

SAFETY OF IMMUNIZATION AND ADVERSE EVENTS FOLLOWING VACCINATION AGAINST HEPATITIS B

Philippe DUCLOS, Immunization Safety Priority Project, Department of Vaccines and Biologicals Health Technology and Pharmaceuticals, World Health Organization, Geneva, Switzerland



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Background

Second only to tobacco as a recognized cause of a major cancer in humans, hepatitis B is preventable with safe and effective vaccines (State of the World's Vaccines and Immunization, 2002). In 2000, according to WHO estimates there were over 5.5 million cases of acute hepatitis B infection and over 520,000 deaths from hepatitis B-related diseases (470,000 from cirrhosis and liver cancer and 52,000 from acute hepatitis B infection).

Hepatitis B vaccines have been available since 1982 and way over 1 billion doses have been used. Considering the major public health burden of hepatitis B infections and the availability of safe and effective vaccines that could prevent most of this burden, in 1992, the World Health Assembly, recommended that hepatitis B vaccines be integrated into national immunization programs.

By the end of 2001, 142 countries were using hepatitis B vaccine in routine immunization schedules. The actual price of the vaccine has been a major deterrent to its introduction in many countries and has limited further use of the vaccine. The use of hepatitis B vaccine has resulted in dramatic reductions in the prevalence of the carrier state in many areas with a reduction in the carrier rate to less than 1% from levels of 15-20% (Kane, 1998; Kane, 1997). Data from Taiwan also show that hepatitis B vaccination reduces the incidence of liver cancer in children (Chang et al., 1997; Hsu et al, 1999).

Over the recent years, however, the safety of hepatitis B vaccine has repeatedly been under attack. A number of controversial adverse events have been purported to be associated with hepatitis B vaccines including rheumatoid arthritis, diabetes, chronic fatigue syndrome, demyelinating diseases (e.g. multiple sclerosis (MS) and more recently lymphoblastic leukemia.

These allegations have generated a large flurry of media coverage challenging the safety of the vaccine and resulted in a number of legal actions. This had a major impact at the global level on the image of the vaccine and its acceptance. In addition to allegations involving specifically the hepatitis B vaccine, a number of safety issues have been raised with respect to specific vaccines components such as thiomersal and aluminium adjuvants also included in other vaccines. This has resulted in the further undue amalgamation of issues and blame over the hepatitis B vaccine.

In this context, the purpose of the following is to summarize information on the safety profile of the hepatitis B vaccine and on the occurrence of adverse events following its administration. Before reviewing this, however, it is important to consider the actual content of the vaccine as well as the various sources of information.

Vaccine preparations

Hepatitis B vaccines (HBV) are composed of highly purified preparations of hepatitis B "s" antigen (HBsAg). This is a glycoprotein that is a component of the outer envelope of hepatitis B virus, and is also found as 22-nm spheres and tubular forms in the serum of people with acute and chronic infection. Vaccines are prepared by harvesting HBs Ag from the plasma of people with chronic infection (plasma derived vaccine) or by inserting plasmids containing the viral gene in yeast or mammalian cells (recombinant DNA vaccine). An adjuvant, aluminium phosphate or aluminium hydroxide, is added to the vaccines that are sometimes preserved with thiomersal. The concentration of HBs Ag varies from 2.5 to 40 µg per dose,

according to which manufacturer is used and the target population (Mahoney et al., 1999).

Although vaccines were initially mostly of the plasma derived type the biggest share of the market is now represented by recombinant vaccines which have become more affordable and plasma derived vaccines will likely be phased out.

Sources of information

In establishing a safety profile for a vaccine, it is important to discriminate between allegations or facts and to consider the source of information and if data is obtained from surveillance or from properly controlled studies. Surveillance, case reports and case series represent an incomplete picture since they only focus on those vaccinated individuals which develop a particular medical condition without consideration neither to un-immunized individuals nor to those vaccinees that remain free of the particular condition of interest.

