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VACCINE SAFETY – A REVIEW AND A STUDY OF NEWBORN HEPATITIS B VACCINE COVERAGE DURING A PERIOD OF CHANGING RECOMMENDATIONS

By

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ABSTRACT

VACCINE SAFETY – A REVIEW AND A STUDY OF NEWBORN HEPATITIS B VACCINE COVERAGE DURING A PERIOD OF CHANGING RECOMMENDATIONS

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Thanks to vaccines, many once-prevalent devastating diseases are now rarely seen in the United States. Despite the remarkable success of the U.S. National Immunization Program, individual safety concerns about vaccines have become a leading topic of public debate.

Temporary changes in the hepatitis B vaccination schedule due to concerns about thimerosal used as a preservative in that vaccine led to the Michigan Thimerosal-Impact Study – an observational study designed to assess the impact of recommendation changes on the proportion of newborns receiving the hepatitis B vaccine before hospital discharge. This study focused on births where the mother's hepatitis B surface antigen (HBsAg) status was unknown, because infants born to women who are not screened for HBsAg are at greater risk of perinatal infection (compared to screened mothers). Furthermore, this study targeted births where the mother's HBsAg status was unknown rather than positive because the Michigan Department of Community Health has a perinatal hepatitis B coordinator that already tracks births to HBsAg-positive women to ensure these infants are treated accordingly. This study's results indicate a need to renew efforts to begin hepatitis B vaccination at birth, especially for infants at higher risk of infection.

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INTRODUCTION

With the exception of safe water, no other health intervention has impacted the improvement of the human condition as much as immunization.[1] During the past century, the average life expectancy of U.S. citizens has increased by 30 years.[2] Thanks to vaccines, many once-prevalent devastating diseases are now rarely seen in the United States.

In 1796, Edward Jenner inoculated James Phipps with cowpox and called the procedure vaccination.[3] Within a few years of Jenner's first scientific demonstration of the use of vaccination against smallpox, people throughout the world embraced the practice. Generations of people have died or become disfigured from smallpox since the disease first appeared in northeastern Africa about 10,000 years before the appearance of Christ.[4] This disease that historically brought down empires today has been eradicated worldwide. The last indigenous case of smallpox occurred in 1977 (Somalia); global eradication was declared two years later by the World Health Organization (WHO).[5]

Protection from vaccine-preventable diseases, such as smallpox, is readily obtained through immunization. While disease management is necessary for the maintenance of a healthy population, the optimal goal is to prevent a disease from ever occurring. In order to understand the basis for recommendations of vaccine usage, it's important to understand the basics of vaccines themselves.

There are two primary mechanisms for acquiring immunity to infectious diseases – active and passive. Active immunity is protection produced by a person's own immune system.[6] It relies on the ability of the host to generate an immune response following exposure to foreign antigens. Passive immunity is the other type of protection, and it is

conferred to a host through products produced by an animal or human, usually via injection (e.g., hepatitis B immunoglobulin).[6] Individuals can acquire immunity against vaccine-preventable diseases through immunization, where the goal is to elicit an immune response that mimics natural infection (i.e., active immunity). There are two basic types of vaccines: live attenuated and inactivated.

Vaccines are referred to as being *attenuated* if the bacteria or viruses they contain have been rendered nonpathogenic (e.g., MMR vaccine and yellow fever vaccine).[3] These live attenuated organisms must then replicate within the host to induce a protective immune response. *Inactivated* vaccines refer to either viruses or bacteria that are killed or components of the microorganism that are extracted and purified (e.g., polio vaccine and pertussis vaccine).[3] Receipt of inactivated vaccines cannot cause the disease they're meant to provide protection against. Several doses are usually required, though, to boost the specific antibody level in the host. Microorganisms can also be genetically altered to produce either live attenuated or inactivated vaccines, a process which can result in *recombinant* vaccines (e.g., hepatitis B vaccine).[6]

Immunization programs can be viewed broadly as serving two purposes. First, vaccines help to prevent individuals from contracting the diseases that they've been inoculated against. Second, vaccination of many individuals within a community helps to establish herd immunity. Herd immunity is a level of immunity in a population that is sufficient to prevent epidemics of a given communicable disease and prevent acquisition of disease by those who can not be immunized (e.g., too young, immunocompromised, concurrent disease states, etc.). Herd immunity is closely related to the basic reproductive rate, which Giesecke defines as:

"...the average number of persons directly infected by an infectious case during his entire infectious period, when he enters a totally susceptible population."[7]

The higher the basic reproductive rate is for an infectious disease, the greater the proportion of a community will have to be immunized to achieve herd immunity and prevent epidemicity. Exemptors (i.e., individuals who refuse vaccination or persons unable to access or receive a vaccine) rely on herd immunity to protect them from vaccine-preventable diseases. The individual freedom of whether or not to vaccinate should be balanced with public health responsibilities, because the decision has both personal as well as public consequences.[8]

Individuals who refuse vaccination may do so for several reasons, including but not limited to: religious or philosophical grounds, medical reasons (e.g., allergies and/or compromising underlying health conditions), or safety concerns. Forty-eight states offer nonmedical exemptions (religious, philosophical) to state immunization laws, in spite of the fact that legislative mandates are key to ensuring that children receive recommended vaccinations in the U.S.[9] It has been suggested that in many states, it's easier for parents to obtain an exemption than it is to get their children immunized.[9] Despite the remarkable success of the U.S. National Immunization Program, individual safety concerns about vaccines have become a leading topic of public debate.

How does one define "safe"? If safe is defined as, "free from damage, danger, or injury"[10] then vaccines are not safe. All vaccines, just like all preventive treatments used in medicine, have possible side effects.

We as American citizens are almost prisoners of our own success. As the incidence of vaccine-preventable diseases has continued to decline, the questions

regarding vaccine safety issues have increased. Public concerns have shifted from the fear of getting disease to health risks from receiving vaccines. Because vaccines are typically given to healthy persons, a higher standard of safety is generally expected than is true for, say - prescription drugs to treat chronic conditions. When one considers the fact that many vaccines in this country are part of a recommended childhood immunization schedule, public tolerance of adverse reactions related to these products is even lower, because now one is considering a degree of risk to healthy youngsters.

Unusual health effects thought to be associated with vaccines may be true adverse reactions or associated temporally with vaccination purely by coincidence. To assure that true adverse reactions are detected as quickly as possible, the Vaccine Adverse Event Reporting System (VAERS) collects reports of adverse immunization events in the United States. VAERS was created in 1990 to unify the national effort for the collection of vaccine-associated adverse events.[11] This passive, open surveillance system places no restrictions on who may submit reports, or when they can submit them. While jointly administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), a private contractor is responsible for data collection and standardization of VAERS reports.[11] Approximately one-fifth of the annual reports received by VAERS are deemed serious enough (e.g., death, hospitalization, disability, etc.) to be followed-up by a health professional. The number of annual reports to this system now totals approximately 10,000 per year,[11] which exceeds the current reported incidence of most vaccine-preventable childhood diseases combined.[12]

Case reports of adverse events are not definitive in assessing vaccine causality, because of methodologic weaknesses such as underreporting and individual bias.[12,13]

Recognizing the need to improve the study of vaccine safety, the CDC began work on the Vaccine Safety Datalink (VSD) project – a large linked database of computerized vaccination and medical records.[12] The problems of underreporting or recall bias are reduced by the VSD project, because the databases are generated routinely and patient records number in the millions. Data collection has now been expanded to include those from infancy through adulthood, bringing the total to about 2% of the U.S. population.[14]

In June 2001, the CDC announced the setting up of the Clinical Immunization Safety Assessment (CISA) Centers Network.[15] The CISA design incorporates desirable attributes of both the VAERS and VSD projects, in an effort to improve the understanding of vaccine safety issues. CISA Centers will combine the detail of individual, patient level adverse events seen by clinicians with the standardization of routine reporting. Beyond enhancement of the understanding of known adverse vaccine reactions, the CISA project will evaluate newly hypothesized relationships originating from both VAERS data and the VSD project.

There is also a federal program designed to compensate families for the adverse effects of vaccines. In 1987, Congress created the National Vaccine Injury Compensation Program (NVIP) fund.[16] Because some companies at the time were threatening to quit the vaccine business, the federal government set up the program as a way to protect manufacturers from lawsuits brought about by injured vaccine recipients. Although the fund has paid out $1.3 billion to 1,700 families since 1988, the program has been labeled by some as being more combative than the court cases it was designed to avoid.[17] This program, however, has been credited with substantially reducing the annual number of lawsuits directed toward vaccine manufacturers.

Overview of the remainder of this thesis

Surveillance systems and compensation funds are some of the initiatives the U.S. immunization program uses to deal with the detection and provision of remedies for vaccine safety issues. The next section of this document will describe several of the most widely publicized vaccine safety concerns affecting the United States and the entire globe. This discussion will lead into a review of the history and safety profile of hepatitis B vaccine, highlighted by a detailed discussion of the scientific plausibility of the alleged association between the vaccine's preservative (thimerosal) and adverse neurologic events.

Temporary changes in the hepatitis B vaccination schedule due to concerns about thimerosal used as a preservative in that vaccine led to the Michigan Thimerosal-Impact Study – an observational study designed to assess the impact of recommendation changes on the proportion of Michigan newborns receiving the hepatitis B vaccine before hospital discharge. The results of this study and other examples to date will lay the groundwork for the conclusion of this manuscript, including recommendations to consider when making changes to proven immunization schedules.

VACCINE SAFETY CONCERNS

As was already mentioned, vaccines are not totally free from possible negative effects. All vaccines have the potential to cause adverse events. A vaccine adverse event refers to any harmful reaction, large (anaphylaxis) or small (sore limb), that occurs following receipt of the vaccine. Vaccine adverse reactions are broadly categorized into three general groups – local, systemic, and allergic.[18] Local reactions are typically the least severe yet most frequent, and they usually manifest as pain, swelling, and/or redness at the site of injection. Systemic reactions are more nonspecific and generally include symptoms such as fever, malaise, and headache. Probably the most severe of the general adverse events is allergic reaction, which rarely results in a dangerous immune system response called anaphylaxis. The most frequently occurring signs and symptoms of anaphylaxis include: urticaria and angioedema; dyspnea and wheezing; and dizziness and hypotension.[19]

Aside from anaphylaxis, some parents have voiced concerns that the increase in vaccine number and doses given to infants might be responsible for various allergic diseases. Anderson et al. performed an ecologic analysis using national and local immunization rates for several routinely administered vaccines to examine their relationship with symptoms of atopic disease in children.[20] Outcomes were measured as the prevalence of allergic rhinoconjunctivitis, atopic eczema, and wheezing in the past 12 months. Immunization rates for tuberculosis, diphtheria, tetanus, and pertussis (DTP), and measles vaccine were sought that corresponded to the approximate year of birth for study groups.

