Hepatitis B vaccination: CDC public relations (PR) material vs. *Medical Veritas*™ rebuttal

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Abstract

The Association of American Physicians & Surgeons (AAPS) and the Centers for Disease Control and Prevention (CDC) demonstrate two divergent schools of thought when it comes to administration of Hepatitis B vaccination, especially with regard to newborns. Several statements from Dr. Jane Orient, Director of AAPS were presented by *Medical Veritas* staff to the CDC via e-mail so that a CDC representative could review AAPS' opposing position and respond. We invite the reader to decide whether or not the available CDC public relations material presented in Appendix 1–3 adequately counters Dr. Orient's assessment, "For most children, the risk of a serious vaccine reaction may be 100 times greater than the risk of hepatitis B."

Keywords: Hepatitis B, adverse vaccine reactions

1. Introduction

Dr. Jane Orient, director of the Association of American Physicians & Surgeons, writes, "Doctors reported only about 10,000 hepatitis B cases in the U.S. in 1997 with only 306 occurring in children under 14. The only babies at risk are those born to hepatitis B-infected mothers. In 1996, only 54 cases of the disease were reported to the Centers for Disease Control and Prevention (CDC) in the 0 to 1 age group. There were 3.9 million births that year, so the observed incidence of hepatitis B in the 0 to 1 age group was just 0.001 percent. In the Vaccine Adverse Event Reporting System (VAERS) there were 1,080 total reports of adverse reactions from hepatitis B vaccine in 1996 alone in the 0 to 1 age group, with 47 deaths reported."

"For most children, the risk of a serious vaccine reaction may be 100 times greater than the risk of hepatitis B. Overall, the incidence of hepatitis B in the U.S. is currently about 4 per 100,000. The risk for most young children is far less; hepatitis B is heavily concentrated in groups at high risk due to occupation, sexual promiscuity, or drug abuse."

2. CDC responds with public relations information

When Medical Veritas staff presented the above facts to the CDC, Duane Kilgus, MPH (Masters of Public Health degree) and Health Education Specialist for the National Immunization Program (NIP), provided the public relations information regarding hepatitis B vaccination shown on the left column of the Table 1 below. The logic of these statements is challenged in the right column of the table. Additional public relations information from the CDC website is provided in Apendices 1-3.

Duane Kilgus, upon receipt of the rebuttal responses wrote, "Thank you for your concerns. I am sorry, this is not a forum for us to debate specific points related to the incidence of disease or adverse reactions. We will take your comments under advisement."

It is interesting that a recent manuscript, *Duration of hepatitis B immunity in low risk children receiving hepatitis B vaccinations from birth* by K. M. Petersen et al. of the Arctic Investigations Program, National Center for Infectious Diseases, CDC, Alaska Native Tribal Health Consortium, (Pediatr Infect Dis J. 2004 Jul;23(7):650-5) concludes, "Anti-HBs disappeared by 5 years of age in most children who were vaccinated with hepatitis B vaccine from birth. Although most children showed immunologic memory, one-third failed to demonstrate an anamnestic response to a booster dose."

Another recent manuscript by independent researchers (Geier MR, Geier DA. Clin Exp Rheumatol. 2004 Nov-Dec;22(6):749-55) found that Hepatitis B vaccine was associated with autoimmune conditions including arthritis, rheumatoid arthritis, myelitis, optic neuritis, multiple sclerosis (MS), Guillain Barre Syndrome (GBS), glomerulonephritis, pancytopenia/thrombocyto-penia, fatigue, and chronic fatigue, and Systemic Lupus Erythematous (SLE). The analysis concluded, "Evidence from biological plausibility, case-reports, case-series, epidemiological, and now for positive re-challenge and exacerbation of symptoms, and events in identical twins was presented. One would have to consider that there is causal relationship between Hepatitis B vaccine and serious autoimmune disorders among certain susceptible vaccine recipients in a defined temporal period following immunization. In immunizing adults, the patient, with the help of their physician, should make an informed consent decision as to whether to be immunized or not, weighing the small risks of the adverse effects of HBV with the risk of exposure to deadly hepatitis B virus."

In response to the question, "For whom is the hepatitis B vaccine recommended?" CDC answers, "Adults who are at increased risk of HBV infection and who should receive the vaccine include: sexually active heterosexual adults with more than one sex partner in the prior 6 months or a history of a sexually transmitted disease; homosexual and bisexual men; illicit injection drug users, persons at occupational risk of infection; hemo-

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dialysis patients; and household and sex contacts of persons with chronic HBV infection; clients and staff of institutions for the developmentally disabled."