Globally, post-marketing surveillance capabilities are improving and more importance is attached to the reporting of suspected links between vaccination and adverse events and signal generation. However surveillance and case-series reports can identify spurious associations and generate false hypotheses. One has therefore to clearly distinguish hypothesis generating and hypothesis testing. Hypothesis testing must be done quickly and to high quality scientific standards. Epidemiological and laboratory investigations need to be carefully conducted to avoid introducing bias; data must be carefully validated and scrutinized before results are communicated.

Establishing a causal relationship between many of the purported adverse events mentioned before and hepatitis B vaccine is difficult: these events are rare, occur in the absence of hepatitis B vaccination and have their peak incidence in the older age groups who did not receive hepatitis B vaccine as part of routine childhood vaccination.

To respond promptly, efficiently and with scientific rigor to vaccine safety issues, in 1999, the World Health Organization (WHO) has established a Global Advisory Committee on Vaccine Safety (GACVS) to provide an independent scientific assessment of vaccine safety issues (GACVS, 1999) and to make scientific recommendations which are intended to assist WHO, national governments and international organizations in formulating their policies regarding vaccine safety issues, including problems which particularly affect developing countries. The committee has published the principles underpinning vaccine adverse event causality assessment that it uses (GACVS, 2000) and has been asked to review a number of hepatitis B related safety issues.

In 1998, the Viral Hepatitis Prevention Board organized a technical consultation on the safety of the hepatitis B vaccine (Halsey et al, 1999). In addition, recently, the US Institute of Medicine (IOM) commissioned an independent comprehensive review paper (Waubant et al, 2002) and went on to review the evidence bearing causality on the relationship between hepatitis B vaccine and central and peripheral nervous system demyelinating diseases in March 2002 (Stratton et al., 2002).

The following summary is based on published literature, information presented at public conference as well as analysis of surveillance data. It also builds on the conclusions of the IOM and on that of the GACVS, which was presented with some yet confidential and unpublished data. Since a comprehensive review of the safety of the hepatitis B vaccine had first been completed in 1994 by the IOM (Stratton et al., 1994), the review focuses on major publications and reviews since that time and attempts to allude to all of the major issues raised.

Adverse events following immunization

Mild adverse reactions

A large number of clinical trials have been reported in the literature. In general, there are minimal reactions reported, such as local pain, myalgia and transient fever, mostly within 24 hours. In summary, mild adverse events have been reported with an approximate frequency of 1-6% for temperature greater than 37.7°C, 3-29% for pain, 3% for erythema, 3% for swelling, and 3% for headache (Zajac, 1986; Andre, 1989; Stevens, 1987; Szmunn, 1980; Francis 1982). Several studies compare reactions after different vaccines (Greenberg, 1996), different concentrations of the same vaccine (Pooverawan, 1993; Tan 1990), different schedules (Goldfard, 1994; Giammanco, 1998), or describe the reactions of a single vaccine

(Soulie, 1991; McMahon, 1992; Leroux-Roels, 1997) without placebo group. All report mild local and general reactions, lasting less than 48 hours. In placebo-controlled studies, these side-effects were reported no more frequently among vaccine recipients than among individuals receiving a placebo with the exception of local pain (Szmuness, 1980; Francis et al. 1982, Lewis et al., 2001). Children have fewer adverse reactions than adults (<10% vs. 30%) (Andre, 1989)

Severe adverse events

Anaphylactic reactions

The estimated incidence of anaphylaxis among vaccine recipients is one per 600,000 vaccine doses distributed. No serious, severe or fatal anaphylactic reaction has been reported. Further vaccination with hepatitis B vaccine is contraindicated in people with a history of anaphylaxis to a previous dose (CDC, 1996).

Chronic fatigue syndrome

In Canada, during 1993–94 a rumour was also raised that vaccination against hepatitis B was responsible for chronic fatigue syndrome (Delage et al., 1993) but no epidemiological data have ever confirmed this allegation (Anonymous, 1993).

