LEADING ARTICLE

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Thiomersal in Vaccines
Is Removal Warranted?

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Abstract

The mercury-based vaccine preservative thiomersal has come under scrutiny in recent months because of its presence in certain vaccines that provide the foundation of childhood immunisation schedules. Over the past decade new vaccines have been added to the recommended childhood schedule, and the relatively smaller bodyweight of infants has led to concern that the cumulative exposure of mercury from infant vaccines may exceed certain guidelines for the human consumption of mercury. In the US, government agencies and professional societies have recently recommended that thiomersal be removed altogether from vaccines. Some involved in developing vaccine policy feel that the evidence to support these safety concerns has not risen to the level required for such a response. This apparent divergence of opinion has left healthcare professionals and the public with uncertainty about the potential health effects from low level exposure to thiomersal as well as the necessity of removing thiomersal from vaccines. At present, scientific investigation has not found conclusive evidence of harm from thiomersal in vaccines. As a precautionary measure, efforts are under way to remove or replace thiomersal from vaccines and providers should anticipate the availability of more vaccine products that are thiomersal-free over the coming years.

The mercury-based vaccine preservative thiomersal[1] has come under public and professional scrutiny in recent months because of its presence in certain vaccines that provide the foundation of childhood immunisation schedules. The World Health Organization (WHO), the European Agency for Evaluation of Medicinal Products (EMEA), and other key agencies continue to recommend the use of vaccines containing this preservative because of the proven benefit of vaccines in preventing death and disease and the lack of data indicating harm. However, government agencies and professional societies in the US have urged manufacturers to remove thiomersal altogether from vaccines, citing the desirability to minimise human exposure to mercury from all sources and the feasibility in the US of formulating childhood vaccines without thiomersal as a preservative.[1] This apparent divergence of opinion has left healthcare professionals and the public with uncertainty about the potential health effects of low level exposure to thiomersal as well as the necessity of removing thiomersal from vaccines.

Questions regarding the safety of thiomersal in vaccines have arisen primarily because of recent

1 The terms thiomersal and thimerosal are regional variations of the same chemical and are interchangeable.

studies suggesting adverse effects in children from *in utero* exposure to methylmercury (a similar organic mercury compound) at levels previously considered safe[2] and a reduction in the recommended limits of methylmercury exposure by the US Environmental Protection Agency (EPA).[3] At the same time, the tolerance of the public for risk without obvious benefit to the individual has diminished.[4] The combination of these factors has led to an altered perception of mercury-containing products. As a result, the gradual removal of the preservative from vaccines is being supported by the US Public Health Service (USPHS), WHO, and industry.[5,6] At present, scientific investigation has not found conclusive evidence of harm from thiomersal in vaccines. The benefits of vaccination in preventing death and disease outweigh the theoretical risks of exposure to thiomersal as a vaccine preservative. As a precautionary measure, efforts are under way to remove or replace thiomersal from vaccines, and providers should anticipate more vaccine products that are thiomersal-free over the coming years.

1. Background

Thiomersal is an organic mercurial compound used for over 60 years as an anti-microbial agent in vaccines and other pharmaceutical products to prevent unwanted bacterial and fungal growth.[7] In certain vaccines, thiomersal is used during the manufacturing processes. It is present in commonly used multi-dose presentations of vaccines such as diphtheria-tetanus-whole cell pertussis (DTP) and tetanus toxoid (TT) as well as certain formulations of diphtheria-tetanus-acellular pertussis (DTaP), hepatitis B and *Haemophilus influenzae* type b (Hib) vaccines, but not in live bacterial or viral vaccines. Vaccine preservatives, including thiomersal, have probably prevented illness and death in countless infants over the years by reducing the risk of contamination of opened multi-dose vials. The use of preservatives in multi-dose vials, however, has not always prevented local infections caused by the introduction of contaminating organisms into multi-dose vials,[8,9] emphasising the importance of proper techniques in administering and handling vaccines.