No significant associations were found between symptoms of atopic disease and vaccination rates using national figures. Negative significant associations were found at the local level between DTP and wheezing, allergic rhinoconjunctivitis, and atopic eczema and between measles vaccine and rhinoconjunctivitis and atopic eczema for the 13- to 14-year old group. Controlling for per capita gross national product (GNP) only slightly decreased significant associations.

Mass immunization of children against a variety of communicable diseases is only one of several factors that affect the immune system early in life, although this practice has increased along with various allergic diseases since the 1950s.[20] This international ecologic study by Anderson et al. does not support the idea that immunization is responsible for increases in atopic disease among children. Although ecologic studies can't exclude associations at the individual level, they may help correct for random variation encountered by values taken at the individual level. The Institute of Medicine's (IOM) Immunization Safety Review Committee recently examined five studies looking at multiple vaccinations and their potential to induce hypersensitivity reactions, and the committee concluded there was not enough evidence to accept or reject a causal relationship.[21]

Vaccines are given to children at multiple points during their development, and coincidental adverse events of many types can happen throughout that time. There are several vaccines that have received considerable publicity in recent years for their alleged associations with adverse events. Some of these safety concerns involve risks that, although rare, appear to be factual in nature, including: fears about live **polio vaccine** producing rare paralysis and **yellow fever vaccine** associated with recent deaths. Other

vaccines have gained notoriety because of their purported risks and the associated damage done to immunization coverage, including: **measles-mumps-rubella (MMR) vaccine** associated with autism-spectrum disorder and **whole-cell pertussis vaccine** leading to adverse neurologic events.

Polio vaccine

The first outbreaks of poliomyelitis were reported in Europe during the early 1800s.[22] Throughout the nineteenth century, epidemics of polio were described in temperate countries of the Northern Hemisphere each summer and autumn.[22] Probably the most well-known American citizen to become paralyzed by polio was President Franklin Delano Roosevelt, who used a wheelchair for the remainder of his life after contracting the disease.

Polio is caused by a virus and is highly contagious. Poliovirus is a member of the genus *Enterovirus*, and there are three serotypes (P1, P2, and P3).[23] The mode of transmission for poliovirus is primarily through the fecal-oral route. After entering through the mouth and multiplying at the site of implantation, the virus enters the blood stream via lymphoid tissue and can go on to infect cells of the central nervous system (CNS).[22]

The majority of all polio infections (greater than 90%) are subclinical, although these infected persons still shed virus in their stool.[23] Less than 1% of all poliovirus infections result in flaccid paralysis, where the disease selectively destroys the motor neurons of the spinal cord and brain. Asymmetrical muscle weakness and diminished deep tendon reflexes are key features of the illness.[23]

Transmission of wild poliovirus stopped in the U.S. in 1979, and vaccination has also led to elimination of polio throughout the Western Hemisphere since 1991 (Peru).[23] In the early vaccine era, the incidence of wild virus cases dramatically decreased following the introduction of Salk inactivated polio vaccine (IPV) in 1955.[6] This decline continued following licensure of Sabin oral live attenuated vaccine (OPV) in 1961-1962.[6]

While the Salk IPV provided excellent individual protection from paralytic poliomyelitis, persons who got IPV received less intestinal immunity than OPV recipients. This made IPV recipients more susceptible to local wild poliovirus replication in the gut, with reduced impact on the continued excretion of wild strains of polio in stool resulting in continued exposure to those in the community[22] (the eIPV – enhanced IPV – vaccine now used worldwide and in the USA is a more potent inducer of intestinal immunity than the original Salk vaccine). The World Health Organization (WHO) recommends the use of OPV alone in developing countries where wild virus is still endemic.[23]

One adverse event that follows receipt of oral poliovirus vaccine, though rarely, is known as vaccine-associated paralytic poliomyelitis (VAPP).[22] VAPP induced by OPV occurred in about 1 out of every 750,000 first doses of the vaccine,[24] and the paralysis that results is identical to that caused by wild poliovirus. The occurrence of VAPP following receipt of oral vaccine is increased in infants if followed by multiple injections of antibiotics (commonly used in some countries to treat infants with febrile illness).[25] The IPV form, which cannot cause paralysis (because it doesn't contain live virus), is the preferred vaccine for routine immunization of children in the United States where wild virus has been eliminated.[26]

Because of the low cost, ease of administration, and capability to provide immunity to susceptible contacts through secondary spread, WHO has continued to support an OPV-only polio eradication policy in many parts of the world.[22] This would indicate that Organization officials have opted for the benefit of possibly eradicating wild-virus polio cases globally, despite the rare (but known) risk associated with oral poliovirus vaccine.

This risk has been evident recently in two regions of the Western Hemisphere that are quite distant from each other. From July 2000-September 2001, an outbreak of poliovirus infection due to a mutant strain of vaccine-derived oral poliovirus (OPV-1) resulted in 21 cases of poliomyelitis on the island of Hispaniola (Dominican Republic and Haiti).[27] The outbreak occurred in areas of low vaccine coverage (Haiti, 20-32% and Dominican Republic, 73-82%), and only one patient had received at least three doses of OPV. After these cases associated with circulating vaccine-derived poliovirus (cVDPV) were discovered, all polioviruses under investigation worldwide were required to undergo additional testing to distinguish wild virus from cVDPV. These new prospective testing requirements also detected three cases of VAPP associated with cVDPV in the Philippines during March-July 2001.[28] No other paralytic cases attributable to cVDPV have been reported since then.

It is believed that the viruses may have been replicating for a while within certain individuals with deficient immune systems living in those communities, with reversion of the circulating strains to augment neurovirulence and improve transmissibility.[28-30] The longer an attenuated virus can replicate in the gut, the more time it has to potentially

revert away from the parent strain (OPV) and towards the wild-type virus.[29] An inadequately vaccinated or immunodeficient host may then pick up the mutated strain.

Poor vaccination rates are one of the most important causes of cVDPV. These episodes of VAPP due to reverted strains are especially noteworthy since both areas (Hispaniola and the Philippines) are believed to have been free of wild-type poliovirus since 1991. The occurrence of VAPP in association with cVDPV in these regions of the world raises the question: what is the appropriate immunization schedule (OPV, IPV, or combined) in developing countries that have few cases of wild-type polio? While a switch to IPV would eliminate the risk of vaccine-associated paralysis in individuals receiving the vaccine, it might not be economically feasible in developing countries. In addition, a switch to IPV would remove the benefit that comes from vaccine virus being introduced into the environment following administration of OPV, which helps to "vaccinate" persons who may not have directly received the vaccine themselves.

Yellow fever vaccine

Early in the nineteenth century, the means of transmission of yellow fever were unclear. Some believed that the disease could be transmitted from one person to another, until Stubbins Firth exposed himself both orally and parentally to fluids of patients dying of yellow fever.[31,32] After Firth didn't fall ill with yellow fever, he concluded the disease was not communicable. When the U.S. occupied Cuba during the Spanish-American War, a study commission (led by Walter Reed) established that *Aedes aegypti* mosquitoes transmitted yellow fever.[31,33] Reed and his commission also determined that yellow fever was caused by a virus, the first disease to be labeled as such.

Yellow fever is an infectious viral disease of the genus *Flavivirus*.[34] After an incubation period of three to six days, typical attacks are characterized by fever, malaise, nausea, and vomiting. Some cases experience a brief remission period followed by hemorrhagic symptoms and liver failure, with up to 40% of individuals succumbing to the disease.[34] Patients who are fortunate enough to recover from yellow fever experience lasting immunity.

In 1937 Theiler and Smith developed an attenuated 17D version of the yellow fever virus, and all the currently produced vaccines are based on this.[31,35] The current vaccine substrains are designated 17DD and 17D-204. The disease is especially problematic in areas densely populated with vector mosquitoes and many susceptible humans. A single injection of vaccine is effective in almost 99% of recipients,[34] and its administration is recommended for inhabitants of, and travelers to, many regions of South America and Africa.

Until recently, the most serious side effects thought to be associated with yellow fever vaccine (for recipients older than 9 months) were severe allergic reactions.[34] But the *Lancet* of July 14, 2001 collated reports of 7 cases of multiple organ system failure (MOSF) (including 6 deaths) following yellow fever vaccination in Brazil, the U.S.A., and Australia.[36-38] The clinical manifestations differed among the cases, and there were no obvious correlations between the three reports. Vaccines produced by different manufacturers had been used on each continent.

In 1998, Brazil included yellow fever vaccine in their national program of childhood immunization in response to one of the largest epizootics in history.[36] Beginning in 1998, the country registered 192 human cases of yellow fever, almost half

of which (46%) died.[36,39] Brazil uses the 17DD substrain of yellow fever vaccine. The two Brazilian fatalities reported in the *Lancet* (ages 5 and 22) that occurred following yellow fever immunization represent two deaths in over 85 million vaccinations in that country between 1990 and 2000.[36] These two patients experienced significant organ damage (e.g., liver necrosis and hemorrhaging) that was confirmed as vaccine derived, based on serum and tissue samples. This demonstration that 17DD vaccine has residual viscerotropism resembling wild-type infection represents a complication not previously reported.[40]

The four U.S. cases (three deaths and one severe illness) involved patients of advanced age, all of whom were older than 63 years.[37] Yellow fever vaccine is recommended for individuals traveling from the United States to areas where the disease is endemic. The United States uses the 17D-204 substrain of yellow fever vaccine. Three of the reports of severe illness were received at the CDC in 1998, while the additional case had been reported to VAERS in 1996.[37] These cases showed less organ damage than the Brazilian fatalities and more involvement of the CNS. The timing between vaccination and illness, clinical features, and isolation of vaccine virus from bodily fluids led the authors to suggest the possibility of a causal association between yellow fever vaccine and illness in these patients.[37]

The one Australian case of MOSF was 56 years old.[38] Australia also uses the 17D-204 substrain of yellow fever vaccine, but from a different manufacturer than the United States uses. The man suffered from extensive hemorrhages, and his liver was found to have large areas of necrosis.[38] His death was attributed to vaccine-derived yellow fever by virus isolation from multiple tissues.

