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Thiomersal in Vaccines

Balancing the Risk of Adverse Effects with the Risk of Vaccine-Preventable Disease

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Abstract

A number of affluent countries are moving to eliminate thiomersal (thimerosal), an ethylmercury preservative, from vaccines as a precautionary measure because of concerns about the potential adverse effects of mercury in infants. The WHO advocates continued use of thiomersal-containing vaccines in developing countries because of their effectiveness, safety, low cost, wide availability and logistical suitability in this setting.

The guidelines for long-term mercury exposure should not be used for evaluating risk from intermittent single day exposures, such as immunisation using thiomersal-containing vaccines. Similar or higher mercury exposures likely occur from breast feeding and the health benefit of eliminating thiomersal from a vaccine, if any, is likely to be very small. On the other hand, the benefits accrued from the use of thiomersal-containing vaccines are considerably greater but vary substantially between affluent and developing regions of the world. Because of the contribution to overall mercury exposure from breast milk and diet in later life, the removal of thiomersal from vaccines would produce no more than a 50% reduction of mercury exposure in infancy and <1% reduction over a lifetime.

Different public policy decisions are appropriate in different settings to achieve the lowest net risk, viewed from the perspectives of the individual vaccinee or on a population basis. In developing regions of the world, at least over the next decade, far more benefit will accrue from protecting children against widely prevalent vaccine-preventable diseases by focusing efforts aimed at improving infant immunisation uptake by using current, inexpensive, domestically-manufactured, thiomersal-containing vaccines, than by investing in thiomersal-free alternatives.

Mercury is a naturally occurring element to which all humans are exposed.[1-6] It is estimated that natural degassing of the earth's crust is responsible for over half of atmospheric mercury emissions (about 2700–6000 tons per year), whereas anthropogenic releases may account for an additional 2000–3000 tons per year.[7] The serious health consequences of short or long-term, high-dose, dietary-organic mercury exposure, which primarily involved the nervous system, were recognised following investigation of outbreaks of illness from the consumption of contaminated fish in Minamata, Japan and contaminated bread in Iraq, during the last century.[1,8-10]

Current questions regarding mercury toxicity are focused on possible neurological adverse effects

at much lower exposure levels. Although exposure to some level of mercury is universal, quantitative assessment has shown that the three largest contributors of mercury exposure to the general population are diet (primarily fish), dental amalgam and some pharmacological products, such as thiomersal (thimerosal)-containing vaccines.[1,5,8,11-13] Thiomersal is an ethylmercury-containing compound and has been used for decades as a preservative in many vaccines.

Since 1999, two different approaches have been followed regarding thiomersal-containing vaccines for childhood immunisation programmes. The US, countries in the European Union (EU) and a few other affluent countries have implemented measures to eliminate childhood exposure to vaccine-derived thiomersal.[14-21] As of 2004, none of the routine single or multivalent vaccines recommended and routinely used to protect preschool children in the EU or US contain thiomersal.[21-23] Elimination of thiomersal from routine childhood immunisation programmes in these jurisdictions has been achieved essentially by exclusive use of single dose, preservative-free vaccine formats.

However, most countries continue to use thiomersal-containing vaccines in their childhood programmes. The WHO continues to endorse using thiomersal-containing vaccines for children, including malnourished, premature or low-birthweight infants.[24-26] The basis of WHO's position is that pharmacokinetic and epidemiological studies have not demonstrated convincing evidence of ethylmercury toxicity from exposure to thiomersal-containing vaccines, whereas use of these vaccines, particularly in regions of high disease burden, has proven highly effective in protecting children.[27,28]

The two different approaches to the issue of thiomersal in vaccines continue to generate confusion among parents, adult vaccine recipients and healthcare workers who administer vaccines. Even in jurisdictions where thiomersal has been eliminated from vaccines routinely administered to infants, there remain thiomersal-containing vaccines that may be recommended for some high-risk children (e.g. vaccines against influenza, Lyme disease, invasive pneumococcal disease or rabies).