According to a new study ("To vaccinate or not to vaccinate--that is the question: why are some mothers opposed to giving their infants hepatitis B vaccine?" by Maayan-Metzger A, Kedem-Friedrich P, and Kuint J, published in *Vaccine* and available online at http://dx.doi.org/10.1016/j.vaccine.2004.10.015 since November 20, 2004), women who complied with hepatitis B vaccination believed that the reason for giving the vaccine was to "protect the baby" and they had "trust in the doctors". Women who prevented their babies from being vaccinated were "more educated and had a higher income level" than the compliant group. The authors concluded that reasons for preventing infant vaccination "were not due to ignorance". Mothers denying vaccination gave explanations such as, (1) "The child is too young"; (2) "Vaccines are dangerous"; (3) "Doctors vaccinate without consideration"; (4) "Vaccines cause trauma to the baby." Ironically, the authors suggested, "In order to overcome this harmful trend, the medical community must supply counter information that encourages vaccination." Editors of *Medical Veritas*™ trust your decision will be an informed one and the more educated one.

Table 1. CDC response vs. Medical Veritas Rebuttal Response

CDC Response	***Medical Veritas* Rebuttal Response**
Nearly every vaccine we have now will show more adverse reactions than cases or deaths from the actual disease because of the success of vaccines. Hepatitis B vaccine at birth has to do with the possibility of maternal transmission of Hepatitis B. I would use these numbers below to make your point.	So, unless a mother is infected, then the baby is not at risk. Yet, the recommendation is to vaccinate anyway? What is the logic or justification for this?
Hepatitis B is the cause of up to 80% of hepatocellular carcinomas, and is second only to tobacco among known human carcinogens. More than 250,000 persons die world wide each year of hepatitis B associated acute and chronic liver disease.	The larger number of the 250,00 persons that die are in other foreign and third world countries; actually about 10,000 Hepatitis B cases were reported in the U.S. in 1997 with 306 cases occurring in children under 14. Perhaps you [Dr. Kilgus] could provide the statistic for number of deaths in the U.S. among children aged 0 to 1? It is unethical to quote large numbers that are not applicable to the conditions of the U.S. Otherwise, based on the world population, we would have to be telling the parents that 1 out of 5 children (or 20%) under the age of 5 dies from starvation. While this statistic is valid for Africa, it is skewed if we limit the discussion to children in the U.S.
Fulminant hepatitis occurs in about 1% or 2% of persons, with mortality rates of 63% to 93%. About 200 to 300 Americans die of fulminant disease each year. Although the consequences of acute HBV infection can be severe, most of the serious complications associated with HBV infection are due to chronic infection. An estimated 3,000 to 4,000 persons die of hepatitis B-related cirrhosis each year in the United States. Persons with chronic HBV infection are at 12 to 300 times higher risk of hepatocellular carcinoma than noncarriers. An estimated 1,000 to 1,500 die each year in the United States of hepatitis B-related liver cancer.	What could all the infants who are virtually at zero risk for Hepatitis B virus possibly have to do with the cohort of older individuals that the CDC discusses here? Why expose infants to adverse reactions of vaccination? CDC states, "Serious systemic adverse reactions and allergic reactions are *rarely reported* following hepatitis B vaccine." In fact, the VAERS passive database likely contains only 10% of the true number of adverse reactions. CDC files contain 32,731 reports of possible reactions following hepatitis B since 1991, including 10,915 emergency room visits, 685 life-threatening reactions, 3,700 hospitalizations, 1,200 disabilities, and 618 deaths. In 1996 alone, VAERS reports 1,080 adverse reactions from hepatitis B vaccine in the 0 to 1 age group, with 47 deaths reported.
The most common adverse reaction following hepatitis B vaccine is pain at the site of injection, reported in 13% to 29% of adults and 3% to 9% of children. Mild systemic complaints, such as fatigue, headache, and irritability have been reported to 11% to 17% of adults and 0% to 20% of children. Low-grade fever (>37.7°C) has been reported in 1% of adults and 0.4% to 6.4% of children. Serious systemic adverse reactions and allergic reactions are rarely reported following hepatitis B vaccine.	It is clear from CDC's own data, as well as that of other researchers, that the hepatitis B vaccination program in the U.S. is a failed concept, causing considerably more harm than good. Further, CDC continues to obscure this truth by using inappropriate and misleading rhetoric disguised as fact.

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Appendix 1. CDC Public Relations: Hepatitis B Vaccine: Fact Sheet

Available at http://www.cdc.gov/ncidod/diseases/hepatitis/b/factvax.htm

Hepatitis B Vaccine: Fact Sheet

First Anti-cancer Vaccine

- Hepatitis B vaccine prevents hepatitis B disease and its serious consequences like hepatocellular carcinoma (liver cancer). Therefore, this is the first anti-cancer vaccine.