It is worth mentioning that all seven adverse events occurred in a small number of vaccine recipients among many others who received the same vaccine. A commentary published in the same issue of the *Lancet* suggested that now is the time for investigating the pathophysiology of wild-type yellow fever virus as compared to attenuated viruses, in addition to host susceptibility factors.[41] Despite the recent adverse events, an Advisory Committee on Immunization Practices (ACIP) working group suggested that persons traveling to areas where yellow fever is known to occur should still be vaccinated.[42] However, providers are cautioned to carefully screen potential recipients based upon where they're planning to travel, to ensure that their destination warrants them getting the vaccine. Two of the persons who succumbed to vaccine-associated MOSF were planning to travel to regions where yellow fever transmission had never even been reported.[42]

Whole-cell pertussis vaccine

The DTP vaccine is a combined vaccine used to prevent three diseases – diphtheria, tetanus, and pertussis. Pertussis (widely known as whooping cough) is an acute infectious disease caused by the bacterium *Bordetella pertussis*.[43] In non-immunized populations, pertussis is among the most lethal diseases of infants and young children, with an estimated 300,000 deaths per year.[44]

B. pertussis produces a toxin that is responsible for the clinical, respiratory features of the disease. The incubation period of pertussis is usually 7-20 days.[43] Pertussis-associated neurologic complications are more common among infants, and encephalopathy and seizures have been reported from 0.2% and 1.4%, respectively, of all cases.[44] Pertussis is highly communicable with a secondary attack rate of 80% among

susceptible household members via contact with respiratory secretions or aerosol droplets.[45-47]

Whole-cell pertussis vaccine was developed in the mid-1930s and combined as DTP in the mid-1940s.[44] Whole-cell DTP vaccines had a fairly high rate of mild and severe side effects, with febrile seizures reported in 1 of every 1,750 doses and encephalopathy occurring very rarely.[44] Concerns about the safety of DTP led to development of an "acellular" pertussis vaccine (DTaP). The acellular pertussis vaccine has been the one in use in the United States since 1996.[44]

Anti-vaccine movements that targeted whole-cell pertussis vaccine provide another example of harm done to immunization coverage when imprudent decisions are made. Adverse neurologic events were first associated with receipt of whole-cell pertussis vaccine in 1933.[47,48] Since that time, several review committees and large-scale studies have examined the issue and arrived at varying conclusions.

Gale et al. conducted a population-based case-control study (as a part of a feasibility assessment) to evaluate adverse whole-cell pertussis vaccine effects in Oregon and Washington.[49] Prospective surveillance was established from August 1987 through July 1988 using a blinded panel of clinicians to identify all cases of serious acute neurological illness (acute encephalopathy, infantile spasms, and complex febrile seizures). The authors observed no increased risk of onset of serious neurological disease in the seven days after DTP exposure. Even with a prospective surveillance system of 218,000 children, the authors admitted that the statistical power would only be able to detect significant odds ratios of at least 2.5 for all incident cases.[49]

Following the study by Gale et al., a 1991 Institute of Medicine report concluded that the available evidence suggested a causal relationship between the receipt of DTP and acute encephalopathy.[50] The Vaccine Safety Datalink Working Group subsequently used VSD records to examine the relation between DTP vaccine and seizures, as well as the outcomes among children with seizures.[51] Using criteria similar to Gale et al. for classifying episodes of seizure, the VSD Working Group found that receipt of DTP vaccine was associated with an increased risk of febrile seizures only on the day of vaccination (R.R., 5.70; 95% C.I., 1.98 to 16.42).

Despite the published associations between DTP vaccine and neurologic complications, public health authorities around the world should carefully weigh the risks and benefits of using DTP vaccine. This controversy may be less of an issue in the U.S., where acellular (DTaP) vaccine has been recommended for use since 1996.[44] However, nearly all developing countries still use DTP vaccine because of its lower cost.[43]

An estimated 45 million cases of pertussis occur annually, and case-fatality rates in developing countries can reach 15%.[52] If these figures are coupled with estimates of adverse events attributable to DTP vaccine, one begins to understand why the decision to completely discontinue pertussis vaccination is imprudent. For example, the 1991 IOM report only translated into an excess number of acute encephalopathy cases in the range of 0-10.5 cases per million doses of DTP administered.[50] The risk of febrile seizures on the day of vaccination reported by the VSD study only equated to approximately 6-9 additional febrile seizures for every 100,000 recipients.[51] Furthermore, the VSD Working Group conducted a follow-up analysis and found that these children were at no greater

risk of subsequent seizures, epilepsy or learning, behavioral, or psychiatric disorders than other children with febrile seizures (in the absence of vaccination).[51]

Another way of examining the importance of DTP immunization is to study the experience of nations where pertussis vaccine coverage declined. Gangarosa et al. compared the pertussis experience of two groups of countries: Group I (Hungary, the former East Germany, Poland, and the U.S.), where high coverage with DTP vaccine was maintained; and Group II (Sweden, Japan, the U.K., the Russian Federation, Ireland, Italy, the former West Germany, and Australia), where anti-DTP movements disrupted vaccination.[53] This study showed overall trends indicating that pertussis incidence was 10-100 times lower in countries where high vaccine coverage was maintained versus countries belonging to Group II. In nations where vaccine coverage was breached, the reasoning behind each story is varied, including: a loss of confidence in vaccine efficacy (Sweden);[54] fear due to fatalities following vaccination (Japan); attitudes, knowledge, and practices of providers (Italy and the former West Germany); and concern about potential nonfatal adverse events (the Russian Federation, the United Kingdom, Ireland, and Australia). It is worth mentioning that the commotion raised in the U.K. spread to Ireland and Australia because of their common ties,[53] providing further evidence that fear about vaccines can be contagious.

Measles-mumps-rubella (MMR) vaccine

Measles, mumps, and rubella are all viral infectious diseases.[55-57] Measles and mumps viruses are paramyxoviruses, while the rubella virus belongs to the family Togaviridae. There is only one antigenic type of measles virus, and its incubation period averages 10-12 days.[55] Diarrhea is the most commonly reported complication of measles

(8%), while the most serious nonfatal sequelae is encephalitis. Acute encephalitis occurs in about 0.1% of cases, and subacute sclerosing panencephalitis (SSPE) is reported in five to ten cases per million measles infections.[58]

The measles-mumps-rubella (MMR) vaccine is a combined vaccine used to prevent all three diseases. Each vaccine has been available as a single antigen preparation. Fever is the most commonly reported adverse event following MMR immunization (5%-15%).[58] While encephalopathy is only noted in less than one per million doses (estimated to be the same as the background rate of encephalitis due to all causes),[58] MMR vaccine has been publicly blamed for another CNS-related disorder – autism spectrum disorder (ASD).

In February 1998, the *Lancet* published an early report by Andrew Wakefield et al. proposing that MMR vaccination might cause autism, possibly by a mechanism involving damage to the gut.[59] The report was based on a case-series of 12 children referred to a London pediatric gastroenterology department, with a history of intestinal problems and presentation of developmental disorders. In eight cases, the child's behavioral problems were pinned upon receipt of MMR vaccine. The average interval from immunization to first notice of behavioral symptoms was six days.[59]

Wakefield et al. described a hypothesis known as the "opioid excess" theory of autism, which postulates that an exogenous influence impairs the cerebral function of patients.[59] The theory proposes that disruption of the gut wall (presumably caused by persistent measles vaccine-strain virus infection) increases intestinal permeability. Gut-derived peptides are increasingly absorbed, initiating a process that leads to disruption of normal brain development.[59]

Autism is a complex and severe developmental disorder marked by cognitive and neurobehavioral deficits.[60] The term "autism-spectrum disorder" (ASD) refers to a continuum of impairments in which patients vary in the severity of their symptoms. The reported time course of developmental problems determines whether a patient's autism is described as early onset or regressive. The majority of autism cases seem to be early onset, presumably due to some sort of brain injury.[61] Regressive autism occurs less often, and follows what is thought to be normal, early development. The two types of presentation (early onset and regressive) are typically not diagnosed until the second year of life.[62] ASD appears to exhibit a strong genetic component, also.[62,63]

The provocative study by Wakefield et al. is marred with shortcomings. The clinical investigation of patients involved the collection of histories from a variety of sources, including parents and health visitors.[59] Eleven of the twelve cases were investigated by the same clinician (J.A. Walker-Smith), who is also cited in the references section of Wakefield's paper as having previously published work on a related hypothesis.[59,64] The investigators should have been blinded for aspects such as clinical assessments. In addition, four of the children had their behavioral assessments done elsewhere, and these results were used to determine their diagnosis for this study.[59]

There was not any patient selection, other than the case-series of 12 children referred to the department, and the underlying population was not clear. A case-series approach is sometimes useful for *generating* new hypotheses, but it shouldn't be used for *testing* hypotheses and stating conclusions. The report announced that eight out of twelve patients had their autistic behavioral problems temporally linked with MMR vaccination.[59] Parents or the child's physician did this linking, but we're told nothing

about the querying procedure or how often a troubled parent rather than a physician made the association.

The Wakefield article set off a flurry of correspondence in the next month's *Lancet*.[65-71] All of the published letters echoed the same sentiment: a genuine fear that the published study results would damage vaccine uptake and lead to a resurgence of measles, mumps, and rubella in the United Kingdom (U.K.). Three of the seven letters[65,67,70] cited the negative pertussis-vaccine movement in Europe as foreshadowing of what can happen when an article with such potential for harm is published.

Wakefield's research was widely reported in the media and generated much public concern. The *British Medical Journal* subsequently reported that U.K. parents believed the MMR vaccine to be even more dangerous than natural measles virus.[72] In the same *Lancet* issue as the aforementioned letters, Wakefield[73] and some of the other study's authors[74] printed their replies. The two letters[73,74] had very different tones. The accompanying authors claimed that they were emphatic about not calling for a change to existing immunization policy,[74] although this did little to soothe frightened parents. Wakefield, in regards to the criticism his work received from the public health community of the United Kingdom, stated:

"...the clinical researcher's obligation is to test hypotheses of disease pathogenesis on the basis of the story as it is presented to him...listen to the patient or the patient's parent, and they will tell you the answer."[73]

These five pages of heated correspondence ended with an editor's reply, which asked the question:

"...are Wakefield and colleagues' observations reproducible?"[75]

From a deductionist's viewpoint, the more appropriate question might be: is Wakefield and colleagues' hypothesis refutable?

