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This edition of *Viral Hepatitis* comprises recommendations, consensus statements, and meeting conclusions produced by, or in collaboration with the Viral Hepatitis Prevention Board, between 1996 and 2003.

Viral Hepatitis Prevention Board (VHPB) recommendations, consensus statements, and meeting conclusions: an overview

Preamble

The following overview comprises the most recent updates of recommendations, consensus statements, and meeting conclusions produced by, or in collaboration with the Viral Hepatitis Prevention Board (VHPB), between 1996 and 2003. We hope this document will become a useful reference tool.

Prevention and control of hepatitis B in the community (1996)¹

Universal vaccination

Infant vaccination programmes

Since 1991, WHO has called for all countries to add hepatitis B vaccine into their national immunisation programmes. Routine immunisation of all infants and/or adolescents should receive the highest priority.

Universal infant and early adolescent vaccination protects individuals from infection immediately but also later in life, whether because of sexual activity, occupational risk or other behaviour such as intravenous drug use. The sooner individuals are vaccinated against hepatitis B the better. Early vaccination protects individuals from childhood infection, which results in high carrier rates and chronic disease. Chronic disease is associated with serious and fatal liver cancer.

Adolescent vaccination programmes

The VHPB supports the recommendation made by the WHO Global Advisory Group of the Expanded Programme on Immunization endorsed by the World Health Assembly in 1992: 'Hepatitis B vaccine should be integrated into the national immunisation programmes, in all countries by 1997. Countries with a low prevalence may consider immunisation of all adolescents as an addition or alternative to infant immunisation.' Adolescent programmes should be directed at young adolescents before the age of 13, and are appropriate in countries where there are structures and resources for delivery of vaccines to young adolescents such as school health services.

Infant plus adolescent vaccination programmes

Combined universal early adolescent and infant vaccination programmes have been shown to have the fastest impact on reducing levels of hepatitis B infection. Vaccination of young adolescents can of course stop once the first group of individuals vaccinated as infants reaches early adolescence.

High-risk strategies plus universal vaccination

High-risk group approaches have failed to control hepatitis B infection in the general population in many countries. But it is good medical practice to protect individuals in these groups. Strategies aimed at vaccinating and changing behaviour in high-

VIRAL HEPATITIS PREVENTION BOARD**Core Members**

Dr Nedret Emiroğlu
WHO, Regional Office for Europe / EPI
Copenhagen, Denmark

Dr Peter Grob
Clinical Immunology
University Hospital Zürich, Switzerland

Dr Johannes Hallauer
Universitätsklinikum Charité
Berlin, Germany

Dr Mark Kane
Children's Vaccine Program at PATH
Seattle, Washington, USA

Dr André Meheus
Epidemiology and Social Medicine
University of Antwerpen, Belgium

Advisers

Dr Selim Badur
Microbiology Department
University of Istanbul, Turkey

Dr Paolo Bonanni
Public Health Department
University of Florence, Italy

Dr José de la Torre
Ministry of Health and Consumers Affairs
Madrid, Spain

Dr Nicole Guérin
Comité Technique Vaccinations
Antony, France

Dr Wolfgang Jilg
Institute for Medical Microbiology and
Hygiene
University of Regensburg, Germany

Dr Daniel Lavanchy
WHO, Division of Communicable Diseases
Geneva, Switzerland

Dr Harold Margolis
CDC, NCID, Division of Viral Hepatitis
Atlanta, Georgia, USA

Dr Daniel Shouval
Hadassah University Hospital, Liver Unit
Jerusalem, Israel

Honorary Advisers

Dr Pietro Crovari
Institute of Hygiene
University of Genoa, Italy

Dr Alain Goudeau
Université de Tours, France

Dr Eric Mast
WHO, Vaccines and Biologicals / EPI
Geneva, Switzerland

Dr Elisabeth McCloy
Dorking, Surrey, United Kingdom

Dr Georges Papaevangelou
National Centre for Viral Hepatitis
Athens School of Hygiene, Greece

Executive Secretary

Dr Pierre Van Damme,
Epidemiology and Social Medicine
University of Antwerpen, Belgium

Executive Secretariat

Ms Emmy Engelen,
Dr Guido François,
Mr Alex Vorsters,
Epidemiology and Social Medicine
University of Antwerpen, Belgium

Rapporteurs

Dr Guido François
Epidemiology and Social Medicine
University of Antwerpen, Belgium

Ms Diana Steimle
European Vaccine Manufacturers
Brussels, Belgium

risk groups should therefore continue. However, also in areas of low endemicity, universal vaccination programmes are needed to eliminate hepatitis B infection, because high-risk strategies alone are clearly failing. Public health officials, health care providers and the public need to be aware of this and take action.

Combined vaccines

The VHPB supports efforts to add hepatitis B vaccination to existing infant and adolescent vaccination programmes. Hepatitis B vaccines can and should be integrated into any existing schedule. In addition, combined vaccines would be useful in hepatitis B control programmes. The VHPB advocates the development and use of combination vaccines, which contain the hepatitis B component. These vaccines require fewer injections, this making them more acceptable to the public and the health care provider, and representing savings on syringes, storage, transportation, record keeping, and training. In addition, it could possibly reduce the number of medical visits required. The implementation of universal hepatitis B vaccination, however, should not be delayed until such combined vaccines are available.

Raising awareness about the dangers of hepatitis B

The VHPB seeks to raise the awareness of health care providers about the dangers of hepatitis B as a community health risk and about the need for hepatitis B immunisation, both for themselves and for their patients. The VHPB also realises the importance of understanding the attitudes, beliefs, and behaviour of health care providers, health policy makers and the general public (especially the parents) when working to improve the success of universal hepatitis B vaccination programmes. The VHPB aims to produce and support educational initiatives targeted at these groups.

Booster strategies

There are no reported cases of clinical hepatitis B or HBV carrier state in individuals who have been vaccinated successfully (> 10 IU/l anti-HBs) in more than 15 years follow-up, despite the loss of detectable antibody in many individuals. Immunological memory induces a rapid anamnestic response in exposed individuals. This can abort clinical hepatitis B or the development of the carrier state. However, some clinically insignificant breakthrough infections have been reported in vaccinated individuals in whom only anti-HBc seroconversion occurred. Given these data, routine administration of booster doses in universal vaccination programmes is not recommended by the VHPB.²

Contraindications to vaccination

There are few absolute contraindications to vaccination. Still, withholding vaccination for inappropriate contraindications has been identified as an important cause of under-immunisation. For hepatitis B vaccination only severe reactions to previous doses and hypersensitivity to one of the vaccine components are considered absolute contraindications. Axillary fever above 38.5 °C is considered as a temporary contraindication.

References

¹ Grosheide P, Van Damme P. Prevention and control of hepatitis B in the community. *Communicable Diseases series* 1996; No 1.

² European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 2000; 355:561-565.

Surveillance of hepatitis B (1996)³

Surveillance is necessary to determine the incidence, prevalence, and burden of a disease. The success of any surveillance system is dependent on the willingness of doctors to report cases of infectious disease. Feedback to reporting physicians is an integral part of any surveillance system. In addition, the role and purpose of surveillance should be stressed from the start of medical training.

Surveillance systems for hepatitis B are necessary to:

- prioritise hepatitis B among other diseases of public health importance;
- measure the impact of vaccination programmes (including the monitoring of adverse effects);
- evaluate prevention programmes;
- ensure that targets for disease reduction and prevention are met.

Surveillance may also alert health officials to outbreaks of disease.

In most European countries notification of acute hepatitis is mandatory, but wide differences between case definitions, and the completeness and methods of reporting exist, making it extremely difficult to draw meaningful conclusions from country-to-country comparisons.

