

Uproar over a little-known preservative, thimerosal, jostles U.S. hepatitis B vaccination policy

In 1997, when Frank Pallone, a Democratic congressman from New Jersey, attached a simple amendment to an FDA reauthorization bill, he could not have predicted that it would cause such a commotion two years later. His amendment ran just 133 words. It gave FDA two years to "compile a list of drugs and foods that contain intentionally introduced mercury compounds and ... [to] provide a quantitative and qualitative analysis of the mercury compounds in the list...." The bill later evolved into the landmark FDA Modernization Act of 1997 (FDAMA) and was signed into law on November 21, 1997. Pallone's amendment undoubtedly sprang from his long interest in environmental causes. But he had unwittingly set into motion a chain of events that would, two years later, bring turmoil to the immunization policy world and fears of harm to the nation's hepatitis B control effort.

Thimerosal, old soldier under a cloud

At first glance, someone looking for a controversy would not choose thimerosal. It has been used as a vaccine preservative since the 1930s, and, until recently, it has generally been viewed as a safe, reliable, and somewhat drab defender against bacterial and fungal contamination. The compound garners only one short paragraph in the 1249-page Plotkin and Orenstein reference book, *Vaccines 3rd Edition (1999)*.

Thimerosal is sometimes added to vaccines during manufacturing as a guarantee against production-related contamination. Its greatest value, however, is in the field, where it acts as a fail-safe against imperfect aseptic handling. It is especially valuable for multidose vaccine vials, in which the re-entry of needles greatly increases the risk of bacterial introduction. Thimerosal's only competitor, 2-phenoxyethanol, is less effective than thimerosal in suppressing potential contaminants like *Pseudomonas aeruginosa*, *E. coli*, and *Staph. aureus*, according to data presented by Dr. Stanley Plotkin at an August workshop on thimerosal safety held at the National Institutes of Health.

The problem with thimerosal is that it contains 49.6% mercury by weight. At high exposure levels, mercury causes neurotoxicity in humans, especially in fetuses and small infants whose brains are still developing. But because of thimerosal's long track record as a defender against vaccine

contamination disasters, discarding it is not easy.

CBER mercury analysis triggered fears

Over a year went by before the FDAMA mercury study got any public attention at FDA. Finally, on December 14, 1998, just 11 months before the congressional deadline, the agency published a notice in the Federal Register requesting manufacturers to provide data on mercury content. The agency published a second, more specific request on April 29, 1999. The work of analyzing the vaccine data fell to FDA's Center for Biologics Evaluation & Research (CBER).

Officials at CBER were aware that thimerosal had surfaced as a safety issue in Europe. In June 1999, the "European FDA", called the Agency for the Evaluation of Medicinal Products (EMA), completed an 18-month inquiry into the risks and benefits of using thimerosal in vaccines. EMA concluded that "although there is no evidence of harm caused by the level of exposure from vaccines, it would be prudent to promote the general use of vaccines without thimerosal...."

One of CBER's first tasks was to simply add up the total amount of mercury given to children through vaccines in the U.S. immunization schedule. Although it may seem surprising that CBER had not done this before, CBER's mission, to ensure the purity, potency, safety, and efficacy of individual products, would never have required such an analysis. CBER researchers soon confirmed that thimerosal was present in over 30 licensed vaccines in the U.S. in concentrations of 0.003% to 0.01%. According to the agency's calculations, an infant six months old who got all vaccine doses on schedule would receive 75 micrograms of mercury from three doses of DTaP, 75 micrograms from three doses of Hib, and 37.5 micrograms from three doses of hepatitis B vaccine – a total of 187.5 micrograms of mercury.

But was this enough mercury to worry about? The analysts next tried to compare the calculated mercury intake with federal guidelines for safe mercury intake, but they immediately ran into difficulty. Thimerosal is metabolized in humans to *ethylmercury*, but all guidelines for safe mercury intake relate only to *methylmercury*. No guideline exists for the ethyl compound. Indeed, the literature on ethylmercury toxicity is so scant that toxicologists do not even know whether ethylmercury is more or less toxic than its methyl cousin. Left with no choice, CBER analysts assumed that the toxicity of the ethyl compound is equivalent to the methyl compound.