The latter question was quickly addressed through a succession of studies and review committees.[76-79] A group of researchers in Finland traced 31 children who developed gastrointestinal symptoms after MMR vaccination (apart from within the first hour), out of about three million vaccinees.[76] Diarrhea was the most commonly reported symptom, and no children developed ASD. Working backwards from patients known to have ASD in North East Thames, Taylor and colleagues showed that, although the known number of cases of ASD had been increasing since the late 1970s, there was not a notable increase after the introduction of MMR vaccine a decade later.[77] They also showed that at age 2 years, MMR vaccination coverage among the identified ASD cases was almost identical to other children in the same birth cohort.

Two separate reviews of the issue have been conducted in the U.S., one by the Institute of Medicine[78] and another at an American Academy of Pediatrics conference.[79] Both reviews resulted in the same conclusion: the available evidence does not support a causal relationship between MMR vaccine and ASD at the population level. However, that MMR vaccine could contribute to ASD in a small percentage of children cannot currently be ruled out.

A high-profile campaign was announced in early 2001 in the U.K. to publicize the lack of causal evidence regarding the issue and reassure parents that MMR vaccine was safe.[80] However, Andrew Wakefield had also opined that the single antigen preparation of each vaccine should be used instead of the combined vaccine[81] and gave already concerned parents something else to consider. In addition to press conferences and

interviews, Wakefield has made two trips across the Atlantic to appear before the U.S. Senate.[82,83] Wakefield and John O'Leary have presented fragmented results in Washington that raise more questions than they answer. It was understandable how these clinicians got a spot on the agenda – Congressman Dan Burton is the chair of the House Committee on Government Reform, and his grandson was diagnosed with regressive autism.

Despite their efforts, the United Kingdom's Department of Health may be losing the battle. It was already reported that, prior to Wakefield's fame, the coverage of MMR vaccine was subtly decreasing;[84] but this subtleness turned overt following a 12% drop in the number of children receiving the vaccine.[85] There have also been reports of mumps outbreaks in Northern Ireland and England.[85,86] In the United Kingdom, trust in government announcements is low, and it's not improving with a government-imposed gag order that prohibits officials (including Prime Minister Tony Blair) from disclosing whether their children have received the MMR vaccine.[87] In February 2002, it was reported that uptake of the MMR vaccine in London is only 73 percent.[88]

HEPATITIS B VIRUS (HBV) VACCINE

Background

Transmissible illnesses that caused jaundice have been reported since antiquity. The earliest recognition that blood or blood products could transmit some forms of jaundice was in 1885, when cases of what was likely hepatitis B were identified following the use of glycerinated human lymph as part of smallpox vaccination.[89,90] The hepatitis B virus (HBV) contains multiple antigens, including hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and hepatitis B *e* antigen (HBeAg).[89,91] Identification of HBsAg in human serum indicates that the person is potentially infectious. In addition, HBV is relatively resistant to decontamination - it can retain infectivity after remaining on inanimate surfaces for at least one month at room temperature.[89,91] The incubation period of HBV infection usually ranges from 45-180 days.[91]

Part of the difficulty in controlling the spread of HBV is its tendency to cause asymptomatic infections, especially among infants and children.[89,91] Even though many individuals will be unaware that they're infected, the most serious complications won't usually occur unless a person develops chronic infection.[92] The risk of chronic infection is highest among infants and young children, and decreases with increasing age.[89,93] Chronic infection is responsible for most HBV-related morbidity and mortality - an estimated 5,000 liver disease deaths occur each year in the U.S. because of chronic HBV infection.[89]

A plasma-derived vaccine was licensed for protection against hepatitis B virus in the U.S. in the early 1980s.[91] Due in part to fears that the vaccine could become

contaminated with other viruses that might be found in human blood, a recombinant vaccine was licensed in the mid-1980s, making it the first of its kind in the United States.[92] The efficacy of hepatitis B vaccine ranges from 80% to 100% in those who follow the recommended schedule of doses.[92] Because HBV can cause primary hepatocellular carcinoma,[89] this vaccine is the first vaccine that prevents cancer, and deaths among children due to hepatocellular cancer have significantly decreased in Taiwan following universal vaccination.[94]

The initial strategy for use of hepatitis B vaccine in the United States was based on vaccinating persons at highest risk for disease (e.g., intravenous drug abusers, promiscuous hetero-/homosexuals, and health care workers).[95,96] However, surveillance data indicated that 30-40% of hepatitis B cases had no identifiable risk factors, and vaccination coverage among high risk groups was very low.[96]

Although a relatively small proportion of the estimated 200,000 to 300,000 HBV infections per year occurred in children during the 1980's, infections prior to age 5 accounted for 20-30% of all chronic cases, thereby perpetuating the endemicity of HBV (albeit at a low level).[97] In 1991, the Advisory Committee on Immunization Practices (ACIP) developed a comprehensive strategy for controlling the virus, which was based on universal screening for HBsAg of all pregnant women and universal vaccination of all infants.[98] The 1991 recommendations called for all infants to begin the vaccine series within the first 6 months of life, and noted that beginning the vaccination series shortly after birth, before discharge from the hospital, was safe and effective.[98] This universal immunization strategy emphasized the importance of U.S. birthing hospitals in preventing vertical transmission of the virus from mothers to newborns. Theoretically, a

sustained program of universal infant vaccination would complement programs aimed at preventing horizontal transmission among adolescents and high-risk adults. As these vaccinated infants grew to adulthood, the pool of susceptible hosts would be low enough to interrupt transmission of the disease. However, widespread use of HBV vaccine has been criticized for its alleged association with demyelinating diseases, as well as because of the vaccine's preservative – thimerosal.

Hepatitis B Vaccine – Safety Concerns

Demyelinating disease

Around the same time that the CDC released its universal immunization strategy, concerns were being voiced that hepatitis B vaccine might be associated with adverse neurologic events.[99,100] Guillain-Barre' syndrome was reported significantly more often than expected after administration of plasma-derived hepatitis B vaccine in one study.[99] However, an Institute of Medicine panel review, as well as other reviewers, found insufficient evidence to support or reject a causal association.[101,102]

In 1991, a Belgian group reported in a case-series that CNS demyelination occurred after vaccination with recombinant hepatitis B vaccine.[100] Their findings were based on only two patients (one already known to have multiple sclerosis (MS)), and the findings appeared as a commentary in the *Lancet*. A larger study (25 cases) reported an association between hepatitis B vaccine and MS in France,[103] although sufficient evidence to support a causal association was not established there, either.[102] More recently, a brief report from Greece suggested a causal link between hepatitis B vaccine and leukoencephalitits.[104] This conclusion was based upon a case report of two separate episodes in the same patient. Only sketchy details were released about the patient's

neurologic history - a questionnaire had been administered, and no preexisting conditions could be demonstrated.

An Institute of Medicine committee currently reviewed the hypothesized association between hepatitis B vaccine and demyelinating neurological disorders, such as multiple sclerosis and Guillain-Barre' syndrome.[105] A review of the epidemiological evidence led the committee to reject the notion of a causal relationship between hepatitis B vaccine and multiple sclerosis; however, not enough evidence currently exists to comment on the relationship between the vaccine and other demyelinating disorders.

Thimerosal preservative

Thimerosal has been used as an antibacterial preservative in many childhood vaccines since the 1930s, and in some hepatitis B vaccines until 2000.[106] Preservatives are often used when vaccines are supplied in multi-dose vials. Repeated entry of syringes into such vials allows for the possible introduction of bacteria and fungi. Multi-dose vials are preferred in certain settings because they generally are less expensive to purchase and store.[106]

In 1976 there was a formal Food and Drug Administration (FDA) assessment and review of any potential harm from repeated exposure to thimerosal. At that time it was concluded that dangerous quantities of mercury were unlikely to result from receipt of biological products (such as thimerosal-containing vaccines) over the course of a lifetime.[106,107] During the next couple of decades, more vaccines containing thimerosal as a preservative were gradually added to the U.S. childhood immunization schedule.

The 1997 FDA Modernization Act called for a review of heavy metal exposures to humans from all potential sources, including foods, work place, environment, and

biologics. Thimerosal was also scrutinized given the increased number of vaccines recommended for children, along with advances made in the understanding of the effects of exposure to mercury.[106] This reassessment indicated that, depending on the vaccines used, some infants might have been receiving total doses of mercury that exceeded Environmental Protection Agency (EPA) guidelines - it is important to note that these guidelines were set according to data from studies on the effects of methylmercury. *Ethylmercury* is the actual metabolite of thimerosal that is found in the human body, not methylmercury. In addition, only the EPA guidelines were found to be surpassed by certain immunization schedules, whereas the Agency for Toxic Substances and Disease Registry (ATSDR), World Health Organization (WHO), and FDA guidelines were not exceeded.[106]

To assess the scientific plausibility regarding exposure to thimerosal and adverse neurologic effects, the author searched the literature for reports of such adverse events in humans and animals. This plausibility assessment has two components: (1) an examination of the causal relationship between the exposure and adverse events, and (2) a discussion of any pathogenic mechanisms that support the alleged associations.

Causal Relationship

Much of what is known about mercury toxicity comes from poisoning episodes over the previous 50 years or so. The consumption of contaminated fish in Minamata, Japan during the late 1950s and early 1960s provided evidence of methylmercury's toxicity.[108] A strange nervous disorder began afflicting villagers in and around the area. During the second half of the 1950s, approximately 6 percent of the children born in that

area developed cerebral palsy.[108] In utero exposure to methylmercury was blamed, because these infants had not eaten contaminated fish.

During the early 1970s, barley and wheat grain treated with methylmercury was distributed to Iraqi farmers.[109] This mercury was presumably added to help stave off fungal contamination. Reported symptoms were similar to those of the Japanese epidemic. Blood mercury levels of infants born just prior to the epidemic were attributed to poisoning via breast milk. In utero exposure, breast milk, or both were implicated as the methods of poisoning for infants born during or after the epidemic.

Bakir et al. studied 15 mother-infant pairs in Iraq by carrying out serum analyses with repeated clinical examination.[110] Six of the affected infants showed irritability and excessive crying, with four of them having severely affected mental power. Although this Iraqi study had a very small sample size, the authors concluded that exposure to methylmercury in the third trimester of pregnancy could lead to damaging effects for the infant.[110] However, there was much variability between when the infants were examined.