For better standardisation of surveillance systems across Europe, the VHPB recommends greater uniformity in formulating case definitions, in submitting surveillance reports, in monitoring vaccine coverage and impact, and in reporting severe adverse events.

Formulating case definitions

The VHPB recommends that all countries formulate a case definition, and support the case definition of viral hepatitis B put forward by the World Health Organization:

- A clinical case of acute viral hepatitis is an acute illness that includes the discrete onset of symptoms and jaundice or elevated serum aminotransferase levels (> 2.5 times the upper limit of normal).
- A confirmed case of hepatitis B is a suspected case that is laboratory confirmed: HBsAg positive or anti-HBc-IgM positive, and anti-HAV-IgM negative.

The serological quality of the tests used is crucial for a firm diagnosis of infection. It is understood, however, that case definitions based on serological tests pose a problem for countries without widespread access to these tests. Methods to detect HBsAg using test procedures such as reverse passive haemagglutination (RPHA) or latex bead technology are very inexpensive, and while not as sensitive as radioimmunoassay (RIA) antigen tests or the enzyme-linked immunosorbent assay (ELISA), are far better than not testing at all.

Submitting surveillance reports

Regardless of the availability of serological tests, all countries are advised to report all cases of jaundice and suspected viral hepatitis. Countries with laboratory facilities can further differentiate between hepatitis A, B, C, and other types of hepatitis. Surveillance reports should be submitted on a regular basis, and at a minimum, once a month.

Data from acute disease reporting systems underestimate the true incidence of hepatitis B virus infection in the community because:

- at least 60 percent of infections in adolescents and adults are asymptomatic or subclinical;
- a high degree of underreporting takes place;
- 90% or more of infections occurring in infants and children are asymptomatic and are therefore not reflected in the reported data.

Although surveillance of acute disease can be an essential parameter, it is insufficient to give a clear picture of the burden of disease. Surveillance of the chronic consequences of HBV (for instance, cirrhosis and HCC) and reporting of disease-specific mortality data is useful to document the burden of disease in the community. Acute case notification should be followed up by further epidemiological investigation and implementation of appropriate control measures. All outbreaks should be investigated immediately and confirmed serologically.

Outbreak investigation and sentinel surveillance may serve as supplementary sources of data on disease surveillance. In addition, sero-surveillance systems are very cost-effective ways of looking at the epidemiological situation of an infectious disease.

Although screening of blood donors is a very efficient system for preventing transmission of blood-borne pathogens, prevalence data from blood donors are not representative of the general population. Certain population groups - such as pregnant women and military personnel - are easily accessible for hepatitis screening, and data collected from these groups are relevant and should be incorporated into surveillance systems. In addition, hospital diagnosis systems should also be considered as additional sources of information.

Monitoring vaccine coverage and impact

All countries should have coverage assessment systems in place for the vaccine-preventable diseases included in the national immunisation schedule. The target age for assessing vaccine coverage is dependent on the chosen vaccination programme and should be clearly defined.

The impact of vaccination programmes on acute and chronic disease cannot be measured until at least 3 to 5 years after implementation. However, countries may decide to conduct serological studies to measure the effectiveness of the vaccination programme: taking serological assessment of markers such as HBsAg and anti-HBc can document a reduction in chronic carrier rates and acute disease.

Reporting severe adverse events

Adverse events monitoring systems are already in place in many countries for tracking adverse events following immunisation; these guidelines should be applied to hepatitis B immunisation programmes as well.

References

³ Viral Hepatitis Prevention Board. Surveillance systems in Europe need strengthening and uniformity. Viral Hepatitis Prevention Board meeting, Athens, Greece, June 24-26, 1996. *Viral Hepatitis* 1997; 5.3.

Prevention of perinatal HBV transmission (1998)⁴

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 HBV carrier women and to prevent 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 these 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, which:

- Allows identification of newborns that require immediate vaccination.
- Allows identification of carrier mothers and prevention of further secondary spread of HBV, as well as representing a health benefit to the mothers.

Most countries currently administer HBIg and vaccine to

infants of carrier mothers, although scientific 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 an injection site other than that of the vaccination site. The schedules most widely used for the hepatitis B vaccine are 0,1,6 and 0,1,2,12 months, both of which have shown to be equally 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 immunisation provider. An organisational framework should be in place, and responsibility for co-ordination of HBsAg screening and follow-up of vaccination of newborns should be well defined.

Where maternal screening programmes do not exist, resources may be better directed towards universal neonatal immunisation 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.

References

⁴ Viral Hepatitis Prevention Board. Viral hepatitis in infants and children: epidemiology and prevention. Viral Hepatitis Prevention Board meeting, Lisbon, Portugal, April 14-16, 1998. *Viral Hepatitis* 1998; 7.1.

Hepatitis B virus mutants and variants (1998)⁵

The present vaccines and vaccination strategies are 90% to 95% effective in reduction of HBV carrier prevalence in immunised cohorts of children, and are highly effective in preventing transmission in other at risk groups. These prevention strategies should be vigorously continued in the 168 countries that have already introduced universal immunisation [data from the World Health Organization, 2003], and should be implemented in all countries where not yet in place.

A much more complete understanding of the potential impact of 'escape' mutants on the epidemiology and prevention of hepatitis B is needed. In order to reach this goal the following activities should be encouraged and implemented:

- The tools to detect HBV mutants and variants should be optimised:
 - There is a need for the evaluation of existing HBsAg diagnostic assays to determine if they detect relevant

HBsAg mutants. This will require the development of a serum panel containing such mutated viruses/antigens, and validation by external quality control.

- A true neutralisation assay is necessary to evaluate the potential of mutants to escape passive or active immunisation or natural immunity.

- Methods to detect and classify mutants should be standardised. A definition of what is a wild type virus is needed.

- There is a need for a surveillance network to detect HBV mutants worldwide.
- Epidemiological studies are needed to determine:
 - The attributable risk of HBV infection from these mutants following post-exposure immunisation;
 - The risk of person-to-person transmission of these mutants in susceptible and immunised humans.
- Research should be encouraged to better understand the mechanisms or pressures for naturally occurring mutants, or induced by passive or active immunisation. For this

reason there is a need either to further characterise and standardise hepatitis B immunoglobulin preparations or to replace these with pools of monoclonal antibodies with defined properties known to neutralise 'S' mutants, and to further study the development of vaccines which might prevent the occurrence of relevant mutants.

References

⁵ Viral Hepatitis Prevention Board. Viral Hepatitis Prevention Board consensus statement on HBV mutants and variants. *Viral Hepatitis* 1999; Fact sheet 4. Prepared from material presented at a VHPB meeting held June 2-4, 1998, in St Petersburg, Russia.

Injection safety and safe blood supply (1998)⁶

Injection safety⁷

The VHPB recommends:

- education of health care providers and the public about the dangers of unsafe injections;
- education of health care providers and the public on appropriate and inappropriate use of injections;
- insistence that a separate sterile needle and a separate sterile syringe be used for each injection, and then properly disposed of;
- use, wherever possible, of auto-disable syringes and the provision of adequate supplies of sterile needles and syringes and sterilising equipment as appropriate;
- routine evaluation of the effectiveness of prevention programmes;
- research into the extent of the problem of unsafe injections in Eastern and Central Europe and the NIS.

A safe blood supply

- All countries should develop a structured blood transfusion service to ensure the safety of blood through proper donor

selection, blood collection and testing, and appropriate medical indication. All donations should be screened for HBsAg, anti-HCV, and anti-HIV.

