VACCINE SAFETY ISSUES

Vaccine Safety Issues

Autism (page 71)

Inflammatory Bowel Disease (IBD) (page 77)

Multiple Immunizations (page 81)

Bovine Spongiform Encephalopathy (BSE) (page 88)

Thimerosal (page 91)

Diabetes (page 95)

Multiple Sclerosis (MS) (page 97)

Shaken Baby Syndrome (SBS) (page 100)

Autism

Autism is a permanent, developmental disability that occurs in all racial, ethnic and social groups and falls into a disease category known as autism-spectrum disorders (ASD). Other ASDs include Asperger's disorder, childhood developmental disorder and pervasive developmental disorder not otherwise specified. Autism is characterized by problems with social interactions, difficulties with communication and by restrictive or repetitive interests and behaviors. The severity of autism can vary among individuals, ranging from poor language and daily living skills, to those who can function well in most settings.[1] Approximately 66% to 89% of individuals with autism also suffer from mental retardation.[2]

Autism is typically diagnosed between 18 to 30 months of age. Some children (approximately 20%) progress through a period of normal development before the onset of symptoms and may subsequently lose some of their earlier acquired skills. No blood or other medical test is available to diagnose autism, and a correct diagnosis depends on extensive, accurate analysis of a child's behavior and developmental history.[3]

A hypothesized link between autism and the measles, mumps and rubella (MMR) vaccine has been refuted by many public health experts and agencies, including the British Medical Research Council,[4] the World Health Organization,[5] the American Medical Association,[6] the American Academy of Pediatrics (AAP)[7] and the Institute of Medicine (IOM)[8] as well as numerous scientific studies.[9-14] This hypothesis was first proposed in 1998 in a small study of 12 children who were referred to a pediatric gastroenterology unit with histories of normal development followed by loss of acquired skills, diarrhea and abdominal pain. All research subjects except one were diagnosed with ulcerative colitis, a form of inflammatory bowel disease (IBD), and eight of the 12 subjects were diagnosed with autism.[15] The investigators proposed that the MMR vaccine might, within 24 hours to a few weeks of immunization, lead to intestinal abnormalities, which in turn could cause impaired intestinal function, allowing toxic intestinal products to reach the brain and cause neurological damage leading to autism. However, researchers explicitly stated that their findings did not prove an association between MMR vaccine and the syndrome they described.[15]

Temporal relationship?

Any evaluation of a temporal relationship between immunization with MMR vaccine and the development of autism must keep in mind that because MMR is administered at the age when many children are diagnosed with autism, it would be expected that most children, regardless of whether or not they have autism, would have received the MMR vaccine. It would be likely that many of the children with autism would have received the vaccine close to the time of their autism diagnosis.[16]

However, two questions need to be considered when assessing whether a temporal relationship exists between MMR vaccination and autism:

(1) Did symptoms of autism develop in children following immunization with the MMR vaccine?

Commentary following the publication of the 1998 study[15] noted that the disease of autism was known well before the MMR vaccine became available and that behavioral changes were almost always preceded by bowel symptoms.[17] A recent report by the AAP that analyzed over 1,000 references in the medical literature notes that most studies of the size and structure of the brains of ASD cases suggest that atypical brain development characteristic of the disease occurs before birth.[7]

At the time the 1998 study was conducted, about 90% of children in the UK had received the MMR vaccine.

Another research group in the United Kingdom attempted to replicate the findings of the 1998 study. These researchers noted a slightly increased relative risk for the association of MMR vaccination and initial parental concern about their child's

GLOSSARY TERMS

Acute
Adverse events
Asperger's disorder
Association
Autism
Autism-spectrum disorder
Bias
Blinded
Cases
Cerebral palsy
Childhood developmental disorder
Chronic
Congenital rubella syndrome
Control
Coverage
Crohn's disease
Disease
Dose-response relationship
Dysfunction
Encephalopathy
Enterocolitis
Fragile X syndrome
Gastroenterology
Gastrointestinal system
Gastrointestinal tract
Genome
HOXAI
Ileal-lymphoid-nodular hyperplasia
Immunization
Incidence
Inflammatory bowel disease
In situ hybridization
In utero
Institute of Medicine
Lymphocytes
Major histcompatibility complex
Measles
Metabolic disorders
MMR vaccine
Morbidity
Mumps
Neuropeptides
Neurotrophins
Nodules
Pervasive developmental disorder
Polymerase chain reaction
Prevalence
Registry
RNA
Risk
Rubella
Seizure
Selection bias
Temporal relationship
Thalidomide
Ulcerative colitis
Vaccine
Vaccination registry
Virus

ACRONYMS

AAP	American Academy of Pediatrics
ASD	Autism-spectrum disorder
HMO	Health maintenance organization
IBD	Inflammatory bowel disease
IOM	Institute of Medicine
MHC	Major histocompatibility complex
MMR	Measles, mumps, rubella
NCES	National Childhood Encephalopathy Study
NIH	National Institutes of Health
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
RNA	Ribonucleic acid

WEB RESOURCES

AUTISM:

National Partnership for Immunization
http://www.partnersforimmunization.org/issues.html

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/autism/default.htm

Johns Hopkins University Institute for Vaccine Safety
http://www.vaccinesafety.edu/cc-mmr.htm

National Network for Immunization Information
http://www.immunizationinfo.org

(continued)

development. However, researchers questioned whether this association may have resulted from the parents' difficulty in recalling the precise age at onset and hence they may have approximated that their child was 18 months of age when they first became concerned.[11] Researchers then conducted a further analysis of this proposed association and found no significant difference in the age at parental concern between children receiving MMR vaccine before the age of 15 months, those receiving vaccine at 15 months of age or later and those not receiving MMR vaccine.[18]

A study conducted in Sweden involving 55 known cases of autism compared autism prevalence rates in populations of children from two communities. The results indicated no difference in autism prevalence between children born after the introduction of the MMR vaccine in Sweden and those born before the vaccine was used.[10]

Before 1980, the majority of parents reporting to the Autism Research Institute stated that their children had autistic symptoms in early infancy. After 1980, over two thirds of the parents reported that their children's symptoms started after age 18 months.[19] The question remains whether this change in reporting of onset of disease is real or biased.

Rates of bowel problems and behavioral regression were compared in children who received the MMR vaccine before their parents became concerned about their development with those of children who either received the vaccine after their parents became concerned or did not receive the vaccine at all. No significant difference between these groups was found.[20]

The United Kingdom's National Childhood Encephalopathy Study (NCES) in 1976-1978 examined 770 cases of children with encephalopathy who previously appeared to be neurologically normal, to ascertain the relationship between immunization and various acute encephalopathic illnesses. Only 16 of these children had received measles vaccine within 7-14 days before the onset of their illness. When children with seizures accompanied with fever were excluded, the findings showed no significant association between measles vaccination and the onset of acute neurological events in previously healthy children.[21]

(2) Has there been an increase in the number of autism cases since the MMR vaccine was licensed?

According to a study done in the United Kingdom, the number of known autism cases has been increasing since 1979, and no sharp increase in cases was observed after the introduction of MMR vaccine in 1988. Among affected individuals, the age at diagnosis was similar whether the child had been vaccinated before or after age 18 months or had not been vaccinated.[11] If MMR vaccine was causing autism, it would be expected that children vaccinated at a younger age would develop autism at a younger age than children vaccinated at older ages.[9]

A recent AAP report noted that the increase in reporting of autism-spectrum disorders in recent years occurred long after the introduction of the MMR vaccine in the US in 1971.[7]

A review of 16 studies in North America, Europe and Japan found no evidence of an increase in autism rates following the introduction of the MMR vaccine.[22]

No change in the proportion of autistic children in the United Kingdom with bowel problems or developmental regression was found over a 20-year period beginning in 1979. This was the period of time when MMR vaccination was introduced in the United Kingdom.[19]

Strength of association?

The findings of the 1998 United Kingdom study described a striking and consistent pattern of ileal-lymphoid-nodular hyperplasia, an abnormality of the mucosal surface of the gastrointestinal tract, in nine of the 12 children examined.[15] The uniformity of these findings combined with the absence of detectable neurological

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccie.chop.edu/concerns.shtml#question7

Immunization Action Coalition
http://www.immunize.org/autism

National Alliance for Autism Research
http://www.naar.org

Institute of Medicine's Measles-Mumps-Rubella Vaccine and Autism Report
http://www.iom.edu/imsafety

abnormality in these children led the researchers to believe that some outside factor was causing the abnormal brain function. However, other investigators suggested that selection bias may have occurred in this study as the report was based on cases referred to a group known to be specifically interested in studying the possible relationship between MMR vaccine and IBD.[16] Such groups or centers are more likely to encounter patients with gastrointestinal disease. A more objective way to determine the prevalence of gastrointestinal symptoms in ASD patients is to evaluate all children with ASD in a particular community.[7]

Dose-response relationship?

If evidence was found that rates of autism were increasing relative to increased use of MMR vaccine, this information would suggest a possible dose-response relationship between MMR use and the development of autism. MMR immunization coverage rates among children born in 1980-1994 and enrolled in California kindergartens were recently compared to the number of autistic children enrolled in the California Department of Developmental Services regional service center system. The increase in the number of autism cases during this time period (373% relative increase) was substantially greater than the increase in MMR immunization coverage rates (14% relative increase). These substantially different increases do not provide evidence to support a causal relationship between the use of MMR and the development of autism.[13]

Data from the United Kingdom general practice research database were used to analyze the relationship between MMR vaccination and the diagnosis of autism in boys over time. Autism incidence rates increased almost fourfold among two to five year old boys born in each year from 1988 to 1993, while the prevalence of MMR vaccination remained relatively steady at over 95% for each year studied.[23] In another United Kingdom study, high, stable MMR immunization rates were observed during a period in which autism incidence was apparently increasing. Also, MMR vaccination coverage among autistic children at age two was found to be nearly identical to that of non-autistic children of the same age in the same London districts. These findings suggest an absence of a dose-response relationship between vaccine coverage and autism.[9]

Replication of findings?

Recent reports from both the IOM Immunization Safety Review Committee and AAP have not found evidence to support the hypothesis that the MMR vaccine causes autism at the population level.[7, 8] Both reports noted that existing epidemiological research shows no overall association between the MMR vaccine and autism. The IOM report did not exclude the possibility that the MMR vaccine could contribute to rare cases of ASD in a very small number of affected children.[8]

Data from a surveillance system created in 1982 when MMR vaccine was first introduced in Finland were analyzed for adverse events associated with MMR vaccination. Comprehensive analysis of 1.8 million individuals and consumption of almost three million vaccine doses during a 14-year follow up revealed no cases of autism, ulcerative colitis, Crohn's disease or any other chronic disorder affecting the gastrointestinal system.[14]

All 498 known cases of ASD among children living in certain districts of London who were born in 1979 or later were evaluated relative to an independent vaccination registry. An association between MMR vaccine and autism could not be identified.[9]

No association was found between IBD and autism in 325,000 French school-age children[24] or in nearly 9,000 children and adolescents at a London psychiatric care center.[25]

Biologic plausibility?

The 1998 British study identified an abnormal pattern of ileal-lymphoid-nodular hyperplasia in nine of the 12 autistic children examined.[15] However, any suggestion that MMR vaccine causes autism requires consideration of at least two additional biologic mechanisms. First, MMR vaccine must be shown to cause the observed intestinal abnormalities. Although nine of the 12 vaccinated children studied displayed this abnormality, suggesting an association between these two factors, this observation does not provide evidence that the MMR vaccine was the cause of the dysfunction. A biologic mechanism explaining how MMR vaccine might cause this intestinal abnormality has yet to be identified.