This article reviews evidence of mercury-related health effects from exposure to thiomersal-containing vaccines in the context of other mercury exposures during infancy and over a lifetime, and assess the potential impact of eliminating thiomersal from vaccines. It also examines the public policy implications of eliminating thiomersal from vaccines as a trade-off between two competing risks (i.e. the risk of potential adverse effects attributable to exposure to thiomersal in vaccines versus the risk of vaccine-preventable illness or death), viewed from individual and population health perspectives.

To obtain relevant papers for this review, an electronic search was undertaken of literature published up to March 2004 using Medline (PubMed). Papers subsequently published up to December 2004 were included during the review of the final proofs. An initial Boolean search strategy using the key words 'thimerosal', 'ethylmercury', 'methylmercury', 'neurodevelopmental disorders', 'adverse effects' and 'autism' was utilised. No electronic search limitations were applied. Additional citations were identified through a PubMed search of related articles and from secondary sources cited in primary references.

1. Quantifying Vaccine-Derived Ethylmercury Exposure

In 1999, it was estimated that American infants could receive a cumulative dose of vaccine-derived ethylmercury as high as 187.5μg during the first 6 months of life and up to 237.5μg ethylmercury by 2 years of age.[29] Exposures for some children at high risk who also received influenza vaccine could have been as high as 200μg and 275μg at 6 months and 2 years of age, respectively. Although exposure of American (and most Western European) infants to thiomersal-containing vaccines used in routine immunisation has since been eliminated, several thiomersal-containing vaccines continue to be used for routinely recommended adult immunisations, which could potentially expose persons to a cumulative 950μg of ethylmercury over a lifetime (table I).

The immunisation schedule for infants recommended by the WHO Expanded Programme on Immunisation (EPI) (table II), representing the core of immunisation programmes in most developing countries, potentially exposes most of the world's children to a level of 112.5μg ethylmercury by 14 weeks of age. *Haemophilus influenzae* type b (Hib)

Table I. Vaccine-derived ethylmercury exposure in US Centers for Disease Control immunisation schedules for children, adolescents and adults[30,31]

Age	Vaccines	Ethylmercury dose (μg)	
		per dose	cumulative to 80 years
4–6 years	DTaP, IPV-4, MMR-2		
11–12 years	Td	25	25
Every 10 years	Td	25	150
Annually from age 50 years	Influenza	25	750
Age 65 years	Pneumococcal	25	25
Total to age 80			**950**

DTaP = diphtheria-tetanus-acellular pertussis; **IPV** = inactivated poliovirus vaccine; **MMR** = measles-mumps-rubella; **Td** = tetanus-diphtheria.

vaccine is gradually being introduced into childhood programmes in the developing world,[32] with three doses of Hib vaccine contributing an additional 75μg of ethylmercury in the first 6 months of life. Current EPI recommendations for routine immunisation of adults focus on preventing perinatal tetanus through immunisation of women of childbearing age with tetanus toxoid (table III).[32]

2. Is There Evidence of Adverse Health Effects from Vaccine-Derived Ethylmercury?

A retrospective cohort study first reported in 2001 by the US Institute of Medicine, Immunization Safety Review Committee, suggested a possible association between vaccine-derived ethylmercury and adverse health effects.[29] This study examined up to 7 years of data for children who were enrolled in three US health maintenance organisations (HMOs). The data analysed were from the Vaccine Safety Datalink, which includes vaccination, clinic, hospital discharge and demographic data from seven US HMOs. Results were inconsistent between HMOs and inconclusive, with weak associations (relative risks <2 per 12.5μg increment in ethylmercury) identified between various cumulative exposures to thiomersal and some neurodevelopmental diagnoses, such as speech delay and attention deficit disorder but not autism. No consistent dose-response relationship was detected.