Safe and Effective

- Medical, scientific and public health communities strongly endorse using hepatitis B vaccine as a safe and effective way to prevent disease and death.
- Scientific data show that hepatitis B vaccines are very safe for infants, children, and adults.
- There is **no confirmed evidence** which indicates that hepatitis B vaccine can cause chronic illnesses.
- To assure a high standard of safety with vaccines, several federal agencies continually assess and research possible or potential health effects that could be associated with vaccines.

Vaccine Schedule

- Printable childhood and adult immunization schedules, 2003: National Immunization Program, CDC
- If the vaccination series is interrupted after the first dose, the second dose should be administered as soon as possible. The second and third doses should be separated by an interval of at least 2 months. If only the third dose is delayed, it should be administered when convenient.
- Recommended dosages and schedules of hepatitis B vaccines

Booster Doses

- Current data show that vaccine-induced hepatitis B surface antibody (anti-HBs) levels may decline over time; however, immune memory (anamnestic anti-HBs response) remains intact indefinitely following immunization. Persons with declining antibody levels are still protected against clinical illness and chronic disease.
- For health care workers with normal immune status who have demonstrated an anti-HBs response following vaccination, booster doses of vaccine are not recommended nor is periodic anti-HBs testing.

Post-vaccination Testing

- After routine vaccination of infants, children, adolescents, or adults post-vaccination testing for adequate antibody response is not necessary.
- Post-vaccination testing IS recommended for persons whose medical management will depend on knowledge of their immune status.

This includes persons who:

- are immunocompromised (e.g., hemodialysis patients)
- received the vaccine in the buttock
- are infants born to HBsAg (hepatitis B surface antigen)-positive mothers
- are healthcare workers who have contact with blood
- are sex partners of persons with chronic hepatitis B virus infection
- Post-vaccination testing should be completed 1-2 months after the third vaccine dose for results to be meaningful. A protective antibody response is 10 or more milliinternational units (>=10mIU/mL).

Adverse Events

- Case reports of unusual illnesses following vaccines are most often related to other causes and not related to a vaccine. Whenever large number of vaccines are given, some adverse events will occur coincidentally after vaccination and be falsely attributed to the vaccine.
- Anyone believing they have had a possible reaction or adverse health effect from a vaccine should report it to their health care provider. The Vaccine Adverse Events Reporting System (1-800-822-7967) receives reports from health care providers and others about vaccine side effects.

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Appendix 2. CDC Public Relations Information: Hepatitis B Vaccine Fact Sheet

Available at http://www.cdc.gov/nip/vacsafe/concerns/hepB/genHepb.htm

Hepatitis B Vaccine
FACT SHEET

> Each year in the United States an estimated 200,000 people are newly infected with hepatitis B virus (HBV), of whom more than 11,000 are hospitalized and 20,000 remain chronically infected. Overall, an estimated 1.25 million people in the United States have chronic HBV infection, and 4,000 to 5,000 people die each year from hepatitis B-related chronic liver disease or liver cancer. Hepatitis B vaccination has contributed to a substantial decrease in infection B particularly in children and adolescents among whom vaccination coverage has been highest. Hepatitis B vaccine is the first vaccine that prevents a type of cancer.

> Concerns about possible adverse effects of hepatitis B vaccine are being taken seriously and carefully controlled scientific studies are underway to examine whether vaccination is associated with serious neurological disease in a small number of people. There is no confirmed scientific evidence that hepatitis B vaccine causes chronic illnesses (including multiple sclerosis, chronic fatigue syndrome, rheumatoid arthritis, optic neuritis or other autoimmune disorders.). Serious adverse events reported after receiving hepatitis B vaccine are very uncommon and may represent coincidence rather than causation. Given the frequency and severity of hepatitis B infection, the benefit of vaccination far outweighs the known and potential risks.

> Hepatitis B infection is acquired by exposure to blood or body fluids from an infected person. It is about 100 times easier to transmit than is HIV, the virus that causes AIDS. Blood and body fluid exposure, while more frequent among some "high risk" groups, can occur among persons of all ages, and social or ethnic groups. When a child acquires hepatitis B infection, it is more likely to become chronic with potentially severe consequences. Antibiotics cannot cure hepatitis B infection - prevention is the best option. This provides a rationale for recommending universal childhood hepatitis B vaccination. This recommendation also is based on the inability to predict which children will go on to become high-risk adolescents and the better coverage of childhood vaccinations programs compared with those for adolescents or adults.