Hair loss

Hair loss has been reported after routine immunization, especially hepatitis B (Wise et al., 1997). Hair loss is a common event; it may be extremely difficult to confirm a causal association with HBV administration. Recent yet unpublished data from CDC using large linked databases, however, do not seem to support this hypothesis (personal communication, Robert Pless)

Diabetes

Claims have been made that administration of vaccines including hepatitis B vaccine can cause type I diabetes (juvenile or insulin-dependent diabetes mellitus – IDDM) in rats (Classen, 1996) and children (Classen et al., 1997). The consensus of current professional opinion accepts there is no link (Karvonen et al, 1999; Jefferson et al., 1998). A panel review of all the evidence to date was held in the United States. This also found no association (Institute for Vaccine Safety Diabetes Workshop Panel, 1999).

Arthritis

Fisher et al. recently reported on a study of adverse events associated with hepatitis B vaccine in US children and claimed having demonstrated an association between chronic arthritis and administration of hepatitis B vaccine in children (Fisher et al., 2000). The same study also alleged an association with ear infection and pharyngitis and nasopharyngitis. This publication was reviewed by the GACVS, which concluded that the several major methodological flaws of this publication invalidated its results.

Problems identified included: the fact that the results obtained contradict the conclusions made by the authors; the very variable distribution of subjects in the various age cohorts casting doubts on the representative of the study population; the lack of consideration given to potential important confounding variables; the fact that definitions of the adverse events were not provided; the absence of plausible biological hypothesis; the serious flaws in the analysis of the results; and the fact that a large proportion of the study population was excluded from the analysis due to missing information on immunization status.

Multiple sclerosis and demyelating disorders

In recent years, following intensive use of the vaccine in France with over 20 millions persons vaccinated, several case reports raised concerns that hepatitis B immunization may be linked to new cases or relapse of MS (Duclos et al. 2001). Articles published in the media stating such a link further fuelled the worry over the safety of the vaccine. As a result of the public and professional concern, on October 1, 1998, the French Authorities temporarily suspended their school-based adolescent hepatitis B vaccine program. They, however, maintained the recommendation of universal infant immunization and the recommendation to administer the vaccine to adults at increased risk and reiterated continued support for adolescent vaccination through primary care physician. The French decision was misquoted and interpreted as a ban of hepatitis B immunization, which generated lots of concern in both developed and developing countries.

Three hypotheses could explain the observed cases of MS following hepatitis B vaccination: 1) coincidence, due to the large number of hepatitis B vaccine doses administered, many of them in age groups where symptoms of MS first occur; 2) “triggering”: an increased risk of symptomatic demyelination following hepatitis B vaccine which would act as a “trigger” in individuals predisposed to develop MS or central nervous system (CNS) demyelinating diseases; and 3) a true causal relationship between hepatitis B vaccination and MS or other CNS demyelinating disease.

As of 2001, over 600 cases of central demyelinating diseases had been reported to the French authorities, the majority in adult females with a close match to the natural epidemiologic distribution of MS (AFSAPS, personal communication). The time between the last dose of vaccine and the onset of the neurological symptoms was distributed from 1 day to 5 years (median: 60 days). No cases were reported among children less than 25 months despite the vaccination of 1.8 million babies. Overall, 9 epidemiological studies (see Table 1) were carried out in order to estimate the association between vaccination with hepatitis B vaccination and the risk of occurrence of demyelinating disease (first attack or relapse of multiple sclerosis). Despite some slightly elevated odds ratio observed in the first initial studies, none of the studies did show a statistically significant elevated risk and the most recently completed and/or published studies do not indicate any excess risk. There is a lack of experimental data to suggest a link. The analysis of data from spontaneous reports and the results of epidemiological studies, do not suggest a causal relationship between MS and hepatitis B. The most plausible explanation regarding MS reported following hepatitis B vaccination remains a coincidental association, if we take into account all available data. Yet, although one can exclude an elevated risk of MS, a weak risk cannot be rejected nor the existence of subpopulations with specific sensitivity and it is not possible to demonstrate an absence of correlation.

