



# VIRAL HEPATITIS

PUBLISHED BY THE VIRAL HEPATITIS PREVENTION BOARD (VHPB)

December 2003  
Volume 12 - Number 1

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## EDITORIAL

This issue of *Viral Hepatitis* examines vaccine safety issues, based on conclusions that were reached during the Viral Hepatitis Prevention Board (VHPB) meeting, held March 13-14, 2003, in Geneva, Switzerland.

In this issue, we review (1) the safety profile of the hepatitis B vaccine; (2) the impact of safety issues on national and international immunisation programmes; and (3) various strategies to help develop a policy that takes anti-vaccination movements and vaccine 'scares' into consideration.

### Immunisation programmes - then and now

Among the various international disease eradication programmes that were launched during the 20th century, the only programme that has been successful so far has been vaccine-based - the eradication of smallpox. Global elimination of polio could be a second possible achievement within the next decade [1]. Fifty to sixty years ago, when most communities in industrialised countries were faced with the devastating impact of polio disease on childhood populations, massive immunisation campaigns were put into place with the full support and gratitude from the general public.

More recently, as vaccine-preventable diseases have begun to disappear as a result of successful vaccination programmes, there is increasing focus on vaccine safety issues. Today, one of the greatest risks to public health is the erosion of public confidence in vaccination. With decreasing disease incidence, unsubstantiated allegations concerning the hepatitis B and measles-mumps-rubella (MMR) vaccines threaten to jeopardise well-established immunisation programmes, resulting in lower vaccination coverage and outbreaks of diseases - in some cases at near-epidemic level - that were previously under control.

While an overwhelming body of scientific evidence supports the overall safety and benefits of hepatitis B vaccine, there remains a clear need to convey this evidence to the general public through clear, consistent and powerful messages in readily understood language.

Recognising the need to enhance vaccine safety communication strategies, the VHPB calls for pooling the resources of local, national, and international bodies, in partnership with the vaccine industry. Just as crucial is the need for active promotion and personal recommendation for vaccination by health care practitioners at local level, and fostering relationships with the media based on mutual trust, respect, and support.

The VHPB also recognises the need for transparency in communicating the outcome of scientific investigations into vaccine safety issues, and remains committed to playing a role in disseminating the results of such studies to a wide audience including the scientific community and the general public.

*Peter Grob and André Meheus,  
on behalf of the Viral Hepatitis Prevention Board*

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This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on **Hepatitis B vaccination: safety issues**. Geneva, Switzerland. March 13-14, 2003.

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## Hepatitis B vaccination: safety issues - a VHPB Symposium Report - Geneva, Switzerland, March 13-14, 2003

### Multiple sclerosis: state of the art

Hepatitis B vaccine has been administered to over 20 million persons in France during recent years. The issue of a possible association between hepatitis B vaccination and development of multiple sclerosis (MS) was first raised in France following thirty-five 'demyelinating events' that were reported between 1991 and 1997 at a hospital in Paris. In 1998, French authorities temporarily suspended school-based adolescent hepatitis B vaccination but, recognising the benefits of the vaccine, continued to support universal infant hepatitis B immunisation programmes, as well as adolescent vaccination through primary care physicians. The vaccine also continued to be recommended for at-risk adults. At that time, the hypothetical risk of demyelinating disease resulting from hepatitis B vaccination was not statistically significant.

Three hypotheses emerged regarding demyelinating disease following hepatitis B vaccination:

- Coincidence based on the high levels of hepatitis B vaccine coverage, particularly among individuals in age groups where MS first occurs;
- Triggering effect from hepatitis B vaccine that would increase the risk of demyelination in individuals predisposed to developing MS or other central nervous system demyelinating disease;
- True causal association between hepatitis B vaccination and MS or other demyelinating disease.

French post-marketing surveillance data (as of 31 December 2000) showed the following:

- More than 700 cases of central nervous system demyelinating diseases closely matching the natural epidemiological distribution of MS in France;
- A time delay between the last dose of hepatitis B vaccine and onset of neurological symptoms of 1 day to 5 years (median: 60 days);
- No cases reported among children < 25 months despite hepatitis B vaccination of 1.8 million babies.

Nine epidemiological studies were carried out between 1986 and 1999 to assess the risk (if any) of a possible association between hepatitis B vaccination and onset or relapse of MS. None of the initial studies showed a statistically significant increase in risk.

#### Hepatitis B vaccination, MS, and the first occurrence of CNS-demyelinating diseases (FCDD) - Summary of studies conducted - [1]

Study	Year	Cases	Controls	OR	CI 95%
FCDD (case-control) [2]	1997	121	121	1.7 (2 m) 1.5 (2-6 m)	0.5-6.3 0.5-5.3
FCDD (case-control) [3]	1998	236	355	1.4 (2 m) 1.8 (2 m) (all subjects)	0.4-4.5 0.7-4.6
MS & FCDD (case-control) [4]	1998	481	2388	1.4 (2 m) 1.5 (12 m)	0.8-2.4 0.6-3.9
MS relapse (self-controlled) [5]	1997-98	24 (before/after)	0.8 (RR)	-	
MS relapse (case crossover) [6]	1998-99	643	<sup>a</sup>	0.7 (m)	0.2-2.2
MS (retrospective cohort) [7]	1988-95	27,229 <sup>b</sup>	107,469 <sup>c</sup>	1.3 (2 m)	0.4-4.8
MS (ecological) [8]	1986-98	5/289,651	9/288,657	0.5 (RR)	
MS (nested case-control) [9]	1999	192	645	0.7 (RR, 24 m) 1.0 (RR, 24 m) (breast cancer controls)	0.3-1.7 0.3-4.2
MS and optic neuritis (case-control) [10]	1995-99	440	950	0.9 (any time) 0.8 (1 year)	0.6-1.5 0.4-1.8

<sup>a</sup> 42-month periods prior to relapse, case crossover

<sup>b</sup> Vaccinated

<sup>c</sup> Non-vaccinated

From among 976 potential studies on demyelinating disease following hepatitis B vaccination, 130 were retrieved in the Cochrane Collaboration database (<http://www.cochrane.org>) for detailed examination, and 23 included for review. Criteria for review were:

- Case definition and comparability of cases and controls (Newcastle-Ottawa Scale);
- Representativeness of exposed cohorts and comparability for cohort studies;
- Appropriateness of selection criteria and comparability of exposure for ecological and case cross-over studies.

Only a few of the studies could be combined. The conclusions were that no single or pooled studies revealed a statistically significant increased risk of demyelinating disease and that the data showed strong evidence against a link with hepatitis B vaccination.

### Conclusions

In June 2002, the Global Advisory Committee on Vaccine Safety (GACVS) ([http://www.who.int/vaccine\\_safety/en/](http://www.who.int/vaccine_safety/en/)) issued the following statement: 'The analysis of data from spontaneous reports and results of epidemiological studies do not support a causal relationship between MS and hepatitis B [vaccination]. The most likely explanation is a coincidence... There is no reason to suggest that the recommendations for universal infant and adolescent immunisation coverage with hepatitis B vaccine should change.' The Institute of Medicine (IOM) also concluded in 2002 that the evidence favoured rejection of a causal relationship between hepatitis B vaccine administered to adults and incident MS or MS relapse.

From a communications perspective, the hepatitis B vaccine crisis in France highlights the extent to which individuals may be influenced by information that is emotional, direct, and personal rather than by scientific data alone. Vaccine advocacy efforts should focus on communicating the risks of non-immunisation as compelling evidence for parents and other caregivers to prevent disease through immunisation.