- Although the most recent and technologically advanced screening assays may not be available in many countries because of financial, logistical or technical constraints, this should not prevent the development of an effective blood-screening programme. The undisputed benefit of screening all blood donations far outweighs concerns over the absolute sensitivity of the available assays.
- The international community should ensure that countries in greatest need receive resources necessary to achieve safe blood use. Manufacturers of reagents are urged to make affordable screening tests available to developing countries.

References

⁶ Viral Hepatitis Prevention Board. Injection safety and a safe blood supply. *Viral Hepatitis* 1998; Fact Sheet 3.

⁷ Further information on injection safety is available on the website of the Safe Injection Global Network: <http://www.injectionsafety.org>

Control of hepatitis A (1999)⁸

Hygiene and adequate sanitary measures are the most important tools to prevent the spread of hepatitis A.

The decision to adopt a routine hepatitis A vaccination of children should take into consideration:

- prevalence and incidence of hepatitis A cases
- frequency of outbreaks
- health impact of hepatitis A compared to other health priorities
- programmatic feasibility of a hepatitis A vaccination programme
- economic evaluation of the different hepatitis A prevention strategies.

Universal hepatitis A childhood vaccination should be considered in communities with repeated outbreaks or where the hepatitis A incidence rate is substantially higher than in the overall country.⁹

If implementation of effective hygiene measures is not achievable, hepatitis A vaccination can be effective and should be considered in controlling an outbreak in small, self-contained communities with high rates of hepatitis A if:

- vaccination can be started early in the outbreak;
- high coverage levels in the target population can be achieved;
- multiple age cohorts are vaccinated.

The vaccination efforts should preferably focus on children. The upper age limit, however, will be determined by the local epidemiology.

Universal hepatitis A childhood vaccination programmes that are currently implemented in some areas of the WHO European region (Israel; Puglia, Italy; Catalonia, Spain) should be followed up and evaluated.

The VHPB endorses hepatitis A vaccination for:

- Travellers (born in low-endemic countries) visiting high-endemic countries, including people who travel frequently as part of their occupation.
- Children of immigrant parents, born in Western Europe (low endemicity) visiting their parents' country of origin (high endemicity).

Hepatitis A vaccination is recommended for persons at

increased risk for hepatitis A or an adverse disease outcome, such as men who have sex with men, intravenous drug users, staff and residents in institutions for the mentally retarded, persons with chronic liver disease (regardless of its aetiology), and haemophiliacs.

Further studies are needed to document the occupational risk of hepatitis A for health care workers.

Post-exposure prophylaxis for hepatitis A:

- IgG is still very effective for post-exposure prophylaxis.
- The effectiveness of hepatitis A vaccine compared to IgG has not yet been fully evaluated.

- In countries where IgG is not routinely used after exposure or where IgG is unavailable, administration of hepatitis A vaccine can be considered and is likely to provide protection.

References

⁸ Viral Hepatitis Prevention Board. Hepatitis A. Epidemiology and prevention including new recommendations. Viral Hepatitis Prevention Board meeting, Nice, France, March 25-27, 1999. *Viral Hepatitis* 1999; 8.1.

⁹ Recommendations of the Advisory Committee on Immunization Practices (ACIP). Prevention of hepatitis A through active or passive immunization. *MMWR* 1999; 48:RR-12.

Prevention and control of hepatitis B in migrant populations (1999)¹⁰

Mass migration and increased mobility are modern phenomena that are having a tremendous impact on the epidemiology of hepatitis B infection and on national prevention programmes.

Mobile populations are heterogeneous and include people from all walks of life and backgrounds. In addition, the speed and efficiency of modern transportation systems make it a challenge to introduce health interventions to mobile populations and to monitor the effectiveness of these programmes.

The VHPB examined the situation in 1999, taking particular note of the immigration trends in Europe, put forward recommendations on how to define the health care problems brought about by mass migration and to formulate national health care policy that will protect the individual and the society.

What follows are definitions of different migrant populations and recommendations on what elements need to be included in successful hepatitis B prevention programmes aimed at migrant populations.

Besides the official migrant populations, unofficial migrants represent a huge and unsolved problem.

Migrant populations

Migrant populations are diverse. Those who would be considered as risk groups for hepatitis A and/or B would include:

- asylum seekers and refugees;
- internal migrants moving from rural to urban areas and back, migrating because of:
 - economic considerations
 - natural disasters and political upheaval
 - development projects
- international guest workers, both seasonal and long-term;
- sex workers;
- frequent travellers:
 - businessmen
 - professionals
 - aircrews
 - seamen

- truck drivers
- civil servants
- military personnel;
- tourists;
- immigrants / permanent migrants;
- unofficial migrants;
- students;
- spouses of international marriages;
- children adopted internationally.

All of these groups have specific health care and psychosocial needs that should be addressed. The VHPB proposes that routine immunisation remains the best tool for the long-term prevention of HBV and HAV, together with education and counselling of migrants and the health care workers who serve these populations.

Recommendations

- HBV prevention should be offered to all migrants coming from high prevalence areas to low prevalence areas. Immunisation programmes should include screening, immunisation (if indicated), and counselling.
- Migrants should be screened for HBsAg and anti-HBc. All susceptible persons should be immunised against HBV.
- When HBV carriers are identified, they should be offered:
 - counselling;
 - an evaluation of the possible treatments available;
 - follow-up for chronic liver disease (including hepatitis A vaccination if indicated);
 - confidentiality.
- Newborns of HBV carrier mothers should be immunised at birth, or as soon after as possible.
- HAV vaccination should be given to frequent travellers at risk and to all military personnel.
- Providing the blood supply is safe, migrants are not a risk for community-wide transmission of HCV.
- Efforts should be made to apply the official recommendations also for unofficial migrants of any category, and ways must be found to take care of these people without compromising their anonymity.

Adopted children¹¹

- Candidate adoptive parents should receive counselling so that they understand fully the issues of international adoption.
- Candidate adoptive parents should have access to reliable information on the hepatitis B status of the perspective 'adopted child' before the adoption takes place. However, they should be aware that not all screening information is reliable.
- The VHPB recommends that the adopted child be re-tested as soon as possible after arriving in the home country of the parents.
- All household contacts should be vaccinated if the adopted child is HBsAg-positive.
- All children in foster care or in institutional care should receive hepatitis B immunisation.

Refugees and asylum seekers

Refugees and asylum seekers fall into two categories: those who are relocated by government programmes and are living in organised camp settings; and those who have moved on their own under no organised programme.

Management in camps

- It is imperative that all relief workers and staff of refugee camps be immunised for hepatitis A and hepatitis B, ideally, before arriving in the camps or alternatively, immediately upon arrival.
- Immunisation of all refugees for hepatitis A to prevent outbreaks of infection in the camps is recommended in low endemic countries. Good general hygiene is also a necessary preventive measure. Vaccination for hepatitis A is not a priority in high endemic countries, but is recommended in countries of intermediate endemicity for hepatitis A.
- As HBV and HCV are also sexually transmitted, information about transmission and prevention should be made available as part of any prevention programme.
- All injections should be delivered according to safe medical practice.

Refugees identified for resettlement and asylum seekers

- Hepatitis B immunisation should be carried out:
 - without anti-HBc screening of children in recipient countries where routine infant immunisation is in place;
 - after anti-HBc screening for all age groups in recipient countries where routine hepatitis B immunisation is not yet implemented.
- Anti-HBc screening and vaccination should be performed in adults.
- Testing should not be related to the outcome of the integration process, but should be performed in the interest of individual and public health.
- Refugees should receive culturally appropriate information on screening and vaccination.
- All countries are strongly encouraged to exchange epidemio-logical information on refugees.

