Executive Summary

ABSTRACT

Immunization advisory bodies recommend that all infants, adolescents, and high-risk adults receive the hepatitis B vaccine for protection from serious liver disease, including cirrhosis and hepatocellular carcinoma. These recommendations have been viewed skeptically by some because of concerns about the safety of the vaccine and because of a perception that hepatitis B infection is not a serious risk to the general population. The Immunization Safety Review Committee reviewed the evidence regarding the hypothesis that the hepatitis B vaccine causes demyelinating neurological disorders, such as multiple sclerosis and Guillain-Barré syndrome.

There is a theoretical basis for the hypothesis that vaccines, including the hepatitis B vaccine, could cause demyelinating disorders. A review of the scant and indirect evidence that relevant biological mechanisms could operate in humans in response to the hepatitis B vaccine to produce disease provides weak support for this theory. However, the committee found that the epidemiological evidence (i.e., from studies of vaccine-exposed populations and their control groups or of patients with these diseases and their control groups) favors rejection of a causal relationship between the hepatitis B vaccine in adults and multiple sclerosis. The evidence was inadequate to accept or reject a causal relationship between the hepatitis B vaccine and all other demyelinating conditions.

Demyelinating disorders are often quite devastating, as are the sequelae of chronic hepatitis B infection. The committee found evidence that some parents and health care workers are skeptical about the vaccine due more to a perception that the vaccine is unnecessary, rather than due to a large concern about the safety of the vaccine. The committee is aware, however, that there are some people who very much object to the vaccine on the basis of the perception that not all infants and children are at risk for hepatitis B infection and on the basis of concerns about the safety. Because of the lack of epidemiological data on conditions other than MS in adults, the committee recommends further attention in the form of research and communication. However, the committee does not recommend that national and federal vaccine advisory bodies review the hepatitis B vaccine on the basis of concerns about demyelinating disorders. See Box ES-1 for a summary of all conclusions and recommendations.

Immunization to protect infants and children from vaccine-preventable diseases is one of the greatest achievements of public health. Immunization is not without risks, however. It is well established, for example, that the oral polio vaccine can on rare occasion cause paralytic polio.

The Immunization Safety Review Committee was established by the Institute of Medicine (IOM) to evaluate the available evidence on a series of immunization safety concerns. The committee is charged with examining three immunization safety hypotheses each year during the three-year study period (2001–2003). While all of the committee members share the view that immunization is generally beneficial, none of them has a vested interest in the specific immunization safety issues that come before the group. In this report, which is the fourth in the series, the committee examines the hypothesis that the hepatitis B vaccine increases the risk for demyelinating disorders of the central or peripheral nervous systems, including multiple sclerosis (MS) and Guillain-Barré syndrome (GBS). The conclusions and recommendations of the committee's first three reports—*Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism* (IOM, 2001a), *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders* (IOM, 2001b), and *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* (IOM, 2002)—are summarized in Appendix A.

For each hypothesis to be examined, the committee assesses both the scientific evidence and the significance of the issue for society.

The *scientific* assessment has two components: an examination of the epidemiological and clinical evidence regarding a possible causal relationship between the immunization and the adverse event; and an examination of biological theory and experimental evidence (from studies in humans, animals, or *in vitro* systems) regarding mechanisms that might be relevant to the hypothesis.

The *significance* assessment addresses such considerations as the burden of the health risks associated with the vaccine-preventable disease and with the adverse event in question, as well as the level of public concern about the safety issue.

The Immunization Safety Review Committee has adopted the framework for assessing causality developed by its predecessors (convened by the IOM in 1991 and 1994 under congressional mandate of P.L. 99-660) to address questions of immunization safety. The categories of causal conclusions used by the committee are as follows:

1. No evidence
2. Evidence is inadequate to accept or reject a causal relationship
3. Evidence favors rejection of a causal relationship
4. Evidence favors acceptance of a causal relationship
5. Evidence establishes a causal relationship.

Assessments begin from a position of neutrality regarding the specific vaccine safety hypothesis under review. That is, there is no presumption that a specific vaccine (or vaccine component) does or does not cause the adverse event in question. The weight of the available clinical and epidemiological evidence determines whether it is possible to shift from that neutral position to a finding for causality ("the evidence favors acceptance of a causal relationship") or away from causality ("the evidence favors rejection of a causal relationship"). The committee does not conclude that the vaccine does not cause the adverse event merely if the evidence is inadequate to support causality. Instead, it maintains a neutral position, concluding that the "evidence is inadequate to accept or reject a causal relationship."