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*Based on a presentation by Dr Philippe Duclos, Department of Vaccines and Biologicals, World Health Organization, Geneva, Switzerland.*

## Infant hepatitis B vaccination and childhood leukaemia

Four studies identified by the Global Advisory Committee on Vaccine Safety (GACVS) considering the potential association between vaccination and acute lymphoblastic leukaemia (ALL) [1] do not support the suggestion of increased risk of leukaemia following hepatitis B vaccination in children.

One additional study [2] suggesting a link between childhood leukaemia and hepatitis B vaccination was carried out among 334 children in the United States - the Northern California Childhood Leukemia Study (NCCLS). The NCCLS was based on data for incident cases of childhood leukaemia (all ages between zero and fourteen years) collected from major medical centres between 1995 and 1999, and a control group, randomly selected from the California birth registry, pair-matched according to date of birth, gender, race, ethnicity, and maternal county or residence at birth.

Eligibility criteria for the control group were:

- Residence in study area and no previous malignancy;
- < 15 years of age at time of diagnosis or for control;
- English-speaking or Spanish-speaking parent.

Parents or physicians provided copies of immunisation records, with the exact dates recorded for all vaccines. The immunisation data were censored on the dates of diagnoses.

Analysis was based on:

- 167 case-birth control pairs:
  - 137 acute lymphoblastic leukemia
  - 133 acute lymphoblastic leukemia with immunisation data
- Pearson's chi-square for demographic and socio-economic characteristics
- Conditional logistic regression to estimate odds ratios as the approximation of relative risk, adjusting for household income.

### Hepatitis B immunization and ALL, NCCLS

Hepatitis B vaccine	Number ALL-control pairs				Adjusted OR 95% CI
	+/+	+/-	-/+	-/-	
Ever	98	7	8	20	0.95 (0.34, 2.67)
≥ 3 doses	75	18	8	32	2.92 (1.18, 7.19)
3 doses in 1 <sup>st</sup> year	52	19	5	57	4.75 (1.67, 13.5)
3 doses in 1 <sup>st</sup> year and BW < 3500 g	14	8	0	13	incalculable

Results showed that:

- DTP, polio, and MMR vaccines are not associated with overall leukaemia or acute lymphoblastic leukaemia;
- 78% of cases and 79% of control group received at least one dose of hepatitis B vaccine:
  - Cases had received more doses than the controls
  - For each dose of hepatitis B vaccine the odds ratio was: (1) All leukaemia: 1.20 (0.89-1.62); (2) Acute lymphoblastic leukaemia: 1.31 (0.92-1.86)
- Adjusting for birth order or day care attendance did not change results.

### Conclusions

The authors of this study point out that the results should be interpreted with caution [2]. Some of the issues that this study raises are:

- The effect of the birth dose compared with later doses was not analysed. If the hypothesis is that the birth dose of hepatitis B vaccine causes childhood leukaemia, then a comparison of exposure to a birth dose among cases and controls is warranted to support that hypothesis. Exposure to subsequent doses could be controlled if the hypothesis is that a birth dose plus cumulative exposure is necessary to cause childhood leukaemia.
- Incompatibility between the findings and observed ecological trends. If the increased risk of leukaemia hypothesised in the study was real, then the national incidence rate of childhood leukaemia should have increased correspondingly, also taking the increased vaccination coverage into account (hepatitis B vaccination coverage with 3 doses for children aged 19-36 months increased from 8% in 1992 to 88% in 1999). The calculated incidence rate would then increase as follows:  $OR \times \text{increase in coverage} = 2.56 \times (88 - 8)\% = 2.05$  times. Yet the incidence rates for childhood leukaemia remained stable since the mid-1980s.
- Thiomersal-free vaccine was not accounted for or analysed.

- The control group was mainly from higher income families with the possibility of having been less likely to be vaccinated.
- The censoring of hepatitis B vaccine doses may suggest that during the prodromal period of ALL, the number of physicians visits was increased with possible vaccination carried out during these visits.
- Folate supplementation has been shown to have a weak association with ALL and may be a possible confounder in this study.
- Immunisation records were missing in some children; sources of vaccination data are not clearly identified; precise dates of vaccination according to the recommended index dates were not analysed and could be different between cases and controls.

GACVS concluded that the suggestion of an association between ALL and hepatitis B vaccine, based only on one study with small numbers, was not convincing. As the design of the study did not preclude a statistical bias, the results do not provide a convincing causal link. Further research is being carried out by the Centers for Disease Control and Prevention (CDC) in the United States using the Vaccine Data Link. However, at this time the issue does not indicate a need to change current immunisation recommendations.

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*Based on a presentation by Dr Hal Margolis, CDC, NCID, Division of Viral Hepatitis, Atlanta, Georgia, USA.*

## Vaccination and autoimmune diseases: what is the risk?

It is generally assumed that autoimmunity results from interactions between genetic traits and environmental factors, among which infection is the most likely cause [1]. Although the prevalence of autoimmune disease (AID) is quite low, in industrialised countries the incidence has increased during the last several years, affecting approximately five percent of the population [2].

Considering the high levels of vaccination coverage resulting from immunisation programmes worldwide, a coincidental temporal association between vaccination and the occurrence of autoimmune disease may be expected. However, no scientific data based on sound epidemiological studies and analyses support the existence of a causal link or triggering association between administration of hepatitis B vaccine and the onset of or the relapse of multiple sclerosis (MS) and other demyelinating diseases. In a case control study [3] that was carried out between 1988 and 1997, six paediatric vaccines were tested within four HMOs: DTP, DTPa, HepB, Hib, MMR, and varicella. The investigators concluded that there was no significant association between any of the recommended childhood vaccines and an increased risk of type 1 diabetes.

### Molecular mimicry

The biological plausibility of a causal link between hepatitis B vaccine and autoimmune disease is not supported by the concept of molecular mimicry. Molecular mimicry occurs when part of a molecule of a given protein closely resembles part of another totally different protein, yet is recognised by the host's immune system as

being similar to the antigenic determinants of the host itself. In order to establish a causal link between the hepatitis B vaccine and autoimmune disease based on molecular mimicry, there would need to be a homology between the hepatitis B surface antigen (HBsAg) and the human myelin protein. However, the hepatitis B vaccine containing that protein does not resemble any other human proteins. Furthermore, the aggregation of HBsAg that occurs during natural hepatitis B infection far outweighs that given with the vaccine, but does not raise the risk of multiple sclerosis [4].

### AID and infection

Infection may induce autoimmune disease through two mechanisms (antigen-specific or antigen non-specific) that can operate independently or together. However, in such cases, an individual will develop an autoimmune disease only if genetically predisposed to that specific condition, which can result in the activation of otherwise dormant autoreactive T cells. In T-cell epitope mimicry, the risk of vaccine-induced autoimmune disease is very low.

A vaccine to prevent an infection associated with autoimmune T-cell pathology would be relevant. Influenza type A virus contains a protein similar to human myelin basic protein. In some studies, influenza infection has been shown to induce exacerbations of relapsing multiple sclerosis in 33% of patients, within the following six weeks [5]. Well-controlled studies, however, have shown that the influenza vaccine does not trigger MS exacerbations but may actually prevent them by preventing primary influenza infection.



These study results are consistent with the lack of increase in disease activity after vaccination with Bacille Calmette-Guérin (BCG). This vaccine has been used as an immunomodulator in patients with relapsing-remitting multiple sclerosis. In a study [7] reported in *Neurology* no adverse effects were reported.