Armed with this assumption, they compared the mercury

intake from vaccines in children six months old, 187.5 micrograms, to the suggested safe limits for methylmercury intake published by three federal agencies: EPA, FDA, and the Agency for Toxic Substances and Disease Registry (ATSDR). It was then that they made a remarkable discovery – the mercury intake through vaccination in the first six months of life exceeded the limit set by EPA.

Sharpening a double-edged sword

The CBER analysts were concerned. Millions of American children under six months old had apparently received, and were continuing to receive, an amount of mercury from vaccines that exceeded a federal guideline. The finding was potentially serious, but it was muddled by several factors. First, the three federal agencies that publish mercury intake guidelines, EPA, FDA, and ATSDR, disagree about the safe limit. EPA's limit is significantly lower than the FDA and ATSDR guidelines. The intake of mercury from vaccination exceeded only the EPA guideline.

Second, EPA's guideline (called the EPA reference dose, or RfD) is truly cautious. It is based on a single episode of methylmercury poisoning in Iraq in which 81 children were exposed to high levels of mercury *in utero*. EPA calculated the RfD by determining the dose that produced a 10% prevalence of adverse neurological effects in the affected children, such as late walking, late talking, and abnormal neurological scores. The agency then placed a 95% confidence interval around this dose and divided the lower bound of the interval by an "uncertainty factor" of 10 to arrive at the RfD.

CBER's finding was also clouded by important differences in the nature of exposure between the Iraqi children and children exposed through vaccination. The Iraqi children sustained long-term daily prenatal exposures, while vaccinated children have intermittent intramuscular doses later in life, as infants. No one, however, could tell CBER exactly how these exposure differences might affect the potential neurotoxicity of mercury.

AAP sounds an alarm

In mid-June, CBER's findings came to attention of Dr. Neal A. Halsey, Director of the Johns Hopkins Institute for Vaccine Safety. Halsey is a pediatrician and a highly respected vaccine expert. When he learned of the CBER findings, he was finishing up a four-year term as chairperson of the AAP Committee on Infectious Diseases, the committee that determines AAP vaccination policy and edits the

renowned *Red Book*.

Long before he heard about the thimerosal findings, Halsey had become worried about the progress of vaccination protest groups in the U.S. They had chalked up significant successes in discrediting childhood vaccination. Five months earlier, a network television program had seriously questioned the nation's hepatitis B vaccination policy *see Hepatitis Control Report, Winter 1998-99 issue*). In May, Congress had held a contentious hearing on the dangers of vaccination (*see Hepatitis Control Report, Spring 1999 issue*). News media and political groups had picked up the anti-vaccination chant. Halsey feared that the tide was turning against childhood vaccination, with potentially dangerous consequences.

Halsey confirmed CBER's calculations and did his own research on mercury, consulting with experts around the country. He became convinced that the findings were worthy of alarm, and he worried that if they became public prematurely, vaccination protesters would use them to stage yet another attack on the nation's immunization programs. Halsey met with officials at CBER on June 22nd and then called Dr. Walter Orenstein, director of CDC's National Immunization Program (NIP). Eight days later, NIP staff flew to Washington to meet with FDA, AAP, and vaccine manufacturers. From the start, Halsey and his colleagues at AAP, including the new chairperson of the Infectious Diseases Committee, Dr. Jon Abramson, took a strong proactive stance. They argued that physicians should be told – soon – about the amount of mercury in vaccines and the conflict with a federal guideline.

Hectic negotiations led to AAP-CDC compromise, but differences lived on

CDC was surprised by the urgent and undoubting position taken by Halsey and his colleagues at AAP. CDC officials argued that there was no need for precipitous action. They pointed out that no child was known to be harmed from thimerosal, and they were loath to undermine confidence in existing vaccines by labeling some vaccines "bad" (thimerosal-containing) and some "good" (thimerosal-free). But, in further discussions through the first few days of July, it became clear that Halsey and AAP would not retreat – they believed that immediate action was needed.