Studies from the Faroe Islands found subtle cognitive deficits that were associated with methylmercury levels previously considered safe.[111] Increased methylmercury exposure from maternal consumption of pilot whale meat was indicated by mercury concentrations in cord blood and maternal hair. Of the original cohort of 1,022 consecutive births, 917 of the children underwent sophisticated neuropsychometric testing.[111] The most pronounced neuropsychological dysfunctions were in the domains of language, attention, and memory. These associations remained even after the exclusion of children with maternal hair mercury concentrations at the highest end of the spectrum.

The same group of authors published another study on the Faroese cohort, but this time including several other biomarkers of methylmercury exposure.[112] This time they analyzed hair from the children at ages 12 months and 7 years, and blood at 7 years was collected also. The same neuropsychologic tests were chosen as before. Results were presented as the change in test performance at age 7 years associated with a doubling of the mercury concentration for the exposure biomarkers.

The cord-blood concentration generally showed greater regression coefficients and lower P values than did the other biomarkers (significance range: <0.001-0.049).[112] The 1-year hair concentrations of children were significantly associated with three of the neuropsychologic test scores, whereas the two 7-year biomarkers did not present much of an association. The cord-blood concentrations were the best predictors of decrements in the domains of language, attention, and memory.[112] Since no exposure markers were obtained between ages 1 and 7 years, the time at which postnatal damage occurred could not be specified.

This North Atlantic population was again the subject of study in another prospective cohort venture.[113] A cohort of 182 births was assembled during a 12-month period. The following samples were collected for exposure assessment of the infant: maternal serum at week 34, cord blood, maternal hair, and transition milk. For the neurologic examination of the newborn, a technique was used at approximately two weeks of age designed to assess functional abilities and the stability of behavioral status during the exam.[113] The cord-blood mercury concentration showed a negative association with neurologic function, as assigned by a neurologic optimality score (NOS). A 10-fold increase in mercury was associated with an NOS decrease of 2 points. It is worth

mentioning that neonatal assessment tools have not always been highly predictive of later functioning. It is also unclear whether this study's 2-point difference in NOS suggests a true difference in morbidity. The predictive value of measuring these outcomes at two weeks of age is unknown to this author, as well.

Stajich conducted a repeated cross-sectional study among newborns in 1997-1998.[114] All of the newborns had been admitted to the Neonatal Intensive Care Unit (NICU) at the Grady Health System in Georgia. Baseline mercury concentrations were measured in the serum of these infants. It was found that vaccination against hepatitis B significantly increased serum mercury levels in both term and preterm infants ($P < 0.01$).[114] Post-vaccination mercury levels were significantly higher among extremely low birthweight (< 1000 gm) and very low birthweight (< 1500 gm) preterm babies compared to term infants ($P < 0.01$). This was the first published study of its kind. There were 15 subjects in total (10 preterm vs. 5 term infants). All of the newborns were NICU admitted, so it's unclear if findings could be generalized to well infants. Most disappointingly, they did not measure the neurologic function of these infants. Therefore it is unknown what the clinical significance of their data represents. This shortcoming is even more frustrating given that their exposure of interest was actually ethylmercury via thimerosal, and not methylmercury like all other previous studies.

A prospective cohort study in Greenland attempted to examine the effects of methylmercury in utero.[115] Pregnant women were invited to participate when they entered birth clinics at the beginning of labor. Methylmercury concentrations were measured via maternal serum and cord blood. The outcomes of interest were gestational length and birthweight of the infant. Gestational length was not shown to be associated with blood

mercury concentrations.[115] Blood mercury of the infant was negatively associated more strongly with birthweight than was maternal blood mercury. Any conclusions drawn from these analyses are limited by the fact that one half of the eligible births were missed.

Another study that assessed similar outcomes was conducted in Tagum, Philippines, where tons of methylmercury had been continually dumped into the river system from mining ores.[116] This cross-sectional study was conducted as part of a prospective cohort study evaluating the long-term effects of mercury exposure. Total mercury concentrations were measured via maternal blood, breast milk, cord blood, and meconium. The prevalence of mercury in meconium was investigated for its relationship to neonatal head circumference. A negative relationship between levels of mercury in cord blood and a smaller head circumference suggested an effect of total mercury on head growth ($P = 0.0469$ for the association).[116] Similar to the previous Greenland study, certain assumptions must be made on the utility of these two studies. The importance of birthweight and head circumference decrements related to increased mercury levels remains to be assessed by future neurodevelopmental evaluation.

The fact that several studies have found significant associations between mercury exposure and adverse effects does not resolve the causal debate, especially since the specific exposures measured have not traditionally been the thimerosal metabolite, ethylmercury. However, not all of the studies to date have found an association between exposure to mercury and adverse neurologic effects. Davidson et al. conducted a prospective cohort study with an inception cohort of mother-child pairs in the Republic of Seychelles.[117] The cohort consisted of 711 pairs of mothers and children. Prenatal mercury exposure of the infant was assessed by measuring the concentration of total

mercury in maternal hair presumably representing levels during pregnancy. Postnatal exposure was similarly determined by measuring total mercury from a segment of the child's hair at 5.5 years of age. At the same time, nurses blinded to exposure status evaluated each child with a test battery consisting of six age-appropriate neurodevelopmental tests. This study also measured and controlled for caregiver IQ and the quality of the home environment.

None of the global tests employed indicated deleterious effects of mercury exposure.[117] The authors commented that results from this study might be pertinent for the U.S., where dietary intake of fish is similar. Seychelles methylmercury levels are much higher than in the U.S. because they eat more fish, not because they consume a few species of fish with extremely high concentration of mercury.[117] Therefore, potential deficits from methylmercury should be seen in the Seychelles before such effects would be seen here. Given that the authors used somewhat global scales to measure the outcome, this study may be less sensitive to certain subtleties than the domain-specific assessments made in the Faroese cohorts. Recall that the studies from the Faroe Islands found significant associations whereas the Seychelles cohort did not.

The inconsistency of results about the effects of methylmercury exposure on child development led to a panel review by the National Academy of Sciences.[118] The review concluded that both the Seychelles and Faroe studies were well-carried out, and that a variety of differences might account for the inconsistencies. Based upon the panel's suggestions, the authors of the Seychelles study reanalyzed their data.[119] They used the same statistical procedures as reported earlier, except that age at testing and tester were included as additional covariates in the regression analyses. In addition, the raw test

scores were used this time around. The reanalysis confirmed their previous findings. They reasserted that consumption of methylmercury-containing fish had no association with adverse events in child development at 5.5 years of age.[119]

In addition to the aforementioned cohort and cross-sectional studies, much of the literature on vaccine-associated neurologic disorders is generated as case reports. Fenichel assessed the neurologic risk of immunization with thimerosal-containing vaccines using data from the Vaccine Injury Compensation Program (VICP).[102] None of the thimerosal-containing vaccines that were reviewed demonstrated a consistent association with any of the neurologic conditions discussed in this manuscript thus far. Niu et al. used data from VAERS and the VSD project to compare the safety experience of thimerosal-containing hepatitis B vaccines at the time.[120] Not only were there no reports of the previously discussed neurologic conditions, but also, no unexpected serious events appeared to be caused by the thimerosal-containing vaccines.

Niu again made use of VAERS data to assess neonatal deaths after receipt of thimerosal-containing hepatitis B vaccines, but this time the number of years of data coverage was increased.[121] In this review of autopsies, no mention was made of causes of death related to CNS damage. In addition, the comparative safety study by Niu et al. only followed subjects for up to 30 days post-administration of the thimerosal-containing vaccines.[120] This may not be sufficient time for the occurrence or reporting of certain neurologic abnormalities.

The fact that inconsistency is a feature of the literature regarding mercury exposure and adverse neurologic effects does not resolve the debate about whether mercury metabolites from thimerosal cause neurologic deficits or disorders. Noteworthy,

the exposure of interest to our discussion (*ethylmercury* via thimerosal) has not been adequately examined, as compared to methyl- and total-mercury. As was already demonstrated in the description of the literature to date, many different outcomes have been used to try and measure the effects of mercury compounds. Various neurologic decrements sought out have included: neurologic abnormalities (e.g., delays in motor function), cognitive deficits (e.g., performance on attention, language, and memory tests), global IQ testing, and neurodevelopmental disorders (e.g., ASD and speech or language delay). The timing of when these adverse effects occur in relation to the exposure of interest is another consideration when sorting out the causal puzzle.

Temporality (often referred to as 'time-order') is a causal criterion that requests the putative cause precedes the effect in time. In general, the most valid study design for the proper establishment of temporality is a prospective cohort study. All of the studies described thus far from the islands of Faroe and Seychelles, as well as in Greenland, were conducted prospectively using cohorts of mothers and their infants. However, there are several problems with interpreting these findings that need to be discussed yet.

First, in their studies of infants from the Faroe Islands, Grandjean et al. found their most significant associations with neurologic impairment using cord-blood measures of mercury.[111-113] Cord blood is more representative of exposure to mercury near delivery than of long-term maternal exposure during pregnancy.[122] Maternal hair concentration is a better representation of repeated prenatal exposures. Second, it is unclear what the most relevant window of exposure is to study. We have demonstrated that mercury compounds can reach the child in utero; but even when Davidson et al. analyzed mercury concentrations using both prenatal (maternal) and postnatal (infant)

markers, no association was found with adverse effects for children.[117] This discussion also points out the limitations of the relevance and stability of using biomarkers to measure exposures.

In terms of a dose-response assessment, one of the Faroe Island studies[112] reported noticing adverse effects in children with a doubling of the mercury concentration for the exposure biomarkers. The relevance of a two-fold increase in exposure to ethylmercury, let alone methylmercury, is unclear. Similarly, Grandjean et al. reported a decreased neurologic optimality score with a 10-fold increase in the cord-blood mercury concentration. Such dramatic jumps between exposure categories need to be refined. Nevertheless, relationships that don't express a dose-response curve only refute those hypotheses that are specific enough to predict them.[123]

Pathogenic Mechanisms

In 2001, the IOM's Immunization Safety Review Committee commissioned a background paper on the toxicity of ethylmercury (L. Magos), as a part of their scientific plausibility assessment on thimerosal-containing vaccines and adverse neurologic events.[124] In regards to the decomposition of methyl- and ethylmercury, methylmercury is more stable; and the decomposition rate of ethylmercury is greater than that of methylmercury (both in vivo and in vitro).[124] The consequence of these different decomposition rates is that ethylmercury's neurotoxic potential declines faster than methylmercury's. In addition to differing stability, a methylmercury molecule is 6% smaller than a molecule of ethylmercury, which facilitates transport through the blood-brain barrier for methylmercury.[124]

Based on the current evidence, L. Magos stated that, "At equal exposure the risk of neurotoxicity is higher from methylmercury than from ethylmercury..." In fact, there doesn't seem to currently be a best hypothesis (if any) regarding the neurotoxic potential of ethylmercury. No direct studies in either animals or humans of thimerosal exposure of a level similar to those from vaccination can currently establish a sound biologic model.