### Conclusions

In conclusion, it does not appear that commonly administered vaccines, such as those against hepatitis B, influenza, and tuberculosis, increase the risk of lapse in patients with multiple sclerosis. The risk of inducing autoimmune disease or triggering underlying autoimmune disease is generally low.

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*Based on a presentation by Dr Paul-Henri Lambert, Department of Pathology and WHO Collaborating Centre for Vaccinology, University of Geneva, Geneva, Switzerland.*

## Aluminium-containing vaccines and macrophagal myofasciitis (MMF): an update

The safety profile of aluminium adjuvants, used in 'human' vaccines for over seventy years in hundreds of millions of people of all age groups, is considered excellent, with reduced incidence and severity of local and systemic reactions following vaccination. Although aluminium-adjuvanted vaccines elicit a number of local reactions of varying degree (e.g., redness, itching) and low-grade fever, the aluminium component, Al(OH)<sub>3</sub> or AlPO<sub>4</sub>, has not been associated with serious adverse events.

In 1993, a new type of histological lesion of unknown origin was observed in a limited number of patients in France. These lesions were subsequently investigated through biopsies of the deltoid muscle following reports from patients with general systemic complaints (myalgia, fatigue, arthralgia, muscle weakness, fever, asthenia). The biopsies revealed the presence of a minute inflammatory focus of macrophages and associated necrosis, called macrophagic myofasciitis (MMF). The localised lesions were known to contain aluminium salts, and the location of the lesions also appeared to coincide with the usual injection site for vaccines in the deltoid muscle. In some cases the lesions persisted for up to eight years.

In order to investigate the suggestion that vaccination and localised symptoms may be associated with a multi-system disorder, the World Health Organization, on the advice of the Global Advisory Committee on Vaccine Safety (GACVS), initiated a broad consultation on this issue in September 1999. The GACVS met with scientists from the *Groupe d'études et de recherche sur les maladies musculaires acquises et dysimmunitaires* (GERMADD), representatives from the vaccine industry, the French Ministry of Health, and the *Agence française de sécurité sanitaire des produits de santé*.

The GACVS concluded from the data, opinions, and discussions presented, that there is no basis for concluding that aluminium-containing vaccines pose a serious health risk or justification for recommending a change in vaccination practices with aluminium-containing vaccines.

Currently, the number of observed cases of MMF is very small, and data concerning the prevalence of MMF lesions in the healthy population are lacking. The generalised symptoms that brought MMF patients to the attention of the medical community are very common. The large variation in the time that elapsed between the administration of the vaccine and the onset of symptoms pleads against a causal link. Epidemiological studies to investigate further a possible association between aluminium-containing vaccines and MMF and general systemic complaints are being conducted.

The conclusions of a recently performed case-control study noted the absence of specific clinical symptoms in individuals with a deltoid biopsy showing an MMF lesion. This adds further evidence in ruling out the initial hypothesis that aluminium-containing vaccines may induce disease.

At present, there are no data that would justify a 'scare.' However, there are reasons for concern at other levels:

- The MMF 'scare' was inspired by the hepatitis B vaccination multiple sclerosis controversy in France;
- Allegations have the potential for affecting public confidence in vaccines and vaccination.

The communication aspects of this issue are challenging. The public should be made aware that MMF is caused by vaccination, but that the lesions are not linked to the generalised clinical symptoms.

*Based on a presentation by Dr Claire-Anne Siegrist, University of Geneva, Geneva, Switzerland.*

## Thiomersal-related changes in vaccination recommendations and hepatitis B vaccine coverage among United States children

Thiomersal, also known as thimerosal, contains small amounts of ethyl mercury, and is used as a preservative in vaccines. Up until 1999, thiomersal was used in the United States in hepatitis B vaccine, and some DTPa (diphtheria-tetanus-acellular pertussis), Hib (*Haemophilus influenzae* type b), and influenza vaccines. In 1999, the US Food and Drug Administration (FDA) reviewed the thiomersal issue and concluded that for some infants mercury exposure from thiomersal-containing vaccines exceeded FDA limits. However, the levels of exposure did not exceed the guidelines issued by the Environmental Protection Agency (EPA), the Agency for Toxic Substances and Disease Registry (ATSDR), or the World Health Organization (WHO).

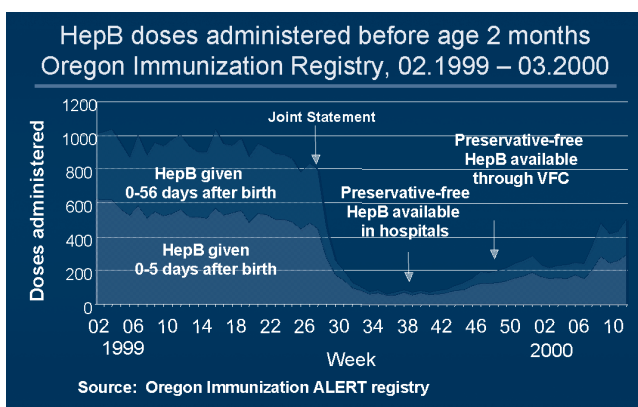
Following discussions in June 1999, representatives from the Centers for Disease Control and Prevention (CDC), FDA, and the American Academy of Pediatrics (AAP), concluded that no health effects from mercury in vaccines were identified. Nevertheless, a joint statement on thiomersal in vaccines was issued in July 1999 by the AAP and the Public Health Service to defer vaccination of infants born to HBsAg-negative women until 2 to 6 months of age. In September 1999, the distribution of thiomersal-free hepatitis B vaccine began, and about one year later, in December 2000, a sufficient supply of preservative-free hepatitis B vaccine was available for all US newborns.

Since 1994, the US has been carrying out a National Immunization Survey, the largest ongoing telephone survey in the United States, and the standard for assessing national vaccine coverage. The survey is conducted through thirty-four thousand telephone interviews carried out every year, and focuses on vaccination verification of children nineteen to thirty-five months of age. Following the changes in hepatitis B vaccine recommendations, the survey sought to determine hepatitis B coverage (birth-dose and 3-dose coverage) among children born before, during, and after the changes in recommendations, and to compare those changes in coverage with other paediatric vaccines.

Following the hepatitis B vaccine thiomersal crisis in the United States, the National Immunization Survey results saw an overall 10 % drop nation-wide in hepatitis B birth dose, from 55% in 1998 to 45% in 2001. For infants (born between February 1998 and May 2000) represented in the 2001 survey, the results show that:

- The birth dose of hepatitis B vaccine and the 3-dose coverage decreased significantly after thiomersal-related recommendations;
- Hepatitis B vaccine birth dose and 3-dose vaccine coverage remained lower than baseline even after preservative-free vaccine was made available;
- Vaccine coverage for other infant vaccines was not reduced after thiomersal recommendations;
- Reductions in birth dose coverage may have led to reductions in 3-dose coverage at 19 months.

From data reflecting immunisation registries for Oregon, the birth dose dropped dramatically:



Other effects of the thiomersal recommendations included infants who were born to mothers with unknown HBsAg status. In Oregon, from among 308 mothers, 147 (49%) were discharged from hospital with no known HBsAg status. Following deferment of the hepatitis B birth dose, hundreds of medical errors were reported in hospital procedures that should have been followed according to basic standards for preventing perinatal and early childhood HBV infection.