If you have any questions on vaccines or vaccine safety, please contact:

The National Immunization Information Hotline
1-800-232-2522 (English)
1-800-232-0233 (Spanish)

Or, visit the following web sites: www.cdc.gov/ncidod/diseases/hepatitis
www.cdc.gov/od/oc/media

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Appendix 3. CDC Public Relations Information: Hepatitis B Vaccine Questions and Answers

Available at http://www.cdc.gov/nip/vacsafe/concerns/hepB/q&a.htm

1. What is hepatitis B?

Hepatitis B is a serious disease caused by the hepatitis B virus (HBV) which is present in the blood and body fluids of an infected individual. The virus can be transmitted from mother to baby at birth as well as through unprotected sexual intercourse, and unsterilized needles. Transmission is also possible with household contacts and from child to child. HBV infection can cause acute illness that leads to loss of appetite; tiredness; pain in muscles, joints, or stomach; diarrhea or vomiting; and yellow skin or eyes (jaundice). HBV can also cause chronic infection, especially in infants and children, that leads to liver damage (cirrhosis), liver cancer, and death. Each year in the United States, an estimated 200,000 people have new HBV infections, of whom more than 11,000 people are hospitalized and 20,000 remain chronically infected. Overall, an estimated 1.25 million people in the United States have chronic HBV infection, and 4,000 to 5,000 people die each year from hepatitis B related chronic liver disease or liver cancer *(Centers for Disease Control and Prevention (CDC), 1990; Margolis, 1991; West, 1992)*.

2. How is hepatitis B vaccine used to prevent hepatitis B and its related complications?

Hepatitis B vaccine prevents both HBV infection and those diseases related to HBV infection. It has been available since 1982. Hepatitis B vaccines currently available in the United States are made using recombinant DNA technology, and contain only a portion of the outer protein of HBV or hepatitis B surface antigen [HBsAg] *(Emini, 1986; Stephenne, 1990)*. The vaccine does not contain any live components. The vaccine is given as a series of three intramuscular doses. More than 95 percent of children and adolescents, and more than 90 percent of young, healthy adults develop adequate antibody to the recommended series of three doses *(Szmuness, 1980; Zajac, 1986; Andre, 1989)*. Persons who respond to hepatitis B vaccine are protected against acute hepatitis B as well as the chronic consequences of HBV infection, including cirrhosis and liver cancer *(CDC, 1991 a; Hadler, 1992)*.

3. For whom is hepatitis B vaccine recommended?

The Advisory Committee on Immunization Practices (ACIP) recommends hepatitis B vaccine for everyone 18 years of age and younger, and for adults over 18 years of age who are at risk for HBV infection *(CDC, 1991 a,b; CDC, 1996; CDC, 1997; ACIP, 1998; Humiston, 1998)*. Hepatitis B vaccine has been recommended as a routine infant vaccination since 1991, and as a routine adolescent vaccination since 1995 *(CDC, 1991,CDC 1996)*. Adults who are at increased risk of HBV infection and who should receive the vaccine include: sexually active heterosexual adults with more than one sex partner in the prior 6 months or a history of a sexually transmitted disease; homosexual and bisexual men; illicit injection drug users, persons at occupational risk of infection; hemodialysis patients; and household and sex contacts of persons with chronic HBV infection; clients and staff of institutions for the developmentally disabled *(CDC, 1991 b)*.

4. Why is vaccination for hepatitis B required by many states for school entry?

Without state and local immunization laws many more people would become sick or die from hepatitis B. Immunization requirements also help protect persons who are too sick to receive the vaccine. This is done by ensuring that a large number of persons are protected with vaccine which prevents transmission of hepatitis B on to others who are not protected. The enforcement of mandatory school immunization laws has significantly increased vaccine coverage (Robbins, 1981). Before hepatitis B vaccine was recommended for all children there were approximately 30,000 infants and children each year who would become infected with hepatitis B (*Margolis, 1991*). Vaccination requirements for enrollment/attendance at day care and programs like Head Start and public and private schools and colleges in the United States, are established at the State and local levels. Laws or regulations are typically enacted by State legislatures with authority granted to State and/or local health departments for rule making, monitoring and enforcement. There are no Federal laws requiring vaccinations for day care, Head Start, school or college attendance.

Rule making is usually based on immunization schedule recommendations established by nationally recognized authorities, including the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatric's (AAP) Red Book Committee. Vaccination requirements between states vary slightly but all states have requirements in some combination against diphtheria, tetanus, pertussis, measles, mumps, rubella and polio. Vaccination against *haemophilus influenzae* type b is required for attendance at day care centers and Head Start programs in most states. More states are adding requirements for vaccination against hepatitis B and varicella (chickenpox) disease to day care and/or school attendance requirements.

In every instance, such requirements have significantly reduced illnesses and death from diseases that vaccines prevent. Vaccine coverage levels are higher in school-age children and those enrolled in licensed day care centers and Head Start programs then among any other comparable group of infants, children or adolescents. These levels have been well documented at or above 95 percent in all states for many years.