Although no firm rules establish the amount of evidence or the quality of the evidence required to support a specific category of causality conclusion, the committee uses standard epidemiological criteria to guide its decisions. The most definitive category is "establishes causality," which is reserved for those relationships where the causal link is unequivocal, as with the oral polio vaccine and vaccine-associated paralytic polio. The next category, "favors acceptance" of a causal relationship, reflects evidence that is strong and generally convincing, although not firm enough to be described as unequivocal or established. "Favors rejection" is the strongest category in the negative direction. The category of "establishes no causal relationship" is not used because it is virtually impossible to prove the absence of a relationship with the same surety that is possible in establishing its presence. If the evidence is not reasonably convincing either in support of or against causality, the category "inadequate to accept or reject a causal relationship" is used. Evidence that is sparse, conflicting, of weak quality, or just suggestive either towards or away from causality falls into this category. The category of "no evidence" is reserved for those cases in which there is a complete absence of clinical or epidemiological evidence.

The sources of evidence considered by the committee in its scientific assessment of causality include epidemiological and clinical studies. Epidemiological studies carry the most weight in a causality assessment. Case reports and case series are generally inadequate by themselves to establish causality.

The committee's scientific assessment includes biological mechanisms, for which it has established three general categories of evidence on biological mechanisms:

(1) Theory only: A reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and that does not contradict known physical and biological principles, but it has not been demonstrated in whole or in part in humans or in model systems. Postulated mechanisms by which a vaccine might cause a specific adverse event but for which no coherent theory ex-

ists would not meet the criteria for this category. Thus, "theoretical only" is not a default category, but one that requires biologically meaningful suppositions.

(2) Experimental evidence that the postulated *mechanism operates* in animals or humans: Experimental evidence often describes effects on just one or a few of the steps in the pathological process required for expression of disease. Showing that multiple components of the theoretical pathways operate in reasonable experimental models increases confidence that the mechanisms could possibly result in disease in humans.

(3) Evidence that a relevant *immunization-related mechanism results in known disease* in humans: For example, a relevant wild-type infection causes the adverse health outcome, or another vaccine has been demonstrated to cause the same adverse outcome by the same or a similar mechanism.

If the committee identifies evidence related to a biological mechanism that could be operational, it will offer a summary judgment of the body of evidence as weak, moderate, or strong. This summary reflects the quantity and the quality of the evidence. Quality includes factors such as the relevance of the evidence to the immunization safety hypothesis and the rigor of the experiment(s).

Published reports that have been subjected to a rigorous peer review process carry the most weight in the committee's assessment. Immunization safety studies and other data reviewed by the committee are funded by a variety of sources—NIH, CDC, vaccine manufacturers, research advocacy organizations, or foundations. The committee relies on editorial and peer review procedures to ensure the disclosure of potential conflicts of interest that might be related to the source of funding for the research study. In general, the committee cannot rely solely on unpublished data in making its scientific assessments (regarding either causality or biological mechanisms) because they have not undergone a formal review and must, therefore, be interpreted with caution.

In reviewing unpublished material, the committee applies generally accepted standards for assessing the quality of scientific evidence, as described above. All unpublished data reviewed by the committee and cited in this report are available—in the form reviewed by the committee—through the public access files of the National Academies. Information about the public access files is available at 202-334-3543 or www.national-academies.org/publicaccess.

DEMYELINATING NEUROLOGICAL DISORDERS

For this review the committee addressed the relationship between hepatitis B vaccine and the following neurological diseases: the central nervous system (CNS) demyelinating diseases of MS (onset or relapse), optic neuritis, acute disseminated encephalomyelitis (ADEM), and transverse myelitis; and the peripheral nervous system (PNS) demyelinating diseases of GBS and brachial neuritis. The committee chose to focus on these specific conditions because they are

serious neurological disorders and known clinical entities. Published epidemiological studies and case reports investigating their association with hepatitis B vaccine are available, and a substantial body of literature exists on the pathophysiology of several of these conditions (e.g., MS, ADEM, and GBS).