In 2001, the US Institute of Medicine (IOM) issued a safety review of thiomersal-containing vaccines and neurodevelopmental disorders. According to the statement, biological plausibility had not been established, and the association rests on '...indirect and incomplete information, primarily from analogies with methyl mercury and levels of maximum mercury exposure given children in vaccines.' In terms of causality, the IOM concluded that '...the evidence is inadequate to accept or reject a causal relationship between exposure to thiomersal from vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder (ADHD), and speech or language delay.' In its significance assessment, the IOM stated that:

- The diseases prevented by the vaccines under discussion are serious and important.
- Understanding the risks of thiomersal is important because of the need for its continued use.
- Many countries still depend on the use of thiomersal in multi-dose vaccine supply.
- Lessons can be learnt from the decision-making process surrounding policy changes for hepatitis B immunisation.
- Concerns about adverse events from thiomersal have the potential to erode the trust in immunisation.

### Conclusions

Changes in vaccination recommendations should be accompanied by effective communication messages. Considering the risks of childhood hepatitis B virus infection, decision-makers need to take into account evidence-based policies when considering changes in immunisation recommendations. Communication about immunisation policy changes must be consistent and issued from organisations that are considered to be the main sources of information for practitioners that immunise children.

Based on a presentation by Dr Hal Margolis, CDC, NCID, Division of Viral Hepatitis, Atlanta, Georgia, USA.

## New communication issues around immunisation

A rapidly changing global environment has led to basic changes in perception of immunisation. For UNICEF, one of its concerns is the divide between industrialised, transitional-economy, and developing countries, and their degree of access to vaccines, basic health care and evidence-based information. UNICEF supplies vaccines for over 40% of the world's children, delivering over 2.8 billion vaccine doses to more than one hundred countries in 2001. However, this represents only 5% of the world's expenditures on vaccines. While the value of the vaccine market has doubled, the value of basic vaccines has dropped by forty percent.

One of the issues is whether countries in transition should be procuring European-manufactured vaccines or vaccines manufactured in developing countries. This divide has led to increasing questions on vaccine quality that, in turn, raises questions regarding the level of trust in vaccines from developing countries.

Other global issues concern the perception of vaccines and vaccination in the absence of disease. As successful immunisation programmes have led to less visible disease threats, the misconception arises that vaccination is no longer needed once vaccine-preventable diseases have disappeared from a community. In a society that has become increasingly engaged in issues concerning product safety, public concern focuses increasingly on vaccine adverse events rather than on prevention and control of communicable diseases.

Locally isolated adverse events become national or international media events, with allegations concerning vaccine safety that can lead to lower coverage and subsequent disease outbreaks.

Biological threats present new challenges to public health organisations, governments, and the vaccine industry in dealing with issues such as smallpox, possible pandemics, and new biological agents for which no vaccines or treatments are available.

Enhancing the perception of vaccines as every child's right and as a public good can be achieved by focusing on the benefits of vaccination rather than on the risks. New communication challenges will require repositioning the value of vaccination as an investment for public health rather than expenditure. Re-branding immunisation for today's global environment and for the future will require a need to view vaccines in a broader context, taking into account national and global security needs. Creating a positive environment for vaccines and vaccination will help prepare for crises and lessen their negative impact, especially if supported by consistent guidance issued from international and national health authorities, and the vaccine industry.

*Based on a presentation by Dr Heidi Larson, UNICEF, New York, New York, USA.*

## International impact of vaccine safety concerns

Vaccine 'scares,' often local in origin, can leave a legacy of doubt, anxiety, and mistrust in the value of vaccination, regardless of the outcome of scientific investigations into the purported allegations. Managing vaccine crises by limiting their short-term and long-term damage to local, national, and international immunisation programmes requires new approaches on the part of the scientific community, governments, and industry in dealing with anti-vaccination sentiment and, very often, a confused general public.

Anti-vaccination groups and their sympathisers are extremely diverse in their views and motives for supporting their cause, representing:

- Parents with legitimate concerns over vaccine safety issues;
- Individuals with religious or philosophical objections to vaccination;
- Adherents to 'natural' or alternative medicine to prevent disease;
- Individuals convinced of conspiracy theories to cast doubt on the benefits of immunisation;
- Individuals opposed to government intervention in personal health issues;
- Lawyers and other individuals with financial or political agendas;
- Scientists reporting hypotheses to the media;
- Opinionated media, equivalent to irresponsible journalism.

### Injection safety

Real issues, such as unsafe injection practices, may arouse little interest within the media. With approximately 16 billion injections administered worldwide each year, approximately 33% of injections in developing countries are unsafe, contributing yearly to approximately 20 million HBV infections, 2 million HCV infections, and 260,000 HIV infections.

The Safe Injection Global Network (SIGN) and GAVI are now contributing to promoting safer injection practices in developing

countries. Fund-eligible countries are now receiving auto-disposable syringes for a three-year period, with 200 million already having been distributed.

### Considerations

- No vaccine is 100% effective;
- All vaccines may have some side effects;
- The decision to use or not use a vaccine must be based on the balance between benefit and risk together with cost-effectiveness;
- Disease burden before immunisation should be taken into account;
- Acknowledge known risks of a vaccine;
- Benefit / risk ratio hugely favours vaccines;
- Diseases return when immunisation stops;
- Surveillance systems for adverse events work and can identify rare events;
- Research is carried out to investigate hypotheses of safety issues;
- When safety concerns are found to be valid, vaccines are removed or changed;
- There are many chronic diseases of unknown aetiology where vaccines may be only one of many possible causes;
- Immunisation programmes should not stop while each hypothesis is investigated;
- Communicate reliable vaccine information sources.

Preparing for vaccine crises, and managing them effectively when they occur require familiarity and complete understanding of the issues at hand, expertise in dealing with the media, and requesting help in investigating incidents from individuals and local experts familiar with the environment and infrastructure.

*Based on a presentation by Dr Mark Kane, Children's Vaccine Program at PATH (Program for Appropriate Technology in Health), Seattle, Washington, USA.*

## COUNTRY REPORTS

### Impact of safety issues in France

#### Hepatitis B immunisation policy

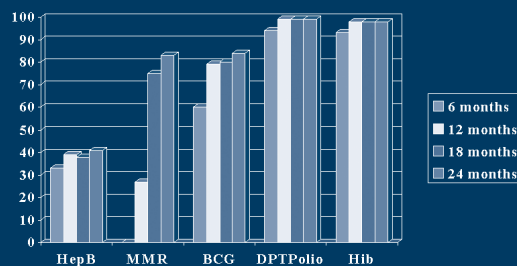
National recommendations for hepatitis B immunisation in France initially focused on targeted vaccination of risk groups. From 1994 to 1998, the policy was extended to include vaccination of infants, and children aged ten to twelve years, with boosters for children eleven to thirteen years of age who had been immunised during infancy. Since 1998, hepatitis B immunisation policy has been based on:

- Vaccination of infants with a 3-dose schedule;
- Vaccination of children aged eleven to thirteen years of age with a 3-dose schedule;
- Clear definition of risk groups, using a 3-dose schedule;
- No boosters after 3 doses except, in some cases, for health care workers and other special groups.

In October 1998, following allegations of an association between hepatitis B vaccine and multiple sclerosis (MS), the French authorities temporarily suspended school-based adolescent hepatitis B immunisation programmes. Recognising the benefits of the vaccine, the authorities continued to support France's universal infant immunisation programmes and adolescent vaccination through primary care physicians. They also continued to recommend vaccination for adults at increased risk. Although data do not support a causal relationship between hepatitis B vaccine and MS, hepatitis B immunisation rates dropped dramatically and have not recovered to their previous higher levels. These rates continue to remain less than satisfactory, with coverage ranging between 25% and 40% among children up to twenty-four months of age. Comparative figures of vaccination coverage levels in France for hepatitis B vaccine, MMR, BCG, DTPolio, and Hib are shown below:

### Vaccination coverage between 6 and 24 months

(through a survey in 2001 on 6779 children)



Gaudelus *et al.* Arch Fr Pediatr, submitted 2003

National measures for 2002-2005 against hepatitis B will include assessment of different strategies for hepatitis B vaccination that focus on:

- Risk groups;
- Reintroduction of compulsory immunisation for health care workers;
- Providing information to private health care workers;
- Providing information to those at occupational risk;
- Assessing various conditions for implementing the recommended strategies.