Consistent with the IOM conclusions that the evidence favoured rejection of a causal relationship between hepatitis B vaccine administered to adults and incident multiple sclerosis or multiple sclerosis relapse, the GACVS committee upon review of available data concluded that there was no evidence based on safety to suggest that WHO should consider altering its recommendations that all countries should have universal infant and/or adolescent immunization programs and continue to immunize adults at increased risk of hepatitis B infection as appropriate.

With respect to other demyelinating diseases, a few articles mention isolated demyelinating cases following hepatitis B vaccination (Shaw, 1988; Herroelen, 1991; Mahassin, 1993; Trevisani 1993; Nadler, 1993; Tartaglino, 1995; Konstantinou et al, 2001). There had also been a suggested possible association between Guillain–Barré syndrome (GBS) and receipt of the first dose of plasma-derived vaccine in the US (CDC, 1991). In 1991, Guillain–Barré syndrome was reported at a very low rate (0.5 per 100 000 vaccine recipients), with no deaths in all reported cases among adults. Current available data indicate no demonstrable association between receipt of either plasma-derived or recombinant vaccine and GBS. At its 2002 review, the IOM concluded but that the evidence was inadequate to accept or reject a causal relationship between hepatitis B vaccine and first episodes of a central nervous system demyelinating disorder, acute disseminated encephalomyelitis, optic neuritis, transverse myelitis, GBS and brachial neuritis. In addition the committee concluded that there was weak evidence for biological mechanisms by which hepatitis B vaccination could possibly influence an individual’s risk of any of the above mentioned demyelinating diseases.

Hepatitis B and Leukaemia

A study recently presented as a poster by Ma et al. (2002) reported an epidemiological association between receipt of hepatitis B vaccine and the risk of acute lymphocytic leukemia (ALL) in a group of 334 children in northern California. This is the first study to ever report such an association. The investigators of the study further suggested that thiomersal may play a role in the mechanism as the effect was more likely to occur with repeated dosing. Additional research is being conducted by the CDC VAERS system using the Vaccine Safety Datalink to verify this hypothesis and further work will also be initiated by WHO. The findings could just be a chance association considering that several hypotheses were being tested on a single data set. This issue was reviewed by the GACVS at its June 2002 meeting in the presence of independent toxicologic and thiomersal experts.

Some animal studies have considered an association between mercury and certain cancers, but this was generally not supported by the literature and it was suggested that such an association was not biologically plausible and that cancers associated with metal carcinogens involves continual or repeated insults before cancer manifests.

The committee concluded that an association between hepatitis B vaccination and acute lymphoblastic leukemia was

suggested from one source which in itself was not convincing together with no strong biological evidence. Associations such as the one described by the authors can appear through a variety of statistical phenomena and may not represent a true causal link. Although the association could not be disregarded at this stage and should be kept under review, the committee concluded that at this stage the risk was only entirely theoretical and contrasted with the proven benefits of hepatitis B immunization.

Aluminium containing vaccines and MMF

Muscle biopsies performed in France in the deltoid of a number of patients with a variety of complaints have revealed in a small number of patients the presence of an inflammatory focus of macrophages. These localized, small inflammatory lesions have been called macrophagic myofasciitis (MMF) and have been found to contain aluminium salts. Since the location of these lesions coincides with the usual site of injection for vaccines, it is quite likely that these microscopic lesions are related to immunization. Groupe d'études et de recherche sur les maladies musculaires acquises et dysimmunitaires (GERMAAD) scientists also hypothesized that vaccination and MMF might be responsible for a disorder affecting many parts of the body (Cherin et al, 1999). However, it is possible that this is only an incidental finding or that the persistence of the lesion results from an underlying disease.