MS is the most common chronic inflammatory demyelinating disease of the CNS in humans. In the United States, approximately 300,000 individuals, about 0.1 percent of the population, have been diagnosed with the disease (Noseworthy et al., 2000). Women are affected approximately twice as often as men. The incidence of the disease is highest in persons between the ages of 20 and 40 years, but it is also diagnosed in children as young as 2 years, and in older individuals. Common presenting symptoms include focal sensory deficits, focal weakness, a loss of vision, double vision, imbalance, and fatigue. The severity of the disease can range from subclinical forms that are diagnosed only after death (from other causes) to hyperacute forms that lead to death within the first few months after disease onset. The cause of MS remains elusive, but susceptibility appears to involve both genetic and environmental factors. Genetic factors are reflected in an increased risk of developing MS among family members of MS patients. The concordance rate among dizygotic (fraternal) twins and other siblings is 2–5 percent and 30–35 percent in monozygotic (identical) twins (Waubant and Stuve, 2002).

Optic neuritis is caused by an inflammation of the optic nerve, with lesions occurring behind the orbit but anterior to the optic chiasm (IOM, 1994). Symptoms include rapid vision loss, pain associated with eye movement, dimmed vision, abnormal color vision, altered depth perception, and Uhthoff's phenomenon—in which visual loss is associated with an increase in body temperature (IOM, 2001c). The majority of cases resolve within a few weeks to months of onset. Optic neuritis can occur as an isolated monophasic disease, or it may be a symptom of other demyelinating diseases such as ADEM or MS.

ADEM, an inflammatory demyelinating disease of the CNS that can result in permanent and severe neurological disability, occurs most commonly in children and adolescents. In contrast to MS, which involves recurring or progressive neurological consequences of demyelination, ADEM is normally defined as a monophasic disorder (that is, relapses do not occur) that results from a discrete episode of inflammatory demyelination. ADEM most often occurs following an infection, and it is associated with several viral pathogens, including the measles, rubella, and varicella zoster viruses.

Transverse myelitis, which also usually occurs after viral or bacterial may represent a variant of ADEM restricted to the spinal cord. Symptoms may begin as pain, weakness, or tingling, but then progress within weeks to paralysis, urinary retention, or loss of bowel control.

GBS is the most common acquired peripheral demyelinating disease in humans. Its incidence is estimated at 1 to 2 cases per 100,000 population per year both in children and adults (IOM, 1994). GBS typically occurs several days or

weeks after an infectious event, commonly a diarrheal illness or a viral upper respiratory infection. From 10 to 30 percent of all cases are associated with *Campylobacter jejuni* infections. An increased risk for GBS has also been linked to exposure to certain vaccines, most notably the 1976 influenza vaccine (the swine flu vaccine).

The characteristic clinical feature of GBS is an acute, rapidly progressive, ascending, and symmetric weakness, with loss of deep tendon reflexes and possible tingling in the feet and hands, and muscle aches (myalgia). Facial, oculomotor, oropharyngeal, and respiratory muscles may also be involved, and some patients may require respiratory support. Most patients will improve and return to normal functioning within 6 to 9 months, but some patients experience relapses or a prolonged disease course with residual neurological deficits.

Brachial neuritis is characterized by a deep, severe pain in the shoulder and upper arm. The pain generally subsides within days or weeks, but weakness and muscle atrophy in the affected arm are common side-effects.

HEPATITIS B VIRAL INFECTION

The hepatitis B virus (HBV) can produce an acute or chronic[1] infection causing inflammation of the liver. Symptoms of acute HBV infection include jaundice, fatigue, joint pain, abdominal pain, loss of appetite, nausea, and diarrhea. About 30 percent of adult infections are asymptomatic (Coleman et al., 1998), but they can become chronic. Among infants infected at birth, the risk of chronic infection is 90 percent; among persons infected as adults, about 6 percent develop chronic infections (CDC, 2001a). Chronic carriers of HBV are at increased risk for cirrhosis and hepatocellular carcinoma (HCC), and 15–25 percent of them die from liver disease (Lee, 1997). Rates of hepatitis B infection vary widely throughout the world. The highest prevalence is found in some regions of Southeast Asia, China, and Africa; in these regions over half of the population will contract acute hepatitis B.

HBV is transmitted through bodily fluids, with the highest viral concentrations found in blood, serum, and wound exudates (Halsey, 2002). HBV can remain viable outside the body for more than 7 days (Mast, 2002) and its relative infectivity is 100 times greater than that of HIV (Hilleman, 2001). Transmission occurs through sexual contact, intravenous drug use and needle sharing, occupational exposure to bodily fluids of infected persons, and contact with an infected family member or contaminated articles in the household. Newborns can be infected by transmission of the virus from an infected mother (also called perinatal transmission).

