaccination is reimbursed at 75% by the national healthcare system.

Since 1995, the recommended intervention for infants of mothers testing positive for HBsAg has been vaccination on a 0,1,6 schedule plus HBIg. A follow-up study found that in 91% of cases infants were given active and passive immunization, while the remainder received only active immunization[1]. It was also found that in only 50% of cases infants were vaccinated within 12 hours of birth, and that 61% received HBIg within 12 hours.

A pilot study conducted in an Antwerp hospital interviewed gynaecologists on their knowledge of recommendations on hepatitis B. It found that the time of screening is not consistent among gynaecologists: testing was done at first consultation, in the first trimester, the third trimester, twice or not at all. Serologic marker requested also varied: 66% tested for HBsAg; 17% for HBsAg + anti-HBs; 7% for HBsAg + anti-HBc; 7% for HBsAg + anti-HBs + anti-HBc; and 3% for anti-HBs + HBeAg.

Hepatitis B control programme

1982	• mandatory immunization of healthcare workers and high-risk groups
1988	• universal screening of pregnant women recommended
1996	• universal immunization of infants recommended

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F FRANCE

Screening of pregnant women

Screening of all pregnant women for HBsAg in the sixth month of pregnancy was made mandatory in France in 1992. Screening is performed free of charge. Neonates of carrier mothers are given the first dose of vaccine and HBIg within 24 hours of birth. Later doses are given at month 1 and 2, and a booster dose is given at month 12. The vaccine is free if it is given in the public sector. If given in the private sector, 65% is covered by social security and the remainder is in some cases paid by insurance.

Hepatitis B control programme

1991	• mandatory immunization of healthcare workers
1992	• universal screening of pregnant women
1994	• universal immunization of adolescents
1995	• universal immunization of infants

The annual incidence of new cases of acute symptomatic hepatitis B in France dropped from 10,000 to 3,000 from 1991 to 1996. Of the individuals with acute symptomatic hepatitis B, 90% were over 20 years of age. Coverage rates among children 0-12 years old are low (approximately 35%), but reach nearly 90% in the 13-15-year-old age group.

Universal vaccination is refunded 65% by the social security system and the remainder of the cost is covered by insurance.

D GERMANY

Screening of pregnant women

In 1984, Germany implemented a strategy of selective screening of pregnant women considered at risk for hepatitis B infection. Healthcare workers, people from endemic countries, contacts of carriers, recipients of blood products, dialysis patients, persons with multiple sex partners and IV drug users were considered high-risk groups. This strategy of selective screening proved a failure at identifying carrier mothers and preventing perinatal transmission on a population basis. A 1996 study conducted in Hanover found that of 912 women in the study, 1.4% were HBsAg positive. Of those who were HBsAg-positive, 30% had no risk factor and none of the German women who were HBsAg-positive indicated a risk factor.

Universal screening of pregnant women became mandatory in 1994. Women are tested free of charge for markers of HBsAg between weeks 32 and 36; testing is reimbursed through the health insurance system. Infants of carrier mothers receive vaccine and HBIg at birth; in all, four doses of vaccine are administered on a 0,1,6,12 month schedule.

Germany has a carrier rate of between 0.3 and 0.8% in the general population. Of 800,000 live births per year, it is estimated that between 750 and 1,500 will become chronic carriers, and that between 200 and 400 will die from the long-term consequences of hepatitis B

infection. The cost of universal screening is put at 20 million DM per year in Germany, while the cost of care and treatment of those infected through perinatal transmission is calculated at approximately 750 million DM.

Hepatitis B control programme

1982	• immunization of risk groups
1994	• universal screening of pregnant women
1995	• universal immunization of infants and adolescents recommended

In Germany, private paediatricians administer the majority of vaccinations. Coverage rates for infant immunization are estimated at 90%, whereas only 10% of adolescents are reached. Estimates are based on vaccine certificates submitted upon school enrolment and on vaccine sales data.