Studies of the biological plausibility of whether MMR use causes autism have focused on attempting to detect measles virus in the intestines of autistic MMR-vaccinated children along with an absence of measles virus in the intestines of non-autistic vaccinated children. Intestinal biopsy samples were tested for the presence of measles virus genome from children both with and without autism. Measles virus was detected in these samples using the techniques of polymerase chain reaction (PCR) and *in situ* hybridization. Seventy-five out of the 90 children with autism were found to have fragments of measles virus in their biopsies while only five out of the 70 children without autism had fragments of measles virus in their biopsies. No information was given by study authors about the immunization status of all 160 children who participated in this study, the length of time post-immunization (for those who had been immunized) that these samples were collected, nor whether the measles virus found in these samples was natural measles virus or vaccine virus, making it difficult to determine if MMR vaccine was associated with this finding. No information was given about whether laboratory personnel performing these tests were blinded as to the diagnosis (autistic or not autistic) of the child associated with each sample.[26] Blinding of laboratory research staff relative to patient status is a key practice necessary for assuring objectivity in clinical research.

Further studies are needed to determine whether the measles vaccine virus can be found in the intestines of autism cases after vaccination with MMR and whether finding measles vaccine virus in the intestine after immunization is abnormal.[7, 27] The report from AAP's New Challenges in Childhood Immunizations Conference noted that physiological interactions, problems with PCR techniques as well as the potential for contamination could affect PCR study results. Therefore, the report recommends that collaborative studies involving multiple laboratories testing coded, unknown specimens be conducted.[7]

Because measles RNA has been found in multiple organs of people without apparent disease,[7] there is a need to determine

whether the presence of measles vaccine virus is associated with the progression to autism in some children. Intestinal biopsies of children who recently received the MMR vaccine and developed autism need to be compared with intestinal biopsies of children who recently received the MMR vaccine and did not develop autism.[27]

A second mechanistic issue in assessing the biologic plausibility of the hypothesis that MMR vaccination causes autism is to determine how intestinal abnormalities might lead to the developmental disabilities characteristic of autism. Although an association between intestinal and central nervous system abnormalities can be suggested, no clinical or experimental data have demonstrated a causal mechanism. Researchers have suggested that this association could result from the action of a gene or physiologic mechanism related to and simultaneously affecting both systems rather than the result of abnormalities in one system (gastrointestinal system) causing the abnormality in the other (nervous system).[7]

Consideration of alternative explanations?

Although the cause of autism is unknown, many factors have been hypothesized to be associated with some forms of autism. A genetic predisposition to ASD has been suggested from observations that boys are nearly four times more likely to develop the disease than girls[23] and also from studies of siblings and twins. Parents with one child with autism have a 50 times greater risk of subsequent children developing autism than parents without an affected child.[28] Up to 75% of identical (having the same genetic make-up) twins either both have autism or both do not have autism while only 3% of fraternal (do not have the same genetic make-up) twins either both have autism or both do not.[29]

Research suggests that as many as 10 genes could be involved in predisposing children to ASD.[30] In 1995, a working group convened by the National Institutes of Health (NIH) reached a consensus that autism probably results from a genetic susceptibility that involves multiple genes. Studies suggest that the gene HOXA1,[31] inherited metabolic disorders[32] and differences in the major histocompatibility complex (MHC) genes[33, 34] may have supportive roles in susceptibility to autism. Studies conducted in families with more than one member diagnosed with an ASD have also identified possible genetic links to ASD.[30, 35]

Studies have shown that children exposed to thalidomide during the first trimester of pregnancy are at an increased risk for developing autism.[36] One study was able to estimate that the risk period for developing autism following receipt of thalidomide occurs before 24 weeks of pregnancy.[21] Another study found evidence for structural brainstem abnormalities in children with autism which only could have occurred during brainstem development *in utero*.[37]

Children with congenital rubella syndrome (exposure to rubella prenatally)[38-44] and fragile X syndrome[21] are also at increased risk of developing autism.

Although some researchers suggest that the MMR vaccine could serve as a trigger in children already genetically predisposed to autism,[45] other possible environmental, infectious and metabolic triggers have been implicated. An extensive review of the autism literature identified 24 medical disorders possibly related to autism or autistic-like conditions. This review noted that the rate of association of autism with these medical disorders ranged from 11% to 37% in published studies.[46]

Factors other than an actual increase in the number of children with autism may influence the determination of autism prevalence rates. Increased knowledge about autism can lead to better recognition of the disease and the provision of more services for autistic patients. Emerging environmental or lifestyle changes might also affect these numbers. Because the California study that observed a 373% increase in the number of autistic cases in recent years used actual numbers of cases instead of rates,[47] the data are influenced by the steadily increasing California population. In other words, even if the rate of autistic children remains the same over time, a larger number of autistic cases will be found in a larger population than in a smaller one.[45]

Some researchers have hypothesized that autism is a result of abnormal development in the brain and that markers of this abnormal development are present in newborns. These researchers found that in children with autism and in those with mental retardation without autism, blood from the earliest days of life contained concentrations of certain neuropeptides and neurotrophins that differed from those observed in children with cerebral palsy or in normal, control children.[48]

Cessation of exposure?

In the absence of evidence of a causal relationship between MMR and autism, eliminating or modifying the use of MMR vaccine would not be expected to alter the risk of developing ASD. By reducing or eliminating children's exposure to the MMR vaccine, their risk of becoming infected with measles, mumps and/or rubella virus would be expected to increase markedly, resulting in much higher incidences of morbidity and mortality due to these diseases. The measles outbreak of 1989-1991, which occurred because of decreased use of the MMR vaccine during the late 1980s, is a compelling example of the public health impact of reducing vaccine use.[49] During this period, 55,467 cases of measles were reported and there were 136 measles-associated deaths.

Specificity of exposure?

Scientific commentary following the 1998 United Kingdom study[15] has argued that the intestinal syndrome described is not clinically unique and that ileal-lymphoid hyperplasia is non-specific.[16] It is not unusual for young children to have collections of lymphocytes in their intestines. In fact, enlarged collections of lymphocytes in the intestine can occur in up to 25% of healthy children.[27] The authors of the 1998 study contend that although small nodules are considered normal, a more exaggerated change was observed in the patients studied.[50]

Consistency with other knowledge?

Home movies were shown to neurodevelopmental specialists who were blinded to whether the children they were watching eventually were or were not diagnosed with autism. These specialists were able to separate autistic from non-autistic children at one year of age with a high degree of accuracy.[51-55]

Children who were eventually diagnosed with autism have also been predicted from home movies taken at two to three months of age.[56] These studies suggest that the first signs of autism are present earlier than thought and that these symptoms occur prior to the receipt of the MMR vaccine.[21]

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Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) is a general medical term used to refer to chronic inflammatory diseases of the intestine. IBD can begin at any age, but it usually develops in persons between the ages of 15 and 30 years. IBD is a rare disease with three to 20 new cases reported per 100,000 persons each year in the US. Two common inflammatory bowel diseases are ulcerative colitis and Crohn's disease. These chronic illnesses can inflame the gastrointestinal tract causing bloody diarrhea, abdominal pain and weight loss. Ulcerative colitis can affect the entire large intestine or the rectum. Crohn's disease mainly affects short segments of both the small and large intestine.[1]

An association between measles vaccination and IBD was first proposed in a 1995 cohort study of vaccinated children in the UK who were enrolled in a 1964 trial of a measles vaccine, and followed until 1994. The incidence of IBD in these children was compared to the incidence of IBD in a group of presumably unvaccinated children enrolled in a study of persons born in Great Britain during one week in 1958. Children in the vaccinated cohort had a three-fold increased risk of Crohn's disease and a 2.5-fold increased risk of ulcerative colitis compared with the unvaccinated children.[2]

The validity of this study has been questioned for several reasons. Vaccinated and unvaccinated groups were followed for different periods of time, with follow up of the vaccinated group being approximately half of that for the unvaccinated group.[3] During the study's evaluation of outcome, vaccinated individuals were asked specifically about Crohn's disease and ulcerative colitis, while unvaccinated individuals were asked about "any longstanding illness, disability or infirmity." Moreover, vaccinated and unvaccinated individuals were selected from different populations.[4] Any of these differences in the selection and assessment of vaccinated and unvaccinated study participants could have significantly biased study outcomes.

Temporal relationship?

The incidence of Crohn's disease has increased since the 1940s, but this trend began some 20 years prior to the introduction of the measles vaccine.[5]

A small 1998 study looked at 12 children who were referred to a pediatric gastroenterology unit with histories of normal development followed by loss of acquired skills, diarrhea and abdominal pain. All research subjects except one were diagnosed with ulcerative colitis. In eight of these 12 children, the onset of behavioral symptoms was attributed by the parent or provider to measles, mumps, rubella (MMR) vaccination.[6] However, other investigators suggested that selection bias may have occurred in this study as the report was based on cases referred to a group known to be specifically interested in studying the possible relationship between the MMR vaccine and IBD.[7]

Using data from a Finnish surveillance system created in 1982 when MMR vaccine was first introduced in Finland, comprehensive analysis of 1.8 million individuals and use of almost three million doses of MMR vaccine during a 14-year follow up revealed no cases of IBD.[8]

Strength of association?

A study looking at all individuals born in Great Britain during a single week in 1970 whose vaccination history was accessed from a survey conducted when the children were five years old found no significant association between measles infection at a young age and later development of Crohn's disease or ulcerative colitis. However, the specific combination of measles and mumps infection in the same year of life between birth and age six years was significantly associated with the development of both ulcerative colitis and Crohn's disease later in life.[9]

Dose-response relationship?

The rate of Crohn's disease reported in Finland from 1986 through 1992 was compared to the proportion of the population receiving measles vaccine. While the

GLOSSARY TERMS

Acute
Antigen
Association
Bias
Cases
Chronic
Cohort study
Controls
Crohn's disease
Disease
Enterocolitis
Epidemic
Gastroenterology
Gastrointestinal tract
Ileal lymphonodular hyperplasia
Immune system
Immunization
Immunogold electron microscopy
Incidence
Inflammation
Inflammatory bowel disease
In situ hybridization
In utero
Lesions
Lymphatic tissue
Lymphocytes
Measles
MMR vaccine
Morbidity
Mumps
Peripheral blood mononuclear cells
Polymerase chain reaction
Risk
RNA
Rubella
Selection bias
Systemic
Temporal relationship
Ulcerative colitis
Vaccine
Vaccine Safety Datalink Project
Virus

ACRONYMS

IBD	Inflammatory bowel disease
MCV	Measles-containing vaccines
MMR	Measles, mumps, rubella
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
RNA	Ribonucleic acid

WEB RESOURCES

The American Gastroenterological Association
http://www.gastro.org/public/ibd.html

KidsHealth for Parents
http://kidshealth.org/parent/medical/digestive/ibd.html

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/autism/ibd.htm

proportion of the population receiving at least one dose of measles vaccine increased over this period, the rate of Crohn's disease remained stable among persons from birth to 24 years of age.[10]

Children five to 16 years of age enrolled in a 1994 national measles, mumps, rubella vaccine campaign targeted at school-age children in England were followed for 16 months. Although each of these children were receiving their second dose of MMR vaccine (their first dose was received around the age of one year), researchers found no increase in hospital admissions for Crohn's disease among this group of children.[11]

Replication of findings?

A study utilizing the Vaccine Safety Datalink Project identified 142 persons with IBD born between 1958 and 1989 and compared each of their vaccination records with those of five matched controls. Researchers found that neither administration of MMR vaccine or other measles-containing vaccines (MCV) nor age at vaccination increased the risk of IBD. Rates of IBD were also not elevated in the time immediately following vaccination with either vaccine (MMR or MCV).[3]

A UK study compared 140 individuals with IBD born in or after 1968 with 280 matched controls and found no association between measles vaccination and Crohn's disease, ulcerative colitis or all IBD combined.[12]

Biological plausibility?

In order to prove that the measles vaccine actually causes IBD, it is necessary to prove that the measles virus is definitely present in gastrointestinal lesions, that it is active and that it can cause an inflammatory response. Researchers would also need to determine whether this reaction was caused by the measles virus or by the attenuated (weakened) measles vaccine virus.[1]

Disease occurs when the virus that causes measles disease infects the respiratory system and then spreads to lymphatic tissue, an important part of our immune system. During the acute infection, lymphocytes in the gastrointestinal tract are infected, but whether this causes chronic inflammation is highly questionable. One theory speculates that the measles virus may persist in the intestine in certain individuals and later trigger a chronic inflammatory infection; however, this has not been proven. Because the MMR vaccine contains a very weak live measles virus, it has been suggested that measles vaccine could cause a similar inflammatory process in the intestine. This theory has not been proven and is speculative.