[1] Chronic infection is defined by having hepatitis B surface antigen (HBsAg) for more than six months (Maddrey, 2000).

HEPATITIS B VACCINE

A vaccine against HBV first became available in the United States in 1982. This vaccine used inactivated alum-adsorbed hepatitis B virus surface antigen (HBsAg) particles purified from human plasma from persons with chronic HBV infections. Plasma-derived hepatitis B vaccine is no longer produced in the United States, but such vaccines are still being produced in other countries. The recombinant hepatitis B vaccines in use in the United States since the late 1980s are produced using *Saccharomyces cerevisiae* (baker's yeast), into which a plasmid containing the gene for HBsAg has been inserted (CDC, 1990). The resulting vaccine consists of HBsAg protein adsorbed with aluminum hydroxide. Three doses of hepatitis B vaccine are required for full immunization. In the United States, current recommendations call for universal immunization of children, with doses administered at birth, at 1 to 2 months, and at 6 to 18 months. For children born to mothers who are HBsAg-negative, the first two doses can be given at 1 to 2 months and 4 months, respectively. Immunization is also recommended for all unimmunized adolescents and for adults at high risk of exposure to HBV, such as health care workers.

EVIDENCE REVIEWED BY THE COMMITTEE

For its evaluation of the hypothesis on hepatitis B vaccine and demyelinating neurological disorders, the committee commissioned a background paper. The committee also held an open scientific meeting in March 2002 (see Appendix B) for presentations on issues germane to the topic. The commissioned paper and all information presented to the committee at the open meeting can be viewed on the project website (www.iom.edu/imsafety). In addition, the committee reviewed an extensive collection of material from the published, peer-reviewed, scientific and medical literature. A reference list of material reviewed by the committee, even if not cited in this report, can be found on its website.

CAUSALITY ASSESSMENT

Most of the epidemiological evidence identified by the committee examines the connection between exposure to hepatitis B vaccine and the incidence of newly diagnosed cases (incident cases) of MS or of a first episode of a CNS demyelinating disorder (CDD, which can be consistent with MS but not yet meet criteria for a diagnosis of MS). One study examined the risk for relapse in patients with diagnosed MS. Some of the studies on MS also examined the risk for other adverse outcomes, but overall, evidence regarding these outcomes is limited. The evidence regarding ADEM, transverse myelitis, and brachial neuritis was largely based on case reports.

From the data reviewed (see Table 1 in the report), **the committee concludes that the evidence favors rejection of a causal relationship between hepatitis B vaccine administered to adults and incident multiple sclerosis. The committee also concludes that the evidence favors rejection of a causal relationship between hepatitis B vaccine administered to adults and multiple sclerosis relapse.** There are no epidemiological data regarding the relationship of hepatitis B vaccination in infants and young children and the risk for MS. The committee cannot extend the causality conclusion based on epidemiological studies in adults to include a possible risk to infants and young children.

Based on the data reviewed (see Table 2 in the report), **the committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and the first episode of a central nervous system demyelinating disorder.** A first episode of CDD might or might not be indicative of MS, which requires more than one episode for diagnosis. The evidence derives from unpublished data, for the most part, and the one published study had methodological weaknesses.

Only one uncontrolled ecological study was available regarding ADEM (Sadovnick and Scheifele, 2000). **The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and ADEM.**

Only one unpublished study was available regarding optic neuritis (DeStefano, 2002) (see also Table 3). Thus, **the committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and optic neuritis.**

Only case reports were available regarding transverse myelitis, GBS, and brachial neuritis. Thus, **the committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and transverse myelitis, GBS, and brachial neuritis.**