GR GREECE

Screening of pregnant women

Universal prenatal screening of pregnant women is mandatory in Greece. Screening is routinely performed once during prenatal visits and twice for mothers considered at high risk of infection. Neonates of carrier mothers are given vaccine and HBIg within 12 hours of birth; the vaccine schedule is 0,1,6 or 0,1,2,12, depending on the vaccine used. Follow-up is done at 12 months when the infant is screened for anti-HBs or anti-HBc. In some high endemic regions, vaccination without screening is carried out, in which cases the schedule followed is 0,1,6 months.

Hepatitis B control programme

1982	• immunization of high-risk groups • universal screening of pregnant women
1994	• universal adolescent immunization
1998	• universal infant immunization

In Greece, the majority of vaccines are delivered through the private sector by paediatricians (61.3%), while 29% of vaccinations are carried out by the public sector. Private sector fees are usually covered by social security or insurance companies. In 1997, almost 60% of children were vaccinated against hepatitis B upon entrance to primary school, up from 36% in 1995.

IS ISRAEL

Screening of pregnant women

Israel has had a policy of mandatory universal neonatal immunization since 1992. The first dose of vaccine is administered the day after birth and the subsequent doses are given at one month and six months. There are approximately 100,000 live births per year in Israel. Because over 98% of deliveries are in a hospital, it is assumed that coverage rates approach 100%. As yet, no studies have been carried out to determine the effectiveness of the programme in preventing hepatitis B transmission. There is no mandatory screening of pregnant women for HBsAg.

Hepatitis B control programme

1992	• universal immunization of neonates • immunization of high-risk groups including healthcare workers, contacts of carriers and other risk groups

Israel is estimated to have between 60,000-80,000 HBsAg carriers, with 1,000 new cases detected every year. The HBsAg carrier rate varies between 0.5% and 4.3% among different ethnic groups. The carrier rate is high among recent immigrants from the southern republics of the former Soviet Union (~15%) and from Ethiopia (16%). The majority of carriers in Israel are anti-HBe positive.

For neonates, the cost of vaccine delivery is covered by the Ministry of Health. In cases where vaccine is given by the private sector, insurance companies reimburse the cost at 50%.

I ITALY

Screening of pregnant women

In Italy, all pregnant women are screened and newborns of HBsAg-positive mothers receive vaccine plus immune globulin within 24 hours of birth. A random sample study in Naples, an area of relatively high endemicity, showed screening coverage at 93%. Of the 3% who were positive, 90% of the babies were vaccinated at birth and the other 10% some days later.

Hepatitis B control programme

1984	• universal screening of pregnant women • immunization of high-risk groups
1991	• universal immunization of infants • catch-up immunization of 12-year-olds for the first 12 years of the programme

Italy's aggressive approach to immunization against hepatitis B over the past 10 years has resulted in a dramatic decline in HBV infection rates as confirmed by follow-up studies. Surveys evaluating the vaccination programmes show that compliance is high, with an average overall coverage rate of 93.6% reported.

Italy is currently conducting a standard EPI cluster survey to evaluate coverage, serological response to immunization, registration of adverse events, calculation of morbidity rates, surveillance on acute cases of disease (with a special focus on vaccinees), and sero-epidemiological studies.

P PORTUGAL

Screening of pregnant women

Universal antenatal screening of pregnant women for hepatitis B surface antigen (HBsAg) has been mandatory in Portugal since 1992. Screening is performed twice during pregnancy for women considered at high risk and once during the sixth month of pregnancy for women who do not fall into a risk category. Screening is free of charge.

All neonates of carrier mothers receive active and passive immunization, with the first dose of vaccine and HBIg administered within 12 hours of birth. The second and third doses of vaccine are delivered at one month and six months. Vaccine and HBIg are administered free of charge.

The proportion of pregnant women screened is not known, although it is assumed to be high as over 95% of pregnant women have access to medical care during pregnancy. A survey of the screening programme is planned; the survey will evaluate screening coverage, the proportion of HBsAg-positive women, and the coverage rates for passive and active immunization among children of carrier mothers.