In 1999, the Institut français de veille sanitaire drew the attention of the WHO to these findings, which had been reported to them by the GERMMAD. On the advice of its GACVS, WHO initiated abroad consultation on this issue (GACVS, 1999).

WHO identified the need to determine why a macrophagic inflammation persists in a very small number of subjects and whether this histological lesion may or may not be responsible for the generalized symptoms in some patients.

These questions can only be addressed by epidemiological studies comparing individuals with and without the lesion. In 1999, WHO recommended that a study be undertaken to establish whether or not there is an association between local MMF lesions and any generalized symptom or condition. This study is now ongoing, and results should be available soon. Preliminary results of animal studies as well as studies of the macrophagic function, however, seem to further support the hypothesis that MMF may actually represent a simple vaccine "tattoo". At its June 2002 meeting the GACVS which reviewed the latest evidence concluded that in light of the data currently available, there was no evidence for a health risk from aluminium containing vaccines, nor any indication to justify changing current vaccination practices

Safety of thiomersal

In 1999, concerns were raised in the United States about exposure to mercury following immunization. This was based on the realization that the cumulative amount of mercury in the infant immunization schedule potentially exceeded the recommended threshold set by one of the United States government agencies for methyl mercury (Freed et al., 2002). Thiomersal, the preservative in some vaccines, contains ethyl mercury not methyl mercury.

The GACVS first assessed this issue in a special meeting in August 2000 and has been reviewing the issue since. Recent expert consultation and data presented to the GACVS on 20-21 June 2002 indicate that the pharmacokinetic profile of ethyl mercury is very different from that of methyl mercury. In particular, the half-life of ethyl mercury is short (probably less than one week) compared to methyl mercury (1.5 months) i.e., exposure to ethyl mercury in blood is comparatively brief. Further, ethyl mercury is actively excreted via the gut unlike methyl mercury that accumulates in the body.

Two independently-conducted epidemiological studies were recently completed in the United Kingdom. These studies further support the safety of thiomersal-containing vaccines in infants at the amounts used in existing vaccines.

On the basis of the foregoing evidence, the GACVS concluded that there is no evidence of toxicity in infants, children or adults exposed to thiomersal (containing ethyl mercury) in vaccines and that there were no reason on grounds of safety to change current immunization practices with thiomersal-containing vaccines.

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Table 1: Hepatitis B vaccination and multiple sclerosis, summary of studies conducted (*the content of this table is based on referenced publication as well as data presented at the 2002 IOM meeting*)

Study	Year	Cases	Control	Odds ratio	CI 95%
FCDD*, E. Touze et al.	1997	121	121	1.7 (2 months)	0.5-6.3
				1.5 (61-180 days)	0.5-5.3
FCDD*, E. Touze et al.	1998	236	355	1.4 (2 months Vacc certificate)	0.4-4.5
				1.8 (all subjects)	0.7-4.6
MS and F CDD, M. Sturkenboom and L. Abenaim	1998	481	6/1	1.4 (2 months)	0.8-2.4
				1.5 (12 months)	0.6-3.9
MSr, Coustans	1997-8	24 (before/after)	0.8 (RR)		
MSr, Confavreux	1998-9	643	*	0.7 (relapse)	0.2-2.1
MS, Zipp	1988-95	27,229§	107,469°	1.3 (2 months)	0.4-4.8
MS, Sadovnick	1986-98	5/289,6519/288,657	0.5 RR		
MS, Ascherio	1999	192	645	0.7 (RR, 24 months) Healthy controls	0.3-1.7
				1 (RR, 24 months) Breast Cancer	0.3-4.2
MS/optic neuritis, CDC, Verstraeten	1995-9	445	3/1	0.8 (non vacc)	0.5-1.4
				0.8 (1 year)	0.4-1.8

*FCDD First occurrence of central demyelinating disease

#2 months periods prior to relapse

§ vaccinated

° non vaccinated