More recently, published studies examining autism and thiomersal-containing vaccines provide evidence that is not consistent with a causal relationship.[33,34] Madsen et al.[33] analysed a national diagnostic registry to assess the incidence of autism in Danish children aged 2–10 years between 1971 and 2000. There was no trend towards increased autism incidence during the period up to 1992 (when thiomersal-containing vaccines were used for childhood immunisations in Denmark). Autism incidence began to rise in 1991 and continued to rise, even after Denmark switched to thiomersal-free vaccines for childhood immunisations during 1992. Autism incidence peaked in 1999, with the highest age-stratified rates among children born between 1993 and 1997. Stehr-Green et al.[34] compared estimated prevalence or reported incidence of childhood au-

Table II. Vaccine-derived ethylmercury exposure for infants immunised as recommended by the WHO Expanded Programme on Immunisation schedule[27]

Age	Vaccines	Hepatitis B vaccine[a]		Ethylmercury dose (μg)	
		scheme 1	scheme 2	scheme 1	scheme 2
Birth	BCG, OPV-0	HBV-1		12.5	
6 weeks	DTP-1, OPV-1, (Hib-1)	HBV-2	HBV-1	37.5 (62.5)[b]	37.5 (62.5)
10 weeks	DTP-2, OPV-2, (Hib-2)		HBV-2	25 (50)	37.5 (62.5)
14 weeks	DTP-3, OPV-3, (Hib-3)	HBV-3	HBV-3	37.5 (62.5)	37.5 (62.5)
9 months	Measles, yellow fever[c]				
Total				**112.5 (187.5)**	**112.5 (187.5)**

a In countries with hepatitis B surface antigen prevalence ≥2%; scheme 1 is recommended in countries with a high risk of perinatal transmission.

b Parentheses indicate ethylmercury dose if the Hib vaccine is also included in the immunisation schedule.

c In countries where yellow fever poses a risk.

BCG = bacilli Calmette-Guérin; **DTP** = diphtheria-tetanus-(whole cell) pertussis; **HBV** = hepatitis B vaccine; **Hib** = *Haemophilus influenzae* type b; **OPV** = oral poliovirus vaccine.

Table III. Vaccine-derived ethylmercury exposure for women of childbearing age (especially pregnant women) immunised as recommended by the WHO Expanded Programme on Immunisation schedule[27]

Vaccine	Timing	Ethylmercury dose (μg)
TT-1	As soon as possible in pregnancy or as early as possible in childbearing years	25
TT-2	At least 4 weeks after TT-1	25
TT-3	At least 6 months after TT-2	25
TT-4 and TT-5	At least 1 year after previous TT dose	50
Total		**125**

TT = tetanus toxoid.

tism with average cumulative doses of vaccine-derived ethylmercury for birth cohorts between the mid-1980s to late 1990s in California, Sweden and Denmark. Although reported incidence (in Sweden and Denmark) and estimated prevalence (in California) of autism-like disorders rose in the late 1980s and accelerated in the early 1990s, the average cumulative vaccine-derived ethylmercury exposures decreased and were eventually eliminated over this period in Sweden and Denmark, while increasing in the US.

In May 2004, the US Institute of Medicine, Immunization Safety Review Committee, investigating whether thiomersal-containing vaccines cause autism, concluded that the body of epidemiological evidence favours rejection of a causal relationship.[35] Subsequently, two published cohort studies in the UK also found no convincing evidence that vaccine-derived thimerosal exposure causes neurodevelopmental disorders. Heron et al.[36] used data from a population-based cohort study of approximately 14 000 children born in 1991 and 1992 from southwest England. Ethylmercury exposure from thiomersal-containing vaccines administered up to 6 months of age was determined from public health immunisation records and analysed against a range of behavioural, speech and motor development criteria that were assessed using validated questionnaires administered to mothers at six specified periods until children were 91 months old. Information on potential confounders (infant gestation birth weight, gender, breastfeeding status and maternal parity, ethnicity, smoking status, education, housing and fish consumption during third trimester) was also collected. Adjusted analyses were most consistent with there being no neurological or behavioural adverse outcome associated with vaccine-derived thiomersal. Andrews et al.[37] retrospectively collected and analysed data on approximately 100 000 term and 2500 pre-term children born in the UK between 1988 and 1997 who had at least 2 years follow-up by general practitioners who were registered with, and contributed to, a research database. Vaccine-derived ethylmercury exposures at 3 and 4 months of age were determined from the research database and analysed against a range of recorded outcome events including neurodevelopmental disorders, autism, problems with behaviour, speech or language, attention deficit disorder, encopresis, enuresis and tics. Potential confounders were not considered. Investigators found no evidence in either term or pre-term children of an association with any of the outcome events, except possibly tics (with which Heron et al.[36] detected no evidence of association).