Hepatitis B control programme

1992	• immunization of risk groups (neonates of carrier mothers, healthcare workers, medical students, haemophiliacs, haemodyalisis patients and others) • universal screening of pregnant women
1994	• universal immunization of adolescents (aged 11-13)
1999	• universal immunization of infants (planned)

All vaccination costs are fully covered by the National Health System.

E SPAIN

Screening of pregnant women

In Spain, the prevalence of HBsAg in pregnant women is 1%, with 6% of these women being hepatitis B e-antigen positive. Universal screening of all pregnant women became mandatory in 1992 for public sector healthcare providers, and was recommended to those working in the private sector.

The immunization strategy for newborns at risk includes passive and active immunization. The first dose of vaccine and a dose of HBIg are administered within the first 24 hours after birth. Vaccine dose two is administered at one month, and dose three at six months. Coverage surveys estimate that 95% of infants receive the first dose of vaccine; uptake is lower for doses two and three.

Hepatitis B control programme

1988	• immunization of risk groups (neonates of carrier mothers, recipients of blood or blood products, IV drug users, healthcare workers, prisoners and staff, contacts of chronic carriers and travellers to endemic areas).
1992	• universal immunization of adolescents (introduced by autonomous region) • universal screening of pregnant women
1994	• universal infant immunization (introduced by autonomous region)

CH SWITZERLAND

Screening of pregnant women

In 1984 selective screening of pregnant women was recommended in Switzerland. Screening was carried out in hospitals that served a high proportion of at-risk women and if the woman had a history of high-risk behaviour. In a 1994 survey to assess the implementation of the screening programme, it was found that of 90 hospitals 67 generally screened all pregnant women, 20 screened only at-risk women, and three did not screen at all. In 1996, the Federal Office of Health recommended universal screening of pregnant women. The cost is covered by the health insurers.

A survey in Zurich conducted from 1987-1991 showed that of 8,988 women screened for HBV markers, 90 were HBsAg-positive and 156 showed markers of anti-HBc only. Of these 246 neonates, 164 received vaccine within a few hours of birth, 34 were vaccinated within 24-36 hours, and 48 did not receive vaccine either because the test results were not communicated or because the physician did not know if newborns of anti-HBc women should receive vaccine.

Hepatitis B control programme

1982	• immunization of risk groups (neonates of carrier mothers, recipients of blood or blood products, IV drug users, healthcare workers, homosexuals, contacts of carriers).
1985	• screening of high-risk pregnant women for HBsAg • screening of refugees for HBsAg
1996	• universal screening of pregnant women
1998	• universal immunization of adolescents recommended

In 1997, the Swiss government made vaccination of adolescents a priority and agreed to finance in part the immunization programmes. In 1998, universal vaccination was implemented. Vaccine coverage is 80% among healthcare workers and 40-50% among IV drug users. More than 80% of women and refugees are screened for HBsAg.

UK UNITED KINGDOM

Screening of pregnant women

The Department of Health 'Green Book' recommends that babies of carrier mothers be vaccinated but universal screening is not compulsory. Both universal screening and selective screening of risk groups are done in the UK; policies vary by region and hospital.

The National Screening Committee, which reviews all screening policies, is currently revising hepatitis B screening programmes and it is expected that a new policy will be announced shortly.

Identified infants of carrier mothers receive vaccine on a 0,1,6 or 0,1,2,12 month schedule. Babies of HBeAg-positive mothers are also given HBIg. Follow-up is done at 12 months to determine if the baby developed anti-HBs or if he/she is still positive and has likely become a carrier.