Additional biological evidence that measles infection increases the risk of IBD is based upon laboratory-based investigations looking for evidence of past or persistent measles infection among people with IBD.

Studies have detected measles virus in the intestines of persons with IBD based on *in situ* hybridization techniques[13] and immunogold electron microscopy.[14] Researchers have since argued that these techniques are not sensitive enough to accurately identify measles virus in the bowel,[15] and other researchers using the same laboratory methods could not identify measles virus in the intestines of patients with IBD.[16] Four studies using the more sensitive and specific polymerase chain reaction (PCR) method found no evidence of measles virus ribonucleic acid (RNA) in the gastrointestinal tissues of patients with Crohn's disease or ulcerative colitis.[16-20]

In a study of 20 patients with chronic intestinal inflammation, measles virus RNA was detected in peripheral blood mononuclear cells (PBMC) using the PCR technique. One of eight patients with Crohn's disease and one of three patients with ulcerative colitis were positive. Measles virus RNA was not detected in PBMC from 28 control patients.[21] These findings were considered by the researchers to be indicative of a potential association between MMR vaccine and the IBD of the individual patients. However, vaccination status was given for only one patient and was not given for any of the controls.

Cessation of Exposure?

In the absence of evidence of a causal relationship between the MMR vaccine and inflammatory bowel disease, eliminating or modifying the existing childhood immunization schedule would not be expected to alter the risk of such infections. By reducing or eliminating children's exposure to the MMR vaccine, their risk of becoming infected with measles, mumps and/or rubella viruses would be expected to increase markedly, resulting in much higher incidences of morbidity and mortality due to these diseases. The measles outbreak of 1989-1991, which occurred because of decreased use of the MMR vaccine during the late 1980s is a compelling example of the public health impact of reducing vaccine use.[22] During this period 55,467 cases of measles were reported and there were 136 measles-associated deaths.

Specificity of Association?

In a recent study of 91 patients with a histologically confirmed diagnosis of ileal lymphonodular hyperplasia and enterocolitis, measles virus was detected in the intestinal tissue of 75 using the PCR technique. In comparison, measles virus was only detected in five of 70 control patients.[23] Commentary following the article noted that the technique used could not identify if the whole virus was present or whether the virus was replicating. Researchers also noted the possibility that the measles virus persistence could be the result of the inability of bodies of patients suffering from a developmental disorder that already existed to clear the virus from their intestines.[24] Further, the PCR methods used could not determine if the measles genomic material identified was the result of a case of measles disease, was from a previous injection with MMR vaccine or was from a previous injection with vaccine that contains only measles vaccine virus.[25]

Consideration of alternative explanations?

There are several unproven theories as to the cause(s) of IBD. A possible genetic predisposition has been proposed because IBD is known to occur in the same family.[26] A possible environmental cause has also been suggested because Crohn's disease most often occurs in people who smoke and in residents of Northern European countries and of urban areas. Other theories propose that IBD is triggered by significant emotional events in a person's life, by other infections, or by the body's immune system reacting to unidentified or unknown antigens causing the immune system to respond inappropriately and resulting in chronic inflammation.[1]

Consistency with other knowledge?

Studies have been conducted to examine the development of IBD following *in utero* exposure to measles and measles infection in early life.

In Utero measles exposure:

A Swedish study of 25,000 pregnancies between 1940 and 1949 found that three of the four babies whose mothers experienced a measles infection while she was carrying them had developed Crohn's disease.[27] This rate of disease was much higher than expected. A later study conducted in Denmark followed 25 babies whose mothers had developed measles during pregnancy and found no cases of Crohn's disease.[28] Another study compared 3,076 individuals exposed *in utero* to viral diseases (including measles) to a matched set of unexposed individuals with follow up through ages 16 to 53 years. Among the non-exposed individuals there was one case of ulcerative colitis and one of Crohn's disease, while among those exposed to measles *in utero* there were no cases of IBD.[29] In both of these studies, the rate of IBD was much less than would be expected had the original findings of the Swedish study been replicated.

Postnatal exposure or infection:

The birth records of 257 Swedish individuals with IBD from 1924 through 1957 were compared to 514 matched controls. Individuals with a history of postnatal infections were 5.5 times more likely to develop IBD than individuals without a history of postnatal infection. But the study did not specifically address whether it was measles infection that accounted for the increased risk.[30]

A study in North Carolina compared 322 individuals with IBD to neighborhood controls or acquaintances and found that childhood infections (not just measles infection) increased the risk of Crohn's disease but not of ulcerative colitis. For measles infection specifically, there was an increased risk of Crohn's disease and ulcerative colitis, but in neither case was the risk statistically significant.[31]

The incidence rate of Crohn's disease and ulcerative colitis in persons less than 30 years of age was evaluated in a group of individuals who were born in a three month time period following five different measles epidemics in Sweden. The actual number of cases of Crohn's disease in this group was 1.46 times higher than the expected number of cases (57 cases were reported compared to the expected number of 39 cases). The number of ulcerative colitis cases in this group was not significantly different from the expected number of cases.[32] A study in the UK that analyzed patients with Crohn's disease diagnosed between 1972 and 1989 found no increased risk for Crohn's disease among children born in years with high measles incidence rates compared with children born in other years.[33]

In the 1970 British Cohort Study, measles infection at 10 years of age or younger was not associated with an increased risk for Crohn's disease or ulcerative colitis by age 26. However, the rare combination of mumps and measles infection in the same year of life was associated with a statistically significant increase of both Crohn's disease and ulcerative colitis.[11]

A Mayo Clinic study followed 662 patients with measles prior to age five during the period from 1950 to 1966 for 10 to 48 years. The number of individuals observed to have Crohn's disease or ulcerative colitis were compared with the number expected based on age and gender-specific population incidence rates. A total of six individuals with Crohn's disease and six with ulcerative colitis were found (compared with 1.9 and 2.0 expected cases, respectively.).[34]

In a study looking at two UK birth cohorts, 26 patients with Crohn's disease and 29 patients with ulcerative colitis were identified. Neither measles nor mumps infection by seven years of age were associated with an increased risk for Crohn's disease or for ulcerative colitis.[35]

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Multiple Immunizations

Currently, there are 11 licensed vaccines in the US that are recommended for universal use by children during the first two years of life.[1,2] These vaccines are administered through as many as 20 separate inoculations. The personal and the public health benefits of these immunizations are extremely important, but the use of syringes and needles to administer vaccines is often frightening and uncomfortable to children, and distressing to parents.[3] Because of the large number of immunizations given to children prior to school entry, particularly those administered during the first two years of life, some parents and others question whether children receive too many immunizations. A national telephone survey in 1999 of parents of children six years of age and younger and expectant parents revealed that 23% questioned the number of immunizations recommended for children and 25% worried that the vaccines might weaken the immune system.[4]

Concerns about the number of immunizations recommended for children and the development of the immune system focus on three issues: (1) the number of inoculations given; (2) the total number of antigens introduced by the immunizations; and (3) whether multiple immunizations might adversely affect the development of the child's immune system. Although the first two concerns were addressed in the section *Vaccines and How They Work*, the third concern, the potential for multiple immunizations to cause abnormal development of the immune system, warrants further consideration.

Some have postulated that the introduction of 123-126 antigens during the first two years of life might result in overstimulation of the immune system potentially leading to abnormal development of the immune system.[2,4-6] The postulated abnormal development might then result in an increased likelihood that the child will be more susceptible to other infectious agents, or to the development of allergies or autoimmune diseases,[5] which are considered indicators of immune system dysfunction. Numerous reports have suggested that as personal and community hygiene has improved in developed countries, the number and types of antigens to which young children are exposed has changed. [5,7-9] The notion that immune system dysfunction might be related to changes in antigen exposure during immune system development is known as the hygiene hypothesis.

As noted in *Vaccines and How They Work*, exposure of the developing immune system to many different bacterial, viral and other antigens is responsible for the development and maturation of B and T cells.[10,11] As currently conceived, postnatal exposure to such agents promotes the development of a subset of helper T cells called Th1 cells.[10] Antigen activated Th1 cells release various cytokines that regulate the normal immune response to viruses, bacteria and other antigens.[10] When a second subset of helper T cells, Th2 cells, are stimulated by antigens, they release certain cytokines that induce B cells to produce a particular type of antibody molecule (termed IgE) that can trigger allergic reactions as well as promoting the development of blood cells called eosinophils that contribute to allergic reactions.[10,11] The hygiene hypothesis suggests that when exposure to various bacteria, viruses and other antigens during postnatal maturation of the immune system is reduced, as might result from increased hygienic practices, the immune system develops a bias toward eliciting Th2-mediated responses to certain antigens.

Reduced exposure to bacterial, viral and other relevant antigens may also influence the development of the immune system by altering the production of a cytokine known as IL-10, which plays a pivotal role in regulating a variety of components of the immune response.[12,14,15] Typical exposure to such antigens in the absence of enhanced hygienic conditions results in the production of IL-10, which limits the ability to develop allergic and autoimmune responses.[8] Under conditions of enhanced hygiene where sustained exposure of the developing immune system to diverse antigens is reduced, production of IL-10 may be reduced. This, in turn, may limit the ability of this cytokine to suppress the activity of cells involved in allergic and autoimmune reactions, thus disposing the person to the develop allergies or autoimmune diseases.[5,8]

GLOSSARY TERMS

Adjuvant
Allergy
Antibody
Antigen
Association
Asthma
Autoimmune disease
B cell
Bacteria
Bias
Bystander activation
Cases
Cell-mediated response
Chronic
Congenital rubella syndrome
Coxsackievirus
Cytokines
Cytomegalovirus
Diabetes
Disease
Dose response relationship
Dysfunction
Eosinophil
Group A streptococcus
Hay fever
Helper T cell
Heterologous infections
Hygiene hypothesis
IgE
IL-4
IL-10
Immune response
Immune system
Immunization
Incidence
Inflammation
Institute of Medicine
Measles
MMR vaccine
Molecular mimicry
Morbidity
Multiple sclerosis
Myelin
Pancreas
Pathogens
Protein
Rheumatic fever
Rheumatic heart disease
Risk
Rubella
Superantigens
T cell
Temporal relationship
Th1 cell
Th2 cell
Thrombocytopenia
Type 1 diabetes
Vaccine
Virus

ACRONYMS

CDC	Centers for Disease Control and Prevention
IgE	Immunoglobulin E
IL-4	Interleukin 4
IL-10	Interleukin 10
IOM	Institute of Medicine
MHC	Major histocompatibility complex
MMR	Measles, mumps, rubella

WEB RESOURCES

American Diabetes Association
http://www.diabetes.org/main/community/info_news/news/vaccines.jsp

Asthma and Allergy Foundation of America
http://www.aafa.org

Institute of Medicine
http://www.iom.edu/iom/iomhome.nsf/pages/multiple+immunizations

Multiple Sclerosis Foundation
http://www.msfacts.org

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/gen/multiplevac.htm

National Institute for Health
http://www.nih.gov/hi/topics/autoimmune/autoimmunity.htm

National Multiple Sclerosis Society
http://www.nmss.org

The Institute of Medicine (IOM) Immunization Safety Review Committee recently examined the scientific evidence surrounding whether multiple immunizations were associated with various types of immune dysfunction that might result from impaired immune system development. The committee found no epidemiological evidence supporting a causal relationship between multiple immunizations and an increase in the incidence of infections by other pathogens or an increase in the likelihood of developing type 1 diabetes, an autoimmune disease associated with immune dysfunction. There was insufficient information available to assess whether multiple immunizations might increase the risk of allergic disease. The committee found only a theoretical link between multiple immunizations and the development of either autoimmune or allergic disease based on current understanding of the biological mechanisms associated with each.[5]

The following more closely examines the work of the IOM committee and others in examining the relationship between multiple immunizations and immune system dysfunction relative to susceptibility to other infections and to the development of allergies or autoimmune diseases.