Within AAP, the issue ascended quickly from Halsey's committee to the executive board. AAP executives felt that their members needed more than just information about thimerosal – they also needed a way to reduce mercury exposure in their tiny patients. They feared that pediatricians

who continued to administer thimerosal-containing vaccines could face a flurry of lawsuits, perhaps claiming that children had acquired learning disabilities from mercury exposure. The discussions quickly veered toward pushing vaccine doses back from the first six months of life to a later time, when infants' bodies were larger and better able to tolerate mercury. Delaying vaccinations against diphtheria-tetanus-pertussis or *Hemophilus influenzae* type b was not practical or could expose children to serious infections. It soon became evident that the delayed vaccine would have to be hepatitis B.

Only two single-antigen pediatric hepatitis B vaccines exist on the U.S. market, Engerix-B (SmithKline Beecham) and Recombivax HB (Merck). Both contain thimerosal and 12.5 micrograms of mercury per 0.5 ml dose. AAP pressed CDC to agree to a delay of the hepatitis B vaccination series, usually started at birth, for children born to hepatitis B surface antigen (HBsAg)-seronegative mothers. The Academy argued that the delay would only be temporary, because both Merck and SmithKline Beecham had promised that they could quickly shift manufacturing to thimerosal-free vaccine, perhaps in just a few months. FDA had already promised to review applications for thimerosal-free hepatitis B vaccine rapidly – within 30 days.

At the CDC Hepatitis Branch in Atlanta, Dr. Harold Margolis, Chief of the Branch, and staff epidemiologist Dr. Eric Mast saw trouble. They and other hepatitis B control advocates had worked hard since 1991 to make infant vaccination routine, and it had become a cornerstone of the CDC-ACIP strategy to eliminate hepatitis B transmission in the U.S. The strategy was working – hepatitis B rates had fallen consistently since the policy was implemented. Margolis and Mast worried that delaying the routine birth dose, even temporarily, would cause hepatitis B vaccination rates to slide. Furthermore, once the policy was changed, it could be difficult to switch back. States were already under pressure from vaccination protest groups to drop hepatitis B vaccination school entry requirements (*see Hepatitis Control Report, Winter 1998-99 issue*). Margolis and Mast began working furiously to build a case against delaying hepatitis B vaccination.

The CDC hepatitis group felt that AAP had not sufficiently accounted for the burden of hepatitis B virus (HBV) infection during childhood. Mast had estimates showing that, in the years before routine vaccination began, 45,000 HBV infections had occurred annually in children less than 10 years old. Of those, 33,000 were in children of HBsAg-seronegative mothers. CDC also had data from the 1998 National Immunization Survey suggesting that a delay in the

birth dose would decrease hepatitis B vaccination completion rates by 15% – perhaps even more in infants born to high-risk mothers.

Negotiations continued with AAP nearly around the clock. Everyone was becoming exhausted. AAP insisted on a six-month delay of hepatitis B vaccination for infants of HBsAg-negative moms. CDC resisted. As the groups continued negotiations over days, worries increased that the story would leak to the press in an uncontrolled way, triggering a general vaccination scare. "Everyone worried that, with the vaccination protest groups looking over our shoulders, if they got the sense that some [toxicological] standard was broken, all hell would break loose," said a senior official who worked on the issue.

Speaking later, AAP's Abramson said, "AAP and CDC diverged on the hepatitis B issue. It was a matter of how safe do you want to be? ... Our perspective was let the individual pediatrician make a judgment for each family. CDC was looking at it from a public health perspective." Finally, after a week of late night meetings involving the AAP executive board, Surgeon General Dr. David Satcher, CDC Director Dr. Jeffrey Koplan and other CDC officials, FDA, the manufacturers, and others, the exhausted group struck a compromise. An AAP-USPHS joint statement was issued on July 7 at 4:15 PM (*see* www.aap.org/advocacy/releases/jointvacc.htm). The statement said in part:

Clinicians and parents can take advantage of the flexibility within the existing schedule for infants born to HBsAg-negative women to postpone the first dose of hepatitis B vaccine from birth until two to six months of age when the infant is considerably larger. Pre-term infants born to HBsAg-negative mothers should similarly receive hepatitis B vaccine, but ideally not until they reach term gestational age and a weight of at least 2.5 kilograms. Because of the substantial risk of disease, there is no change in the recommendations for infants of HBsAg-positive mothers or of mothers whose status is unknown. Also, in populations where HBsAg screening of pregnant women is not routinely performed, vaccination of all infants at birth should be maintained, as is currently recommended.