Sex workers

Sex workers include men, women, and transgender persons who provide sex for money or remuneration. Immigrants have rapidly become a major proportion of the sex worker population in many countries. In the EU, an average of 40% of sex workers are foreign born. Immigrant sex workers carry with them the viral hepatitis epidemiology of their country of origin, although in some cases the prevalence rates of HBV and HCV may be higher or lower than that found in their countries of origin.

Although sex work is illegal in many countries, the goal of disease prevention is to ensure that these people are served by the public health authority and that they have access to health care services.

Sex workers are at occupational risk of sexually transmitted infections, including hepatitis B and, to a lesser extent, hepatitis A. Drug use among sex workers may increase the risk of infection by blood-borne pathogens, particularly hepatitis C.

Clients of sex workers are at increased risk of HBV infection and this risk is highest from those immigrant workers from countries with a high endemicity of infection. The limited data available suggest that legal residents of a country working in the sex trade are more likely than illegal immigrant workers to practice safe sex. However, it is essential that the extent of these practices be determined.

- Routine immunisation of all sex workers should be carried out, irrespective of the person's legal status. Vaccination programmes should be adapted to meet the needs of these diverse populations in order to achieve high levels of coverage.
- As many sex workers have no insurance coverage and limited access to health care, hepatitis B immunisation should be available at no charge. Clients should also receive vaccination at no charge.
- Vaccination should be initiated irrespective of whether completion of the three-dose series can be ensured.
- There is a need to extend currently existing outreach and prevention programmes for sex workers to include immigrant sex workers.
- Health education messages should be directed at both the sex workers and the clients.

Confidentiality and appropriate counselling are essential to the success of any prevention programme targeting sex workers.

References

¹⁰ Viral Hepatitis Prevention Board. Population movement: magnitude and nature of the problems involved. Viral Hepatitis Prevention Board meeting, Venice, Italy, September 16-17, 1999. *Viral Hepatitis* 2000; 8.2.

¹¹ Viral Hepatitis Prevention Board. You're adopting a child from abroad. What you should know about hepatitis B. *Viral Hepatitis* 2000; Fact Sheet 5.

Economic evaluation of vaccination programmes (2000)¹²

Although economic evaluations of viral hepatitis vaccination have had shortcomings, the availability of these analyses have allowed conclusions to be drawn for HBV vaccination, and to a lesser extent for targeted HAV vaccination. In all areas where the overall HBV chronic infection rate exceeds 0.5% and the prevalence of all markers is higher than 5%, universal vaccination of either neonates, infants, or adolescents is desirable on the basis of economic and epidemiological arguments (although in high-endemicity areas other competing interventions may be equally or more attractive). In very low-endemicity areas (where these percentages are lower), there is insufficient evidence to show a preference for universal over selective HBV vaccination.¹³ To date, there have been too few analyses of universal childhood HAV vaccination strategies to make general statements about the relative efficiency of such programmes. In order to facilitate such analyses in the future, the greatest need appears to be for reliable acute disease surveillance. The economic and epidemiological impact of HAV vaccination of adult at-risk groups in low endemicity areas (on which almost all evaluations have been focused) was usually found to be relatively unattractive compared with other health care interventions.

Future analyses of vaccination programmes should benefit from addressing the potential shortcomings we have discussed in this article.¹² Namely, better overall transparency and validation, more careful choice of models (tailored to the infection and the target groups) and time spans, and more extensive sensitivity analyses seem most pressing to improve the quality of and comparability between such analyses. Furthermore, it is in the general interest that any

economic evaluation (also nonvaccine-related) adheres more closely to the overall general guidelines. This needs to be monitored by peer reviewers, who might have to referee lengthy papers when the subject is a model-based economic evaluation. Indeed, a well-balanced analysis demands transparent and clear descriptions of all relevant epidemiological, disease model and cost-related aspects. Therefore editors should be prepared to accept that such a paper could be relatively long, particularly when the modelling and epidemiological aspects are complex, as for many vaccination programmes.

Finally, to improve the credibility of economic evaluation it seems desirable that general guidelines become less ambiguous about potentially important elements (in the case of the vaccination, discounting of health gains and future unrelated costs). Nonetheless, economic evaluation should be only one of the many considerations that come into play. Moreover, in order to be a useful tool in decision making, it should not only be used at convenience to introduce new interventions, but also to cancel existing practices that are both inefficient and inequitable.

References

¹² Beutels P, Edmunds WJ, Antoñanzas F, De Wit GA, Evans D, Feilden R *et al.* Economic evaluation of vaccination programmes. *Pharmacoeconomics* 2002; 20:1-7. Prepared from material presented at a VHPB meeting held October 12-13, 2002, in Istanbul, Turkey.

¹³ Beutels P. Economic evaluations of hepatitis B immunisation: a global review of recent studies (1994-2000). *Health Econ* 2001; 10:751-774.

Hepatitis B vaccination: How to reach risk groups (2001)¹⁴

Injecting drug users (IDUs)

- Hepatitis B vaccination of injecting drug users, ideally as soon as possible after the start of their drug use, is recommended.
- Injecting drug users should undergo pre-vaccination testing for serological markers of HBV infection.
- If chronic infection is diagnosed, referral of IDUs to individual care services for counselling and treatment, and referral of the IDU's household contacts and sex partners to preventive services is recommended.
- Injecting drug users, especially those known to be infected with HIV, should be subject to follow-up testing for anti-HBs after completion of their vaccination series, and to counselling if they do not respond to the vaccination. The importance of communicating the test results to clients and to their regular health care provider is recognised.
- A one-stop service integrating multiple viral hepatitis prevention services (such as prevention counselling, screening for HBV / HCV and risk-based HAV, and hepatitis B / hepatitis A vaccination) with HIV and sexually

transmitted infections services, drug rehabilitation programmes, and other drug-related services, should be established.

- The establishment of needle-exchange programmes, as an efficient means of preventing HBV infection and other blood-borne infections, is recommended.
- The client's anonymity should be guaranteed and his or her identity known only by a unique code number.

Health care and other workers with occupational risks for hepatitis B

- The level of risk of HBV infection among health care workers, trainees, and those in related occupations is dependent upon the frequency of their percutaneous or mucosal exposure to blood or other body fluids.
- As a consequence, hepatitis B vaccination is recommended for the following groups: (1) Health care workers with frequent exposure to blood or other body material; (2) Students or trainees upon their acceptance to schools of medicine, dentistry, nursing, laboratory technology, or

related areas, prior to their first potential contact with blood in a professional setting; (3) Interim health care workers, all the more so since this group is less subject to monitoring than health care workers with a permanent appointment.

- Many other occupational groups face the risk of exposure to blood or other body fluids and are therefore at risk of hepatitis B virus infection. Risk assessment should be performed on the basis of: (1) The prevalence of markers of past or current HBV infection in such groups; (2) The reported frequency of exposure to blood or other body fluids in these groups, taking geographical differences in endemicity into account.
- The need to consider vaccination strategies is recognised for groups of individuals with: (1) A higher reported prevalence of hepatitis B (e.g., tattooists); (2) Firemen, policemen, waste disposal workers, and other utility workers, who are potentially at risk of frequent exposure to blood or other body fluids, despite the fact that the prevalence of HBV markers in these categories is not higher than in the general population.
- A compilation of all bibliographic information on diseases that may be contracted as a result of performing other specific tasks would be most valuable when considering additional risk-group recommendations and risk-assessment criteria.