Susceptibility to Other Infections

The idea that administration of multiple immunizations could lead to a child becoming more susceptible to other infections reflects the notion that if the immune system is busy responding to vaccine-associated antigens, its ability to respond to real infections may be impaired. Infections due to agents other than those targeted by vaccines are referred to as heterologous infections in the IOM report.[5]

Temporal relationship?

In order to determine whether use of increasing numbers of immunizations has led to increased susceptibility to other infections, rates of infections in children would need to be compared to the number of immunizations given over time. If the rate of childhood infections increased as the number of vaccines doses given increased, a temporal relationship could be established. However, no such studies have been conducted. In lieu of such studies, a number of investigators have examined morbidity and mortality data among immunized children in the US and abroad using various study designs. The seven studies reviewed by the IOM committee failed individually as well as collectively to demonstrate a causal relationship between immunization and susceptibility to heterologous infections.[5] None of the studies specifically attempted to determine the relationship between multiple immunizations and the risk of developing such infections.

Strength of association?

A strong association between the receipt of multiple immunizations and increased susceptibility to other infections would mean that those children receiving the fewest immunizations would acquire the fewest heterologous infections, while those receiving the greatest number of immunizations would experience the greatest number of such infections. Again, the studies reviewed by the IOM committee were not specifically designed to assess the role of multiple immunizations. Within the context of the designs used, there was no evidence that immunization increased the risk of heterologous infections.[5]

Dose-response relationship?

One approach to assessing the risk of heterologous infection would necessitate placing different cohorts of children on different immunization schedules so that the members of each cohort received a different number of immunizations. The children would be monitored for a biologically relevant period of time, and all infections recorded and the causative agent(s) determined. If there was a statistical association between increasing numbers of immunizations and increasing incidence of infection, the study would provide scientific evidence of a temporal relationship. Such studies have not been conducted and would be lengthy and costly, and the ethical basis for such studies would be subject to question.

In lieu of such studies, a number of investigators have examined morbidity and mortality data among immunized children in the US and abroad using various study designs. The seven studies reviewed by the IOM committee failed individually as well as collectively to demonstrate a causal relationship between immunization and susceptibility to heterologous infections.[5] None of the studies examined by the IOM committee[5] were specifically designed to determine if increasing the number of immunizations increased susceptibility to heterologous infection.

Replication of findings?

There are no published studies demonstrating a relationship or absence of a relationship between multiple immunizations and susceptibility to heterologous infections. The results of the seven studies reviewed by the IOM committee were highly variable, and flaws in the design of these studies further limited assessment of the reproducibility of the findings.[5]

Biologic plausibility?

Laboratory research has shown that when multiple antigens are given at one time, the strength, type and effectiveness of the immune response to each will differ in comparison to the response observed when each is given separately.[12,13] A variety of mechanisms, such as suppression of the ability of the immune system to respond to certain antigens, ineffective presentation of certain antigens or the overwhelming of the immune system,[10,11] have been suggested to explain such observations. Although none of these mechanisms have been shown to apply to the multiple immunizations given to children, the IOM committee concluded that such mechanisms could, in theory, influence the susceptibility to heterologous infections of children receiving multiple immunizations.[5]

Consideration of alternative explanations?

Susceptibility to infectious diseases is influenced by many factors, including exposure, dose, immune status, personal hygiene, patterns of gene expression and others.[13,14] Any or all of these factors could influence whether a person receiving multiple immunizations would be at increased risk for developing heterologous infections. Thus, there are many alternative explanations that might account for susceptibility to such infections, and only careful, well-defined scientific studies would be able to determine the role of each.

Cessation of exposure?

In the absence of evidence of a causal relationship between multiple immunizations and susceptibility to heterologous infections, eliminating or modifying the existing childhood immunization schedule would not be expected to alter the risk of such infections. By reducing or eliminating children's exposure to multiple immunizations, their risk of becoming infected by pathogens responsible for vaccine-preventable diseases would be expected to increase markedly, resulting in much higher incidences of morbidity and mortality due to these diseases. The measles outbreak of 1989-1991, which occurred because of decreased use of the MMR vaccine during the late 1980s is a compelling example of the public health impact of reducing vaccine use.[15] During this period 55,467 cases of measles were reported and there were 136 measles-associated deaths.

Consistency with other knowledge?

If exposure to multiple immunizations was specifically associated with increased susceptibility to heterologous infections, one would expect that as children progress through the recommended schedule of immunizations there would be an increase in the number of cases of infectious diseases reported, particularly those that are not vaccine preventable. Infectious disease statistics available from the Centers for Disease Control and Prevention (CDC)[16] do not suggest that the incidence of infectious diseases increases with age over the first six years of life.

Immunizations have been used effectively to prevent infectious diseases in the US for nearly 200 years. The use of vaccines has accelerated in recent years resulting in both an increase in the number of diseases that can be prevented by vaccination and in an increase in the number of immunizations given. Throughout this period, the incidence of both vaccine-preventable diseases as well as other infectious diseases has declined.[16] At this time there is no scientific evidence that multiple immunizations increase the risk of heterologous infections.

Susceptibility to Allergic Reactions

Speculation that multiple immunizations might be associated with allergic disease reflect the increasing incidence of asthma and some allergies in the US and in other countries over the past 40 years.[7,8] The hygiene hypothesis offers a biologically-based, but unproven, explanation for the increased incidence of allergic disease. Although this trend began many years before the inception of the current vaccination schedule for children, some have suggested that multiple immunizations of children whose immune systems are theoretically predisposed to Th2 responses may trigger allergic reactions.

The IOM committee focused on epidemiologic studies of hay fever and asthma in evaluating the relationship between multiple immunizations and the development of allergic disease. Generally, more information is available about these two diseases than is available about other allergic diseases. The committee noted that the six germane studies suffered from a variety of design and methodological flaws, and therefore concluded that the available data were insufficient to determine whether there was a causal relationship between multiple immunization and the incidence of hay fever and asthma.[5] As mentioned above in the discussion of susceptibility to heterologous infections, designing and conducting an appropriate study for assessing causality would pose a considerable challenge.

Temporal relationships?

Allergic disease may become apparent at different ages in different people.[17] Food allergies and asthma are often diagnosed in children less than three years of age, although many outgrow the symptoms.[17] For example, the incidence of asthma among children less than one year old was three to four times greater than the incidence among children one to four years of age.[18] Hay fever may not be diagnosed until the person is an adolescent or adult. It is unclear whether the appearance of allergic disease is temporally associated with the age range during which most childhood immunizations are given.

Strength of association?

In the absence of information supporting or refuting an association between multiple immunizations and allergic disease, as represented by the IOM committee's consideration of hay fever and asthma,[5] it is not feasible to assess the strength of the association. A strong association between the receipt of multiple immunizations and increased susceptibility to asthma and hay fever likely would mean that the incidence of these diseases would be lowest among children receiving the fewest immunizations, and greatest among those receiving the greatest number of immunizations.

Dose-response relationship?

In evaluating the relationship between multiple immunizations and allergic disease, one would expect a lower incidence of disease among those given low doses (few immunizations) and a greater incidence of allergic disease among those given high doses (more immunizations). The dearth of relevant data[5] precludes assessing whether a dose-response relationship exists in this case.

Replication of findings?

The IOM committee report[5] did not identify any studies demonstrating a relationship or absence of a relationship between multiple immunizations and susceptibility to developing hay fever or asthma.

Biologic plausibility?

Allergic reactions are typically Th2 cell-mediated and result from IgE antibodies directed against antigens associated with insects, toxins, pollen and other materials in the environment.[19] Much of the asthma reported among children in impoverished urban areas is attributed to allergens associated with cockroaches.[20] Although progress has been made in understanding allergic reactions, the factors responsible for initiating a Th2/IgE response remain incompletely understood.

A variety of experimental data support the hygiene hypothesis, yet it remains a theoretical concept.[5,8,9] If improved personal and community hygiene alters antigen exposure during the development the immune system and leads to abnormal regulation of the immune response, then the response could be skewed in the direction of allergic responses.[5] The IOM committee concluded

that too little is known about the mechanisms that might link the hygiene hypothesis, multiple immunizations and risk of developing allergy to consider such a linkage to be more than a theoretical possibility.[5]

The IOM committee[5] noted that a number of the recommended vaccines include alum as an adjuvant, i.e., a substance that is incorporated into a vaccine to enhance the immune response to the vaccine without eliciting an immune response to itself.[10,11] The adjuvant effect of alum is apparently related to its ability to induce the production of the cytokine IL-4 by certain immunologically active cells, which in turn promotes Th2 cell-mediated responses.[5] Because a number of vaccines given to children contain alum, the IOM committee concluded that there is a theoretical possibility that multiple immunizations could predispose the immune system to eliciting Th2 responses.[5] The committee was unable to assess whether this theoretical possibility might increase the risk of developing hay fever or asthma.

Consideration of alternative explanations?

The increase in the incidence of allergic disease observed over the past four decades coincides with a period of profound changes in American lifestyles, some of which may be reflected in the hygiene hypothesis. The changes in the incidence of allergic disease and lifestyle changes both pre-date the period during which the number of immunizations given to children increased. The likelihood that a person will develop an allergic disease is influenced by a variety of factors, including exposure to allergens and genetic predisposition.[21] For example, children of parents who have allergies are more likely to have allergic reactions than children of parents who do not have allergies.[21] The genetic factors responsible for such associations have yet to be determined. Similarly, no data are available to assess whether and how these genes might influence the responses to multiple vaccines.

Cessation of exposure?

In the absence of evidence of a causal relationship between multiple immunizations and susceptibility to developing allergic disease, the risks of developing allergic disease are unlikely to be altered by eliminating or modifying the existing childhood immunization schedule. As noted in the section on heterologous infection, reducing or eliminating the immunization of children would result in outbreaks of vaccine-preventable diseases.

Specificity of association?

If exposure to multiple immunizations was specifically associated with increased risk of developing allergic disease, one would expect that as children progress through the recommended schedule of immunizations there would be an increase in the number of cases of allergic disease. Although Th2 responses are known to contribute to allergic diseases, Th2 responses also are observed among people infected with parasitic worms.[5] Such infections are relatively common in many developing countries were the incidence of asthma and allergy are low. Hence, the hygiene hypothesis cannot fully account for the observed patterns of allergic disease.

Consistency with other knowledge?

Immunizations have been used effectively to prevent infectious diseases in the US for nearly 200 years. The use of vaccines has accelerated in recent years resulting in both an increase in the number of diseases that can be prevented by vaccination and in an increase in the number of immunizations given. Throughout this period, the incidence of both vaccine-preventable diseases as well as other infectious diseases has declined.[15] At this time, there is no scientific evidence that multiple immunizations increase the risk of developing allergic disease.

Susceptibility to Autoimmune Disease

Over the past several decades, the incidence of autoimmune diseases like type 1 diabetes and multiple sclerosis, have increased.[5] Autoimmune disease occurs when the immune system produces immune effectors that directly damage the person's own cells, tissues and organs. Autoimmune diseases may be systemic, where the symptoms are manifest in a variety of tissues and organs such as multiple sclerosis, or they may be organ-specific, such as type 1 diabetes which effects the pancreas.[22] Although some autoimmune diseases may be diagnosed during childhood, most do not become apparent until the second, third or even fourth decade of life. In general, autoimmune diseases are more commonly diagnosed in females than males,[22] although the reasons for this disparity have yet to be determined.

The normal immune system includes both B and T cells that possess cell surface receptors capable of recognizing and binding to self antigens, i.e., molecules that are normally present in the tissues and organs of the body. A variety of mechanisms have been postulated to account for the immunological tolerance to self antigens that prevent the activation of these cells.[22,23] Even so, normal individuals typically sustain some modest degree of ongoing self-reactivity.[22,23] When the mechanisms that hold these autoimmune effectors in check are compromised, autoimmune disease results.[22,23]

The IOM committee focused on epidemiologic studies of type 1 diabetes in evaluating the relationship between multiple immunizations and the development of autoimmune disease. Generally, more is known about type 1 diabetes than is known about other autoimmune diseases. The committee noted that although the eight relevant studies differed in design, there was no evidence of a causal relationship between multiple immunizations and type 1 diabetes.[5]

Temporal association?