BIOLOGICAL MECHANISMS ASSESSMENT

Three mechanisms—molecular mimicry, bystander activation, and superantigen stimulation—can be posited as the theoretical ways in which immunization of any kind (either through infection or vaccination) could cause the development of demyelinating diseases of the central and peripheral nervous systems. Molecular mimicry refers to the process of a microbial antigenic determinant cross-reacting with a self-protein. If the self-protein is a myelin-related protein, the subsequent immunological response could lead to autoimmune demyelination. Bystander activation refers to a process of a microbial infection (or other stimulus) leading to the release of a large quantity of normally sequestered host proteins and the subsequent destruction of host tissue, which could include cen-

tral or peripheral myelin. Superantigens are proteins that are produced by viruses and bacteria and that activate T cells either by direct activation of auto-reactive T cells (regardless of antigen specificity) or activation of humoral responses. Superantigens can also lead to the release of inflammatory mediators such as cytokines, which could participate in demyelinating processes. It is conceivable that antigenic stimulation from vaccines generally, and from hepatitis B vaccine in particular, could trigger any of these three potentially damaging mechanisms. Thus, there is a theoretical basis for an association between vaccine-induced immune response and demyelination. Biological evidence exists regarding some components of this theory. The most well-established animal model for MS and ADEM is experimental autoimmune encephalomyelitis (EAE). EAE is an autoimmune syndrome induced in susceptible strains of mice and rats. The inducing agent is usually immunization with myelin antigens or the transfer of T lymphocytes reactive against myelin proteins. The similarities between EAE models and MS and ADEM indicate that immunization with certain antigens in humans could trigger autoimmune processes that produce demyelinating injuries.

The most studied rodent model for peripheral demyelinating disease is experimental allergic neuritis (EAN). EAN can be induced by active immunization with a homogenate of whole peripheral nerve tissue or with peripheral myelin extracts, combined with complete Freund's adjuvant. (Hahn, 1996). A related model, experimental neuritis, is similar but requires that a triggering agent (such as various viruses or antigens) be administered concomitantly with the myelin tissue (Hjorth et al., 1984). In this model, the swine influenza vaccine was shown to trigger autoimmune responses and peripheral demyelination. In none of these models, however, has hepatitis B surface antigen been shown to trigger disease.

There is no significant homology between the amino acid sequences of HBsAg—the main component of the hepatitis B vaccine—and the myelin proteins MOG, MBP, and PLP. This makes it unlikely that a T cell-mediated immune response against these CNS autoantigens would be triggered by the hepatitis B vaccine on the basis of molecular mimicry.

There is some evidence linking the hepatitis B vaccine with alopecia (hair loss) in humans (Wise et al., 1997). At least one form of alopecia (alopecia areata) is hypothesized to be autoimmune-mediated. However, the pathophysiological similarities between alopecia and demyelinating conditions are not strong, and the relationship between hepatitis B vaccine and alopecia is not established as causal.

Several vaccines other than hepatitis B vaccine are associated with demyelinating diseases of either the central or peripheral nervous system. Both rabies and measles vaccines are rarely associated with ADEM, and the swine influenza vaccine used in 1976–1977 in the United States was associated with an increased risk of developing GBS (CDC, 2001b). In addition, an IOM committee

found that tetanus-toxoid-containing vaccines are causally associated with brachial neuritis (IOM, 1994).

In summary, the committee concludes that there is a theoretical basis for mechanisms by which a vaccine could cause demyelinating disease. There is no reason why the hepatitis B vaccine could not also function in this way. The biological evidence, however, for hepatitis B vaccine-induced mechanisms or for hepatitis B vaccine-associated clinical disease in humans is neither extensive nor is it directly relevant. Because none of the evidence is specific to the hepatitis B vaccine, **the committee concludes that there is weak evidence for biological mechanisms by which hepatitis B vaccination could possibly influence an individual's risk of the central or peripheral nervous system disorders of MS, first episode of CDD, ADEM, optic neuritis, transverse myelitis, GBS, or brachial neuritis.**

SIGNIFICANCE ASSESSMENT

In formulating the breadth and direction of the recommended public health response, the committee considers not only its conclusions regarding causality and biological mechanisms but also the significance of the immunization safety issues for society—the context in which policy decisions must be made. Public concerns about immunization safety must be examined carefully because most vaccines are given to healthy children not only for their direct protection but also to help protect others in the population.

The hepatitis B vaccine issue initially gained attention because of reports, collected in the 3 years after its introduction, of demyelinating disease, particularly GBS, occurring after vaccination (Shaw et al., 1988). More recently, and particularly in France, concern has arisen that the vaccine might be associated with the onset or exacerbation of MS. In addition, there are concerns about the need for universal immunization of infants and young children against a disease that many people, including some pediatricians, believe is not a major or immediate threat to the health of most infants.