A few days later, AAP issued an "Interim Report to Clinicians" sharpening its own position:

At this time, the only thimerosal-free hepatitis B vaccine available (COMVAX) also contains Hib

vaccine (PRP-OMP). The product is not approved for use before 6 weeks of age because of decreased response to the Hib component. For that reason, where available, this thimerosal-free vaccine may be given to infants born to HBsAg negative women beginning at the two months visit. If thimerosal-free vaccine is not available, hepatitis B virus vaccination should be initiated at 6 months of age....

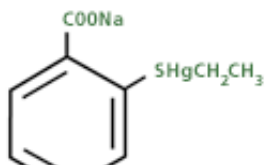
CDC issued its own supplemental guidance on July 14 (*see* <http://www.cdc.gov/nip/news/thimerosal-guidance.htm>), saying:

Many hospitals have instituted policies to vaccinate all children at birth regardless of HBsAg status as a means of ensuring that all the infants of HBsAg positive women and infants of women with an unknown HBsAg status are vaccinated at birth. These hospitals should continue current policies until procedures are or can be put in place to guarantee the proper management of all births to prevent perinatal HBV transmission....

CDC also said "hepatitis B vaccination at birth should be continued for infants born to HBsAg-negative mothers belonging to populations at risk for early childhood HBV infections, including Asian Pacific Islanders, immigrant populations from countries in which HBV is of high or intermediate endemicity..., and households with persons with chronic HBV infection."

The AAP and CDC policies remain slightly at odds. AAP prefers that infants of HBsAg-seropositive moms be delayed until two months if COMVAX is available, or until six months if it is not. CDC prefers that hepatitis B vaccine be administered according to the current recommendations of the ACIP, which allow vaccination to begin at two months (*see* editor's postscript).

Facts about thimerosal and mercury



Thimerosal is a water-soluble, cream-colored crystalline powder. It is 49.6% mercury by weight. In the human body, thimerosal is metabolized to ethylmercury and thiosalicylate. The literature on thimerosal metabolism and excretion is limited and old. Case reports have demonstrated toxicity after massive overdoses.

Toxicological information on the chief metabolite of thimerosal, ethylmercury, is extremely limited. During the

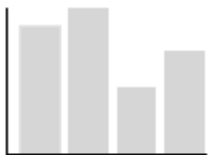
recent controversy over the safety of thimerosal in vaccines, toxicologists have assumed that the toxicity of ethylmercury is equivalent to the toxicity of methylmercury. The toxicity of methylmercury is complex and depends on the type, level, and duration of exposure. The primary environmental exposure is through consumption of predator fish. A 6-ounce can of tuna fish contains an average of 17 micrograms of mercury. A pediatric dose of hepatitis B vaccine contains 12.5 micrograms.

The major toxicity of mercury is manifested in the central nervous system. Forty years ago, when women at Minamata Bay, Japan, ate fish contaminated with methylmercury from pollutants, their children were exposed to high levels in utero and were born with severe developmental and neurologic disorders. Methylmercury poisoning also occurred in Iraq following consumption of seed grain that had been treated with a fungicide containing methylmercury. In both the Japanese and Iraqi episodes, exposures to methylmercury were very high.

Two population-based studies are often cited as the basis for calculations on the neurotoxicity of mercury in utero. In the first, a study from the Seychelles, infants were exposed to mercury in utero when their mothers ate a high daily consumption of methylmercury-containing fish. The mothers had mean mercury levels in hair of 6.8 ppm. No developmental defects were detected. In the second, a study from the Faroe Islands, infants were born to mothers with mean hair levels of 4.3 ppm. In contrast to the Seychelles mothers, these mothers were exposed to mercury through intermittent "bolus" consumption of pilot whale meat. Lower scores on memory, attention, and language tests were associated with methylmercury exposure in the children (see Mercury Study Report to Congress, EPA, 1997).