Sex workers

- Sex workers include all persons who provide sex for money or other forms of remuneration. Sex workers are at occupational risk of sexually transmitted infections, including hepatitis B. For this group, see also the conclusions below for 'Persons who engage in unsafe sexual behaviour.'
- Routine hepatitis B immunisation of all sex workers is recommended, irrespective of their legal status.
- Hepatitis B immunisation should be free of charge for this group, because many sex workers are not covered by health insurance and have only limited access to health care services.
- It is recognised that special attention should be given to: (1) Vaccination programmes adapted to the needs of this group; (2) Health education messages addressed to sex workers and their clients; (3) Confidentiality and appropriate counselling; (4) Anonymity achieved, e.g., by assigning a unique code number to the sex worker; (5) Promotion of outreach programmes and accelerated vaccination schedules, to guarantee higher vaccination coverage.

Persons who engage in unsafe sexual behaviour

- Hepatitis B vaccination is recommended for all adolescents and adults who engage in unsafe sexual behaviour. These groups include: (1) Heterosexuals having sexual contact with HBV infected persons or with multiple partners; (2) Men who have sex with men; (3) Persons attending sexually transmitted infections clinics; (4) Sex workers.
- A one-stop service should be established integrating multiple viral hepatitis prevention services (such as prevention counselling, selective screening for HBV or

HCV, and hepatitis B vaccination) together with HIV and sexually transmitted infections services.

- Pre-vaccination screening of sexually active homosexual and bisexual men is recommended.
- Persons who engage in unsafe sexual behaviour should be subject to follow-up testing for anti-HBs after completion of their vaccination series, and to counselling if they do not respond to the vaccination.
- If chronic hepatitis B infection is diagnosed, referral of clients to individual health care services for counselling and treatment, and referral of the clients' household contacts and sex partners to preventive services is recommended.
- The importance of the expansion of outreach programmes and the integration of vaccination and information programmes (e.g., for MSM) into non-clinical sites is recognised.

Household and other social contacts of persons with HBV infection

- Persons who have casual contact with acute hepatitis B patients or chronic HBsAg carriers at schools and offices are at low risk of catching HBV infection.
- Hepatitis B vaccination is not recommended for these persons unless in special circumstances, such as the occurrence of behavioural problems (biting or scratching) or medical conditions (severe skin disease) that might facilitate transmission.
- Some European countries recommend vaccination of day-care children and staff where they have contact with high-risk children.
- Vaccination of all household contacts of persons identified as acute hepatitis B patients or chronic HBsAg carriers is recommended.

Pregnant women and at-risk neonates

- In general, where universal screening of pregnant women for HBsAg exists, countries may wish to continue such screening programmes.
- Women who present for delivery without having been screened during their pregnancy should be tested immediately, and their newborns vaccinated within twelve hours after birth, irrespective of the screening test results.
- Infants born to mothers who are HBsAg-positive should receive the hepatitis B vaccine within 12 hours (and certainly not later than 24 hours) after birth. As no sufficient data supporting the additional value of administering HBIG at birth are available, this procedure is not recommended. This point of view is, however, not intended to promote modification of currently implemented national policies.
- Efficient implementation of universal screening procedures for pregnant women and vaccination of newborns requires: (1) Awareness among public health authorities, health care providers, and the general public of the importance of prevention of HBV infection; (2) A well-organised structure; (3) Trained personnel; (4) Good communication; (5) Sufficient resources and supplies (needles, vaccines, etc.).
- In general, where maternal screening programmes do not

exist, the available resources may be better directed towards universal neonatal immunisation programmes.

- Control of perinatal transmission can be achieved if the first dose of vaccine is delivered at birth.

Haemodialysis patients and patients receiving blood or blood products

- Screening for hepatitis B markers in blood donors is recommended.
- Pre-vaccination testing for hepatitis B markers in patients who have already received multiple blood transfusions is recommended.
- Vaccination of the following groups is recommended: (1) Haemophiliacs and those frequently receiving blood or blood products; (2) Haemodialysis patients and candidates for haemodialysis, who should be vaccinated early in the course of their renal disease; (3) Transplant patients and candidates for transplant.
- These patients should be subject to follow-up testing for anti-HBs after completion of their vaccination series, and to counselling if they do not respond to the vaccination. Booster vaccination is recommended for all of them, to maintain protective levels of antibody.
- HBsAg-positive haemodialysis patients and haemodialysis machines should be isolated.
- Staff in haemodialysis units should be vaccinated prior to their first contact with haemodialysis patients.
- Patients receiving clotting-factor concentrates should receive subcutaneous hepatitis B vaccination, as soon as possible after diagnosis of their clotting disorder.

Prisoners and prison staff

- Common objectives should form the basis for hepatitis B prevention programmes within European prisons.
- Hepatitis B vaccination for all inmates upon entry into prisons or correctional facilities is recommended.
- Vaccination policies that link vaccination of prison staff and prisoners in order to achieve higher vaccine uptake

levels should be considered.

- The introduction of accelerated immunisation schedules with the aim of achieving higher vaccine uptake levels among prisoners is recommended.
- Post-vaccination anti-HBs levels among prisoners and staff should be tested and recorded.
- Inmates injecting drugs should be permitted access to drug rehabilitation programmes.
- Confidential computerised records should be introduced.

Travellers

- Hepatitis B is of intermediate or high endemicity in all African countries, Latin America, Eastern Europe, most parts of Asia (except Japan), the Pacific Islands, and Arctic regions.
- Travellers to such countries are at risk of HBV infection, particularly through sexual transmission and through percutaneous transmission, via needle sharing, blood transfusion, injections, acupuncture, tattooing, etc. Travel to these areas provides an ideal catch-up opportunity for hepatitis B vaccination.
- Hepatitis B vaccination of the following groups or individuals when travelling to areas with intermediate or high endemicity is recommended: (1) Travelling health care workers; (2) Young children who will be in day-care or residential settings; (3) Travellers likely to engage in sexual or needle-sharing activities; (4) Travellers who may need to undergo medical or dental procedures; (5) Travellers planning to undergo invasive cosmetic procedures; (6) Other travellers staying in areas of intermediate or high endemicity for more than one month, and frequent travellers making shorter trips to these areas.

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¹⁴ Viral Hepatitis Prevention Board. Hepatitis B vaccination: How to reach risk groups. Viral Hepatitis Prevention Board meeting, Ghent, Belgium, March 15-16, 2001. *Viral Hepatitis* 2001; 10.1.

Combined hepatitis B vaccines (2001)¹⁵

Benefits of combined vaccines

- Reduced number of injections per visit, and reduced total number of injections overall, leading to:
 - Reduced number of exposures to possible injection pain;
 - Less or no exposure to thiomersal;
 - Less time spent in doctor visits;
 - Less waste and increased injection safety with fewer syringes;
 - Reduced immunisation programme costs.
- Improved vaccination coverage;
- Simplified implementation of immunisation programmes;
- Facilitated addition of new antigens into existing immunisation programmes;
- Facilitated harmonisation of antigens;
- Decreased disease prevalence and burden;
- Facilitated data collection through easier documentation;
- Reduced costs of storage, transport, cold chain (not valid

for developing countries);

- May present a new opportunity to move towards harmonising vaccination calendars in the European Union.

Combined vaccines - drawbacks and issues

- Possible barriers to the use of certain combination vaccines based on complex issues regarding harmonisation of European vaccination schedules are due to:
 - Different epidemiological patterns per country / region;
 - Different national recommendations for compulsory and facultative immunisations;
 - Different national traditions and attitudes towards health care reimbursement;
 - Complexity of policy and decision making at national level involving many associations of physicians and health insurance providers.