2. Toxicity Profile

Thiomersal is 49.6% mercury by weight and metabolised to ethylmercury and thiosalicylate.[7,10] In humans, the only identified risk from thiomersal at doses used in vaccines are hypersensitivity reactions.[11] The preservative has been reported to cause neuro- and nephrotoxicity in accidental poisoning episodes at doses much higher than those used in vaccines.[12-16] However, the precise dose-response relationship of thiomersal toxicity remains uncertain.

Toxicity data from low dose exposure to ethylmercury are not available, but may be similar to that from low dose exposure to other organic mercurials such as methylmercury.[17] Maternal methylmercury exposure via the oral route in Iraq and Japan was documented to cause neurological abnormalities such as developmental delay in infants exposed *in utero*.[18-21] The human brain seems particularly vulnerable to methylmercury during its developmental period. Additional data from low dose exposure to methylmercury derived from studies of two distinct island populations exposed through seafood consumption have resulted in conflicting conclusions.[2,22,23] Some of these studies have demonstrated subtle abnormalities, detectable only by sophisticated neuro-psychometric testing, at methylmercury levels previously thought to be safe.[2]

No guidelines exist for acceptable exposure to ethylmercury. Therefore, for risk assessment purposes, guidelines for methylmercury exposure have been used to determine whether the mercury dose from vaccines approaches a level of concern. Application of these guidelines assumes that the toxicity of ethylmercury is the same as methylmercury (still an open question). Organisations such as WHO, the US EPA, the US Agency for Toxic Substances and Disease Registry (ATSDR), and the US Food and Drug Administration (FDA) provide recommended limits on methylmercury exposure in the diet.[24-28] Suggested levels range from 0.7

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Table I. Mercury exposure from thiomersal in typical immunization schedules (reproduced from Clements et al.,[31] with permission)

Age	Vaccines	Hepatitis B (HB) vaccine		Mercury dose (μg)	
		scheme A	scheme B	scheme A	scheme B
Birth	BCG, OPV 0	HB 1		12.5	
6 weeks	DTP 1 , OPV 1, Hib 1	HB 2	HB 1	62.5	62.5
10 weeks	DTP 2 , OPV 2, Hib 2		HB 2	50	62.5
14 weeks	DTP 3 , OPV 3, Hib 3	HB 3	HB 3	62.5	62.5
9 months	Measles, yellow fever				
Total potential exposure of infants				**187.5**	**187.5**

BCG = bacillus Calmette-Guerin; **DTP** = diptheria-tetanus-whole cell pertussis; **Hib** = Haemophilus influenzae type b; **OPV** = oral poliomyelitis vaccine.

μg/kg bodyweight per week (EPA) to 3.3 μg/kg bodyweight per week (WHO). This range results from the different primary data sources, intended applications of these guidelines, and uncertainty factors or safety margins built into these recommendations. For example, the EPA reference dose has a 10-fold uncertainty factor that is intended to be protective for the developing fetus. Of note, the guidelines produced by these agencies are meant to be starting points for evaluation of mercury exposure, and not absolute levels above which toxicity occurs.

In a plausible scenario, a female infant at the lowest fifth percentile of bodyweight[29] between birth and 14 weeks [the period during which most infant vaccines are given in the Expanded Programme on Immunisation (EPI)] is limited to a total methylmercury exposure of between 34μg (using EPA guidelines to determine recommended limits) and 159μg (if WHO guidelines are used). Table 1 shows the exposure that would take place under the schedule recommended by the EPI,[30,31] although maximum exposure would be less if available formulations without thiomersal were used. During the first 14 weeks of life, an infant may receive 3 doses of DTP vaccine for a maximum total of 75μg of ethylmercury. If hepatitis B vaccine is added to the immunisation schedule, the maximum exposure to ethylmercury during the first 14 weeks of life is 112.5μg. Adding Hib vaccine, the total ethylmercury dose reaches 187.5μg. This suggests that some infants may receive cumulative exposure to ethylmercury from vaccines that, while not associated with acute toxicity, nonetheless may be of concern and exceeds various agency recommendations for methylmercury exposure.