3. Are Adverse Health Effects from Vaccine-Derived Ethylmercury Plausible?

Plausibility of a possible association between vaccine-derived ethylmercury exposure and mercury-related health effects has been based on the following:

- Presumed similarities in pharmacokinetics and toxicological effects of ethyl- and methylmercury.
- Hypersensitivity reactions after low-dose exposures to thiomersal-containing products.
- Measurable increases in blood mercury following immunisation of infants with thiomersal-containing vaccines.
- Evidence of a dose-response effect from high-dose, acute and chronic occupational and dietary exposures to ethylmercury.

3.1 Are the Pharmacokinetics of Ethyl- and Methylmercury Comparable?

The pharmacokinetics and toxicology of methylmercury have been studied far more extensively than for ethylmercury.[5,29,38] Similar pharmacokinetics and toxicology at lower doses were initially postulated because of their related chemical structures and similar health effects at higher doses.[8,12,15,39] Current regulatory guidelines for organic mercury exposure have therefore been essentially based on the properties and toxicology of methylmercury.[40-43]

The metabolism and toxicological mechanisms of action of ethyl- and methylmercury are complex,[29] and significant differences in the pharmacokinetics between these two compounds are being recognised.[11,12,44,45] Two important differences are the significantly shorter half-life of ethylmercury in blood and less movement of ethylmercury through the blood-brain barrier into the central nervous system.[11,46,47] Magos[46] estimated an allometrically corrected half-life of 18 days for mercury administered as thiomersal, which was within 10% of the measured blood mercury levels reported by Pichichero et al.[11] Data presented by Magos indicate that transient accumulation of blood mercury still results from vaccination with thiomersal-containing vaccines at the 4–6 weeks dose intervals recommended by the WHO/EPI routine infant immunisation schedule for developing countries, although it is significantly less than the estimates based on the longer half-life of methylmercury.[12,46] At the longer 6–8 week primary immunisation dose intervals typically recommended for infants in developed countries, no significant accumulation in blood mercury occurs.[46,47]

3.2 Are the Toxicological Effects of Early Methylmercury Exposure Relevant to Ethylmercury?

Long-term, prospective population-based studies of long-term, low-dose prenatal and dietary mercury exposure to children in the Seychelles Islands,[48,49] Faeroe Islands,[50,51] and New Zealand[52] are based on methylmercury intake. In the Seychelles, chronic, low-dose *in utero* mercury exposures result from mothers eating a predominantly fish-based diet, whereas the fish consumption of Faeroes mothers intermittently changes to the consumption of the meat and blubber of pilot whales.

The Seychelles study,[49] which used maternal and child hair to evaluate prenatal and childhood mercury exposure, respectively, and primarily global neuropsychiatric scales to assess outcome, found no neurological impairment among children up to 9 years of age. The Faeroe Islands study,[51] which used umbilical cord blood and child hair to evaluate prenatal and postnatal mercury exposure, respectively, and domain-specific neuropsychiatric testing to assess outcome, reported subtle neurological deficits in memory, attention and language scores among the 7-year-old children tested. Postnatal mercury exposure was less predictive of these effects than prenatal exposure. Infant neurodevelopment test results have not consistently been shown to predict later dysfunction.[53,54]

The New Zealand study[52] correlated prenatal methylmercury exposure, estimated from analysis of maternal hair samples collected during pregnancy, with scholastic and psychological test results in 6- and 7-year-old children. A possible subtle mercury effect was detected but only after excluding one 'outlier' infant-mother pair from the analysis because of a maternal hair mercury level of 86 mg/kg, which was more than four times that of the other mothers.