In the United States and many other countries, the current strategy for preventing HBV infection emphasizes universal immunization of infants, with the initial vaccine dose given soon after birth. When hepatitis B vaccines first became available in the 1980s, the prevention strategy in the United States focused on immunizing populations, pregnant women in particular, considered at high risk for HBV infection. This strategy was later expanded to include all pregnant women (CDC, 1990). These approaches proved unsuccessful in reducing hepatitis B infections because vaccination rates in many high-risk populations remained low. Moreover, in the 1980s, up to 30 percent of HBV cases in adults could not be linked to known risk factors (Alter et al., 1990).

Infant immunization was also recommended because HBV infections occurred in children of mothers who were HBsAg-negative (CDC, 1991). CDC

has estimated that in 1991, prior to the recommendation for universal infant immunization, approximately 16,000 children between the ages of 0 to 9 years acquired nonperinatal HBV infections (Armstrong et al., 2001).

CDC used these figures to calculate the impact of infant immunization for the 1998 birth cohort (Armstrong et al., 2001). Those estimates indicate that without immunization approximately 6,800 perinatal infections and 18,700 nonperinatal infections of children 0 to 9 years old would have occurred. About 12,100[2] of these children would develop chronic infections, and about 3,000 of them would eventually die from cirrhosis or HCC. With 90 percent of children now receiving three doses of hepatitis B vaccine by age 2, it is estimated that as many as 2,700 deaths from cirrhosis or HCC will be averted (years or decades after immunization) in the 1998 birth cohort.

Overall, the committee found little indication that safety concerns are a major barrier to acceptance of hepatitis B vaccination in the United States. The widespread acceptance of the vaccine is reflected in the increases in coverage rates among young children since the mid-1990s. In 1995, 68 percent of children ages 19–35 months, had received three doses of hepatitis B vaccine. For 2000, the National Immunization Survey data show 90.3 percent coverage among children ages 19–35 months (CDC, 2001c) Although concern about neurological disorders following immunization is justified on the basis of their total burden to individuals and to society and the known relationship of some vaccines to some neurological conditions, the hepatitis B vaccine prevents serious and usually fatal liver disease. However, the benefits of hepatitis B vaccine are realized long after immunization, and because the population at highest risk of hepatitis B infection is in adolescents, young adults, and members of high-risk occupations, the recommendation to universally immunize newborns and infants is difficult for some parents and clinicians to understand. The theoretical risks of the vaccine are salient for them, but the benefits to infants are not. **The committee concludes that concerns about the hepatitis B vaccine remain significant in the minds of some parents and workers who are required to take the vaccine because of occupational risk.**

[2] Chronic infection could be expected to occur in approximately 60% of the children infected before age 2 and in 25% of the children infected between ages 2 and 9 years (Armstrong et al., 2001). Of those chronically infected, approximately 25% would die from cirrhosis or HCC several decades after infection.

RECOMMENDATIONS FOR PUBLIC HEALTH RESPONSE

Policy Review

The scientific and policy issues considered by the committee lead to recommendations for targeted public health attention. Because the hepatitis B vaccine is recommended by federal and national advisory bodies for use in infants and is required for school entry and for employment in the health care and other high-risk fields, and because the rationale for immunization of infants and children is not well understood by some parents and health care providers, public health attention in the form of research and communication is required. However, **the committee does not recommend a policy review of the hepatitis B vaccine by any of the national and federal vaccine advisory bodies on the basis of concerns about demyelinating neurological disorders.**

Research

Although the committee concluded that the epidemiological evidence is inadequate to accept or reject a causal relationship between the hepatitis B vaccine and most of the demyelinating disorders it reviewed, the committee found a theoretical basis for the hypothesis when it considered biological mechanisms. The committee identified only limited and indirect evidence that the biological mechanisms could be operational. Because none was specific to the hepatitis B vaccine, the summary judgment was that the evidence was weak. Given this, and the fact that the committee identified very little information about the effects of the vaccine on demyelinating disorders in infants and children, the committee recommends further research.