Guidelines for methylmercury exposure have been based on neurodevelopmental outcome in children whose mothers were exposed to methylmercury in the diet during pregnancy, raising the issue of vaccination during pregnancy with thiomersal-containing vaccines. Maternal exposure to mercury from TT vaccine does not reach levels of concern because of the greater bodyweight of adult women, although the impact on the more susceptible fetal brain is uncertain and needs more evaluation (table II).

3. Does Mercury in Vaccines Pose a Risk?

Several gaps in our knowledge of the toxicity of thiomersal make it problematic to identify the precise risks from the preservative in vaccines. These gaps include lack of data on the comparative toxicity of ethylmercury compared with methylmercury, the metabolism and elimination from the body of ethylmercury compared with methylmercury, the level of risk to the fetus in relationship to maternal exposure from thiomersal in vaccines, the effect of intermittent intramuscular bolus doses of thiomersal from vaccines compared with daily low dose oral exposure to methylmercury, and susceptibility of the infant compared with the fetus to adverse effects from organic mercurials. Moreover, uncertainty exists regarding background mercury exposure from other sources such as the diet. At the

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Table II. Mercury exposure in women of childbearing age, especially pregnant women (reproduced from Clements et al.,[31] with permission

Exposure through tetanus toxoid (TT) vaccination	Mercury dose (μg)
TT1 – as soon as possible in pregnancy or as early as possible in the childbearing years	25
TT2 – at least 4 weeks after TT1	25
TT3 – at leaset 6 months after TT2	25
TT4 and TT5 – at least 1 year after the previous dose	50
Total exposure	**125**

time of the FDA risk assessment, no population-based studies had been conducted evaluating neurodevelopmental outcome with exposure to thiomersal in vaccines. While this risk assessment did not find evidence of acute or chronic neurotoxicity, the possibility of subtle neuro-developmental abnormalities from cumulative exposure of infants to thiomersal in vaccines could not be excluded due to these gaps in scientific knowledge.[32]

Why has this theoretical risk assumed such significance that policy changes are now being considered? The public's overall tolerance for risk in the absence of obvious benefit to the individual has greatly diminished, particularly when the source of risk is perceived as man-made and potentially avoidable.[4] For example, the remarkable success of immunisation programmes to decrease the incidence of vaccine-preventable diseases in industrialised countries has resulted in a lessened awareness of the risks associated with these diseases.[33,34] As the risk of infection from such diseases declines, parents are less tolerant of adverse events from vaccines they may not consider relevant to their needs. Thus, the potential risk of adverse effects from vaccines has assumed greater prominence. The recognition of the potential cumulative levels of ethylmercury from vaccines in national immunisation schedules, along with the consensus that mercury exposure from all sources should be minimised, has led to a paradigm shift in the perception of risk from thiomersal.

4. Consequences of Change

The goal of reducing mercury exposure from thiomersal in vaccines creates several problems for national immunisation programmes. At one extreme, concerns about thiomersal in vaccines could lead to vital vaccines being withdrawn from production, and immunisation providers refraining from immunising children with thiomersal-containing vaccines. This would likely result in an increased morbidity and mortality from vaccine-preventable diseases. Moreover, if thiomersal were to be withdrawn from vaccines without providing a suitable alternative, the risk from contamination of multi-dose vials would increase and lives would be put at risk from bacteraemia or toxic shock syndrome. At the other extreme, if the issue were to be ignored, children might receive increasing amounts of thiomersal as more vaccines were introduced into national immunisation schedules.