Mercury exposure of infants to thiomersal-containing vaccines differs from exposures in the Seychelles, Faeroes and New Zealand studies in several key respects. First, ethylmercury is less neurotoxic than methylmercury. Second, the timing of the exposure is different with only postnatal exposure associated with infant vaccination. Third, the route of exposure (parenteral vs oral) is different and fourth, the exposure from vaccination is intermittent rather than more continuous as in the Seychelles, Faeroes and New Zealand studies.[15,29,55]

3.3 Hypersensitivity Reactions after Low-Dose Exposures to Thiomersal-Containing Products

Thiomersal has been implicated in contact allergy (delayed-type hypersensitivity) skin reactions.[53,56,57] Between 1% to 16% of tested individuals exhibit allergic reactions on skin patch testing.[53]

Immediate hypersensitivity (e.g. anaphylaxis) and immune complex-mediated disorders (e.g. glomerulonephritis) have also been reported in association with exposure to thiomersal-containing products, although it is uncertain if thiomersal was the responsible allergen.[14,29]

3.4 Changes in Blood Mercury after use of Thiomersal-Containing Vaccines in Infants

Two studies have examined changes in blood mercury following immunisation with thiomersal-containing vaccines.[11,58] Pichichero et al.[11] compared the blood mercury levels of vaccine-derived thiomersal-exposed and control infants who were 2 months and 6 months of age. The cumulative mean vaccine-derived ethylmercury exposures were 45.6μg and 111.3μg for the 2- and 6-month-old infants, respectively. Twelve of 17 exposed 2-month-old infants had detectable blood mercury at a mean concentration of 8.2 nmol/L (or 1.6 μg/L), [SD = 4.9 nmol/L], whereas for 6-month-old exposed infants, 9 of 16 had detectable blood mercury at a mean concentration of 5.2 nmol/L (or 1.0 μg/L), [SD = 1.2 nmol/L]. By comparison, only one of eight 2-month-old control infants had detectable blood mercury of 4.65 nmol/L (or 0.9 μg/L) and none of seven 6-month-old control infants had detectable blood mercury. Prenatal mercury exposure, which was assessed by maternal hair analysis, did not differ, with mean mercury concentrations of 0.45 μg/g and 0.32 μg/g for mothers of vaccinated and control infants respectively ($p = 0.22$).

Stajich et al.[58] reported that immunisation with a single dose of hepatitis B vaccine containing 12.5μg of ethylmercury resulted in an increase in mean mercury blood level in pre-term infants from a baseline level of 0.54 μg/L (SD = ±0.79) to 7.36 μg/L (SD = ± 4.99), whereas in term infants an increase from a baseline of 0.04 μg/L (SD = ±0.09) to 2.24 μg/L (SD = ± 0.58) was detected, when measured 2–3 days after vaccination. Although pre-term infants received higher μg/kg doses than term infants, the ratio of prevaccination blood mercury concentration between pre-term and term infants was greater than the corresponding ratio of post-vaccination blood mercury concentration. This indicates that pre-term infants excreted a greater proportion of the mercury dose per kg bodyweight than term infants.[46,47]

It remains uncertain whether the higher levels of blood mercury detected in low-weight or pre-term infants following immunisation with thiomersal-containing vaccines pose any measurable toxicological risk.[47]

3.5 Evidence of Dose-Response Relationship from High-Dose Exposures to Ethylmercury

A report of short-term, high-dose exposure to ethylmercury in Iraq documented tremor with or without paraesthesia in three individuals with blood mercury concentrations of 1000, 1500, and 1700 μg/L, while no adverse effect was observed in an exposed fourth individual, who had a blood mercury level of 650 μg/L.[59] In China during the early 1980s, consumption of ethylmercury-treated rice caused a range of neurological symptoms including weakness, dizziness, numbness, paraesthesia and ataxia that were recognised in the mildest-affected persons at total dose exposure levels of 0.5–1 mg/kg bodyweight.[60] Magos[44] reported that no adverse effect was observed at blood mercury levels between 140 and 650 μg/L in five adults, assessed 11–22 days after exposure to varying doses of ethylmercury from contaminated food, infusion or topical application of ethylmercury-containing therapeutic/pharmaceutical products.[42] In this same review, the lowest observable adverse effect level was at a blood mercury level of 1000 μg/L.[42]

The lowest blood levels associated with adverse effects are approximately 1000 times higher than levels measured in 2-month-old infants following exposures reported by Pichichero et al.[11] Although dose-response relationships have been constructed for prenatal exposures to methylmercury,[61-64] no relationship between dose and response has been established for postnatal exposures to ethylmercury at the doses delivered through vaccines.[27]