- Potential decrease in immunisation programme flexibility with increase in number of antigens per dose.
- Shrinking market of vaccine manufacturers (due to mergers) places immunisation programmes at potential risk if a manufacturer of a combined vaccine chooses to stop production and no other supply source exists.
- Increasing complexity and costs of clinical development and trials involving:
 - Need for testing safety and efficacy of each vaccine component;
 - Ethical implications in conducting clinical trials with huge numbers of participants to test against different immunisation schedules;
 - Need to establish new minimum potency and protection levels;
 - Need for new reference materials;
 - Analysis of adverse reactions;
 - Surrogate markers.
- Combined vaccines with a hepatitis B component cannot be used for newborn immunisation since the non-hepatitis B components of combination vaccines have reduced immunogenicity in children less than six weeks of age. The monovalent hepatitis B vaccine must continue to be used as the birth dose.
- More long-term studies will be needed to evaluate when booster vaccinations are needed using hexavalent vaccines with a hepatitis B component, especially in immunisation schedules with only three vaccinations in the first year of life with no booster vaccination.
- Quality issues of hexavalent vaccines focus on the cumulative stability of vaccine intermediates, resulting in the Committee for Proprietary Medicinal Products (CPMP) recommendations that have been accepted by manufacturers in assuring that intermediates exceeding a certain age will not be used in the manufacture of vaccines.
- Efficacy issues highlight the need for establishing better or other markers of protection.
- While immunological responses against Hib may be lower in hexavalent vaccines, they still remain at clinically acceptable protective levels.

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Escape hepatitis B virus mutants: a threat? (2001)¹⁶

The list of different types of HBV escape mutants is getting longer. At least theoretically, it cannot be excluded that the growing selection pressure may allow the variants to out-compete the wild-type and even reach a comparable prevalence. This consideration, combined with the manifold known survival strategies of HBV and its additional strategic possibilities that have not properly been investigated yet, is a possible cause for concern. Therefore, there is no choice but to formulate proposals in preparation of any evolving situation.

The most urgent goal should be to gain a more complete understanding of the potential impact of escape mutants on the epidemiology and prevention of hepatitis B. This can best be achieved by increasing the activities at different levels. The present diagnostic assays should be reconsidered and their ability to detect mutants should be evaluated. An *in vitro* neutralisation assay to evaluate the capacity of mutants to escape immune attack would be welcome. Epidemiological studies are necessary to monitor the occurrence and geographical spread of HBV mutants, the induction of mutations after post-immunisation exposure, and the risk of transmission in susceptible and immunised individuals. Fundamental and applied research is needed to improve the present perception of the biological characteristics of HBV variation and to further explore the possibilities of new types of vaccines.

Although it has been shown that two commercial hepatitis B vaccines protected chimpanzees against infection by the prototype G145R mutant, a number of proposals have been made to improve the immunogenicity of current vaccines. Inclusion of the preS region, thus taking advantage of the

characteristics of both the preS1 and preS2 proteins, is an interesting possibility. PreS1 binds directly to the hepatocyte receptor and preS2 contains the albumin receptor. The preS region contains a number of B and T cell epitopes and may be an important target for the identification and elimination of infected hepatocytes. PreS2 is highly immunogenic because it contains a strong T cell epitope and is able to provoke an anti-HBs response in mice that fail to respond to HBsAg-based vaccines. So far, similar attempts with preS1 and/or preS2 sequences in man have not revealed much benefit compared with the standard vaccines. More recently, attempts have been made to produce mammalian or yeast cell derived recombinant preS vaccines containing both preS1 and preS2. Some have been evaluated in healthy adults and children, and proved to be highly immunogenic, but because of an imperfect design of the trials, the results were not conclusive and comparison with conventional vaccines remained difficult. It is clear that this line of research deserves further development.

Generalised incorporation of preS in hepatitis B vaccines may, however, not yield a definitive solution, because it might in the future be accompanied by the emergence of preS deletion escape mutants. It has been suggested that the design of future, effective vaccines may need to take into consideration vaccine escape HBsAg mutant sequences themselves, derived from the second *a* loop or from outside the determinant. Of particular importance would be G145, in combination with R145.

Other types of mutants, diagnosis escape mutants, are not only clinically important, but also cause significant obstacles in immunoassays designed for the detection of HBsAg. An

unanswered question is how to develop more reliable assays for the future. Proposals in this regard have been formulated by a number of authors and involve the inclusion of variant S or preS sequences and screening for HBV DNA or antibody to HBcAg. The relevance of this consideration is obvious when it comes to planning appropriate treatment schemes for patients or guaranteeing the safety of donor blood.

It is clear that this discussion is not closed and it is undoubtedly wise to be prepared for any further evolution. The currently available vaccines are safe and effective and should be globally used in universal vaccination programmes. In terms of vaccine design, incorporation of escape mutant sequences into the present HBsAg based preparations is a possibility at present, although new mutants could emerge and undermine the value of this strategy. Apart from the mentioned experimental vaccines under investigation, potentially powerful alternatives based on blocking viral gene expression at different levels are being explored, to complement existing or future therapeutic and prophylactic strategies. Genetic antiviral strategies include the application of ribozymes (RNA enzymes), antisense oligonucleotides,

and the intracellular synthesis of interfering peptides or proteins. The latter way represents a type of intracellular immunisation whereby the resulting fusion proteins yield dominant negative (DN) HBV mutants capable of significantly suppressing viral replication. This approach is especially promising because the creation of DN mutants is relatively independent from sequence variation in the viral genome and thus minimises the risk of selecting escape mutants. These and other innovative approaches to come, combined with the results of the human genome project and the exciting developments in the field of pharmacogenomics, will lead to the need to drastically redefine hitherto invariable basic concepts such as susceptibility, infection risk, herd immunity, diagnosis, treatment, prevention, and escape, and contain nothing less than the germs of a revolution in the battle against viral and other pathogens.

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Public health challenges for controlling HCV infection (2002)¹⁷

1. In spite of the advances that have been made in our understanding of hepatitis C virus (HCV) biology, the epidemiology and natural history of HCV infection, and the progress in the primary and secondary prevention of HCV infection that has been made, major public health efforts to prevent and control this infection in the global population are still required.

2. Although the first clinical trials of a therapeutic type against HCV are under way, there is no short-term prospect for the introduction of any kind of vaccine against this virus. The conclusions and recommendations arising from this meeting are made in the context that hepatitis C would not be a vaccine-preventable disease in the foreseeable future.

3. Hepatitis C prevention should be viewed in the context of: (1) Primary prevention of newly infected persons; (2) Secondary prevention of transmission from known infected persons to others; (3) Tertiary prevention of the consequences of chronic HCV infection.

4. Primary prevention should focus on identifying persons at increased risk of HCV infection and providing HCV testing, counselling and health education concerning risk and harm reduction, and substance abuse treatment where appropriate.

5. There is a need for health education and awareness campaigns about HCV to be targeted both to the general public and to health care providers. Only a relatively small proportion of individuals infected with HCV are currently aware of their infection. Moreover, even in 2002, a large number of medical professionals are not sufficiently aware of HCV infection and its implications, and may fail to

recognise the disease in their patients. In order to envision appropriate counselling, this lack of awareness by health care professionals of risk factors for infection, diagnostic tests and recent advances in treatment options also needs to be rectified. In short, all health care providers need to be better informed about HCV infection and how to manage and counsel their patients with this infection. Collaboration with patient support groups should be sought and developed.

6. There is a need to identify those infected with HCV to achieve the goals of secondary and tertiary prevention, which includes counselling to reduce the risk of transmission through donating blood, serum, or organs; injecting drug use; and high risk sexual practices. These persons also need medical evaluation for possible treatment in order to prevent progression of their chronic liver disease. They need additional counselling with regard to: (1) Reduction of further liver injury from the consequences of alcohol consumption and co-infection with other hepatitis viruses and HIV; (2) Vaccination against hepatitis A and B, influenza, and possibly against *Streptococcus pneumoniae* infection.