Vaccination requirements for day care and school attendance are also successful in other ways. For example, children with leukemia or who suffer from problems with their immune system may not receive some vaccines. The effect of compulsory and mass vaccination programs is to better reduce the likelihood of exposure of these children to diseases that could be life-threatening. The greater the number of children who refuse vaccination, the greater the risk of disease is to persons who can not be immunized because of health reasons. Likewise, the community benefits by having a large number of persons vaccinated and protected from disease. High coverage levels limit the introduction or spread of disease, benefiting everyone.

The 1996 ACIP recommendations on adolescent immunization is jointly endorsed by the AAP, the American Academy of Family Physicians, and the American Medical Association. The statement reads in part: "In the United States, state vaccination laws and regulations for kindergarten through grade 12 are effective in ensuring high coverage levels among school attendees and have led to a marked decline of overall morbidity and mortality from vaccine-preventable diseases. Additional state laws and regulations requiring documentation of up-to-date immunization of adolescents, or a reliable history of disease-related immunity, at entry into sixth grade would ensure implementation of these recommendations and would lead to further reduction in transmission of vaccine-preventable diseases."

5. Why not vaccinate children in those families where there is the highest risk of HBV infection, rather than vaccinating all infants/children?

Routine immunization of infants and adolescents is recommended for several reasons. One is that there is a large disease burden attributable

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to HBV infections that occur among children. Approximately 30,000 infants and children were infected each year before routine infant hepatitis B immunization began and CDC estimates that one-third of the chronic HBV infections in the United States come from infected infants and young children. The majority of these infections occur among children of mothers who are not infected with HBV and thus would not be prevented by perinatal hepatitis B prevention programs. Other than for infants born to HBV infected pregnant women, there is no way to identify and selectively vaccinate those children at risk of infection (*Margolis, 1991)*.

Another reason we vaccinate infants and older children is that it will provide them protection against exposure to HBV infection when they are older adolescents and adults. While most HBV infections occur among older adolescents and young adults, vaccination of persons in high risk groups has generally not been a successful public health strategy. In addition, about 30 percent of persons do not know where they acquired their acute HBV infection *(Alter, 1990)*.

6. Is hepatitis B vaccine safe?

Hepatitis B vaccines have been shown to be very safe when given to infants, children or adults *(CDC, 1991 a; Greenberg, 1993)*. More than 20 million persons have received hepatitis B vaccine in the United States and more than 500 million persons have received the vaccine worldwide. The most common side effects from hepatitis B vaccination are pain at the injection site and mild to moderate fever *(Szmuness, 1980; Francis, 1982; Zajac, 1986; Stevens, 1985; Andre, 1989; Greenberg, 1993)*. Studies show that these side effects are reported no more frequently among those vaccinated than among persons not receiving vaccine *(Szmuness, 1980; Francis, 1982)*. Among children receiving both hepatitis B vaccine and diphtheria-tetanus-pertussis (DTP) vaccine, these mild side effects have been observed no more frequently than among children receiving DTP vaccine alone *(CDC, 1991 a; Greenberg, 1993)*.

Whenever large numbers of individuals are vaccinated, rare reports of subsequent adverse events occur. In order to determine whether they are caused by or are just coincidental events following vaccination requires further study. Such reports do not mean that the vaccine is unsafe, since millions of persons have received the vaccine without any problem.

7. Is there an association between hepatitis B vaccine and serious side effects?

Serious side effects reported after receiving hepatitis B vaccine are very uncommon *(Andre, 1989; CDC, 1991 a; Greenberg, 1993; Niu, 1996)*. While reported, there is no confirmed scientific evidence that hepatitis B vaccine causes chronic illness, including multiple sclerosis, chronic fatigue syndrome, rheumatoid arthritis, or autoimmune disorders. There is no risk of HBV infection from the vaccine.

Large-scale hepatitis B immunization programs in Taiwan, Alaska, and New Zealand have observed no association between vaccination and the occurrence of serious adverse events. Furthermore, surveillance of adverse events in the United States after hepatitis B vaccination have not shown a clear association between hepatitis B vaccine and the occurrence of serious adverse events including Guillain-Barre' syndrome, transverse myelitis, optic neuritis, and seizures *(Shaw, 1988; CDC, 1991 a; Niu, 1996; Niu 1998 CDC, unpublished data)*. Additional evaluations are ongoing. A recent study suggested persons developing rheumatoid arthritis after hepatitis b vaccination were genetically at-risk for rheumatoid arthritis (*Pope, 1998*).

A low rate of anaphylaxis (hives, difficulty breathing, shock) has been observed in vaccine recipients based on reports to the Vaccine Adverse Event Reporting System (VAERS), with an estimated incidence of 1 in 600,000 vaccine doses distributed. One case has been reported in 100,763 children (10-11 years old) vaccinated with recombinant vaccine in British Columbia and no cases were observed in 166,757 children vaccinated in New Zealand. Although none of the persons who developed anaphylaxis died, anaphylactic reactions can be life-threatening, and therefore further vaccination with hepatitis B vaccine is contraindicated in persons with a history of anaphylaxis after a previous dose of vaccine. There have been rare reports of hair loss after hepatitis B vaccination, with the majority of individuals regrowing their hair (*Wise, 1997*). Studies are in progress to better quantify the possible slight risk of hair loss.