Limited animal studies have looked at the toxicity of thimerosal (ethylmercury). Doses of 1 to 6 ug/kg/day in adult squirrel monkeys resulted in detectable inorganic mercury within the brain.[125] However, no histopathological changes were observed. The literature is much more abundant with studies that examined methylmercury exposure in animals. Gunderson et al. studied crab-eating macaque infants, where the cases had mothers who were dosed with 50-70 ug/kg/day of methylmercury.[126] Animals were administered different sets of visual recognition memory tests. Infant crab-eating macaques exposed prenatally to methylmercury performed at a significantly lower level than did controls ($p < 0.02$).[126]

The effects of in utero methylmercury exposure were also studied using 7- to 9-year old *Macaca fascicularis'*.[127] The subjects were surviving offspring, infants of females that had been exposed during pregnancy to doses of methylmercury ranging from 0-90 ug/kg/day. Monkeys exposed in utero to methylmercury showed no deficits in performance when compared to age-matched controls, as measured by performance on a spatial delayed alternation task.[127]

Difficulties in the interpretation of these animal studies are obvious. Varying sources of mercury, exposure doses, and outcome measures adds even more uncertainty to the utility of results. The toxicity of low doses of methylmercury and

ethylmercury/thimerosal has been assumed to be similar. Given the inconsistencies presented thus far of studies examining just methylmercury, these prior assumptions involving ethylmercury need to be tested. Nevertheless, the supposition that ethylmercury's actions are analogous to methylmercury's has driven the bulk of thinking behind thimerosal-related recommendation and policy changes.

Because no guidelines existed for ethylmercury exposure, the FDA's 1998 risk assessment from thimerosal in vaccines used the guidelines for safe exposure to methylmercury as a guide.[106] The finding that potential exposure to mercury from recommended childhood vaccines (during the first six months of life) could exceed the EPA guidelines, in addition to their literature review of whether thimerosal actually posed a true health risk, led the FDA to begin talks with manufacturers in April 1999 about developing thimerosal-free vaccines.[106] The FDA planned to send a formal letter to vaccine manufacturers in July 1999 regarding the topic, at which time the public would become aware of the issue.[128]

Fearing potential damage to the public's trust in the immunization system, representatives of several organizations involved in U.S. immunization policy were quickly summoned to discuss an appropriate plan of action. Disagreements were widespread and heated between attendees of a June 30, 1999 meeting.[128] Some participants believed that all thimerosal-containing vaccines should have been immediately removed from the market, whereas others doubted the accuracy of the FDA's evidence that receipt of thimerosal from vaccines was harmful. Over the course of the July 4, 1999 holiday weekend, AAP and USPHS officials agreed to release a joint statement that the birth dose of the hepatitis B vaccine be temporarily delayed for infants

of HBsAg-negative status mothers.[128] However, the timing and speed with which the recommendations were developed led some public health officials to wonder if the joint statement had been interpreted correctly by physicians and hospital staff, which eventually led to the *Michigan study on the impact of thimerosal recommendations on infant hepatitis B immunization among infants born to women of unknown HBsAg status.*

The Michigan Study

Introduction

Women who are not screened for hepatitis B surface antigen (HBsAg) are more likely to be HBsAg-positive compared to women who receive prenatal screening,[129] and their infants are less likely to be vaccinated appropriately.[130] For infants born to women of unknown HBsAg status who are actually HBsAg-positive, the consequences are potentially serious and long lasting. The risk of perinatal infection for an infant born to an HBsAg-positive woman who is also hepatitis B *e* antigen-positive (rates of hepatitis B *e* antigen positivity average between 20-30%, depending on maternal origin[97]) is as high as 90%.[93,97,131] As many as 90% of perinatally infected infants develop chronic infection, and up to 25% of HBV-infected newborns will subsequently die of the consequences of chronic liver disease during adulthood.[132]

Screening all pregnant women for HBsAg and immunizing all infants with hepatitis B vaccine are the cornerstones of efforts to prevent perinatal and early childhood hepatitis B virus transmission. Vaccination beginning at birth (the birth dose) is recommended for all children born to HBsAg-positive women and women whose HBsAg status is unknown and is the preferred schedule for all infants.[98] Hospitals and practitioners who want to provide the birth dose only to infants born to women who are

HBsAg-positive and HBsAg-unknown must carefully track HBsAg screening status, rapidly assess the infant's risk of early childhood infection, and ensure that vaccine is provided to infants at risk within 12 hours of birth.

By 1999, many birthing hospitals had recognized the potential for error in tracking the HBsAg status of pregnant women and the difficulty in assessing each infant's risk of early childhood infection. These hospitals established routine policies and practices to prevent perinatal infection by initiating the hepatitis B vaccine series before hospital discharge for all newborn infants, providing a safety net for infants born to HBsAg-positive women who were not identified through screening, whose HBsAg status is unknown to the birthing hospital, or whose HBsAg status is misidentified.

The secure position of the birth dose as part of the vaccination strategy towards eliminating hepatitis B was threatened in July of 1999, when the AAP and the USPHS jointly recommended reducing infant exposure to thimerosal. Specific recommendations were made to postpone the first hepatitis B vaccine dose until two to six months of age for infants born to HBsAg-negative women.[133] Recommendations for infants born to HBsAg-positive women, or to women whose HBsAg status was unknown, did not change.[133] These temporary changes in the recommended routine hepatitis B vaccination schedule were made because of the flexibility of the hepatitis B schedule for infants born to HBsAg-negative women, and were to be discontinued when preservative-free hepatitis B vaccines were licensed. The rationale at the time was that any potential harm that might result from exposure to mercury in the vaccine would be less when the newborn was larger and the neurological system was more fully developed. The recommendations

received wide publicity, and were transmitted to AAP members via fax134 and by a website posting.

By mid-September 1999, adequate supplies of preservative-free hepatitis B vaccine were available for all newborn infants in the United States. The USPHS then advocated a return to previous infant hepatitis B vaccination practices, including administering the first dose of hepatitis B vaccine to all newborn infants in hospitals that had discontinued the practice.[135] But by August 1999, the National Immunization Program was already reporting data that indicated that the recommendation changes had not been correctly interpreted (CDC, unpublished data, 1999). Several reports suggested that the change in recommendations led to disruptions in vaccination practices that could potentially have an impact on coverage rates of infants born to unscreened and even HBsAg-positive women. Surveys of hospitals in Wisconsin,[136] Chicago,[137] and Colorado[138] demonstrated significant decreases in the number of hospitals that offered universal hepatitis B vaccination of all newborns after the recommendation changes, and substantial increases in the percentage of hospitals that did not routinely vaccinate infants born to HBsAg-positive women.[136,138] Vaccine coverage of infants less than 5 days old declined 28% in Oregon, and vaccination of infants < 1 month old declined 50% in Oklahoma during May – June 2000, compared to May – June of 1999.[139] A national survey sample of 773 hospitals in December 1999 indicated similar trends.[140] In Michigan, an unvaccinated infant born at a hospital that had suspended its birth dose policy died from fulminant hepatitis B in December 1999. Although the mother had been tested prenatally and was positive for HBsAg, her lab results had been erroneously reported to the hospital to be "hepatitis-negative".[139,141]

A group of researchers (including the author) conducted a study among newborns in Michigan to assess the impact of the disruption in routine hepatitis B immunization of newborns born to women whose HBsAg status was unknown. We focused on births where the mother's HBsAg status was unknown, because infants born to unscreened mothers are at greater risk of perinatal infection (compared to screened mothers). Furthermore, we decided to focus on births where the mother's HBsAg status was unknown rather than positive because the Michigan Department of Community Health has a perinatal hepatitis B coordinator that already tracks births to HBsAg-positive women to ensure these infants are treated accordingly. Infants born to women that are not screened do not receive this type of case management, so the likelihood of missing vaccination is much higher.

Methods

We addressed the primary hypothesis that infants born to mothers who were not screened for hepatitis B surface antigen were less likely to receive timely immunoprophylaxis after the recommendations changed in July 1999, and that these changes persisted during 2000, long after hepatitis B vaccine that did not have thimerosal as a preservative became widely available.

We used a standardized form to collect demographic information, maternal HBsAg status, and infant hepatitis B vaccination among Michigan infants born during three, 60-day time periods. The first time period, March 1 to April 30, 1999 (T1), was used to assess the baseline proportion of infants born to women of unknown HBsAg status before the recommendation changes in July 1999. The second time period, July 15 to September 15, 1999 (T2), provided data from the time immediately after the Joint

Statement was issued to the approximate time when preservative-free hepatitis B vaccine first became available, and the USPHS requested that hospitals resume their previous newborn immunization practices. The third time period, March 1 to April 30, 2000 (T3), was chosen to represent a time frame when preservative-free hepatitis B vaccine was widely available, and hospitals should have had an opportunity to resume their previous vaccination practices. During 2000 and 2001, all MI birthing hospitals were contacted to determine current and previous policies for offering the first dose of hepatitis B vaccine during the delivery admission.

Infants born during the three time periods were identified by obtaining birth records from the Newborn Screening Division of the Michigan Department of Community Health (MDCH). Michigan newborn screening cards, which have been required by law for all Michigan infants since 1987, contain a field requesting the HBsAg status of the infant's mother (*"Mother Hepatitis B Surface Antigen Tested? Don't Know __; NO __; YES __; Date ____; Result: Positive __; Negative __").*

The schema we employed was a two-phase approach. The first phase was a pilot study. We requested hospital charts for the mother and newborn from 200 births with maternal HBsAg status of "Don't Know". The requested charts were evenly divided between five birthing hospitals in the state of Michigan (i.e., approximately 40 births per hospital). The births at each hospital were evenly distributed across the three time frames of the study (e.g., 13/14/13). Our request to review 200 births yielded information on only 156 births (78%), and few of these women (11%) turned out to truly have unknown HBsAg statuses.