One measure that is expected to help increase hepatitis B immunisation is the use of hexavalent vaccines for infants that are recommended but not yet (2003) on the market.

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

### Impact of safety issues in Israel

The overall compliance rate for all vaccines in Israel's infant immunisation schedule, including hepatitis B vaccine, is 95%.

#### Infant immunisation schedule - Israel\*

	HBV	DTP	Polio	Hib	MMR	HAV
Day 1, month 1	+					
Month 2		+	+ inj.	+		
Month 4		+	+0, inj.	+		
Month 6	+	+	+0	+		
Month 12		+	+0, inj.	+	+	
Months 18 + 24						+
6 years			+0, inj.		+	
7 years		+				
14 years		+	+0			

\* 95% compliance

Adverse events following hepatitis B immunisation are rarely seen in Israel. In an eleven-year period, with over four million hepatitis B vaccine doses administered, there have been only seventy-three adverse events reported, most of them mild and local. Fifteen of

these reported adverse events were described as anaphylactoid reactions or 'fainting,' but none of them was considered to be true anaphylaxis or any other life-threatening event. In the last thirty years, there has been only one case of litigation concerning hepatitis B vaccine.

A national compensation law has been in place in Israel since 1989 for vaccinees that experienced adverse events. The law stipulates that compensation would be awarded on the basis that the vaccine had been administered according to medical / legal requirements. However, approval of monetary compensation in lawsuits sometimes depends on the quality of legal advice plaintiffs may receive. This situation has implications for persons who, because of financial reasons, may not have access to costly legal services. In order to help rectify this situation, Israel is currently trying to establish a programme to provide State legal aid to assist people who are unable to afford legal services.

Some of the reasons for delaying or refusing vaccination in Israel include negligence of parents, use of alternative medicine, and religious / ideological grounds. Adverse events are not considered a major factor in delaying or refusing vaccination, and the numbers citing such events are small.

Israel's high uptake rates are evidence to its success in reducing vaccine-preventable diseases.

Based on a presentation by Dr Daniel Shouval, Liver Unit, Hadassah Hebrew University Hospital, Jerusalem, Israel.



## Impact of safety issues in Germany

### Hepatitis B immunisation policy

Selective hepatitis B immunisation was introduced in Germany in 1982, targeting risk groups such as health care workers, injecting drug users, among others. Universal infant and adolescent vaccination against hepatitis B have been recommended in Germany since 1995.

### Perception of vaccines and vaccination

Vaccine safety issues in Germany are not of major concern either to health care professionals or to the general public. Neither the thiomersal nor the MMR vaccine issues resulted in lower coverage levels. In 1998, following the temporary suspension of school-based adolescent hepatitis B immunisation in France, there was some negative spillover into the border regions with Germany. However, this resulted in a very slight, short-term drop in local coverage, and did not have a negative impact on other geographical areas in Germany. The *Paul-Ehrlich-Institut* and the European Agency for the Evaluation of Medicinal Products (EMA) both issued press releases stating that they had no toxicological concerns with the hepatitis B vaccine - statements that helped to counter potential negative impact on hepatitis B coverage rates in Germany.

### Management, assessment and evaluation of adverse events following vaccination

Legal requirements for managing adverse events following

vaccination are mandated by German Federal law under the *Infektionsschutzgesetz* (Protection against Infection Act), which went into force on 1 January 2001. The law provides for a case definition of adverse events following vaccination. All physicians are obliged to report suspected cases of adverse events following vaccination to the local public health office, which are then sent to the *Paul-Ehrlich-Institut*, responsible for the administration and licensing of sera and vaccines.

The assessment of reported adverse events is based on probability of cause, using various criteria such as timely plausible relationship, causal relationship, known reactions, drug anamneses, de-challenge and re-challenge.

Evaluation of an adverse event is based on WHO criteria, such as certain, probable / likely, possible, unlikely, conditional / unclassified, and unassessable / unclassifiable.

Germany also has a vaccine injury compensation programme that is financed by each of the Federal States (*Länder*).

There is wide acceptance of infant hepatitis B vaccination with the recently licensed hexavalent vaccines. There is a high uptake of these new vaccines by paediatricians in Germany, with fewer injections and office visits as the main advantages for parents.

*Based on a presentation by Dr Johannes Hallauer, Health Systems Research, University Clinic Charité, Berlin, Germany.*

## Impact of safety issues in Scotland

In 1991, the World Health Organization recommended that all countries adopt universal hepatitis B vaccination regardless of the national level of prevalence of infection [1]. The United Kingdom (UK) is one of the few countries in Europe where universal hepatitis B immunisation has not been implemented. Current UK policy of selective hepatitis B immunisation of risk groups is based on the low incidence of hepatitis B. This policy is under review by the UK Joint Committee on Vaccination and Immunisation (JCVI).

A pilot study [2] was carried out in Scotland, where hepatitis B vaccine was offered to all eleven- to twelve-year old pupils in Greater Glasgow in order to assess the feasibility of introducing universal hepatitis B immunisation. The study comprised 10,832 pupils; consent to participate was received from 92% of the school roll. This study represents the first assessment in the UK of the practicalities and acceptability of universal adolescent hepatitis B immunisation in the school system. Glasgow has one of the highest levels of injecting drug use and deprivation in Europe, with considerable religious and ethnic diversity.

Pupils, parents, teachers, school nurses, as well as Members of the Scottish Parliament received health education material via press releases, information leaflets, a telephone helpline, and a website. Through focus group discussions, the study sought to examine knowledge and attitudes of pupils and their parents regarding:

- Perceptions of acceptability and attitudes to hepatitis B vaccine;
- Factors that could influence uptake;
- Reasons for participation and non-participation in the pilot study.

After obtaining written informed consent from pupils and parents, hepatitis B vaccine was administered by the School Health Services using a three-phase, 0-, 1- and 7-month schedule.

Vaccine uptake was as follows:

- 91.2% - at least 1 dose
- 89.2% - at least 2 doses
- 80.1% - at least 3 doses

Serious adverse events were recorded during the second and third visits. However, no serious adverse events that were detected could be definitely related to vaccination.

The high uptake reflects the fact that neither pupils, parents, the media, nor politicians had major safety concerns regarding hepatitis B immunisation. This is remarkable in light of a UK vaccination climate that is extremely sensitive to vaccine safety allegations, particularly those regarding MMR vaccine, thiomersal-containing vaccines, and acellular and whole-cell pertussis vaccines.

### Summary and conclusions

- Proactive and objective health education and vaccine-related materials can help to achieve high uptake of hepatitis B vaccine in young UK adolescents;
- Hepatitis B vaccination uptake is similar to uptake of other routine school vaccinations;
- Hepatitis B vaccine has a good safety profile with no significant safety concerns.

### References

- [1] World Health Organization. Expanded Programme on Immunisation - Global Advisory Group Part I. *Wkly Epidemiol Rec* 1992; 67:11-15.
- [2] Bramley JC, Wallace LA, Ahmed S *et al*. Universal hepatitis B vaccination of UK adolescents: a feasibility and acceptability study. *Commun Dis Public Health* 2002; 5:318-320.