The natural history of most autoimmune diseases is characterized by late onset, diversity of affected target organs, a preponderance of cases among females and other unique features. These disease characteristics suggest that there is no temporal relationship between the receipt of multiple immunizations during the first six years of life and the onset of autoimmune disease.[22,23]

Strength of association?

In the absence of an association between multiple immunizations and autoimmune disease as exemplified by type 1 diabetes,[5]

it is not possible to evaluate the strength of the association. A strong association between the receipt of multiple immunizations and risk of developing type 1 diabetes likely would be manifest by a pattern in which the incidence of this disease would be lowest among children receiving the fewest immunizations, while the incidence would greatest among those receiving the greatest number of immunizations.

Dose-response relationship?

If exposure to multiple immunizations was specifically associated with increased risk of developing autoimmune disease, one would expect that as children progress through the recommended schedule of immunizations there would be an increase in the number of cases of this disease. Although the number of reported cases of autoimmune disease in the US are not well characterized, at least in the case of type 1 diabetes, the incidence seems to be increasing.[5] Evidence from several studies has failed to demonstrate a relationship between immunization and type 1 diabetes,[5] although none of the studies specifically addressed disease incidence relative to the number of immunizations given.

Replication of findings?

The IOM committee report[5] did not identify any studies demonstrating or refuting a relationship between multiple immunizations and susceptibility to developing type 1 diabetes. Because most existing studies of the potential relationships between vaccination and autoimmune disease generally consider single vaccine series, there are little or no data addressing possible relationships between multiple immunizations and autoimmune disease.

Biologic plausibility?

Autoimmunity is an incompletely understood phenomenon that has been associated with a variety of biological mechanisms.[22,23] These include a skewing of the immune response from one directed against a foreign antigen to one that is directed against a biochemically similar self antigen. In this case, the foreign antigen is said to mimic the self antigen, i.e., molecular mimicry. It has been suggested that autoimmunity may result when inappropriate presentation of self antigens occur, resulting in a strong immune responses, or when there is breakdown of regulatory mechanisms that ordinarily limit the ability of the immune system to respond to self antigens or that lead to inappropriate recognition of self antigens.[22,23] Inflammation at sites of infection could contribute to the induction of such mechanisms.[31] It is unclear whether any of these possible mechanisms are activated as a result of receiving multiple immunizations.

The IOM committee report[5] concluded that molecular mimicry could potentially be a factor in the induction of type 1 diabetes. The concept of molecular mimicry as it applies to the immune response suggests that some foreign antigens may be sufficiently similar in structure to certain self antigens such that the immune response directed against the foreign antigen might cross react with the self antigen.[22,23,25] This, in turn, could lead to production of a self-reactive immune response that gives rise to chronic or recurrent autoimmune disease.

A classic example of molecular mimicry is autoimmune-mediated rheumatic fever that occurs in some people as a consequence of Group A streptococcal infections. In this case, antibodies against the bacterial antigens bind to structurally similar proteins found in the heart.[26] These localized antibody/self antigen interactions contribute to the onset of rheumatic heart disease. Infections by coxsackievirus, cytomegalovirus, and rubella virus have been associated with type 1 diabetes.[27] This evidence along with the association of congenital rubella syndrome with type 1 diabetes led the IOM committee to conclude that molecular mimicry could constitute a linkage between immunization and autoimmune disease, although the role of multiple immunizations in such a relationship remains to be determined.[5]

It also has been proposed that infectious agents may induce the activation of an autoimmune response by acting as superantigens or through bystander activation.[24,28] T cells typically are activated when a receptor on the cell surface specifically recognizes and binds to an antigen that is presented by an appropriate MHC molecule (see *Vaccines and How They Work*). Superantigens are antigens that stimulate T cells by direct interaction between the antigen and the receptor molecule independent of the receptor's antigen binding site. The former might be envisioned as inserting a key into a lock in a door handle to open a door, while superantigen activation might be seen as touching the key to the surface of the handle to open the door. Superantigens stimulate T cells independently of the specificity of the cell. Thus, antigens from invading bacteria or viruses could activate T cells that recognize self antigens.[24] Once activated these cells could trigger chronic or episodic autoimmune disease.

As described in *Vaccines and How They Work*, large numbers of inflammatory cells are recruited to a site of infection. T cells activated by antigens as well as other cells at the infection site release a complex mix of cytokines and other regulatory molecules into the local environment. Hence, immune cells present at the site, but not specifically participating in the response, may become activated by virtue of being present when and where these molecules are released.[24] Some of these activated bystander cells may trigger the onset of autoimmune disease. The cytokine-rich environment also could induce antigen presenting cells to inappropriately present self antigens, again setting the stage for the development of autoimmune disease.[24] Processes such as these that alter regulation of the immune response lend support to the hygiene hypothesis as it applies to autoimmune disease.[8]

Scientific evidence exists for the various mechanisms outlined above that might link infections with the risk of developing autoimmune disease.[22,23,24] Other research suggests that susceptibility to developing autoimmune disease is influenced by a variety of other factors, including genetic background.[29,30,31] Whether and how the various mechanisms that have been proposed to explain these relationships apply to vaccines remains unclear. A recent review suggests that in most cases there are few data implicating vaccines in the induction of autoimmune disease.[29] One possible exception is an apparent increase in the risk of developing thrombocytopenia, an autoimmune-mediated blood disorder, after MMR immunization. However, this risk is small relative to the risk of developing one or more of these infections in the absence of immunization.[29] Most existing studies of the

potential relationship between vaccination and autoimmune disease generally consider single vaccine series, and have not specifically addressed possible relationships between multiple immunizations and autoimmune disease.

Consideration of alternative explanations?

In addition to exposure to infectious agents, genetic and environmental factors have been associated with the development of autoimmune diseases.[22,23,29-31] In the absence of definitive evidence linking multiple immunizations to the development of autoimmune disease, these other factors need to be considered in any attempt to explain how multiple immunizations might be causally related to autoimmune disease.

Cessation of exposure?

In the absence of evidence of a causal relationship between multiple immunizations and susceptibility to developing an autoimmune disease, the risks of developing such diseases are unlikely to be altered by eliminating or modifying the existing childhood immunization schedule. As noted in the section on heterologous infection, reducing or eliminating the immunization of children would result in outbreaks of vaccine-preventable diseases.

Specificity of association?

If exposure to multiple immunizations was specifically associated with increased risk of developing autoimmune disease, one would expect that as children progress through the recommended schedule of immunizations there would be an increase in the number of cases of such disease. Although the number of reported cases of autoimmune disease in the US are not well characterized, at least in the case of type 1 diabetes the incidence seems to be increasing.[5] Evidence from several studies has failed to demonstrate a relationship between immunization and type 1 diabetes,[29] although none of the studies specifically addressed disease incidence relative to the number of immunizations given.

Consistency with other knowledge?

At this time there is no scientific evidence that multiple immunizations increase the risk of developing autoimmune disease.

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Bovine Spongiform Encephalopathy (BSE)

Bovine spongiform encephalopathy (BSE) is an incompletely understood infectious disease of cattle. First described in the United Kingdom in 1986, this neurodegenerative disease of the brain results in apprehension, loss of orientation and locomotor disturbances that can lead to frenzied behavior.[1] Hence, the name "mad cow disease." The brain tissue of affected cows is characterized by cell damage and loss, and by the formation of vacuoles, small clear areas within the brain tissue that give it a sponge-like (spongiform) appearance.[2]

Prior to 1986, cattle were not known to develop spongiform encephalopathies. However, this type of disease has been observed in sheep for over 200 years. This disease, known as scrapie, is particularly common in the United Kingdom. Although cattle and sheep have historically co-existed on farms, no prior evidence existed of direct sheep to cow transmission of scrapie, nor did evidence that scrapie could be transmitted to humans. Spongiform encephalopathies were known to affect a variety of animals, and each was considered to be species-specific.[2]

For many years, European farmers fed cattle high protein supplements prepared from livestock carcasses, including those of sheep, which were boiled and treated with organic solvents to produce meat and bone meals.[1, 2] During the early 1980s, these rendering practices were changed to reduce reliance on solvents. Although not previously known to infect cattle, these changes are believed to have facilitated the transmission of the scrapie agent to cattle via the feed supplements.[1, 3]

The causative agent for scrapie and the other spongiform encephalopathies was first described in 1982 as an atypical form of a protein (referred to as a prion) normally found in the brain.[4] A variety of studies give credence to the prion hypothesis, yet other hypotheses have been advanced, suggesting that a virus or virino may be the infectious agent.[2,5]

Creutzfeldt-Jakob disease (CJD) and kuru are prion-associated spongiform encephalopathies that occur in humans. Symptoms of these diseases typically progress from memory loss and confusion, to behavioral and locomotor abnormalities, to a host of neurological problems.[3] In the case of CJD, which occurs at a rate of less than one per million worldwide, the disease progresses extremely rapidly. The interval between diagnosis and death is typically four months.[3] The etiology and epidemiology of CJD are not well characterized, but the disease tends to be diagnosed in people 50 years of age and older. Kuru is the prototypical human prion disease and has been reported only among members of a small population native to Papua New Guinea.[6] This population is unique in that during the mid-20th century, funeral practices included ritual consumption of brain tissue from the deceased.[6] Those persons engaging in such practices, regardless of age, were at risk of developing kuru. This disease occurred among individuals representing a wide range of ages. The interval between initial exposure to the kuru prion and the onset of disease was as much as 30 years. Since then, kuru has been largely eradicated through the cessation of such practices.[7] There is no known treatment for any of the prion-associated diseases.[3]

Soon after the diagnosis of the first case of BSE in the UK in 1986, public health professionals expressed concern that humans exposed to BSE-tainted beef products may be at increased risk for developing BSE- or CJD-like disease.[2, 3, 8] Efforts were initiated to eliminate the disease by culling cattle exhibiting BSE symptoms and, ultimately, banning all animal-derived feed supplements. Over 4.5 million asymptomatic cattle also were destroyed on the presumption of possible exposure to the BSE prion.[8]

A public health surveillance program was initiated in the United Kingdom in 1990 and by early 1996 10 cases of CJD-like disease were attributed to exposure to the BSE prion.[1, 8] Because each affected person was less than 45 years of age and, on autopsy, was found to share a unique type of spongiform change in the brain, the disease was designated new variant CJD or nvCJD, later shortened to vCJD. Symptoms of vCJD include psychiatric and sensory changes and altered electroencephalographic

GLOSSARY TERMS

Association
Bovine spongiform encephalopathy
Case ascertainment
Cases
Creutzfeldt-Jakob disease
Disease
Dose-response relationship
Electroencephalographic
Encephalopathy
Epidemiology
Etiology
Immunization
Kuru
Neurodegenerative disease
Phase I study
Prion
Protein
Rendering
Risk
Scrapie
Serum
Solvents
Spongiform encephalopathies
Temporal relationship
Vaccine
Virino
Virus

ACRONYMS

BSE	Bovine spongiform encephalopathy
CJD	Creutzfeldt-Jakob disease
CBER	Center for Biologics Evaluation and Research (FDA)
FDA	Food and Drug Administration
nvCJD	New variant Creutzfeldt-Jacob disease
vCJD	Variant Creutzfeldt-Jacob disease

WEB RESOURCES

National Partnership for Immunization
http://www.partnersforimmunization.org/what.html

Public Health Service Recommendations
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4950a4.htm

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/bse/default.htm

Food and Drug Administration
http://www.fda.gov/cber/bse/bse.htm

National Network for Immunization Information
http://www.immunizationinfo.org/healthprofessionals/index.cfm

patterns; the average duration of symptoms was 14 months.[3] Through early February 2001, 98 confirmed or probable cases of vCJD had been reported; 94 cases were in the United Kingdom, three in France and one in Ireland.[9]

These cases are presumed to have resulted from dietary exposure to meat or meat products derived from BSE-afflicted cattle.[1-3, 8] However, little information is available regarding their level of exposure, i.e., how much beef they ate, the types of products, how they were prepared, etc. An investigation of a cluster of five cases of vCJD within a small area in central England where a limited number of cattle producers supply the area's beef, implicated specific butchering practices that led to contamination of meat by brain tissue from affected animals.[10]

In 1997, the death of a young woman with vCJD raised further questions about the dose, incubation period and medium of exposure because of her 10-year history as a vegetarian.[11] Because of her abstinence from beef, the possibility was raised that the BSE prion may have been transmitted via dairy products or through cosmetics or pharmaceutical products that contain gelatins or other materials derived from cattle. Ten years of intense vCJD case ascertainment practices in the United Kingdom has not revealed any such associations.