Based upon the results of a similar venture that had just been completed in Oregon in which hepatitis B vaccine coverage levels were measured before and after July 1999 (Corwith-Jensen H, et al, Abstract 653, National Immunization Conference, Denver, CO, 2002), we calculated an initial sample size estimate. Prior to the thimerosal announcement, 81% of infants in the Oregon study were vaccinated before hospital discharge. Immediately following the Joint Statement, this figure dropped to 4%; and one year later when thimerosal-free vaccine was widely available, only 62% of infants born to women of unknown HBsAg status were being vaccinated before discharge. Using these vaccination figures, the initial sample size estimate for the Michigan study was 146 births to women that were truly unscreened. The adjusted sample size estimate that accounted for the small proportion of unscreened mothers located during the pilot phase was 1,340 births (146/11%). This was the number of births to be reviewed in order to find an adequate number of newborns born to unscreened mothers. However, during the pilot phase only 88% of the birth records were suitable for use (due to missing charts, mismatched maternal-infant pairs, etc.). Thus in order to protect from decreased power, 1,521 (1,340/88%) births needed to be requested to compensate for low pull rates and a lack of cooperation at the hospitals.

To improve efficiency of data collection efforts, we excluded infants born at any birthing hospital that reported greater than 40% of its births to MDCH as maternal HBsAg status *"Don't Know"* or missing, or had <15 births for which maternal HBsAg status was reported as *"Don't Know"*. After all of our exclusion criteria were implemented, 19 hospitals remained. Four of these were excluded because of prior difficulty getting into these hospitals for data abstraction (per MDCH). So from the 15

hospitals that remained (n=4,179 total births in the three exposure periods [this total includes multiple births to one mother]), we requested access to the medical records of 1,520 (36%) randomly selected maternal-infant pairs. Appointments were scheduled for MDCH staff to visit hospitals and abstract data from subjects' records.

The exposure status of an infant was based upon whether or not he/she was born during T1, T2 or T3. The outcome of interest was whether or not an infant received the first dose of the hepatitis B vaccination series before he/she was discharged from the hospital. When hour of vaccination was also specified, infants were further classified according to whether or not they were treated within 12 hours of birth (the recommended interval). The same chart abstraction form was used for recording information on both exposure status and outcome. Though data on exposure and outcome were gathered simultaneously, we analyzed and interpreted this data as for a cohort study, since the time order is clear (vaccination status is subsequent to period of delivery).

After the completion of data entry, every tenth birth was systematically reviewed for discrepancies between database tables and abstraction forms. Data tables were subsequently imported into SAS/STAT (Cary, NC) for appropriate analyses. PROC UNIVARIATE was also used to check for outlying data values. Results were first analyzed using the FREQ procedure in SAS to calculate chi-square statistics ($\chi 2$) and p-values. In the presence of small expected values, Fisher's exact test was used.

Results

Nineteen hospitals met the inclusion criteria, and after four hospitals were excluded (see above), 13 agreed to participate (Table 1). All of these hospitals reported that, before the Joint Statement was released, they had a policy to offer a birth dose of

hepatitis B vaccine to all infants. After the Joint Statement, all 13 hospitals stopped these policies. By the time of follow up in 2000-2001, 9 of 13 had resumed the previous policy of offering hepatitis B vaccine to all newborns, and 2 more hospitals reported that they planned to resume in late 2001 or 2002.

TABLE 1. Average annual birth rate (1998-1999) of participating hospitals, by hospital.

Hospital	**# 01**	**# 02**	**# 03**	**# 04**	**# 05**	**# 06**	**# 07**
Average annual birth rate	**1,681**	**779**	**3,074**	**625**	**1,861**	**3,024**	**4,655**
Hospital	**# 08**	**# 09**	**# 10**	**# 11**	**# 12**	**# 13**	**Avg.**
Average annual birth rate	**3,879**	**3,310**	**2,239**	**4,509**	**5,954**	**6,089**	**3,206**

Of 68,776 total Michigan births during these three time periods (T1, T2, and T3), 9,206 had maternal HBsAg status recorded as *"Don't Know"*. We requested 1,520 births for review that were evenly distributed across T1 (3/1/99 – 4/30/99), T2 (7/15/99 – 9/15/99) and T3 (3/1/00 – 4/30/00). Hospital personnel allowed access to the maternal and infant medical records for 89% of requested births (1,355/1,520). After the completion of data collection, 89% of these births could be used for subsequent analyses (1,201/1,355). The remaining 154 were excluded because some or all of the screening and vaccination information was missing from the chart. Of these 1,201 births, 216 (18%) were to women whose HBsAg status was truly unknown at the time of hospital

discharge. For the remaining 985 infants, maternal HBsAg status actually was recorded in the chart (HBsAg (+)=5 mothers and HBsAg (-)=980 mothers). It appeared that maternal hepatitis B screening status was independent of the time frames of the study (Pearson Chi-Square Statistic [χ^2]=4.15, p-value=0.13) [Table 2].

TABLE 2. Results of maternal HBsAg status upon medical record review, by recommendation period.

		T1*	T2*	T3*	Total	P-value
	Number of charts reviewed (%)	418 (34.8)	389 (32.4)	394 (32.8)	1,201	
Maternal HBsAg	Screened (%)	343 (34.8)	308 (31.3)	334 (33.9)	985 (82.0)	
	Unknown (%)	75 (34.7)	81 (37.5)	60 (27.8)	216 (18.0)	0.13

***Denotes the three exclusive time periods under study: T1 = March-April 1999, T2=July 15-September 15, 1999, and T3=March-April 2000.**

The median age of the 216 women of unknown HBsAg status was 26.6 years (range 14-43 years), compared to 26.9 years for the women of known HBsAg status (range 14-57 years). Table 3 summarizes other demographic and prenatal care characteristics. Maternal characteristics did not differ significantly by time periods of the study.

TABLE 3. Demographic and prenatal care characteristics of 1,201 Michigan women by HBsAg status, 1999-2000.

Characteristic	Number (%)	
	HBsAg status – unknown (n=216)	HBsAg status – known (n=985)
Race		
White	85 (39.4)	450 (45.7)
Black	120 (55.6)	438 (44.5)
Other	11 (5.0)	97 (9.9)
First child	52 (24.1)	258 (26.2)
First prenatal visit during first trimester*	33 (35.1)	549 (55.7)
Greater than or equal to 5 prenatal visits*	32 (39.5)	669 (67.9)
Received screening during admission for delivery	6 (2.8)	66 (6.7)
Delivery time period		
March 1-April 30, 1999	75 (34.7)	343 (34.8)
July 15-September 15, 1999	81 (37.5)	308 (31.3)
March 1-April 30, 2000	60 (27.8)	334 (33.9)

***Data unavailable for many women.**

Of infants born to women of unknown HBsAg status during T1, 14/74 (19%) received the vaccine within 12 hours of birth, compared to 1/79 (1%) infant born during T2 (p=0.0002). While only 8/58 (14%) of infants born during T3 received the vaccine within 12 hours of birth, this was not significantly different from the proportion during T1. Four infants vaccinated before discharge did not have a time of vaccination recorded.

For most infants born to unscreened women during T2, vaccination was not only delayed beyond 12 hours, but also did not occur before discharge. **Of infants born to unscreened women during T2, 6/81 (7%) received a dose of hepatitis B vaccine**

before hospital discharge, compared to 40/75 (53%) infants born during T1 (χ^2=39.50, p<0.0001) [Table 4]. However, the proportion of infants vaccinated before hospital discharge during T3 (34/60 [57%]) did not significantly differ from T1.

TABLE 4. Proportion of Michigan infants born to women of unknown HBsAg status who were vaccinated before discharge or within 12 hours, by time period.

Time Period	Vaccinated before discharge, n/total (%)	P-value	Vaccinated within 12 hours of birth, n/total (%)	P-value
T1	40/75 (53)	Ref.	14/74* (19)	Ref.
T2	6/81 (7)	<0.0001	1/80* (1)	<0.001
T3	34/60 (57)	NS§	8/58* (14)	NS§

*** Time of vaccination not available for one infant born during T1, one infant born during T2, and 2 infants born during T3.**
NS§ = not statistically significant

When the analysis was restricted to infants who received vaccine before discharge, a larger proportion (14/39 [36%]) in T1 received the vaccine within 12 hours (as would be recommended if the mother were known to be antigen positive), compared to T2 (1/5 [20%]) and T3 (8/32) [25%], but these differences in proportions were not statistically significant. We also analyzed the data with the outcome defined as the hospitals having offered the vaccine (even if the parents refused it). Reanalysis using this outcome yielded no qualitative difference, as only five infants were different with regard to the two outcomes, including two born during T1, one during T2 and two during T3.

Discussion

The primary goal of our study was to quantify the impact of changing recommendations on the vaccination of infants against hepatitis B. Specifically, we were most interested in those newborns whose mothers' HBsAg status was unknown. Women who have not been screened or have not received prenatal care demonstrate a higher

prevalence of chronic HBV infection.[129] Therefore, babies born to unscreened mothers are at higher risk of infection as compared to those born to screened women, and as a group these infants must be considered as 'high risk.'

Previous studies have shown that many hospitals discontinued policies that provided for hepatitis B vaccination of all newborns after the Joint Statement was issued, and that these policies were not promptly reinstated in some hospitals, even after preservative-free hepatitis B vaccine became available. Our study demonstrates that a significant decline in timely hepatitis B vaccine coverage occurred among infants born to women of unknown HBsAg status immediately after the Joint Statement was released. In Michigan, timely hepatitis B vaccination of infants born to women of unknown HBsAg status virtually ceased within our study hospitals in July and September of 1999, despite specific language in the Joint Statement indicating that hepatitis B vaccination practices for these infants had not changed. Changes in vaccination coverage during the three time periods coincided with changes in routine vaccination policies. This study provides further evidence that rapid policy changes associated with evolving, largely theoretical concerns about the safety of thimerosal were misinterpreted.

Our study revealed that 18% of the births reviewed involved mothers whose HBsAg status was unknown. This figure is higher than the 13% that was reported from the state of Michigan's "Assessment of Progress Toward Goals to Prevent Perinatal HBV Transmission," (unpublished results, MDCH, 1998). However, that survey was based upon all pregnant women in the state, whereas our study is much more limited in its scope. Our target population included only those infants born in Michigan across several study periods whose mothers were unlikely, based upon maternal HBsAg information

from newborn screening cards, to have been screened for hepatitis B. Although, information from screening cards indicating that a mother's HBsAg status was unknown was likely a random process at each hospital (i.e., varied by who filled out the card on what day), rather than being due to factors specific to these women. Nevertheless, the proportion of unscreened mothers presented above (13%) is not meant to be compared directly to our study's findings.