Any presumed risk of adverse events associated with hepatitis B vaccination must be balanced with the expected 4,000 to 5,000 HBV-related liver disease deaths that would occur without immunization, assuming a 5 percent lifetime risk of HBV infection.

8. Does hepatitis B vaccination cause demyelinating diseases such as multiple sclerosis (MS)?

The scientific evidence to date does not support hepatitis B vaccination causing MS or other demyelinating diseases.

Multiple sclerosis is a disease of the central nervous system characterized by the destruction of the myelin sheath surrounding neurons, resulting in the formation of "plaques." MS is a progressive and usually fluctuating disease with exacerbations (patients feeling worse) and remissions (patients feeling better) over many decades. Eventually, in most patients, remissions do not reach baseline levels and permanent disability and sometimes death occurs. The cause of MS is unknown. The most widely held hypothesis is that MS occurs in patients with a genetic susceptibility and that some environmental factors "trigger" exacerbations. MS is 3 times more common in women than men, with diagnosis usually made as young adults.

The concern that hepatitis B vaccination may cause MS or exacerbate it derives from case reports and media attention in France and, more recently, televised news reports in the United States. However, it is possible that these MS case reports are purely coincidental to hepatitis B vaccination. Carefully controlled studies (currently underway) are needed to determine the nature of these reports.

Other than these case reports, what then is the current scientific evidence that hepatitis B vaccination causes MS or other demyelinating diseases? First, extensive pre-licensure clinical trials did not document such an effect. Second, hundreds of millions of persons worldwide have been immunized without developing MS (or any other autoimmune disease). This finding provides important negative evidence as well as an appropriate framework for assessing this possible association-namely, that if vaccination causes MS, it does so extremely rarely.

Third, prospective studies of MS patients have shown that exacerbations appeared to be more frequent after nonspecific viral illnesses *(Sibley, 1985)*. This is presumably due to generalized stimulation of the immune system that occurs with such infections *(Owen, 1980)*. There have been reports of exacerbations of MS following immunization of persons who already had MS but no evidence that vaccination increases the rate of MS in otherwise healthy persons. Given the large number of vaccinations administered worldwide, it is not surprising that surveillance systems in the U.S., France, and elsewhere *(Quast, 1991)*, have received some reports of MS temporally (coincidentally) associated with vaccinations. As with all such case reports, however, they only constitute signals of possible causal associations. Further controlled studies are necessary to establish causation.

A recent (and largest to date) multi-center randomized double-blind placebo controlled trial of influenza immunization in 104 MS patients

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failed to show any difference in attack rate or disease progression over 6 months between vaccines and placebo recipients *(Miller, 1997)*. This study suggests that even if a vaccine can exacerbate MS, it must do so only among a small minority of MS patients.

Fourth, whether vaccinations actually cause an overall excess of MS in the population (vs. being just one of multiple possible triggers for MS in genetically susceptible individuals, without causing an excess of MS) can only be evaluated in a population-based study.

Finally, MS is an autoimmune disorder in which a person's antibodies attack the body's own myelin (a sheath that covers the nerves). According to the "molecular mimicry" hypothesis, the hepatitis b vaccine must somehow be similar to the myelin in three dimensional structure thus provoking anti-myelin antibodies to form. However, recent research (as yet unpublished) using genetic sequencing has not shown a similarity between hepatitis B vaccine and myelin basic protein. This research raises doubts about the validity of the "molecular mimicry" hypothesis.

Although scientific evidence to date does not support hepatitis B vaccination causing multiple sclerosis (MS) or other demyelinating diseases, studies are currently being organized in the Vaccine Safety Datalink project at CDC and elsewhere because of public concern about this issue in France and other places and because there is little available research on this specific topic *(Chen, 1997)*. Computerized medical records on approximately 5 million or 2 percent of the U.S. population are available in this study. It will probably be at least one year, however, before any results are available.

In the meantime, the concern regarding a suggested association between vaccination and MS or any other chronic illness must be weighed against the very strong evidence that vaccines have in protecting against disease and death.

9. Are there any studies being conducted to examine what relationship, if any, exists between the hepatitis B vaccine and multiple sclerosis (MS)?

YES, there are at least six research projects underway. In recent years, several unproven theories have caused concern in the general public by suggesting there is an association between the hepatitis B vaccine and demyelinating disorders, including MS. As a result, the research studies described below were developed to investigate these hypotheses further.