Cattle-derived products, e.g., blood, serum, purified proteins (enzymes, etc.), gelatins and extracts, may be used in the production of vaccines. Several independent panels of scientists have evaluated the possibility that the BSE prion might be transmitted to humans via a vaccine. The US Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) convened a joint meeting of the Transmissible Spongiform Encephalopathy Committee and the Vaccines and Related Biological Products Advisory Committee during 2000. They concluded that there was no evidence that vCJD has occurred in the US and that there is no evidence that any vaccines are contaminated with the BSE prion. Indeed, the probability of any such contamination is remote, i.e., on the order of one in two billion doses for a bacterial toxoid vaccine or one in 40 billion doses for a vial vaccine.[12] A current list of vaccines using bovine-derived materials from countries on the US Department of Agriculture BSE list or from countries in which the status of BSE is unknown can be found at www.fda.gov/cber/bse/bse.htm#usda. There is no evidence that vCJD has been transmitted to people by vaccination.[13] A review of 52 of the vCJD cases reported in the UK found no evidence of an association between vaccination and vCJD disease.[14]

In the interest of assuring public confidence in the safety of vaccines, given their public health value, the US Public Health Service subsequently recommended that all vaccine manufacturers obtain cattle-derived materials used in vaccine production only from countries where there is no known risk of BSE.[15]

Temporal relationship?

Although the available data suggest a temporal relationship between dietary exposure to BSE and the onset of vCJD, the absence of any association between vaccination and vCJD negates a temporal association between the two.

Strength of association?

The small number of cases of vCJD reported to date in the UK relative to the numbers of people presumably eating beef and beef products during the early and mid 1980s suggest that factors other than beef consumption alone influence BSE transmission and/or disease onset. Indeed, evidence does suggest that people expressing a particular gene may be susceptible to developing vCJD under appropriate, but ill-defined, exposure to the relevant prion.[16] Hence, the association between dietary exposure and disease is not strong. In the absence of any association between vaccination and vCJD, the strength of an association cannot be assessed.

Dose-response relationship?

A dose response relationship has not been established relative to dietary exposure to BSE-tainted meat and meat products. Because no alternative routes of exposure, e.g., vaccination, have been identified, it is impossible to collect meaningful dose response data with respect to other routes of exposure.

Replication of findings?

In the absence of evidence of a causal relationship between vCJD and vaccination, there are no studies to be replicated.

Biologic plausibility?

Although the data support the biologic plausibility of BSE prion transmission to humans via contaminated meat and meat products, and the subsequent development of vCJD, the biologic plausibility that the disease agent can be transmitted with vaccines is considered remote and hypothetical.

Consideration of alternative explanations?

An atypical protein or prion has been identified as the agent responsible for BSE, and a variant of that agent is considered to be responsible for causing vCJD. Some investigators consider the prion to be a marker for a virus or virino that may be the disease-eliciting agent. Such distinctions have limited relevance to the vaccine issue given the absence of an association between immunization and vCJD.

Cessation of exposure?

Steps taken in the United Kingdom subsequent to the identification of BSE and its potential association with vCJD resulted in the virtual elimination of BSE from food animals. Thus, humans are no longer exposed to BSE-tainted meats and meat products. This is expected to result in decreasing numbers of case reports, although the prolonged (and undefined) incubation period and duration suggest that the number of cases reported annually may continue to increase for some period of time.[17,18] Because vaccines are not known to be contaminated with the BSE prion, halting exposure to vaccines would serve no purpose relative to vCJD but would significantly compromise the public's protection against serious infectious diseases.

Specificity of the association?

The association between dietary exposure to BSE-tainted meats and meat products and vCJD is weak given the inability to link cases to specific exposures. In the absence of evidence suggesting an association between vaccines and vCJD, there are no grounds for trying to ascertain specificity of association.

Consistency with other knowledge?

That the occurrence of vCJD is limited to Western Europe, that it is not associated with vaccination, and that there is no evidence to suggest that vaccines in use elsewhere are associated with vCJD, indicates a consistency of knowledge that excludes vaccines from consideration as a possible source of vCJD.

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Thimerosal

Thimerosal is a preservative that has been used in some vaccines and other products since the 1930s as a safeguard against contamination after multi-dose vaccine vials are opened. Disease outbreaks have occurred following contamination of multi-dose vaccine vials in the US and other countries. For example, in April 1995, three infants died in India from toxic shock syndrome after they received contaminated measles vaccine at one health center. While use of thimerosal as a preservative does not eliminate the possibility of bacterial contamination, it can greatly reduce its likelihood. The vaccines used in the US that can contain thimerosal as a preservative include diphtheria, tetanus, acellular pertussis (DTaP), *Haemophilus influenzae* type b (Hib), hepatitis B, influenza, rabies, varicella and pneumococcal polysaccharide.[1] However, all vaccines on the currently recommended childhood immunization schedule for children age six years or younger are available without thimerosal in the US.[3]

According to the Food and Drug Administration (FDA) Modernization Act of 1997, the FDA is required to review and assess the risk of all mercury-containing foods and drugs. Because ethyl mercury is contained in thimerosal, US vaccine manufacturers were requested under this Act to provide more detailed information about the thimerosal content of their vaccines that contain this compound as a preservative.[1, 2] In 1999, FDA review of this information suggested that some infants who have received all of their recommended vaccines may be exposed to levels of ethyl mercury in vaccines that could exceed the Environmental Protection Agency (EPA) guidelines established for the intake of methyl mercury, a related compound known to be associated with adverse health effects.

Vaccine surveillance systems have revealed that other than local, mild vaccine reactions, no adverse events have been associated with thimerosal in vaccines. However, in an effort to maintain high standards of safety and to enhance public confidence in vaccines, federal agencies and public health officials recommended that thimerosal be removed from vaccines. On July 7, 1999, the American Academy of Pediatrics (AAP) and the US Public Health Service (PHS) jointly announced that they would collaborate with the FDA and vaccine manufacturers to make sure that thimerosal was removed from all vaccines.[2] As mentioned above, today all recommended childhood vaccines for children age six years of age or younger are now available thimerosal-free.[3]

Recently, the question has been raised as to whether or not the use of vaccines containing thimerosal might cause neurodevelopmental disorders, specifically autism, attention deficit/hypersensitivity disorder and speech and language delay. While thimerosal-free vaccines are now available, the question remains whether the past inclusion of thimerosal in vaccines may have caused neurodevelopmental problems in some children. In addition, thimerosal-containing vaccines remain in use in the developing world where use of multi-dose vials of vaccine require this preservative.

Temporal relationship?

Some individuals experience local skin reactions such as redness and swelling or hypersensitivity reactions such as contact allergy following injection with products containing thimerosal.[1,4,5] The prevalence of thimerosal hypersensitivity in selected populations varies from 1% to 18%. There is a predominance in young adults, particularly those 20 to 30 years of age.[6]

Strength of Association?

Phase I of a Vaccine Safety Datalink Project study screened a health maintenance organization's (HMO's) records for potential associations between thimerosal-containing vaccines and selected outcomes. A statistically significant but weak association was found between various cumulative exposures to thimerosal-containing vaccines and unspecified developmental delays, tics, attention deficit disorder, language and speech delay and general neurodevelopmental delays. No association was found between exposures to thimerosal and other neurological disorders, including

GLOSSARY TERMS

Advisory Committee on Immunization Practices
Allergy
Association
Attention deficit disorder
Autism
Cases
Chelation therapy
Chronic
Coma
Disease
Dose response relationship
DTaP
Ethyl mercury
Haemophilus influenzae type b
Hepatitis
Hepatitis B
Hypersensitivity
Immunization
Influenza
Institute of Medicine
Measles
Methyl mercury
Neurodevelopmental disorders
Pertussis
Phase II study
Pneumococcal polysaccharide
Prevalence
Rabies
Risk
Seizure
Temporal relationship
Tetanus
Thimerosal
Toxic shock syndrome
Vaccine
Vaccine Safety Datalink Project
Varicella

ACRONYMS

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ATSDR	Agency for Toxic Substances and Disease Registry
DTaP	Diphtheria, tetanus, acellular pertussis
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
Hib	*Haemophilus influenzae* type b
HMO	Health maintenance organization
IOM	Institute of Medicine
NIH	National Institutes of Health
PHS	United States Public Health Service
WHO	World Health Organization

WEB RESOURCES

National Partnership for Immunization
http://www.partnersforimmunization.org/issues.html

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/thimerosal

Johns Hopkins University's Institute of Vaccine Safety
http://www.vaccinesafety.edu

Immunization Action Coalition
http://www.immunize.org/thimerosal

Food and Drug Administration
http://www.fda.gov/bbs/topics/news/2001/new00756.html

autism or renal disorders.[7, 8] Reanalysis of these data generated results that differed slightly from the original analysis. However, the magnitude of the associations was generally consistent with those in the preliminary analysis.

A second component of this study was designed to test the hypotheses generated in the first phase. A sufficient number of cases of attention deficit/hypersensitivity disorder and speech delays were available for analyses. No significant differences in the risk of developing either attention deficit/hypersensitivity disorder or speech delays was found comparing persons who had been vaccinated with thimerosal-containing vaccines and those who had not. But because the sample size of this study was small the study is limited in its ability to detect whether these disorders might be found in a very small percentage of the population.[8,9]

Dose-response relationship?

Low-dose exposure of humans to either thimerosal or ethyl mercury, such as that received from vaccines, has not been demonstrated to be associated with effects on the nervous system. Instead, only hypersensitivity reactions such as contact allergy have been reported.[4, 5] The hypothesis that thimerosal exposure through the recommended childhood immunization schedule has caused neurodevelopmental disorders is not supported by clinical or experimental evidence.

Extremely high-dose exposure to thimerosal[10-15] and ethyl mercury[16-20] have been reported to produce toxic effects. Persons exposed to high doses of either thimerosal or ethyl mercury experienced mainly neurologic symptoms, including restlessness, slurred speech, confusion, unsteady gait, coma, impaired vision, hand tremors and death.

Prenatal exposure to low doses of methyl mercury has also been associated in some studies with subtle neurodevelopmental abnormalities.[21] Two large prospective studies are currently examining methyl mercury exposure from consumption of pilot whale meat in the Faroe Islands and from consumption of ocean fish in the Republic of Seychelles. In the Faroe Islands, a group of 1,000 children born in 1986-1987 are being followed through seven years of age. Analyses so far have found that prenatal exposure to methyl mercury based on measurement of the mercury content of the umbilical cord blood at the time of birth is associated with subtle attention, memory and language deficits.[22, 23] Two groups of over 700 children being followed in Seychelles have found no adverse associations between prenatal or postnatal exposure to methyl mercury and childhood developmental outcomes through 5.5 years of age. Exposures were determined by measuring the mercury concentration in maternal and child hair.[24-26]

Replication of findings?