Hepatitis B control programme

- screening of pregnant women (advised but not obligatory)
- immunization of high-risk groups

PREVENTION OF VERTICAL TRANSMISSION OF HB
OVERVIEW OF SCREENING POLICIES OF SELECT COUNTRIES

Country	Universal screening	Recommended	Mandatory	Screen for	Timing	Reimbursed	Intervention (month)
Belgium	Yes	Yes	No	HBsAg	1st trimester	75%	0,1,6 + HBIg
France	Yes	Yes	Since '92	HBsAg	Month 6	Partial	0,1,2,12 + HBIg
Germany	Yes	Yes	Since '94	HBsAg	Week 32 - 36	Yes	0,1,6,12 + HBIg
Greece	Yes	Yes	No	HBsAg	Month 3, again at month 6 for high-risk mothers	Partial	HBIg + 0,1,6 or 0,1,2,12
Israel	No, policy of universal vaccination at birth	Optional	No	HBsAg	1st trimester	Partial	0, 1,6
Italy	Yes	Yes	Since '91	HBsAg	Month 6 -9	Partial	0,1,2,11/12 + HBIg
Portugal	Yes	Yes	Since '94	HBsAg	high-risk mothers tested twice, others once	Yes	0,1,6 + HBIg
Spain	Yes	Yes	Since '92 for the public sector	HBsAg	Week 12	Partial	0,1,6 + HBIg
Switzerland	Yes	Yes	No	HBsAg	Week 8 - 18	Yes	0,1,6 + HBIg or 0,2,12 + HBIg
UK	Universal and selective, depending on area	Yes	No	HBsAg HBeAg	Week 8 - 12	Partial	0,1,6 or 0,1,2,12 or 0,1,6 or 0,1,2,12 + HBIg (if HBeAg-positive)

HEPATITIS B VACCINE EFFECTIVE IN PREVENTING VERTICAL TRANSMISSION

The severity of outcome of infection is inversely related to the age at which a person becomes infected. HBeAg-positive mothers have a 70-90% probability of infecting their newborn babies perinatally; almost 90% of these infected infants will become HBV carriers and they have a 30-50% probability of developing chronic hepatitis.

A recent literature search was carried out to investigate the factors that influence the protective efficacy of hepatitis B vaccine when given to newborns of hepatitis B carrier mothers. It was determined that vaccine, administered with or without immune globulin (HBIg), is effective in preventing vertical transmission and chronic disease.

The search looked at the effectiveness of different vaccine doses and schedules, and tried to determine the importance of immune globulin in preventing infection and disease. It was found that good protection levels can be achieved with both high and low dosages of vaccine. This can be attained without the use of HBIg, although with lower dosages, simultaneous use of HBIg was more important than with higher doses to elicit good protection.

Timing appeared to be the most important factor in achieving protective efficacy: high levels of protection were achieved with high dosages of vaccine without concomitant use of HBIg, provided the first dose of vaccine was given at birth and the second dose at one month. Giving the second dose at two months reduced the level of protection.

Strategies for preventing perinatal transmission include screening all pregnant women to identify carrier mothers, and administering vaccine with or without HBIg to the neonate. Where screening programmes do not exist, good control of perinatal transmission can be achieved through programmes of universal neonatal immunization without HBIg, provided the first dose of vaccine is administered within 12 hours of birth and a high dose of vaccine is used.

Protective efficacy achieved with vaccine among high-risk infants

Study	Dose (µg)	HBIg at birth	No. of recipients	Vaccination schedule (months)	Protective efficacy (%)
1	5	+	20	0,1,6	89
2	2.5	-	29	0,1,2,12	66
3	10	+	56	0,1,2,(12)	98
	20	+	54	0,1,2,(12)	92
	20	+	60	0,1,6	96
4	5	-	15	not specified	100
	10	-	18	not specified	100
	20	-	28	not specified	94
5	2.5	+	76	0,1,5	not specified
	5	+	for both	0,1,5	100
6	5	+	19	0,1,6	89
7	10	_	57	0,1,2,(12)	95
	10	+	64	0,1,2,(12)	98
	10	-	54	0,1,6	95
	10	+	59	0,1,6	100
8	5	+	351	0,1,6 or 0,1,9	92
9	20	+	26	0,1,2,(12)	95
	20	-	23	0,1,2,(12)	90

Adapted from a review of published studies on the efficacy of recombinant DNA HB vaccines in neonates

Reference

André FE and Zuckerman AJ. Review: protective efficacy of hepatitis B vaccines in neonates. Journal of Medical Virology 1994; 44: 144-151.