Local vaccine production accounts for as much as 60% or more of the market in developing countries. Local manufacturers would be seriously disadvantaged if they were forced to reduce or eliminate thiomersal from their products. For example, conversion to mono-dose vials would require significant changes in the manufacturing filling process because of the greatly increased number of vials, resulting in an estimated 6- to 10-fold increase in production cost (J. Lloyd, personal communication). Moreover, replacement of higher volume multi-dose containers with mono-dose vials would place increased demands on the cold chain (i.e. maintaining the vaccine at the required temperature during transport to the clinic.) Even if suitable mercury-free preservatives were to be developed in the future, local manufacturers would not necessarily have automatic access due to patent and proprietary concerns.

Like so many situations in healthcare, the WHO and national vaccine programmes are faced with balancing benefits and risk. On the one hand there is the theoretical and incompletely defined risk of thiomersal in vaccines. On the other is the known, life-threatening risk of vaccine-preventable diseases if vaccines are not used, and the risk of con-

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tamination from using vaccines without a preservative. The WHO has gone on record as continuing to recommend thiomersal-containing vaccines where preservatives are essential to maintain the sterility of the product.[35] At the same time, the organisation is working with partner organisations and industry to reduce exposure to mercury in vaccines. Efforts in this direction will need to be targeted at short and long term solutions, but work in both areas is being carried out in parallel. This approach was endorsed by the WHO Expert Committee on Biological Standardisation at its meeting in November 1999.

5. Policy in the US

It has been recognised for some time that there is a need to minimise exposure to mercury from all sources such as food (especially certain fish), pharmaceuticals and biological products. Recent studies have suggested the potential for adverse neurodevelopmental consequences in infants whose mothers were exposed during pregnancy to low levels of methylmercury.[2] The addition of new vaccines to the recommended childhood immunisation schedule during the past decade has increased the potential exposure of infants to mercury from vaccines. In July 1999, an FDA review mandated by the US Congress found that some infants might receive more mercury from vaccines than was considered acceptable according to certain national guidelines.[32] The USPHS and American Academy of Pediatrics (AAP) issued a joint statement concerning thiomersal in vaccines[1] and the AAP released an interim report to clinicians[36] recommending that thiomersal be removed from vaccines as soon as possible, while maintaining efforts to ensure high vaccination levels. These events prompted international debate about preservatives and their safety as well as controversy over immunisation recommendations for thiomersal-containing vaccines. One recommendation in the joint statement and interim report to clinicians was deferral of hepatitis B vaccination until 2 to 6 months of age for infants born to mothers at low risk of hepatitis B disease. An editorial in *JAMA* soon followed suggesting that the authorities should express a preference for thiomersal-free DTaP and Hib vaccines for infants.[37]

The policy to delay hepatitis B vaccination prompted some disagreement and confusion. Some claimed it elevated a theoretical risk above an actual risk.[38] A US Centers for Disease Control and Prevention (CDC) survey performed shortly after publication of the joint statement revealed that 9% of hospitals in the US reported that they no longer routinely vaccinate any newborn, regardless of the hepatitis status of the mother.[1] The precipitous manner in which policy changes were made may have contributed to confusion and errors in implementation. However, there is general consensus in the US among government agencies and professional societies that reduction in mercury exposure from thiomersal in vaccines is merited.

6. Developments in the US Since the Original Risk Assessment

The USPHS and various US vaccine advisory bodies including the AAP, the Advisory Committee on Immunization Practices (ACIP), and the American Academy of Family Physicians continue to recommend the policy of moving rapidly to vaccines that are free of thiomersal as a preservative.[1,39] With the approval in the US of a single-antigen thiomersal-free hepatitis B vaccine in August 1999, the ACIP recommended that the birth dose of hepatitis B vaccine be resumed for all infants.[40] The FDA approved an additional preservative-free hepatitis B vaccine in March 2000. Additional proposals to remove thiomersal from other vaccines have been announced by manufacturers of vaccines licensed in the US.