Several agencies, including the EPA, Agency for Toxic Substance and Disease Registry (ATSDR), FDA and World Health Organization (WHO), have developed guidelines for intake of methyl mercury. A significant safety margin was incorporated into all federal mercury exposure guidelines.[27] The methyl mercury exposure limits calculated by these agencies are not considered to be the limits above which injury is certain to occur. Rather, they are general limits of exposure below which these organizations are confident that adverse effects will not occur.[4] Although the total amount of mercury found in all recommended childhood vaccines exceeded EPA guidelines,[21] which incorporates a ten-fold safety margin, they did not exceed guidelines recommended by the FDA (the agency responsible for the safety of vaccines), ATSDR[28] and WHO.[29]

Biologic plausibility?

At high doses, mercury compounds are well-established to be toxic to the nervous system.[28,30,31] Methyl mercury has been of particular concern to the public because high doses have been associated with health effects.[32] Two groups are most vulnerable to the effects of methyl mercury: the fetus and pregnant women. If a pregnant woman ingests methyl mercury at high concentrations, the developing fetus may develop brain damage, mental retardation, lack of coordination, blindness, seizures and an inability to speak. Premature babies are more vulnerable because they tend to be very small and their brain is not as developed as a full term baby. Because the guidelines for mercury exposure are based on amount of mercury per weight, children may be at greater risk of mercury exposure than are adults. This increased risk is due to greater exposure per pound of body weight and because children may be inherently more sensitive than adults as their nervous systems are still developing.[1] These serious health concerns led federal agencies to develop intake guidelines for methyl mercury.

No guidelines have been established for the ethyl mercury found in thimerosal, but experts agree that methyl mercury guidelines are appropriate to use when evaluating ethyl mercury. However, differences between methyl and ethyl mercury and their effects have been shown. Ethyl mercury is converted faster than methyl mercury into mercuric mercury.[10] Studies in mice have found that after administration of ethyl mercury more mercury was found in the blood and kidney—compared with methyl mercury—and less in the brain than after administration with methyl mercury.[33] Because of this faster conversion, researchers believe that ethyl mercury may remain in the body for a shorter period of time and be eliminated faster by urination than methyl mercury.[4]

Once both ethyl and methyl mercury reach the brain they are metabolized to the inorganic compound mercuric mercury. Ethyl mercury that enters the brain is more rapidly converted to mercuric mercury than methyl mercury that enters the brain. But once these compounds have been converted to mercuric mercury in the brain, they do not as readily cross the blood-brain barrier to move into the bloodstream for elimination.[4]

The Institute of Medicine (IOM) Immunization Safety Review Committee concluded that although the proposed association between exposure to thimerosal-containing vaccines and neurodevelopmental disorders has not been established, the hypothesis is biologically plausible.[4]

Consideration of alternative explanations?

Many causes of various neurodevelopmental disorders, such as genetic and environmental factors, have been hypothesized.[4] Some of these have been discussed in the *Autism* section on page 74.

Cessation of exposure?

The trace amounts of mercury contained in vaccines have not been found to cause any serious health problems in infants or young children. Recent studies by the National Institutes of Health (NIH) showed that the levels of mercury contained in the blood of immunized children are similar to those in unimmunized children.[34]

AAP, the Advisory Committee on Immunization Practices (ACIP) and the Surgeon General all recommend that parents do not let their children miss a vaccination when safe and effective vaccines are available. The risks of not vaccinating children far outweigh the unknown and probably much smaller risk, if any, of cumulative exposure to thimerosal-containing vaccines over the first six months of life.[2, 35]

Specificity of exposure?

Other than local hypersensitivity reactions, there is no evidence of any harm caused by the level of exposure that children may have encountered when immunized with thimerosal-containing vaccines under the existing immunization schedule.[1]

The acceptable levels of mercury exposure calculated by the EPA were based upon studies of children of women who had chronically ingested fish containing high levels of methyl mercury. These studies were then used to extrapolate acceptable levels of exposure of young children to trace levels of ethyl mercury contained in vaccines.[27] These EPA studies are under continuing scrutiny and have been criticized on a variety of scientific grounds.[36,37]

Consistency with other knowledge?

Some researchers have proposed that the similarities between autism and the toxic effects of mercury are evidence of an association.[38] However, the mechanisms causing these similar symptoms vary. For example, impaired ability to focus vision is associated with both mercury toxicity and autism. However, in the case of mercury toxicity, this impairment is due to problems with motor control of eye muscles. But in the case of autism, the visual impairment is related to joint use, which is most likely a problem of social reciprocity, not motor control.[4]

Another argument that has been made for the proposed association between thimerosal and autism is based on the observation that some autistic children have abnormal blood-metal profiles. But the presence of abnormal metal profiles in autistic children does not mean that the metal burden is the cause of autism. An inability to metabolize heavy metals such as mercury may occur as a result of autism rather than the cause of the disease. Further, a favorable response to chelation therapy (therapy used to reduce the concentration of metals in the blood) is not proof that the mercury levels caused the neurological dysfunction. Chelation therapy is non-specific, and the observed effects could be caused by the removal of other metals or by other factors.[4]

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Diabetes

Diabetes is a condition that prevents the body from being able to make enough insulin and/or being able to use the insulin that the body does make. Insulin is needed to help the body to use sugar absorbed from the bloodstream. People with diabetes have high blood sugar levels. Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), is an autoimmune disease that occurs primarily in children, but the disease has been found in persons of all ages.[1]

A 10-year follow-up of Finnish children who participated in a trial of the safety and effectiveness of the *Haemophilus influenzae* type b (Hib) vaccine looked at the possible association between this vaccine and type 1 diabetes. The study concluded that no significant relationship existed between the vaccine and diabetes.[1] However, another researcher analyzed the same data and claimed that an association did exist.[2] This sparked concern about whether a relationship between the two does exist and about whether the timing of hepatitis B vaccine delivery, which coincides with the Hib schedule, may affect the risk of developing diabetes.[3] However, the association between hepatitis B vaccine and/or other vaccines and IDDM has been refuted by many immunization experts and safety studies as noted below.

Temporal relationship?

One report suggests that the greatest increase in type 1 diabetes in New Zealand occurred in children under four years of age, coinciding with the period when Hib vaccine was introduced there in the mid-1980s.[4] However, figures from these studies show that cases of diabetes have continued to increase from 1976 to 1996, with one new case every two years. These figures suggest that the introduction of the hepatitis B vaccine in 1987/88 did not alter this rate of increase.[5]

Strength of association?

A 1999 Finnish study reported a relative risk of 1.01 (essentially no risk) of developing type 1 diabetes when comparing children born before the vaccination period with those vaccinated at 24 months of age.[1] Reanalysis of these data by another research group found an increased relative risk of 1.26 when they compared those children receiving vaccine and those not receiving the vaccine, which indicates only a small increased risk of developing diabetes.[4]

Replication of findings?

The only evidence suggesting a possible association between the risk of developing diabetes and vaccination has come from one research group.[6, 7] Based on animal experiments and on comparisons of diabetes rates between countries with different immunization schedules, this group suggested that certain vaccines given at birth may decrease the chance of developing diabetes as compared to vaccination after two months of age.[6] Researchers who have examined the relationship between vaccination and diabetes without regard to time of administration have not found an increased risk of diabetes with vaccination.[8-12]

In 1998, a review of the current state of knowledge of IDDM and its possible links to human vaccination was published. Evidence of a causal link in humans was examined by reviewing 12 large trials and two meta-analyses of pediatric vaccines. This review found that the international scientific literature was insufficient to determine whether a possible link exists between onset of IDDM and vaccination.[13]

An Institute for Vaccine Safety Workshop in March 1998, concluded that no vaccines have been shown to increase the risk of type 1 diabetes in humans. Workshop participants included 30 experts on the pathogenesis of diabetes, autoimmune disease, epidemiology, biostatistics, vaccines and adverse events associated with vaccines.[14]

A study of more than 1,000 children born in the health maintenance organizations (HMOs) involved in the Vaccine Safety Datalink Project from 1988 through 1997 observed that children vaccinated against hepatitis B virus or Hib were not at

GLOSSARY TERMS

Adverse events
Association
Autoimmune disease
Beta cell
Biostatistics
Cases
Diabetes
Disease
Haemophilus influenzae type b
Hepatitis
Hepatitis B
Hib vaccine
Immunization
Incidence
Insulin
Insulin-dependent diabetes mellitus
Non-obese diabetic mice
Pathogenesis
Relative risk
Risk
Temporal relationship
Type I diabetes
Vaccine
Vaccine Safety Datalink Project
Virus

ACRONYMS

DTaP	Diphtheria, tetanus, acellular pertussis
Hib	*Haemophilus influenzae* type b
HMO	Health maintenance organization
IDDM	Insulin-dependent diabetes mellitus
NOD	Non-obese diabetic

WEB RESOURCES

American Diabetes Association
http://www.diabetes.org/main/community/info_news/news/vaccines.jsp

National Partnership for Immunization
http://www.partnersforimmunization.org/issues.html

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/diabetes

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/concerns.shtml

increased risk of developing type 1 diabetes. Furthermore, the age at which the children were vaccinated was not likely to affect the risk of developing the disorder.[3,15]

Biologic plausibility?

A possible link between hepatitis B vaccination and insulin-dependent diabetes mellitus (IDDM) was first suggested after the demonstration of a relationship between the timing of administration of the DTP vaccine and the development of IDDM in non-obese diabetic (NOD) mice.[5] However, findings from animal studies[7] cannot be directly applied to people due to large biological differences between the two, in part because most NOD mice are genetically predisposed to developing IDDM.[16]

Consideration of alternative explanations?

Other genetic and environmental triggers for the development of IDDM have been suggested and continue to be explored. Damage to the pancreatic beta cells has been found to lead to type 1 diabetes in genetically susceptible individuals. This damage is believed to be induced by environmental factors.[1]

Cessation of exposure?

In the absence of evidence of a causal relationship between immunizations and the development of diabetes, the risks of developing diabetes are unlikely to be altered by eliminating or modifying the existing childhood immunization schedule. Reducing or eliminating the immunization of children have in the past resulted in outbreaks of vaccine-preventable diseases.[17]

Specificity of the association?

Although the incidence of diabetes is increasing throughout the world, the increase has occurred in countries with or without the introduction of new vaccines.[18]

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Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a neurologic disorder associated with autoimmune-mediated destruction of myelin, the coating of the nerve fibers of the brain and spinal cord. Depending on the extent and location of destroyed coating, a wide range of symptoms result.[1] Although neurologists are aided by magnetic resonance imaging (MRI), analysis of the fluid obtained by lumbar puncture and other techniques in the identification of this disease,[1] diagnosis of MS is usually made after multiple occurrences of traditional symptoms.[2]

In the US, approximately 300,000 individuals have been diagnosed with MS. The highest incidence of disease is between the ages of 20 and 40 years. More women than men are affected, and MS is found more frequently in Caucasians than in other ethnic groups.[3]

The history of concern over the potential association between MS and vaccination with hepatitis B vaccine began following the 1994 initiation of a national immunization campaign targeting newborns and adolescents in France. An increasing number of reports suggesting that MS might develop within months of vaccination with hepatitis B vaccine led to increased public concern in France about this issue and to the launch of epidemiological studies to investigate a possible association between hepatitis B vaccination and MS.[4]

Temporal relationship?

Much of the available information suggesting this potential association is based upon the number of cases of MS or other demyelinating diseases occurring after vaccination that were reported to French health authorities and vaccine manufacturers.[1] Despite these reports, French data collected through June 1998 show a rate of 0.6 case of MS per 100,000 persons vaccinated, which is a lower rate than the expected incidence in the same population (estimated at one to three cases per 100,000 population).[1, 5]

A case for a temporal relationship between the hepatitis B vaccine and MS might be made if, following the introduction of the hepatitis B vaccine in a certain area, the average age of developing MS in that area became closer to the recommended age for hepatitis B vaccination. A case might also be made if after the introduction of the hepatitis B vaccine in a population the proportion of males and females with the disease within that population began to mirror the rates of vaccination with hepatitis B vaccines within each sex. The average age of people with MS and the distribution of this disease among males and females has not changed with the introduction of the hepatitis B vaccine in the US.[2,6]

Results of a study utilizing Vaccine Safety Datalink Project data to evaluate the timing of hepatitis B vaccination and the risk of developing MS did not find that vaccination triggered the development of MS.[7]

Strength of the association?