Surveillance

The committee emphasizes the need for continuing surveillance of hepatitis B vaccine recipients and possible adverse events. MS rarely appears in childhood but begins to appear in early adulthood (Noseworthy et al., 2000; Waubant and Stuve, 2002). The evidence that the onset of MS may appear a decade or more after exposure to a risk factor (environmental or microbial) raises the possibility that long-term follow-up might be needed to determine an effect on the rate of MS. Because the hepatitis B vaccine has been routinely administered to newborns and infants since 1991, surveillance of this exposed and aging group provides an opportunity to study its incidence of MS. The incidence of other central and peripheral nervous system disorders, such as optic neuritis, CDD first episode, ADEM, GBS, brachial neuritis, and transverse myelitis should also be examined in this group. In addition, there should be continued surveillance of health care workers who have received the vaccine. **The committee recommends surveillance of MS and other central and peripheral nervous system**

demyelinating disorders, specifically in health care workers and those born since 1991.

Surveillance of these outcomes would be strengthened by having standard diagnostic approaches and case definitions to permit epidemiological investigations. The lack of standardized case definition for adverse events following vaccination is a recurring concern for the committee and for all who study immunization safety. Specifically, **the committee recommends the development of case definitions and guidance for diagnostic evaluation of the demyelinating disorders it has reviewed for purposes of improved vaccine adverse event surveillance and, when appropriate, causality assessment.** The committee notes and encourages the work recently begun by the Brighton Collaboration to develop, through an international consensus process, a set of standard definitions for adverse events (brightoncollaboration.org); as well as the newly established Clinical Immunization Safety Assessment centers (www.cdc.gov/programs/immun8.htm). The committee has not reviewed these efforts in sufficient detail to recommend whether or not the entities behind them can or should assume the responsibility for this recommendation, or whether a distinct effort is needed.

Infection with the hepatitis B virus increases the risk of developing cirrhosis and hepatocellular carcinoma (El-Serag, 2001). Surveillance of these secondary outcomes of hepatitis B infection may provide a clearer understanding of the impact of the hepatitis B vaccination program. Continued surveillance of acute infections also remains important for the same reason. Furthermore, because hepatitis B infections can be asymptomatic, supplemental surveillance, such as the serological testing that has been conducted as part of the National Health and Nutrition Examination Survey, is needed for more accurate estimates of incidence and prevalence. Therefore, **the committee recommends continued surveillance of hepatitis B disease and increased surveillance of secondary diseases, such as cirrhosis and hepatocellular carcinoma.**

Basic and Clinical Science

The committee has not recommended large-scale epidemiological studies at this time to address concern about the demyelinating conditions it has reviewed. But, in recognition of its inability to reject causality for most of these conditions, and of the limited evidence regarding biological mechanisms, **the committee recommends continued research in animal and *in vitro* models, as well as in humans, on the mechanisms of immune-mediated neurologic disease possibly associated with exposure to vaccines.**

Communication

The committee searched for web-based materials aimed at an information-seeking parent, but it found several barriers. Similarly, the concerned public may spend a great deal of time seeking meaningful information, often without success. If an individual approaches the task stressed or concerned about the issue, it is likely that the search process will only increase that frustration. Thus, the committee is concerned that the public's need for relevant information is not being effectively met. **The committee again recommends that government agencies and professional organizations responsible for immunizations critically evaluate their communication services with increased understanding of, and input from, the intended users.** It is important to ensure that the content and format of the communication methods and tools are appropriate, readily accessible, and relevant to the public.

BOX ES-1 Committee Conclusions and Recommendations

SCIENTIFIC ASSESSMENT

Causality Conclusions

The committee concludes that the evidence favors rejection of a causal relationship between hepatitis B vaccine administered to adults and incident multiple sclerosis.

The committee also concludes that the evidence favors rejection of a causal relationship between hepatitis B vaccine administered to adults and multiple sclerosis relapse.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and the first episode of a central nervous system demyelinating disorder.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and ADEM.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and optic neuritis.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and transverse myelitis.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and GBS.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and brachial neuritis.

continued

Box ES-1 continued

SIGNIFICANCE ASSESSMENT

The committee concludes that concerns about the hepatitis B vaccine remain significant in the minds of some parents and workers who are required to take the vaccine because of occupational risk.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review

The committee does not recommend a policy review of the hepatitis B vaccine by any of the national and federal vaccine advisory bodies on the basis of concerns about demyelinating neurological disorders.

The committee recommends continued surveillance of hepatitis B disease and increased surveillance of secondary diseases such as cirrhosis and hepatocellular carcinoma.

Basic and Clinical Science

The committee recommends continued research in animal and *in vitro* models, as well as in humans, on the mechanisms of immune-mediated neurological disease possibly associated with exposure to vaccines.