7. Because of overlapping routes of transmission and populations that are at risk for viral hepatitis, HIV/AIDS, and other sexually transmitted infections, it is important that identification and prevention strategies should be integrated.

8. The problem of identifying all individuals infected with HCV and bringing them under medical attention is compounded by the fact that a large proportion of individuals with HCV infection live in developing and transitional economy countries where resources are scarce, screening of blood and blood products is not performed, the diagnosis of

HCV infection is difficult, and treatment is not affordable.

9. There is still insufficient epidemiological data on the prevalence and incidence of HCV infection in many countries. Therefore, further studies, particularly evaluating the general population are warranted in most places. The complexity of reporting highlights the need for organisations such as WHO, CDC, and VHPB to develop guidelines on methods to obtain representative population-based HCV infection prevalence data and case definitions for reporting purposes.

10. Injecting drug use continues to be the source of HCV infections in most developed and some transitional economy countries. Because a high proportion of incarcerated persons have used injection drugs, there is a high prevalence (30-80%) of HCV infection in this population. This stresses the importance of the use of harm-reduction (harm-minimisation) procedures in prisons.

11. To minimise the spread of HCV among intravenous drug users, harm reduction involves more than just needle and syringe exchange. It must also involve swabs, filters, spoons, water, and any other equipment used. One of the major actions recommended is the necessity for needle exchange programmes to be introduced on a far larger scale, including the use of commercially available drug-paraphernalia (e.g., Stericup®). Collaboration with patient support groups should be sought to enhance the impact of prevention programmes.

12. Evidence-based information on nosocomial infections dramatically proves the impact of unsafe injection procedures, and the resulting high chronic HCV infection rates. In some countries unsafe injection techniques are now the predominant mode of acquisition of HCV infection. Particularly important in this regard are the following:

- Using only sterilised medical equipment. Unsafe medical injections may be eliminated by: (1) Changing behaviour among patients and health care workers to decrease injection overuse and improve injection safety; (2) Providing access to necessary equipment and supplies.
- Applying proper management of sharp waste.
- Recent literature has stressed that in haemodialysis units, in particular, recommended procedures are not being carried out adequately, and hand-washing techniques remain faulty.

13. Multidose vials are also a cause of nosocomial transmission of HCV. Therefore:

- Single-dose vials should be used wherever possible. If multidose vials must be used, the septum should always be pierced with a sterile needle, and a needle must not be left in place in the stopper.
- Each injection should be prepared in a clean designated area where blood or body fluid contamination is unlikely.

14. Other routes of infection, such as through sexual activity or intra-familial transmission, play a much lesser role in spreading HCV.

15. Testing for HCV:

- Of all patients with persistently raised serum ALT levels, 15% prove to be chronically infected with HCV. It is recommended that individuals with persistently raised serum ALT levels that are unexplained should be tested for HCV. Screening of the whole population is, however, not recommended.
- Patients with defined extrahepatic manifestations of HCV should be tested for the virus.
- It is self-evident that testing for HCV should be undertaken only if appropriate counselling can be given and appropriate treatment is available.

16. Disease progression - Controversy still exists over the proportion of patients acutely infected with HCV who progress to cirrhosis. Hospital-based data on patients with symptomatic chronic HCV infection give far higher rates of progression to cirrhosis than do analyses of all patients infected with the virus. When patients in the Irish outbreak of HCV infection caused by contaminated anti-D immunoglobulins were followed-up, only 2% developed cirrhosis, and in other large-scale studies in children with post-transfusion HCV infection and in intravenous drug users less than 5% progressed to cirrhosis.

17. In order to reduce the morbidity and mortality caused by HCV infection, the objective of treatment should be:

- Cure by completely eliminating HCV and normalising serum ALT levels.

If this is not possible, the objectives should be to:

- Stop disease progression;
- Improve quality of life;
- Reduce transmission of the virus;
- Reduce the pool of chronic carriers.

18. Despite a greater awareness of HCV infection, earlier diagnosis through improved laboratory techniques, and the recent introduction of more effective treatment, the overall outcome of HCV infection has not improved appreciably in recent years.

19. Treatment of chronic HCV infection with interferon does result in viral clearance in some patients, and in others it slows down progression to fibrosis. More recently, controlled trials have demonstrated that combined treatment with pegylated interferon and ribavirin has produced a greater number of sustained responses, depending on the genotype of the virus. Higher response rates are obtained with 6 months of treatment in patients with genotypes 2 and 3. Treatment of persons infected with genotype 1 produces less encouraging results and there is also the need to treat for 12 months.

20. Treatment of acute community-acquired HCV infections in younger patients appears to have a higher success rate with respect to viral clearance and progression to chronic

infection. If confirmed, early treatment with interferon alone or in combination with other drugs should reduce the burden of HCV disease.

21. In spite of the advances in the treatment of HCV infection, given the fact that the majority of patients infected with this virus are not under medical care, the overall impact of therapy on the number of patients who are chronically infected with HCV is relatively small.

22. The VHPB aims to contribute to the prevention and control of hepatitis C by: (1) Raising awareness among health care providers and policymakers of the public health significance of hepatitis C; (2) Informing them about the risk

of HCV transmission through blood or blood products, injecting drug use, and high-risk sexual practices; (3) Stressing the potential impact of preventive strategies, including the effect on the prevalence of other infectious diseases such as hepatitis B and HIV/AIDS; (4) Collecting and collating epidemiological data on hepatitis C, especially in Europe.

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Hepatitis B vaccination: safety issues (2003)¹⁸

The scientifically proven benefits of vaccination in general and more specifically those of hepatitis B vaccination are overwhelming and outweigh by far any suggested risk. Currently, 168 countries have implemented universal infant and / or adolescent vaccination against hepatitis B, and there is no reason to change these policies based on fears of an alleged and unsubstantiated link with multiple sclerosis or other disorders.

1. The VHPB remains fully committed to the current recommendations for continued universal as well as risk-group hepatitis B vaccination programmes, and sees no evidence for establishing any links between the hepatitis B vaccine and certain diseases. Hepatitis B vaccine remains one of the safest and most effective vaccines. It protects people of all ages against hepatitis B virus infection and the wide spectrum of liver diseases that the infection can cause.

2. No hard scientific data support the existence of a causal link between hepatitis B vaccination and the development of multiple sclerosis (MS). There is also no evidence to support any biological plausibility of a link: molecular mimicry would need to be based on an homology between the hepatitis B surface antigen and the human myelin protein, and no such homology can be found. Any temporal association appears to be a coincidental one. WHO's Global Advisory Committee on Vaccine Safety (GACVS), the Institute of Medicine (IOM), and the VHPB support this point of view.

3. The only evidence of potential adverse events that may result from administration of thiomersal-containing vaccines is a small risk of hypersensitivity, such as skin rash and swelling, at the injection site. There is no stringent reason, therefore, to stop the use of thiomersal-containing vaccines in current immunisation programmes, with the balance of benefits over risks of such vaccines being overwhelmingly positive.

4. No causality between the administration of aluminium-containing vaccines and general systemic complaints has been demonstrated. The general public needs to know and

understand that although this type of histological muscle lesion is caused by vaccination, the lesions are not linked to the generalised clinical symptoms. This issue is relevant as a communications challenge having considerable potential for affecting public confidence in vaccination.