The first two research projects were sponsored by the French Medications Agency, an organization similar to the United States Food and Drug Administration (FDA). One was a case-control study based on clinical reports of demyelinating disorders that were seen in 11 neurology centers across France. The second was also a case-control study. This research project was based on approximately 4 million patients receiving care through general practices in the United Kingdom. A third project was done by one of the vaccine manufacturers. Preliminary results from all three studies were shared with the French Medications Agency and the Viral Hepatitis Prevention Board in September 1998. These results are not yet available to others. If determined to be scientifically sound, these papers will be published in peer-reviewed medical journals in the near future.

The CDC's National Immunization Program (NIP) is using the Vaccine Safety Datalink (VSD) Project to examine whether there is an increased risk of MS following hepatitis B vaccination. The VSD contains data on more than 6 million people which is collected from four health maintenance organizations on the west coast. All vaccines administered within the study population are recorded. Available data include vaccine type, date of vaccination, concurrent vaccinations, the manufacturer, lot number and injection site. After vaccine administration, the medical records are monitored for potential health effects occur around the time of immunization. In this project, a case-control research design is being used to study patients 18 to 49 years of age without a prior diagnosis of MS or optic neuritis. NIP anticipates that within the study population, about 500 patients will be diagnosed with MS by a physician using specific criteria. This study is being funded and organized by CDC in collaboration with Kaiser Permanente HMO's in Portland, Oregon, Northern California, and Southern California, and Group Health Cooperative of Puget Sound in Seattle, Washington. Research results will be available within the next few years.

Data from the Harvard Nurses Health Study (NHS) are being used to examine whether a possible relationship between hepatitis B vaccine and MS exists. NHS data collection began in 1976 and longitudinal follow-up is on-going. The study population includes a randomly selected cohort of nurses age 25-55. Researchers are using a nested case-control design with approximately 200 MS cases having been identified. Cases are being verified by follow-up questionnaires to the patient's physician as well as classification by a blinded panel of neurologists. Two control groups are being used. Every MS patient will be matched with five healthy controls and one control with a diagnosis of breast cancer (to control for recall bias). This study is being supported by Merck and results are expected during the fall of 1999.

Researchers at the University of Lyon in France are examining whether immunization (with any vaccine) increases the short-term risk of relapse in patients already diagnosed with MS. This project, known as the VACCIMUS study, employs a case-crossover design (where cases also serve as controls). The study includes 600 MS patients identified from neurology departments belonging to a network specializing in MS. Researchers will compare vaccination history in the three months prior to a relapse with a control period. This project is funded, in part, by Pasteur Merieux Connaught and results are expected in the fall of 1999.

10. Does the scientific evidence support a causal link between hepatitis B vaccine and infant deaths?

No. The National Center for Health Statistics, the primary Federal organization responsible for the collection, analysis, and report of health statistics, shows a consistent decline in new born deaths (infants from birth to 30 days of age) since 1935. Much of this decline is due to great improvements in sanitation, health care, and infectious disease control that have taken place during this time. Since 1991, infants have been receiving hepatitis B vaccine on a routine basis starting as early as the first day of life. Examination of newborn deaths during this time does not reveal any increase in reports, but continues to show a steady decrease in numbers of newborn deaths (*Kiely, 1998*). In a review of the 1991-1994 reports to VAERS, there were no unusual reports believed to be causally related to hepatitis b vaccine that occurred in infants given the vaccine (*Niu et al., 1996*).

Some persons have questioned whether Sudden Infant Death Syndrome (SIDS) deaths could be related to vaccines. Several studies have looked at an association between SIDS and vaccines. The Institute of Medicine reviewed these studies and concluded that there was no evidence to prove a relationship existed between DTP and SIDS (*IOM,1991*). Almost all infants are vaccinated during the first year of life. Therefore, any infant with a medical illness or who dies is likely to have been vaccinated earlier in life. Since vaccinations are usually administered at ages 2 months, 4 months and 6 months, a statistically measurable chance of any event, death or otherwise, can occur within 24 hours of vaccinations by coincidence alone (*AAP, 1995*). Medical scientists have no convincing evidence or proof that there is a connection between SIDS and vaccines. In fact, deaths from SIDS have been decreasing in the past few years (*Willinger et al., 1998*). If SIDS were