To assess the potential health effects in infants of exposure to thiomersal in vaccines, the CDC sought epidemiological data to examine selected outcomes with varying exposure levels. The results of a recent study in the US were presented to a peer review group and later to the public.[41] This retrospective analysis examined whether there was a link between the degree of exposure of infants to thiomersal-containing vaccines and the develop-

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ment of certain neurological and renal sequelae. The investigators analysed computer records derived from 2 health maintenance organisations on the West Coast of the US. The screening analysis found weak (relative risk less than 2) but statistically-significant associations between exposure to thiomersal-containing vaccines before the age of 6 months and tic disorders, attention deficit disorders (ADD), and speech and language disorders. The analysis did not find an association with other neurological and renal disorders. The investigators then used another, smaller database from the East Coast for a more focused study to test the hypotheses that tic disorders, ADD, and speech and language disorders are associated with thiomersal exposure before 6 months of age. This study did not confirm an association. Taken together, the results of the two studies are inconclusive as to an effect of thimerosal on neurological outcomes. The WHO is actively seeking additional data using retrospective studies, and is applying to existing databases methodologies similar to those that were used in these studies. In the US, additional studies to address the gaps in knowledge regarding potential health effects of thiomersal in vaccines are planned, including animal toxicology studies and further epidemiological assessments.

To address the uncertainty in the scientific community regarding the effects of low level exposure to methylmercury and the lack of consensus between various US agencies on the most appropriate methylmercury exposure limits, the US Congress solicited the independent scientific advice of the National Academies of Sciences'(NAS) National Research Council. The National Research Council's findings, released in July 2000, concluded that the 'EPA's reference dose is scientifically justifiable for protecting the health of the vast majority of Americans'.[42,43] The committee found strong scientific evidence in both humans and animals linking methylmercury exposure and certain neurological deficits such as poor performance on test of attention and motor function. This report emphasised the need for further evaluation of the many uncertainties involving the health effects of methylmercury, including the most sensitive time of exposure during development, the mechanisms of toxicity, and the role of individual factors such as genetics, health status and nutrition. The NAS report is currently under review by other US agencies responsible for developing methylmercury exposure guidelines.

7. The Future

In the US, recent progress in reducing exposure to thiomersal in vaccines has relied on reformulation of thiomersal-containing products into monodose vials, which do not require a preservative. This is not an option for many countries relying on multi-dose vials for vaccine storage and delivery. As a result, the WHO, the United Nations Children's Fund and other key agencies supplying vaccines to developing countries will continue to recommend vaccines containing this preservative for the foreseeable future. Work is under way evaluating the suitability of existing preservatives and finding new preservatives as replacements for thiomersal in vaccines. However, even if replacements are found quickly, there may be a time lag of months to years before commercial availability because the safety and efficacy of a new preservative must be established. Vaccines containing a new preservative may require re-licensing and, even with 'fast track' regulatory attention, could take over a year to bring on line. Combination vaccines as well as new vaccine technologies currently under development may further reduce exposure to thiomersal or the need for preservatives altogether. There is an inevitable trend towards thiomersal-free vaccine products, and greater availability of vaccines formulated without thiomersal as a preservative or containing only residual trace amounts. As complete removal of thiomersal in all vaccines may not be possible in the near future, further research is under way to address the gaps in knowledge to better understand the human health effects of low level exposure to thiomersal.

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8. Conclusion

Thiomersal has long been used as a preservative in vaccines. Risk assessment raises the possibility of a theoretical risk of neuro-developmental toxicity in infants receiving vaccines containing thiomersal. However, the risk of death and illness from vaccine-preventable diseases, especially in areas with high disease burdens, outweighs the theoretical risk of exposure to thiomersal in vaccines. The benefits of immunisation are apparent even in countries where high vaccination rates have significantly decreased the burden of vaccine-preventable disease because of the risk of resurgence of life-threatening diseases such as pertussis and diphtheria. Nevertheless, an evolving understanding of the potential health risks of low level exposure to organic mercury compounds, the feasibility of developing alternatives to thiomersal, and the paradigm shift that has occurred in the public perception of risk have led to the process of reducing and removing thiomersal from vaccines.

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