Communication

The committee again recommends that government agencies and professional organizations responsible for immunizations critically evaluate their communication services with increased understanding of, and input from, the intended users.

REFERENCES

Alter MJ, Hadler SC, Margolis HS, Alexander WJ, Hu PY, Judson FN, Mares A, Miller JK, Moyer LA. 1990. The changing epidemiology of hepatitis B in the United States. Need for alternative vaccination strategies. *JAMA* 263(9):1218–22.

Armstrong GL, Mast EE, Wojczynski M, Margolis H. 2001. Childhood hepatitis B virus infections in the United States before hepatitis B immunization. *Pediatrics* 108(5):1123–1128.

CDC (Centers for Disease Control and Prevention). 1990. Protection against viral hepatitis. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 39(RR-2):1–26.

CDC. 1991. Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR*; 40((RR-13)):1–19 .

CDC. 2001a. Viral hepatitis B: Fact sheet.

CDC. 2001b. Influenza Vaccine 2001–2002. *Vaccine Information Sheet.*

CDC. 2001c. National, state, and urban area vaccination coverage levels among children aged 19–35 months—United States, 2000. *MMWR Morb Mortal Wkly Rep* 50(30):637–41.

Coleman PJ, McQuillan GM, Moyer LA, Lambert SB, Margolis HS. 1998. Incidence of hepatitis B virus infection in the United States, 1976–1994: estimates from the National Health and Nutrition Examination Surveys. *J Infect Dis* 178(4):954–9.

DeStefano F. 2002. Risk of Demyelinating Disease After Hepatitis B Vaccination: The Vaccine Safety Datalink. *Presentation to Immunization Safety Review Committee.*

El-Serag HB. 2001. Epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 5(1):87–107, vi.

Hahn AF. 1996. Experimental allergic neuritis (EAN) as a model for the immune-mediated demyelinating neuropathies. *Rev Neurol (Paris)* 152(5):328–32.

Halsey NA. Recommendations for Newborn and Infant Hepatitis B Vaccination: Historical Perspective. *Presentation to Immunization Safety Review Committee.* 2002.

Hilleman MR. 2001. Overview of the pathogenesis, prophylaxis and therapeusis of viral hepatitis B, with focus on reduction to practical applications. *Vaccine* 19(15–16):1837–48.

Hjorth RN, Bonde GM, Piner E, Hartzell RW, Rorke LB, Rubin BA. 1984. Experimental neuritis induced by a mixture of neural antigens and influenza vaccines. A possible model for Guillain-Barre syndrome. *J Neuroimmunol* 6(1):1–8.

IOM (Institute of Medicine). 1994. *Adverse Events Associated ith Childhood Vaccines: Evidence Bearing on Causality*. Washington, DC: National Academy Press.

IOM. 2001a. *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism*. Washington, DC: National Academy Press.

IOM. 2001b. *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders*. Washington, DC: National Academy Press.

IOM. 2001c. *Multiple Sclerosis: Current Status and Strategies for the Future*. Washington, DC: National Academy Press;

IOM. 2002. *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction*. Washington, DC: National Academy Press.

Lee WM. 1997. Hepatitis B virus infection. *N Engl J Med* 337(24):1733–45.

Maddrey WC. 2000. Hepatitis B: An important public health issue. *J Med Virol* 61(3):362–6.

Mast E. Recent Analyses of Hepatitis B Viral Infections in Children. *Presentation to Immunization Safety Review Committee.* 2002.

Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. 2000. Multiple sclerosis. *N Engl J Med* 343(13):938–52.

Sadovnick AD, Scheifele DW. 2000. School-based hepatitis B vaccination programme and adolescent multiple sclerosis. *Lancet* 355(9203):549–50.

Shaw FE Jr, Graham DJ, Guess HA, Milstien JB, Johnson JM, Schatz GC, Hadler SC, Kuritsky JN, Hiner EE, Bregman DJ, Maynard JE. 1988. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years. *Am J Epidemiol* 127(2):337–52.

Waubant E, Stuve O. Suspected mechanisms involved in multiple sclerosis and putative role of hepatitis B vaccine in multiple sclerosis. *Commissioned Background Paper for IOM Immunization Safety Review Committee.* 2002.

Wise RP, Kiminyo KP, Salive ME. 1997. Hair loss after routine immunizations. *JAMA* 278(14):1176–8.