Reaction in the real world

In the weeks after the AAP and CDC statements were issued, state health departments reacted in a variety of ways. At least one state, New Hampshire, recommended no change in the hepatitis B vaccination schedule. At the other extreme, New Mexico opted for a full one-year delay. Most states have adopted a 2- or a 2-6 month delay for infants of HBsAg-seronegative women, and many of those states recommend COMVAX at two months.



Suggested
limits for
safe
methylmercury

Some physicians have criticized the new recommendations. "I can't believe the Academy doesn't think it has stubbed its toe on this one," said one prominent Texas pediatrician who is a

member of AAP. "It's too much too fast. I mean, it's crazy." Dr. Paul Offit, chief of infectious disease at the Children's Hospital of Philadelphia and a member of ACIP, told *The Philadelphia Inquirer* that the fear of trace mercury in vaccines was "a theoretical and unproven problem which has been elevated to a level of importance that doesn't make sense." Others have taken the opposite view – some leaders within AAP believe that the Academy did not go far enough to protect infants against mercury. But pediatricians in both camps feel obligated to follow the new policies for fear of legal liability if they diverge.

Informal surveys indicate that hospitals have changed their hepatitis B vaccination policies rapidly to comply with the new recommendations, often on orders from their legal departments. The consequences have not always been good. Dr. Barbara Watson, chief of immunization at the Philadelphia City Health Department, told attendees at the August NIH thimerosal workshop that she personally knew of three infants of HBsAg-seropositive mothers who missed being vaccinated in hospital because of confusion caused by the policy change.

At the August NIH workshop, Dr. Eric Mast showed a CDC analysis estimating that 246 infants of HBsAg-seronegative mothers and 200 infants of mothers with unknown HBsAg status would become infected nationwide as a result of the new policy, assuming it lasted six months and produced a 15% to 25% drop in the newborn vaccination rate.

The aftermath

The nation's most well-known vaccination protester is pleased with the change in hepatitis B vaccination policy. Barbara Loe Fisher, President of the National Vaccine Information Center in Vienna, Virginia, said in a press release that the new policy "will result in the deaths and injury of fewer babies.... Eliminating mercury from childhood vaccines is an important safety initiative and we hope that further evaluation of the cumulative toxic effects of other vaccine ingredients, such as aluminum used as an adjuvant, will also be undertaken"

But a physician from WHO, Dr. John Clements, said at the NIH workshop that "the U.S. has gone on its due process to identify a problem and correct it. But there is a knock-on effect which the world must bear as a consequence." Clements pointed out that only multidose, multipuncture vaccine vials can be used in developing countries because of cost and cold-chain considerations. Removing thimerosal from these vials is not an option for WHO, at least for the

next several years, he said.

The foreseeable future

The long-term effect of the controversy on hepatitis B vaccination rates remains murky. Vaccine manufacturers have agreed to provide a plan to eliminate or reduce the mercury content of vaccines as soon as possible (see editor's postscript). AAP and CDC plan to monitor immunization practices, immunization coverage, and vaccine preventable disease levels. ACIP will take up the thimerosal issue at its October meeting.

In an August interview, Dr. Halsey defended the thimerosal decision-making process used by AAP and CDC. It would not have been possible to deal with thimerosal in the usual public forums like ACIP, Halsey said, because the presence of vaccination protesters would have made rational discussion hopeless. Deliberations were handled in the only way possible, he said. But Halsey acknowledged that many of his immunization colleagues are angry with him and miffed about the way the issue was handled.

Halsey said he does not believe that delaying the first dose of hepatitis B vaccine in HBsAg-seronegative mothers will have a major impact. He does worry, however, about the effects, real and perceived, that mercury may have on vaccinated infants. He pointed out that, to truly assess infants' exposure to mercury, the intake from thimerosal must be added to the intake from all other sources, especially maternal fish consumption. For infants born to women with high mercury consumption, he said, "no one knows what dose of mercury, if any, from vaccines is safe.... We can say there is no evidence of harm, but the truth is no one has looked."