The time periods of our study were not related to the rigor with which mothers were screened for hepatitis B. The study periods (which varied by vaccine recommendations at the time) were, however, significantly associated with infant vaccination proportions. Newborns of mothers with unknown HBsAg status were much less likely to be vaccinated during the time period after the Joint Statement was released (T2). Infants born soon after thimerosal-free vaccine became widely available (T3) were also less likely to be vaccinated compared to infants born during T1, although the difference in proportions vaccinated did not reach the level of statistical significance. However, given the fact that vaccination of these newborns was already quite low during T1 (53%), it is not surprising that we were unable to show a significant difference one year later (T3).

An important aspect of our study worth noting is that we actually conducted chart review to confirm maternal screening status and infant vaccination, whereas previous surveys relied on interview responses from hospital personnel to generate their conclusions. Because we did not assess vaccination data beyond the year 2000, our vaccine coverage data may not reflect the current situation. Our results should be

interpreted as indicating that hospitals were slow to return to practices in place before the Joint Statement, even if they may well have returned to them eventually.

It is unknown whether our findings reflect a nationwide reduction during the alert period in first dose hepatitis B vaccine coverage for infants born to women of unknown HBsAg status. We only examined birth records at a subset of Michigan hospitals that consistently filled out information on maternal HBsAg status on newborn screening cards. These hospitals may not have been representative of all Michigan birthing hospitals or those in other states. By virtue of the exclusion criteria we employed, small rural hospitals (usually staffed by family practice physicians) would be underrepresented in our study; and hospital size, location, and makeup of the hospital attending staff strongly influence birthdosing practices.[136] However, hospitals that were unable or unwilling to adequately complete newborn screening cards would probably not be more likely to successfully screen and provide timely vaccination to infants born to unscreened women. In addition, a similar pattern and magnitude in reduction of coverage for infants born to women of unknown HBsAg status was observed in Oregon (Corwith-Jensen H, et al, Abstract 653, National Immunization Conference, Denver, CO, 2002).

Several explanations for the observed effects on newborn vaccine coverage are possible. First, there may have been confusion about which infants should have vaccination deferred, despite the specific language used in the Joint Statement. In a Colorado survey done in early 2000 of persons who identified themselves as being responsible for nursery vaccination policy, 71% learned of the Joint Statement recommendations from colleagues or the news media, rather than from the health department or a professional society.[138] The precise language used to delineate which

infants should have vaccine deferred may have been lost in summaries provided by colleagues or the news media.

Secondly, practitioners and hospitals may have considered the theoretical risk from thimerosal exposure to exceed the risk of perinatal infection due to missed immunoprophylaxis for infants born to women of unknown HBsAg status. The haste with which the Joint Statement was developed and publicized may have led practitioners and hospitals to conclude that reducing exposure to thimerosal in vaccines was a public health emergency for all infants.

Finally, practitioners and other delivery hospital personnel may not have been aware that infants born to women of unknown HBsAg status were no longer being routinely immunized. Practitioners may have assumed that prenatal screening could successfully identify all HBsAg-positive women, and grown accustomed to the safety net that universal hepatitis B vaccination of newborns provided. Formerly (before the Joint Statement – T1), each nursery probably had a routine involving the ascertainment of hepatitis B information about every birth, when practically all newborns were receiving the birth dose of vaccine. But after the thimerosal alert, the absence of such a routine probably allowed for oversights that wouldn't have happened during times of near-universal birth dosing, resulting in newborns being discharged without any hospital staff ever checking the maternal record for hepatitis B status.

Misinterpretation of public health and professional society recommendations regarding thimerosal might have been avoided if a more deliberate process had been followed as recommendations were developed. The need for urgent changes in vaccination policy, without review by the Advisory Committee on Immunization

Practices (ACIP) and the National Vaccine Advisory Committee (NVAC)[128], was not supported by the existing data. At the time the Joint Statement was issued, no harm from the mercury in thimerosal-containing vaccines had been demonstrated, and there was no consensus about the risk of exposure to the quantities of mercury-containing compounds present in vaccines.

Since the universal immunization strategy was released in 1991, the number of children born to HBsAg-positive women in the U.S. has risen substantially.[142] It is well known that timely immunoprophylaxis provides the best means for interrupting transmission of hepatitis B virus. For example, the 1998 U.S. birth cohort would have experienced 6,800 perinatal infections and 18,700 more infections due to horizontal transmission by 10 years of age if no vaccination had taken place.[142] Infants born to women of unknown HBsAg status should be treated as though the mother is a chronic carrier of hepatitis B.

Inadequate immunoprophylaxis of infants born to HBsAg-positive women has been associated with a failure to document maternal screening results in the delivery room prior to birth.[143] Based upon our results from babies delivered by mothers with unknown HBsAg statuses, we can only speculate on what happened to babies of HBsAg-positive mothers. Before the Joint Statement, many hospitals relied upon provision of hepatitis B vaccine to all infants at birth as a safety net, so that infants whose mothers were unscreened but HBsAg-positive would automatically get immunoprophylaxis without the need to wait for lab results and make a decision at delivery. After the Joint Statement, these hospitals would have returned to a policy of making the decision on a case-by-case basis, thus introducing the opportunity for error. In addition, it seems likely

that hospitals that missed vaccinating unscreened mothers' newborns would have a greater potential to miss administering vaccine to some infants born to HBsAg-positive women also. In fact, this sort of error was documented in the case of the Michigan infant alluded to earlier.

The recommendation changes that occurred in July 1999 were not based on a proven causal relationship. The effects of exposure to methylmercury were assumed to hold true for ethylmercury, which is the metabolite of thimerosal preservative. Available data does indicate, however, that the toxicological properties and pattern of tissue disposition for ethylmercury compounds are qualitatively similar to those of the methylmercury compounds.[144,145] The recommendation changes in July 1999 were the result of a cautious approach when making alterations to proven immunization programs. The theoretical risk posed by thimerosal-preservative in vaccines was viewed as being greater than the known benefits of vaccinating newborns prior to discharge. However, the detrimental effects seen on infant vaccination coverage in Michigan should be viewed as a caution when changes to existing immunization schedules are considered in the future.

Beginning hepatitis B vaccination at birth for all infants has been the preferred schedule advocated by the AAP since their policy was first published in Pediatrics in 1992,[146] as it was in 1999 before the Joint Statement. The ACIP recently stated its preference for the birth dose schedule. Our data indicates that there is a need to renew efforts to begin hepatitis B vaccination at birth, especially for infants at higher risk of infection. Although hepatitis B vaccine coverage of infants born to unscreened women in Michigan returned to near baseline (57% by discharge, 14% within the first 12 hours of life) by mid 2000, physicians and birthing centers must increase vaccine coverage for

these newborns beyond this unacceptably low level. Efforts to improve hepatitis B vaccine birth dose coverage in Michigan are underway, and include provision of free vaccine and educational resources to hospitals and staff. A recent report from MDCH indicated that 83 of 102 (81.4%) birthing hospitals in Michigan have now implemented or reinstated policies to offer hepatitis B vaccine to all newborns prior to discharge.[147] Hopefully these policies will help provide better protection for Michigan newborns against hepatitis B, especially among those at highest risk of infection.

CONCLUSION

The examples of damage done to immunization coverage discussed in this thesis should serve as a warning when dealing with vaccine safety issues. In the case of Andrew Wakefield and colleagues' findings, the warning pertains to responsibility – the responsibility researchers have to apply appropriate criteria for determining causality when publishing their results. In response to criticism his efforts have received relating MMR vaccination to autism, Wakefield stated:

"Assumptions of vaccine safety, based upon inadequate safety trials and dogma contribute largely to confusion and public loss of confidence in vaccination."[73]

Ironically, Wakefield's own crusade has been at the forefront of this confusion, and he has not wavered despite several studies that have refuted his conclusions at the group level.[76-79] The editor of the *Lancet* defended the journal's decision to publish the controversial report, mentioning the fact that the journal did run a commissioned commentary in the same issue by Chen and DeStefano.[148] However, common sense tells us which of the two references (Wakefield or Chen & DeStefano) a media journalist is going to pick up on.

Whereas health officials in the United Kingdom have backed the safety of the MMR vaccine, other examples of diminished vaccination coverage can be attributed to public health policymakers. Unlike the MMR controversy, it appears as though a causal relationship may exist between whole-cell pertussis vaccine (DTP) and certain adverse, neurologic events (e.g., acute encephalopathy).[50] Despite such findings, the estimated 45 million cases of pertussis that occur annually are more than enough reason to be cautious when examining immunization policy. Although anti-vaccine movements have had some

beneficial effects (e.g., promoting interest in funding research for improving vaccine safety and surveillance of adverse events), the DTP controversy provides a strong international example of imprudent policy decisions leading to outbreaks of disease.[53] For example, following the elimination of whole-cell pertussis vaccine use in Japan, a pertussis epidemic occurred with more than 13,000 cases and 41 deaths.[53]

Although it's not currently known whether thimerosal-related policy changes led to a nationwide rise in perinatal infections with hepatitis B virus, the Michigan study presented here demonstrated decreased vaccine coverage among a group of high-risk children in this state. Abrupt changes in established vaccination recommendations, originally intended only to pertain to low risk children (i.e., infants whose mothers' were known to be HBsAg-negative), led to decreased coverage among higher risk children. The unintended impact of the thimerosal controversy on hepatitis B vaccine coverage of infants born to women of unknown HBsAg status should serve to remind public health and professional associations that changes in established recommendations, especially if they occur without timely communication and education of health-care providers, may result in unexpected changes in vaccination practices. Anticipating the need for public health to respond to future safety controversies, the IOM report on thimerosal-containing vaccines also called for "...a review and assessment of how public health policy decisions are made under uncertainty" as well as research on how to improve strategies used to communicate rapid changes in vaccine policy.[124]

The need may also currently exist for research on how to boost public confidence in U.S. immunization policy. One hundred years ago, this confidence was easily obtained by making vaccination the popular thing to do.[149] In London at the time, there was public

apathy regarding the need for smallpox vaccination. But once a member of the local stock exchange donned a red ribbon on the vaccinated arm (indicating to others not to press against the arm), the act of smallpox vaccination became fashionable, and "a thousand ribboned arms may be met in five minutes anywhere in the city."[149] However, it will take more than a simple fashion statement for public health officials today to regain the level of public support for immunization that existed just a few years ago.

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