5. A hypothetical link between vaccination and acute lymphoblastic leukaemia (ALL) in children has been investigated in a number of studies. The results of the only study that suggested a link between hepatitis B vaccination and ALL, hypothetically attributed to thiomersal, were not convincing, based only on a small number of cases, and other thiomersal-containing vaccines not implicated. At this moment, there are no other scientific data supporting such an association and no need to change current immunisation recommendations.

6. There is currently enough evidence to conclude that people suffering from autoimmune diseases can be vaccinated.

7. Hepatitis B immunisation programmes: selected countries

France

As a consequence of France's temporary suspension in 1998 of school-based adolescent hepatitis B immunisation programmes, following allegations of an association between the hepatitis B vaccine and multiple sclerosis, immunisation rates dropped dramatically, in infants as well as in adolescents. Although these safety allegations have since been refuted and communicated to the general public and medical practitioners, hepatitis B immunisation coverage has not yet recovered to its previous higher level. One measure that is expected to help increase hepatitis B immunisation in France is the use of hexavalent vaccines for infants. These new vaccines are recommended in France but are not yet on the market.

Germany

Vaccine safety issues in Germany are not of major concern to the general public or to health care practitioners. Universal

infant and adolescent hepatitis B immunisation have been recommended in Germany since 1995, and there is now wide acceptance of infant hepatitis B vaccination with the recently licensed hexavalent vaccines. The high uptake of these new vaccines by paediatricians in Germany may be attributed, in part, to the fact that fewer injections and less office visits are required, and are regarded as major advantages among parents for their children's immunisations.

Scotland

A pilot study in Glasgow demonstrated that through promotion of proactive and objective health education and vaccine-related materials, it is possible to achieve high uptake of hepatitis B vaccine in young adolescents, similar to uptake of other routine school immunisations. In the United Kingdom, the current policy (2003) of selective hepatitis B immunisation of risk groups, based on the low incidence of hepatitis B, is under review by the UK Joint Committee of Vaccination and Immunisation (JCVI).

Israel

The overall compliance rate for all vaccines in Israel's infant immunisation schedule, including hepatitis B, is 95%. Adverse events following hepatitis B immunisation are rarely seen in Israel, and only one case of litigation concerning the hepatitis B vaccine has occurred in thirty years. The high uptake rates in Israel attest to its success in reducing vaccine-preventable diseases.

8. Changes in immunisation policy should be evidence-based. Rapid changes in vaccination recommendations, such as those based on vaccine 'scares,' should not be encouraged. All changes in vaccination recommendations should be accompanied by effective communication strategies. This communication must come from organisations that are recognised as a reliable source of information by medical practitioners.

9. A rapidly changing global environment has led to basic changes in perception of immunisation that require a reassessment of issues concerning:

- The divide between industrialised, transitional-economy, and developing countries, and their degree of access to vaccines, basic health care, and evidence-based information;
- The challenge of appropriate response by the scientific / health care, regulatory, and vaccine industry sectors to increasing demands by the general public for consistent, reliable, and readily understandable information relating to vaccine safety, quality, and efficacy, and to the vaccine preventable-disease itself;
- The need for better understanding and increased public awareness of the level of regulations and quality control for vaccines, in order to appreciate better the quality of the currently available vaccines and to make informed decisions.

10. Creating a positive environment for immunisation can

be achieved by repositioning the value of vaccines and vaccination. This new environment will need to be supported by evidence-based information that will ease the task of health care decision-makers in developing proactive communication strategies to deal with crises that have the potential to have a negative impact on vaccine coverage, and on the consequent health status of children.

11. While the scientific community needs to deal rapidly with vaccine safety issues as soon as they arise, there also needs to be rapid follow-up communication to health care professionals and the general public regarding the outcome of such investigations. As research is carried out to investigate hypotheses of vaccine safety concerns, delays in communicating the results of these investigations may have a negative impact on immunisation programmes, and may delay the introduction of certain vaccines in certain countries. The VHPB, therefore, encourages publication of the results of such studies, as well as those of clinical trials, to make this information accessible to many different audiences.

12. A wide range of issues concerning vaccine safety is being taken up by anti-vaccination groups as well as by other groups whose concerns may reflect local customs, religious, political, or other beliefs. Responding to media / anti-vaccination allegations thus requires:

- Familiarity with issues that may reflect unique or local beliefs and attitudes;
- Cultivating relations with the media by responding to vaccine safety issues in a timely and appropriate way, and being seen as a reliable, trustworthy partner in communication;
- Learning where to go for reliable, helpful information and where to seek help in investigating local incidents.

13. Trends have been observed in immunisation coverage following vaccine injury compensation lawsuits, which show dramatic drops in coverage for the relevant vaccine and corresponding geographical area. Previous higher coverage levels are sometimes not attained even after safety allegations have been refuted.

14. To provide a basic framework for vaccine litigation issues, United Nations-developed regulations, while having no legal basis, could provide a model to be followed by the European countries and to provide an impetus for implementation at national level.

15. Vaccine 'scares' continue to have an impact on immunisation coverage. In order to respond to this challenge, there is a need to develop vaccine communication strategies that provide a balance between evidence-based information and advocacy / lobbying activities. Improving communications at international level requires:

- Consensus among authorities on key issues;
- Ability to provide credible, scientific data, either proactively or in timely response to a crisis situation;
- Compiling independent, international reviews of vaccine

safety issues, together with relevant statements from authoritative neutral organisations;

- Strong international collaboration, with direct, early and clear statements agreed by authorities and other key parties, prior to public communications.

16. The vaccine industry recognises that vaccine issues (including safety and supply) need to be dealt with through partnerships forged at different levels:

- At company level, recognising the importance of internal stakeholders;
- Through vaccine industry associations;
- With health authorities and expert groups.

17. The vaccine industry needs to be proactive in identifying resources and in adapting information to different types of audiences. Lobbying activities will also have their place in vaccine communications, as legislators often do not have the time to read to be kept informed of ongoing developments in the vaccine community.

18. A new environment surrounding vaccine issues includes not only traditional players (health authorities, scientific media, patients, health professionals and the industry) but also newer players who must be taken into account in vaccine communications. Patient action groups, the legal profession, the lay media who will be as crucial in crisis management as the specialised press, and the Internet. It is important for the industry to act on the precept that understanding issues does not necessarily bring support to an issue, but that support must also be gained through trust.

19. International collaborative working groups, such as the Brighton Collaboration, are developing standardised

definitions for adverse events following immunisation, in order to allow comparability of data in developing guidelines for clinical trials and surveillance systems.

20. Loss of public confidence in vaccination is one of the greatest threats to public health, and needs to be addressed by local, national and international bodies, pooling resources, to prepare for possible causes that might be taken up by anti-vaccination groups or the media. The health care community needs to actively promote and personally recommend the benefits and safety of vaccination in language that is readily and easily understood by the intended audience.

21. Previous vaccine 'scares' should provide a model for dealing with possible future crises, with the scientific community and health departments providing information to the public of any new, credible evidence of adverse events. Vaccine 'scares' should be dealt with through encouraging open debate and undertaking further studies, if necessary.

22. The vaccine community needs the media and must, therefore, be willing to communicate in a responsible, professional, and timely manner to allegations of adverse events. Journalists, as one of the main communication links with the general public, will need to be informed and convinced of the safety, effectiveness, and benefits of vaccination.

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For further information, please contact:
VHPB Executive Secretariat
Centre for the Evaluation of Vaccination
WHO Collaborating Centre for Prevention and Control of Viral Hepatitis
Department of Epidemiology and Social Medicine
University of Antwerpen
Universiteitsplein 1
B-2610 Antwerpen, Belgium

Tel +32 (0)3 820 25 23 Fax +32 (0)3 820 26 40
E-mail: emmy.engelen@ua.ac.be

<http://www.vhpb.org>