A case-control study was conducted in two large cohorts of nurses in the US. The analyses included 192 women with MS and 645 matched controls (534 healthy controls and 111 with breast cancer). The relative risk of MS associated with exposure to the hepatitis B vaccine at any time before the onset of the disease was 0.9. The relative risk associated with hepatitis B vaccination within two years before the onset of MS was 0.7.[5]

A study of Vaccine Safety Datalink Project data also assessed the association between hepatitis B vaccination and the development of demyelinating diseases of the central nervous system in adults. The immunization status of 440 participants with MS were compared with that of 950 matched controls. The relative risk of developing MS associated with hepatitis B vaccination was 0.8 using a doctor's diagnosis and 0.9 using a specialist's diagnosis. Results did not support the hypothesis that hepatitis B vaccination causes or triggers the development of MS.[7]

GLOSSARY TERMS

Acute
Acute disseminated encephalomyelitis
Amino acids
Antigen
Association
B cell
Bacteria
Bystander activation
Case control study
Cases
Controls
Demyelinating
Disease
Dose response relationship
Epidemiological studies
Etiology
Experimental autoimmune encephalomyelitis
Hepatitis
Hepatitis B
Immune system
Immunization
Incidence
Inflammation
Influenza
Institute of Medicine
Interferon gamma
Lumbar puncture
Macrophage
Magnetic resonance imaging
Measles
Molecular mimicry
Multiple sclerosis
Mumps
Myelin
Neurologic disorder
Polymerase protein
Prevalence
Protein
Rabies
Relative risk
Risk
Rubella
Superantigens
T cell
Temporal relationship
Vaccine
Vaccine Safety Datalink Project
Varicella
Virus

ACRONYMS

ADEM	Acute disseminated encephalomyelitis
EAE	Experimental autoimmune encephalomyelitis
IOM	Institute of Medicine
MMR	Measles, mumps, rubella
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
WHO	World Health Organization

WEB RESOURCES

National Partnership for Immunization
http://www.partnersforimmunization.org/issues.html

National Immunization Program
http://www.cdc.gov/nip/vacsafe/conerns/MS/default.htm

Johns Hopkins University's Institute for Vaccine Safety
http://www.vaccinesafety.edu/hepb-nejm.htm

Multiple Sclerosis Foundation
http://www.msfacts.org

National Multiple Sclerosis Society
http://www.nmss.org

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/concerns.shtml

Two unpublished case control studies performed in England and France reported a statistically non-significant relative risk of 1.4 linking the hepatitis B vaccine with the occurrence of demyelinating disease within a period of two months after vaccination.[1]

Dose-response relationship?

In a case-control study of US nurses, no association was found between the number of doses of vaccine received by an individual and an increased risk of MS.[5]

Replication of findings?

The Institute of Medicine (IOM) Immunization Safety Review Committee found that currently available epidemiological evidence favors rejection of a causal relationship between the hepatitis B vaccine use by adults and MS.[8]

A group of international experts convened by the World Health Organization (WHO) met in 1998 to examine all of the post-marketing surveillance studies from the different vaccine manufacturers in North America. None of these studies showed any evidence of an increased risk of MS.[6]

Biologic plausibility?

Theoretical biological mechanisms that might explain an association between MS and hepatitis B vaccination include the concepts of molecular mimicry, bystander activation and superantigens (see the discussion of autoimmunity in the section *Multiple Immunizations*). These mechanisms have been demonstrated in mouse studies of experimental autoimmune encephalomyelitis (EAE), the archetypal model for MS.[8]

Molecular mimicry refers to immunologically similar microbial antigenic determinants and self antigens that when recognized by the immune system, can lead to autoimmune destruction of the host tissue.[9] No such similarity exists between the amino acid sequences of the hepatitis B surface antigen, the main component of the hepatitis B vaccine and the proteins making up human nerve fibers.[2] Animal studies have shown that a part of rabbit myelin shares six consecutive amino acids with a hepatitis virus polymerase protein and causes brain inflammation when injected in a rabbit.[1] But a relationship has not been found between hepatitis B virus polymerase protein and human myelin. Likewise, the hepatitis B vaccine does not contain the polymerase protein from the hepatitis B virus.[1]

Bystander activation refers to the non-specific stimulation of inflammatory cells associated with the normal response to an infection. Upon activation, these cells release large quantities of cytokines and other factors that contribute to the destruction of host tissue. Superantigens, natural proteins produced by certain viruses and bacteria, may also activate T cells, B cells or macrophages to cause destruction of myelin in mice.[10] However, no conclusive evidence exists that molecular mimicry, bystander activation or superantigens cause MS onset or MS exacerbations.[2]

Consideration of alternative explanations?

Infection by known or unknown organisms often precedes the onset of MS, MS relapses and/or MS exacerbations. Most researchers believe that MS disease progression results from a combination of infection and autoimmune events in genetically susceptible individuals.[9]

For the past 100 years, many different infections and viruses have been suggested as possible causes of MS. However, none of these hypotheses has been accepted because intensive scientific investigation has failed to demonstrate any causal relationships.[11] But data have shown that multiple factors, including genetic and environmental factors, can contribute to the development of this disease.[1]

Evidence exists of genetic involvement in the development of MS. Parents and siblings of MS patients have a 10 to 20 times greater risk of developing the disease than does the general population. In fact, 15% to 20% of persons with MS have another family member who has the disease. While 30% to 35% of identical (having the same genetic make-up) twins either both have MS or both do not have MS, only 2% to 5% of fraternal (do not have the same genetic make-up) twins either both have MS or both do not.[2] Although one particular region on chromosome 6p21 has been strongly associated with MS, studies have suggested that as many 15 to 20 other genomic regions may contribute to MS susceptibility.[12]

Environmental impacts on MS disease have been demonstrated by several epidemiological studies showing that individuals who migrated after age 15 from regions of high disease prevalence to regions of low disease prevalence, or vice versa, carry their native risk for contracting MS.[13,14] Further environmental involvement is suggested by reports of localized clusters, defined areas of unexpected high prevalence of MS and a higher prevalence of disease in the northern latitudes.[2]

Psychological stress,[15] immediate post-partum upper respiratory viral infections, interferon gamma, experimental drugs[2] and infections[8] have all also been implicated in causing MS relapses.

Cessation of exposure?

In the absence of evidence of a causal relationship between hepatitis B immunization and the development of MS, the risks of developing MS are unlikely to be altered by eliminating or modifying the existing immunization schedule. Reducing or eliminating immunization has in the past resulted in outbreaks of vaccine-preventable diseases.[16]

Specificity of the association?

Cases of MS in British Columbia were investigated in adolescents before and after the introduction of a grade six (11-12 year old students) hepatitis B vaccination program. Onset of MS among adolescents aged 11-17 years of age was determined from hospital medical records and the database of the provincial MS clinic. All pediatric neurologists in the province were also contacted to confirm that all cases known to them were assessed in the specified settings. Nine cases of adolescent-onset MS occurred among 288,657 students who had attended grade six prior to the vaccination campaign (January 1986 – September 1992) and five cases occurred out of a total of 289,651 grade six students from October 1992 to September 1998, of whom 267,412 (92.3%) completed the full hepatitis B vaccine series. These numbers were not significantly different.[17]

Consistency with other knowledge?

Infection with natural hepatitis B virus has not been proven to cause MS or to worsen clinical disease symptoms. If the virus does not cause MS or worsen existing disease, then the likelihood that the vaccine can do so is extremely low.[3,18]

Acute disseminated encephalomyelitis (ADEM) is a rare disease of the central nervous system that usually affects infants and young children. The disease is very similar to MS except that one episode of neurologic symptoms occurs rather than the multiple episodes characteristic of MS.[19] After the introduction of the first vaccine against rabies in humans, 0.1% of vaccinees were reported to have contracted ADEM. This vaccine was manufactured from rabbit cells containing rabies virus, and the immunization thus initiated the human equivalent of EAE.[2] Measles, rubella and varicella viruses and, less commonly, influenza and mumps viruses have been shown to cause ADEM. The incidence of ADEM after measles infection is approximately one out of 1,000 infections, whereas after varicella and rubella it is less than one out of 10,000 and one out of 20,000 respectively.

Despite the fact that vaccines do not contain this rabbit tissue anymore, ADEM is sometimes still reported after various vaccinations. The incidence of post-immunization ADEM is one to two per million for live measles vaccine immunizations, i.e., significantly lower than that for post-measles development of ADEM. It is most commonly associated with measles, mumps, rubella (MMR) vaccinations but more recently has been associated with two recombinant hepatitis B vaccines.[2]

A case-crossover study (equivalent to a case-control approach in which patients serve as their own controls) of 643 patients with relapses of MS between 1993 and 1997 in the European Database for Multiple Sclerosis was conducted to assess whether vaccinations increase the risk of relapse in MS. No increase in the relative risk of relapse associated with exposure to any vaccination during the previous one, two or three months was found.[18] This study did not address long-term effects of vaccination or changes in the etiology of the disease and excluded patients with frequent relapses (within one year of each other).[20]

No evidence exists that vaccines in children cause more or less frequent demyelinating disease than in adults.[2] In a retrospective study of 134,698 individuals enrolled in a US healthcare database from 1988 to 1995, the incidence of demyelinating diseases was not increased after hepatitis B vaccination in the general population or among children under age 14 years.[21] In another report, hepatitis B vaccine in children ages 11 to 12 years did not increase the risk of developing MS or ADEM in adolescence.[22]

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Shaken Baby Syndrome (SBS)

Shaken Baby Syndrome (SBS), a serious form of child maltreatment, usually involves infants less than six months of age and is often overlooked or underdiagnosed.[1] This medical condition is due to mechanical injury that can result in brain swelling and bleeding inside the brain or on the retina of the eye. Death or permanent brain damage are frequent outcomes in SBS. In recent years, a defense has surfaced in criminal cases involving SBS that alleges that the child was injured by an injection of diphtheria, tetanus, whole cell pertussis (DTP) vaccine. DTP vaccine is no longer used in the US as it has been replaced with diphtheria, tetanus, acellular pertussis (DTaP) vaccine.

Replication of findings?

Scientific studies have not provided evidence to support a causal relationship between DTP immunization and serious acute neurologic illness resulting in permanent neurologic injury.[2] An article from the United Kingdom dismisses the theory that pertussis vaccine can cause permanent brain damage in infants on scientific grounds.[3]

Biologic plausibility?

No medical reports have proposed that this pathology could be related to DTP immunization.[2]

Consideration of alternative explanations?

In highly contested child abuse criminal trials, even speculative possibilities can be sufficient to raise a reasonable doubt concerning a defendant's guilt, since juries do not want to believe that caretakers are capable of violent assault on helpless children.[2]

Cessation of exposure?

In the absence of evidence of a causal relationship between DTP immunization and SBS, the risks of SBS are unlikely to be altered by eliminating or modifying the existing immunization schedule. Reducing or eliminating immunization has in the past resulted in outbreaks of vaccine-preventable diseases.[4]

Specificity of the association?

The pathology and progression of SBS varies greatly from the adverse events that have been associated with DTP vaccine. Rare cases of inflammation of the brain and spinal cord have been reported following DTP vaccination, but the mechanical injuries seen in SBS are very different from these adverse events.[2]

GLOSSARY TERMS

Acute
Adverse events
Association
Cases
Cytokines
Disease
Immunization
Inflammation
Pathology
Pertussis
Risk
Shaken Baby Syndrome
Tetanus

ACRONYMS

DTaP	Diphtheria, tetanus, acellular pertussis
DTP	Diphtheria, tetanus, whole cell pertussis
SBS	Shaken Baby Syndrome

WEB RESOURCES

National Partnership for Immunization
http://www.partnersforimmunization.org/issues.html

National Center on Shaken Baby Syndrome
http://www.dontshake.com/sbsfall00dtp.html

American Academy of Pediatrics
http://www.aap.org/policy/t0039.html

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