Based on information presented by Dr Francis André, SmithKline Beecham, Rixensart, Belgium.

EVALUATING IMMUNIZATION PROGRAMMES

It is necessary to monitor immunization programmes to determine how successfully they are being carried out, to establish what percentage of the target population is being reached and to pinpoint programme weaknesses. Coverage assessment is an important part of the evaluation and makes it possible to determine programme impact. For HB, this would mean concentrating on infant or adolescent immunization, depending on the country programme.

Immunization coverage is defined as the proportion of the target population receiving a vaccine or series of vaccines (the numerator), divided by the total target population (the denominator). Various methods can be used to determine the numerator and the denominator.

The numerator may be defined as the number of children immunized by age two; the number of doses delivered, divided by the number of doses in a complete vaccine course; an estimate of the number of doses of vaccine imported, licensed, sold or prescribed, with a correcting factor for wastage; the number of children immunized at school; or the number of doses distributed to the public health sector.

The denominator may be based on the number of children in the relevant age group living in the area; the number of children in the target age group extrapolated from the total resident population; the number of births in the previous or current year; the number of school-age children; or the number of vaccination certificates submitted. The numerator and denominator must be relevant to one another.

Several methods for estimating coverage exist:
1. The method can be exhaustive, meaning it uses immunization records, data from computerised systems or health certificates, and takes into account the immunization status of every individual.
2. Estimates can be based on number of doses sold.
3. Estimates can be based on national or randomised surveys.

Evaluation programmes should also include:
- a system for investigating outbreaks of disease;
- a system for monitoring adverse events.

Overview of evaluation programmes

- **Belgium** has no systematic programme for evaluating vaccination programmes, although a national system to standardize coverage assessment and programme evaluation is planned. The system would include a computerized child health registry accessible to GPs, paediatricians, mother and child clinics, and school health systems. Coverage is now estimated from vaccine doses sold, and from sero-surveys, school surveys and school entrance certificates.
- Coverage evaluation in **France** for infants is based on certificates of health for children 24 months of age which detail vaccine history. Data is also culled from vaccine sales figures, vaccine prescriptions, school surveys and a bi-annual national family survey.
- In **Germany**, vaccination is mostly carried out by the private sector, making coverage assessment problematic. No timely monitoring programme is in place. Vaccination certifications are checked at school entry and provide data on five to six-year-olds. Vaccine sales data are other indicators and suggest 85% coverage for DTPa, Hib, IVP and HB in infants, and 70-80% for MMR. HB vaccination among adolescents is a problem, as only 10% of this group are vaccinated.
- Universal infant immunization is new in **Greece**. Information will be collected from school entrance certificates. Doctors will be required to report to the local health authority each vaccine course delivered. Surveys of the health registry and of army recruits are currently carried out.
- **Israel** has universal neonatal immunization. Because nearly all babies are born in hospital and data from the national child clinics is readily available, coverage assessment (for dose one) is complete. Specific studies are carried out to collect further information.
- Information on infant vaccine coverage is available from immunization registers in **Italy**. The standard EPI cluster survey is also used to collect data on immunization programmes. Random telephone check-ups and home visits verify the accuracy of information. Local studies and sero-surveys provide other sources of information. Adverse events are reported by physicians to the Ministry of Health.
- **Portugal** relies on local and national surveys to evaluate immunization programmes and coverage.
- Coverage data in **Spain** is available on public sector employees. Data on universal immunization programmes is collected by the autonomous regions and sent to the Ministry of Health which calculates national coverage rates. National surveys are also used to collect data.
- In **Switzerland** it is anticipated that 90% of HB immunization will be carried out by the private sector, making programme assessment difficult. Additionally, while vaccination will be federally mandated, implementation will be done at the district level (canton), further complicating national programme assessment.
- The **UK** has selective vaccination of high-risk groups and babies of carrier mothers; no formal system for measuring coverage among risk groups such as IVDU and patients at STD clinics is in place as this has proved too problematic. In general, coverage is determined by doses distributed and from data on a computerized child health registry maintained for each district. Seroprevalence studies which look at antibody levels per age group are also used to estimate coverage.