*Based on a presentation by Dr Claire Bramley, Scottish Centre for Infection and Environmental Health, Glasgow, Scotland, UK.*

## The Global Advisory Committee on Vaccine Safety and its communication strategy

The Global Vaccine Advisory Committee on Vaccine Safety (GACVS) ([http://www.who.int/vaccine\\_safety/en/](http://www.who.int/vaccine_safety/en/)) was set up in 1999 by the World Health Organization (WHO) to provide reliable and independent assessment of vaccine safety issues. The Advisory Committee comprises experts from a wide range of disciplines, such as epidemiology, internal medicine, paediatrics, infectious diseases, public health, immunology, among others, and operates under strict rules protecting confidentiality and prohibiting conflict of interest. Meeting twice each year, its primary objectives are:

- To respond promptly, efficiently, independently, and with scientific rigour to vaccine safety issues of global or national importance;
- To review the latest scientific knowledge relevant to vaccine safety issues in collaboration with all parties involved, including experts from national authorities, academia, and industry;
- To identify possible causal relationships between vaccines and adverse events;
- To set up ad hoc expert teams to monitor and evaluate major concerns associated with vaccines and to commission research relevant to purported associations; and
- To decide which vaccine safety issues should be reviewed.

As vaccine-preventable diseases begin to disappear, thanks to mass immunisation programmes, many communities have no knowledge of diseases such as measles, diphtheria, and poliomyelitis, among others. Some recent (unsubstantiated) vaccine safety scares that emerged during the last several years have had a negative impact on vaccine coverage. The measles-mumps-rubella (MMR) vaccine and its alleged association with autism and inflammatory bowel disease has led to an upsurge of measles cases in the United Kingdom and Ireland, nearly reaching epidemic proportions in some

areas. Similarly, in 1998 in France a hepatitis B vaccine scare purportedly linking the vaccine with multiple sclerosis (MS) has contributed to lower hepatitis B vaccine coverage resulting in a large cohort of adolescents who may be unprotected by the vaccine. In June 2002, the GACVS concluded that spontaneous reports and results of epidemiological studies do not support a causal relationship between hepatitis B vaccine and MS, and that there is no reason to suggest that recommendations for universal infant and adolescent immunisation coverage with hepatitis B vaccine should change.

Other vaccine safety issues that the GACVS have assessed include macrophagic myofasciitis (MMF), thiomersal, immunisation and autoimmune diseases, among others.

In order to deal with rumours that can damage the effectiveness of immunisation efforts, scientific data and strong international collaboration will be needed to counter negative perceptions of vaccines. Improvements in communication should consist of:

- Consistent messages delivered by key authorities;
- Credible scientific data that are readily accessible when crises occur;
- Independent international reviews of issues and dissemination of authoritative statements issued by neutral organisations;
- Direct, proactive, and clear communications reflecting consensus among authorities and stakeholders prior to issuing public statements.

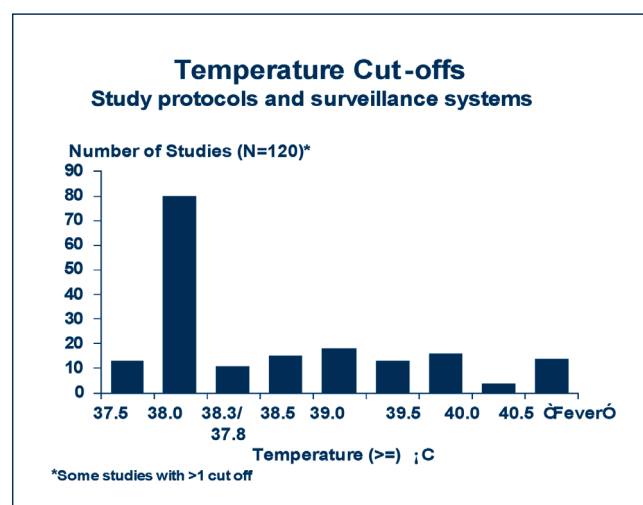
*Based on a presentation by Dr Philippe Duclos, Department of Vaccines and Biologicals, World Health Organization, Geneva, Switzerland.*

## The Brighton Collaboration: comparability of vaccine safety data

The Brighton Collaboration is an independent international voluntary collaboration aiming to facilitate the development, evaluation, and dissemination of high quality information about the safety of human vaccines. The Collaboration was officially launched in autumn 2000, and currently includes about 500 researchers and other professionals from vaccine safety, public health, pharmaceutical, and regulatory agencies involved in addressing the problems of information quality on vaccine safety. The Collaboration's first task is the development of standardised case definitions for adverse events following immunisation (AEFI) together with guidelines for collection, analysis, and presentation of vaccine safety data [1].

The Brighton Collaboration considers that standardised case definitions of AEFI are a key element for scientific assessment of immunisation safety as they provide a common 'vocabulary' and understanding of AEFI and thus allow for comparability of data from clinical trials and surveillance. The demonstration of the current variability of case definitions included the spectrum of temperature cut-off values used to define fever in 120 study protocols and surveillance systems as shown in the figure [2].

Brighton Collaboration definitions and guidelines are developed in a four-step process: (a) Systematic search of existing case definitions and guidelines; (b) Development of draft definitions and guidelines in AEFI Working Groups; (c) Review and evaluation



of drafts by a wide Reference Group comprising organisations concerned with vaccine safety; (d) Finalisation and dissemination via the Brighton Collaboration website (<http://brightoncollaboration.org>) and other channels for worldwide use free of charge.

The first six AEFI definitions developed by the Collaboration are (1) fever; (2) local reactions; (3) intussusception; (4) persistent crying; (5) generalised convulsive seizure; (6) hypotonic - hyporesponsive episode [3].

The Collaboration aims to expand its global network of experts concerned with immunisation safety, and to facilitate decision-making by sharing its knowledge with health professionals, vaccine providers, and vaccine recipients.

## References

- [1] Bonhöffer J, Kohl K, Chen R *et al.* The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). *Vaccine* 2002; 21:298-302.
- [2] Kohl KS, Bonhöffer J, Chen RT *et al.* The Brighton Collaboration: enhancing comparability of vaccine safety data. ISPE Commentary. *Pharmacoepidemiol Drug Saf* 2003; 12:1-6.
- [3] Definitions are available at: <http://brightoncollaboration.org/en/index/aeafi.html>

*Based on a presentation by Dr Jan Bonhöffer, Brighton Collaboration and University Children's Hospital, Basel, Switzerland.*

## Communication: the industry perspective

The hepatitis B vaccine crisis that occurred during the 1990s has been the most serious crisis for vaccine manufacturers in Europe. Major changes in the risk environment of vaccinology during that time had a profound impact on the vaccine industry's management of risk assessment and communication. One of the major pitfalls that occurred during this time was the industry's slow response to the crisis, based in part on the lack of a well-defined strategy in dealing with the management of scientific communication to the media and the lay public. An overall lack of consistency in messages issued by industry as well as by health authorities, may have contributed to lower levels of trust and confidence, and of the credibility of the vaccine industry.

### Understanding the environment

The years 1996 through 1999 may be considered a learning period during which the industry and other stakeholders recognised the need to re-evaluate their communication strategies in an environment increasingly focused on safety issues and adverse events. Since then, the traditional interplay among health authorities, scientific media, patients, health professionals, and industry has become more complex. New players - the lay media, patient action groups, the legal profession, and the Internet - have the potential to influence public perception of vaccination as a risk rather than a benefit, resulting in lower vaccination coverage and increased rates of infection.