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some how related to hepatitis B vaccines we would expect to see an increase in SIDS deaths since 1991 after hepatitis B vaccine was recommended for all infants. A few years ago some people had questioned whether the Diphtheria, Pertussis, Tetanus (DPT) vaccine was somehow related to SIDS deaths. In one study, scientists examined data from the National Institute of Child Health and Human Development's, Sudden Infant Death Syndrome Cooperative Epidemiological Study. The results confirmed earlier preliminary findings that DTP immunization was not a key factor in the occurrence of SIDS (*Hoffman et a., 1987*). In another analysis of the question looking at VAERS data scientists determined how many cases of SIDS would be expected to occur around the time a DPT vaccine is given based on chance alone. Based on birth and immunization rates, and the incidence of SIDS, scientists expected approximately 34 cases of SIDS to occur within 24 hours of receipt of DPT vaccine based purely on chance. Therefore 34 cases of SIDS would be expected to be reported to the Vaccine Adverse Event Reporting System unrelated to the vaccine but occurring around the time DPT vaccine was given. The average number of observed reports of all deaths, not just SIDS, within 24 hours of DTP reported to the Vaccine Adverse Event Reporting System was 22 reports for the year the analysis took place (*AAP, 1992*). Today more is understood about the cause of SIDS. Recent evidence shows that babies who are positioned on their stomach have a greater risk of SIDS. Scientists believe that this sleeping position may interfere with the babies ability to breathe properly resulting in the increased risk of SIDS death (*AAP, 1992*).

11. How is vaccine safety monitored after it is licensed for use?

The Vaccine Adverse Event Reporting System (VAERS) ensures the safety of vaccines distributed in the United States. VAERS reports are usually submitted by health care professionals or vaccine manufacturers, however anyone can submit a report to VAERS. VAERS is administered, monitored and analyzed jointly by the CDC and FDA. Persons who wish to report a possible health effect related to a vaccine should notify their health care provider and can also call the VAERS program at 1-800-822-7967.

12. Can the Vaccine Adverse Event Reporting System (VAERS) be used to determine the number of side effects that occur after people receive hepatitis B vaccine?

No. There are several reasons why numbers of cases from VAERS can not be used to determine numbers of side effects that occur after people receive vaccines. First, VAERS accepts all reports of adverse health events which follow vaccination regardless of the cause. Therefore VAERS contains a mix of vaccine-caused side effects and health effects not related to vaccines. Second, the same case may be reported to VAERS more than once. This can happen when different people file the same report. For instance, a health care provider, a parent and a manufacturer may all send VAERS the same report resulting in several entries of the same case into the data base. Other reports are filed more than once because vaccines are typically given in combination with other vaccines so the same report may be filed separately under each vaccine. Reports are also filed separately from the same case under each adverse effect listed. For instance, one report that listed fever and headache and persistent crying would be filed separately into the system under each health effect reported. In addition the details and diagnosis of a given report may be incomplete or inaccurate depending on a person's access to complete clinical information. Without fully understanding these and other limitations, VAERS data can easily be misinterpreted or analyzed incorrectly leading to false conclusions about reports of health effects occurring after vaccine administration. (*Chen et al., 1994; Ellenberg et al., 1997*).

Serious health events reported to VAERS, such as reports of death, are followed up by VAERS staff. Autopsy and death certificate records are requested and reviewed for each death report. Follow up for other serious reports is done to collect additional clinical information including recovery status. The vast majority of death reports to VAERS are later determined not to be related to vaccines.

Scientists use VAERS data to look at overall trends or unusual occurrences. In a review of the 1991-1994 reports to VAERS, no unusual reports felt causally related to hepatitis b vaccine occurred in infants given the vaccine were found. (*Niu et al., 1996*). Of the 12 million doses of hepatitis B vaccine given in these age groups, the vast majority reported no side effects. Another study reviewed preliminary VAERS data which at first suggested that more severe adverse events may occur in children receiving one brand of hepatitis B vaccine, however further analysis found that this was false and not a true difference. This study showed some of the problems involved with interpreting VAERS data (*Niu et al., 1998*).

In addition, data from the National Center for Health Statistics, the primary Federal organization responsible for the collection, analysis, and reports of health statistics, show a consistent decline in new born deaths (infants from birth to 30 days of age) since 1935. Much of this decline is due to great improvements in sanitation, health care, and infectious disease control that have taken place during this time. Since 1991, infants have been receiving hepatitis B vaccine on a routine basis starting as early as the first day of life. Examination of newborn deaths during this time does not reveal any increase in reports, but continues to show a steady decrease in numbers of newborn deaths (*Kiely, 1998*).

13. Where can I find more information about hepatitis B and hepatitis B vaccine?

Further information regarding hepatitis B and hepatitis B vaccine can be obtained by contacting the Hepatitis Hotline of the Hepatitis Branch, CDC at 1-888-4HEP-CDC (or 1-888-443-7232) and by contacting your local or State health department. For information about vaccines contact the National Immunization Program, CDC Information Hotline at 1-800-232-2522 (English) or 1-800-232-0233 (Spanish); or visit the CDC National Immunization Program website at http:/www.cdc.gov/nip, or the CDC Hepatitis Branch web site at http://www.cdc.gov/ncidod/diseases/hepatitis/hepatitis.htm

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