THE DURATION OF PROTECTION AGAINST HB INFECTION AFTER IMMUNIZATION AND IMPLICATIONS FOR BOOSTER POLICY

A review of the published literature on the long-term immunologic memory for HBsAg after a course of hepatitis B vaccine concluded that healthy vaccinees retain immunologic memory for a period of at least 5-12 years, even though the levels of antibody (anti-HBs) fall below the recognised protective level of 10mIU/mL.[1] Protection persists because vaccinees develop immunologic memory. Although additional studies are needed to define better the limits of immunologic memory, it does not appear that routine booster vaccination is needed to sustain protection for at least five years, and perhaps longer.

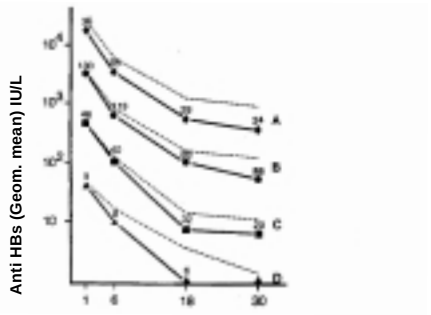
Although safe and effective hepatitis B vaccines have been in widespread use for over 15 years, the duration of vaccine-induced protection against hepatitis B infection is still a subject of debate. How long protection is thought to last has implications when setting national vaccination policy.

Subjects of debate include:

- How long is immunity expected to last after vaccination?
- What are the standards for measuring immunity (e.g. Is immunity contingent on the continuing presence of antibody?)?
- Is booster vaccination necessary to sustain immunity?

What constitutes a protective response to vaccination? A protective immune response to a course of vaccine is considered to be achieved if the vaccinee shows antibody development at a serum concentration of at least 10 mIU/mL one month after administration of a full course of vaccine. This has been found to be the case in multiple randomised, double-blind placebo controlled trials, and many vaccine advisory groups including the World Health Organization (WHO) have endorsed the development of 10 mIU/mL of anti-HBs as indicating a successful response to vaccination. However, a number of national advisory bodies have set the more conservative level of 100 mIU/mL as conferring immunity. The rationale is that this higher level will compensate for inter-laboratory variation in testing.

The level of antibody declines after vaccination



(from ref. 2)

The level of antibody does decline after vaccination (see graph).[2] Because of persistent immunologic memory, however, immunity to infection is not lost as antibody declines. After vaccination, memory cells develop which react to antigenic stimulation, thus leading to production of more anti-HBs. Immunologic memory is demonstrated by the rapid rise in the titre of anti-HBs following a booster dose of vaccine. The chart below illustrates immunologic memory by showing the response of healthy vaccinees to booster vaccination.

Demonstration of immunologic memory through booster vaccination

			Anti-HBs response to booster vaccination		
			% with 10 mIU/mL		
Age at first vaccination	Time since first vaccination	Number	Pre-boost	Post-boost	Fold rise in GMT (time)
Infants[3]	12 years	14	100%	100%	8 (7 days) 62 (29 days)
Children[4,5]	5 years	308	85%	99%	54 (10 days) 79 (9 days)
Adolescents[6]	5.5 years	71	90%	100%	72 (11 days)
Adults[7]	6 years	302	67%	97%	70 (1 month)

If memory sustains immunity, then extended surveillance should find very few clinically significant breakthrough infections. In a study by Hadler et al[8] this was the case:

Long-term protection in homosexual male responders to hepatitis B vaccine[8]

				Number (%) of HBV events		
Group	Number	Surveillance period	% retaining >10 mIU/mL anti-HBs	anti-HBs↑	anti-HBc	HBsAg
Vaccine	634	8 1/2 years	46%	22 (28%)	46 (58%)	2 (2.5%)
Placebo	529	16 months	—	2 (1.6%)	47 (36%)	80 (62%)

As vaccine-induced antibody declined, many vaccinees displayed serologic evidence of exposure to HBV. However, the events in almost all exposed vaccinees involved only boosts in the titre of anti-HBs sometimes accompanied by seroconversion for anti-HBc. No vaccinee became ill, and only two of 80 events (2.5%) involved seroconversion for HBsAg, signalling a clinically significant breakthrough infection. By contrast, 80 of 129 events (62%) in unimmunized placebo recipients were clinically significant HBsAg-positive infections.