### Risk assessment and managing crises

Some of the common features that characterise a vaccine 'scare' are:

- Claims of a causal link between a vaccine and a disease or a condition whose aetiology is often unknown or unclear;
- Claims of an association made by one investigator or a small group of investigators;
- Claims of an association not confirmed by peers or subsequent research;
- Claims that are made with no apparent concern for potential harm from public loss of confidence and refusal to vaccinate children.

While each vaccine crisis is unique, the following precepts, based more on attitude rather than on procedure, can be applied in dealing with uncertainty during crises:

- Be proactive - do not wait to be confronted;
- Listen to all who are genuinely concerned - the general public, the media, and the scientific community;
- Say what is being done to reduce uncertainty;
- Admit and explain reasons for cautiousness;
- Acknowledge if you have been slow to respond to the issue.

External communication on vaccine safety relies as much on the lay press as on scientific media. Vaccine companies at local level have set up monitoring networks to alert local media of articles in the scientific press, thereby anticipating potential issues that could have an impact on public perception of vaccines. Development of key messages, position papers, fact sheets, and other related tools, are major tasks for vaccine company communication departments, which are made up of multi-disciplinary teams and media-trained spokespersons.

### Vaccine advocacy

Vaccine advocacy is carried out at company level through internal stakeholders, as well as through partnerships with health authorities and expert groups (e.g., CDC, WHO, VHPB, among others), and through national and European vaccine industry associations. The European Vaccine Manufacturers (EVM) work closely together with EU authorities and other stakeholders on a wide range of vaccine-related issues. The EVM website ([www.evm-vaccines.org](http://www.evm-vaccines.org)) provides information on twenty-four vaccine-preventable diseases, and EU legislation having an impact on the European vaccine industry. EVM also publishes a quarterly newsletter and information sheets dealing with issues of current concern (e.g., influenza pandemic preparedness, biological threats, and vaccine safety, among others).

### Vaccine development

The impact of safety issues on vaccine development has resulted in:

- Extensive pre-licensure safety studies;
- Post-licensure pharmaco-epidemiological studies;
- Epidemiological surveillance, including vaccine and disease registries;
- Overall increase in costs for vaccine development and compliance.

### Conclusions - the way forward

- Industry and third parties in the vaccine community need to build and maintain partnerships at many levels - regional, national, and international.
- Post-marketing surveillance systems need to be set up to identify: (1) disease epidemiology; (2) disease burden; (3) adverse events.
- Industry must be more proactive in communicating and adapting information and key messages to different types of audiences.
- Trust is a key component in building support with the community and media on vaccine safety issues.

*Based on a presentation by Dr Luc Hessel, Aventis Pasteur MSD, Lyon, France, prepared in collaboration with Dr Hugues Bogaerts, GlaxoSmithKline Biologicals, Rixensart, Belgium.*

## Immunization Action Coalition / Hepatitis B Coalition

The Immunization Action Coalition (IAC) was founded in Minnesota in 1990 as a grassroots coalition to prevent hepatitis B in refugee children. IAC has expanded its activities and now publishes information on all vaccine-preventable diseases and vaccines for children and adults. Funding sources include the CDC, vaccine companies, foundations, professional organizations, and the public.

### IAC's main aim is prevention of disease by:

- Keeping health professionals informed about current vaccine recommendations;
- Providing information about technical aspects of vaccine delivery, print materials;
- Providing materials to the public;
- Involvement in vaccine policy discussions;
- Facilitating communication about the safety, efficacy, and use of vaccines.

### Electronic and print versions of the following publications are available from IAC:

- *NEEDLE TIPS* - targeted to health professionals who provide care to children and adults - [www.immunize.org/nt](http://www.immunize.org/nt)
- *VACCINATE ADULTS!* - targeted to health professionals who provide care to adult patients - [www.immunize.org/va](http://www.immunize.org/va)
- *VACCINATE WOMEN* - targeted to providers of health care in obstetrics and gynaecology - [www.immunize.org/vw](http://www.immunize.org/vw)
- *IAC EXPRESS* - weekly electronic immunisation news service - [www.immunize.org/express](http://www.immunize.org/express)
- *HEP EXPRESS* - electronic news service providing information on viral hepatitis sent every three weeks - [www.hepprograms.org/hepexpress](http://www.hepprograms.org/hepexpress)

### Vaccine and immunisation information is available on the following websites from IAC:

- [www.immunize.org](http://www.immunize.org) - provides vaccine information for health professionals
- [www.vaccineinformation.org](http://www.vaccineinformation.org) - provides vaccine information for the public and media
- [www.hepprograms.org](http://www.hepprograms.org) - presents a database of hepatitis prevention programmes

### For other links to the IAC website, see:

- Unprotected People - [www.immunize.org/stories](http://www.immunize.org/stories)
- Directory of Immunization Resources - [www.immunize.org/resources](http://www.immunize.org/resources)
- VISs (Vaccine Information Statements) - [www.immunize.org/vis](http://www.immunize.org/vis)
- Rules for Childhood Immunization - [www.immunize.org/childrules](http://www.immunize.org/childrules)
- Rules for Adult Immunization - [www.immunize.org/adultrules](http://www.immunize.org/adultrules)
- Photographs - [www.vaccineinformation.org](http://www.vaccineinformation.org)
- ACIP Statements - [www.immunize.org/acip](http://www.immunize.org/acip)
- AAP Statements - [www.immunize.org/aap](http://www.immunize.org/aap)
- Free Print Materials - [www.immunize.org/free](http://www.immunize.org/free)
- 'Immunization Techniques' video - [www.immunize.org/iztech](http://www.immunize.org/iztech)
- IAC Catalog - [www.immunize.org/catalog](http://www.immunize.org/catalog)
- Hepatitis B Birth Dose - [www.immunize.org/birthdose](http://www.immunize.org/birthdose)
- Vaccine Safety - [www.immunize.org/safety](http://www.immunize.org/safety)

Based on a presentation by Dr Deborah L. Wexler, Immunization Action Coalition, St. Paul, Minnesota, USA.

## Impact of litigation issues on hepatitis B vaccination

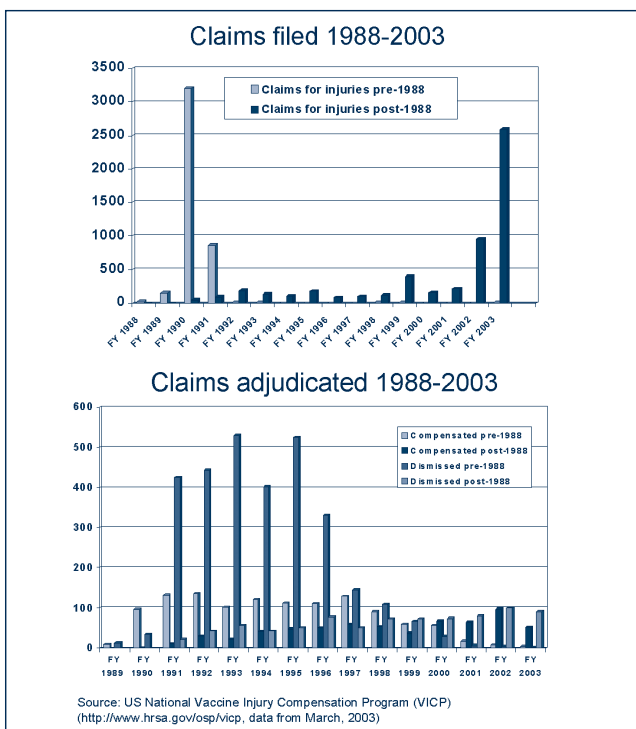
In many countries, compensation for injuries that result from medical malpractice is covered under liability law, and negligence needs to be proven. In vaccine injury claims, the situation is quite different in that negligence is often not an issue. Adverse events following immunisation may be unpredictable in certain individuals, and may result from products that were otherwise properly manufactured and administered

### United States

In the United States, the Vaccine Injury Compensation Program was established in 1986 under the National Childhood Vaccine Injury Act, and went into effect in October 1988. To qualify for compensation in the United States, the following criteria must be met:

- Must show that an injury listed on a 'Vaccine Injury Table' has occurred. This table is considered a 'presumption of causation'; however, compensation may not be awarded if the Court determines that the injury or death was due to an alternative cause unrelated to the vaccine;
- Proof that a vaccine significantly aggravated a pre-existing condition;
- Proof that the vaccine caused the condition;
- The injury must have lasted at least 6 months or resulted in hospitalisation and surgical intervention.

From over 7,000 vaccine injury claims filed in the United States between 1988 and 2003, less than one third qualified for compensation:





For hepatitis B vaccine injury claims in the United States, the only adverse event listed on the official Vaccine Injury Table is anaphylaxis and its sequelae. Other claims that require proof of causation have been filed but are currently under review or on hold.

### Canada

In Québec, Canada, a vaccine injury compensation programme was introduced under a new division of the Public Health Protection Act. The Regulations governing this programme were adopted in November 1987, and the first applications for compensation were filed in 1988. The legal process for filing a claim is based on the following:

- A claim must be made within 3 years following date of immunisation.
- There are no limitations on which vaccines are eligible for compensation.
- A medical evaluation committee, which reviews the application for compensation, is made up of three physicians
  - the first appointed by the Minister of Health, the second by the claimant, and the third by the first two physicians.
- The duties of the evaluation committee consist of:
  - Evaluating the case and the illness incurred;
  - Evaluating causation between the illness and the immunisation;
  - Evaluating compensation based on the public auto insurance plan.
- The evaluation must deal with and consider the following:
  - Clinical history, including a statement of relevant physical and mental ailments, intercurrent illness, and medical history;
  - A physical examination, particularly of the system affected by the immunisation.

Between 1997 and 2000, 117 vaccine injury claims were processed in Québec, of which 20 (17%) were compensated.

### Impact of litigation

During the 1990s, anti-vaccination groups continued to focus on issues regarding freedom of choice in vaccination and what they perceived as coercion by public health authorities regarding vaccination policies. The focus of these groups also shifted to vaccine injury claims related to chronic or ill-defined conditions where causative associations are difficult to establish since the underlying aetiology is not known or fully understood. The mass immunisation campaigns against measles that were being carried

out in Canada during the mid-1990s also provided a focal point for opposition by anti-vaccine activists in some communities.

In Canada, the province of Manitoba began a hepatitis B immunisation programme in November 1998. The timing of this campaign unfortunately coincided with France's suspension in October 1998 of school-based adolescent hepatitis B immunisation. Although parents in Manitoba had already submitted consent forms for their children's hepatitis B vaccination, opposition was mounted from anti-vaccine groups. Consequently, many parents actually reversed their consent, and the programme was only able to achieve 50% vaccine coverage, a figure which to date has not recovered to its previous level. Current estimates of immunisation coverage in the school-based programme is just over 70%, in contrast to coverage of over 90% in other provinces with similar programmes.

### Vaccination mandates

In the United States, there are no national immunisation laws, but State-based laws exist governing school immunisation requirements. The antigens that are covered by the requirements vary by State, as do the availability of exemptions. All State laws have exemptions for medical contra-indications to immunisation, and most have religious exemptions, but a minority also has philosophical exemptions - a figure that is increasing. In contrast, Canada has only three provinces with school entry immunisation requirements, covering only the basic antigens, and allows full philosophical exemptions.

While mandatory immunisation may not be needed or appropriate for all societies, school-age immunisation requirements can help protect children against vaccine-preventable diseases by ensuring against failure to vaccinate due to apathy or neglect (providing an opportunity to check the immunisation status of school-age children), and to provide information on the benefits of vaccination and risks of childhood diseases. Misconceptions about real and perceived vaccine safety issues still persist despite efforts to educate the public. However, rational vaccine injury compensation plans that are evidence-based, and rational verdicts in the case of litigation, can serve as opportunities to educate.

*Based on a presentation by Dr Robert Pless, Immunization and Respiratory Infections Division, Centre for Infectious Disease Prevention and Control, Health Canada, Canada.*

## Countering the anti-vaccination movement and 'scares' - working with the media

Recent UK media coverage of a controversial research report [1], hypothesising an association between MMR vaccine and autism and inflammatory bowel disease, has resulted in lowered coverage of MMR vaccination in the UK and Ireland, with some spill-over into other English-speaking countries such as Canada, Australia, and the United States. The alleged link between MMR vaccine and autism remains unsubstantiated and discredited by other researchers [2, 3], the Departments of Health in the UK and Ireland, the World Health Organization [4], and the Centers for Disease Control and Prevention in the United States [5], among others. The overwhelming scientific evidence for the overall safety of MMR vaccine has been reinforced through public health promotion campaigns, and comprehensive fact sheets distributed at physicians' surgeries and health clinics. Despite such reassurances, the MMR 'scare' has led to lowered levels of coverage and outbreaks of childhood measles that, in some areas of the UK and Ireland, are now at near-epidemic levels.

### Communicating with the media

Anti-vaccination lobbyists, often supported by the media, have been able to advance their agenda through vaccine crises, and have called for repeated televised debates on the MMR issue. Although there is now enough scientific evidence in support of MMR vaccine safety to declare the hypothesis dead, further debate with anti-vaccination proponents on a defunct issue may lend further credibility to their arguments in the mind of the general public.

Risk communication by the medical community may itself be a threat to vaccination if the use of language does not allow the general public to easily understand statements made by health authorities regarding risk and probability, and association and causality.

Medical experts using scientific arguments that are articulated in purely logical, rationalist language, may fail to convince an audience

that is more attuned and receptive to the emotional language of a mother who is sincerely convinced that her child's autism was caused by MMR vaccination. Vital as it is to have comprehensive and scientifically accurate information to counter vaccine 'scares' and fears, such support is limited unless it is communicated in a timely and appropriately straightforward, easily understood language. Responses must be on an appropriate level; for example, emotion cannot be countered by cold fact, an individual human tragedy cannot be met with scientific evidence.

Physicians and other medical professionals need to seek active media involvement in vaccine safety issues, and publicly acknowledge any reasonably firm new evidence of true adverse reactions if credibility is to be maintained. Active, positive collaboration with journalists, especially at local level, can help to build trust in local health care staff and spokespersons, particularly when actively encouraging and personally recommending vaccination as the best and safest way to protect the community.

## Conclusions of the meeting

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

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*Based on a presentation by Dr Robert Aston, Bolton, Lancashire, United Kingdom.*

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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The Viral Hepatitis Prevention Board (VHPB) is supported by grants from the pharmaceutical industry (GlaxoSmithKline Biologicals, Aventis Pasteur MSD, Merck Vaccine Division), several universities in Europe, and other institutions. The VHPB has strict operational and scientific independence. The VHPB Executive Secretariat also benefits from being located at the Department of Epidemiology and Social Medicine of the University of Antwerpen, Belgium, where it has the infrastructure and administrative services at its disposal.

*Viral Hepatitis* is produced and published by the VHPB – Scientific editor: Guido François; Editor and copywriter: Diana Steimle – Photogravure made by Ability Design, Antwerpen, Belgium. Printed by WILDA, Antwerpen, Belgium.

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