The authors of the review of published literature[1], from which the examples in the previous tables are drawn, concluded that:

- There is no medical evidence suggesting that healthy vaccinees lose immunity simply because the level of anti-HBs drops below 10mIU/mL.
- Immuno-compromised vaccinees (e.g. dialysis patients, persons with HIV, etc) should be monitored and do need a booster if anti-HBs drops below 10mIU/mL. In these cases, it cannot be assumed that immunologic memory is robust enough to offer protection if the titre drops below the recognised protective level.
- Current studies show that in healthy vaccinees immunologic memory provides effective protection for at least 5-12 years.
- Additional studies are warranted to better define the duration of immunologic memory in various vaccinee populations and to study the long-term immunity in persons vaccinated at infancy.

These findings have implications on the development of booster policy, and suggest that limited resources might be maximised by focusing on the delivery of the first vaccination series in universal vaccination programmes, rather than on promoting booster vaccination. In certain situations booster vaccination would be warranted, for instance for immuno-compromised individuals or when a booster dose can be given with less total cost as a component of a combined vaccine.

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Further reading

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Based on information presented by Dr David West, Merck Research Laboratories, West Point, PA, USA.

VHPB RECOMMENDATIONS ON PREVENTION OF PERINATAL HBV TRANSMISSION

Perinatal transmission is one of the most efficient and devastating modes of transmitting hepatitis B virus because 60 to 90% of infected newborns become chronic carriers of the virus.

The main objective of maternal screening is to identify HB carrier women and to prevent hepatitis B carriage in their infants; this can be achieved by screening all pregnant women for HBsAg and vaccinating newborns of carrier mothers. Control of perinatal transmission can also be achieved by universal newborn vaccination starting at birth.

Where screening of pregnant women for HBsAg exists, countries may wish to continue screening programmes. If this is the case, any screening programme should include all pregnant women, as selective screening of pregnant women (focused on risk groups) misses a significant proportion of carrier mothers. Screening for HBsAg should be part of routine antenatal care.

Women who present for delivery without having been screened for HBsAg should be tested immediately. Their newborns should be vaccinated within 12 hours of birth, irrespective of the results of the screening test.

Most industrial countries have carried out universal screening of pregnant women for many years:

- It allows identification of newborns who require immediate vaccination.
- It allows identification of carrier mothers and prevention of further secondary spread of HBV, as well as representing a health benefit to the mothers.
- In infants of carrier mothers, it offers the opportunity to implement universal infant immunization in combination with other infant vaccination programmes.

Most countries currently administer HBIg and vaccine to infants of carrier mothers, although recent evidence suggests that vaccine alone may be just as effective. Vaccine should be given within 12 hours of birth. In cases where HBIg is given, it should be administered within 12 hours of birth at another injection site than the vaccine. The schedules most widely used are 0,1,6 and 0,1,2,12 months, both of which have shown to be effective.

Effective programmes for the prevention of perinatal transmission require transfer of information to the mother, and among the antenatal care centre, the delivery unit and the infant immunization provider. An organizational framework should be in place, and responsibility for coordination of HBsAg screening and follow-up of vaccination of newborns should be well defined. Countries should systematically monitor and evaluate prevention programmes.

Where maternal screening programmes do not exist, resources may be better directed towards universal neonatal immunization programmes. Control of perinatal transmission can be achieved if the first dose of vaccine is delivered at birth.

HBsAg-positive mothers should not be discouraged from breast-feeding.

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