4. Mercury Exposure Guidelines: Their Limitations and Assumptions

There have been no studies specifically designed to evaluate a 'no observed effect level' for ethylmercury,[1] although Magos[44] has interpolated data from published case reports. Although no 'tolerable

daily intake' level for ethylmercury has been proposed,[65] various agencies have published recommended mercury exposure limits that provide policy-making guidance in managing long-term population exposure.[40-43,66-68] In general, these limits are intended to be protective of the fetus.[3,5,14,69] These exposure limits are back-calculated from hair or blood concentrations that are at a steady state and are intended for application to long-term, average daily intake of methylmercury from all sources (Health Canada, WHO, US Environmental Protection Agency and US FDA) or for *a minimum* of 1 year (Agency for Toxic Substances and Disease Registry), below which there is no known, appreciable health risk.[8,29,70] The exposure limits do not represent absolute levels above which toxicity occurs.[1,15,27,29,70] As these recommendations are intended to apply to average long-term, rather than a maximum single-day exposure, care must be taken to compare exposures averaged over a suitable time base. It is not meaningful to compare these guidelines with single-day exposures, such as the day on which a patient receives one or more thiomersal-containing vaccines.

To illustrate how these exposure guidelines can be misinterpreted by using inappropriate averaging times,[71] hypothetical 'worst-case' scenarios of calculated cumulative exposure limit to methylmercury exposure are depicted in figure 1 for infants at 14 weeks of age (corresponding with completion of EPI-recommended vaccinations at 14 weeks age), 6 months of age (approximating completion of similar primary vaccinations in developed countries) and at 1 year of age. These scenarios assume that a newborn female infant in the lowest fifth percentile of mean bodyweight receives all vaccines according to

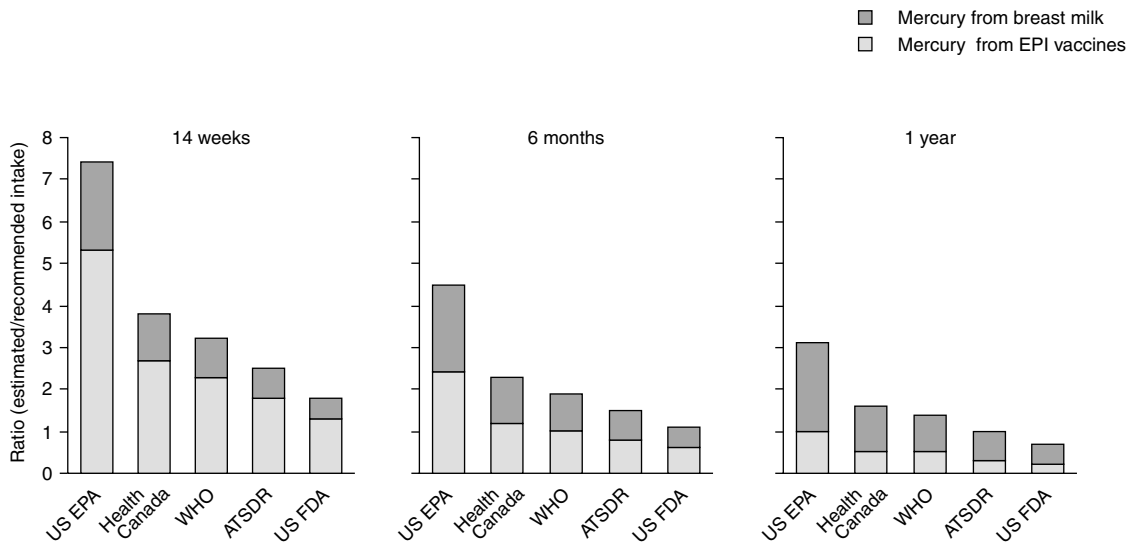

Fig. 1. Ratios of average weekly exposure to mercury from thiomersal-containing vaccines and/or breast milk, compared with agencies' exposure recommendations for methylmercury averaged over 14 weeks, 6 months and 1 year – hypothetical 'worst-case scenarios' for infants aged 14 weeks, 6 months and 1 year and based on fifth percentile of female infant bodyweight. Thiomersal-containing vaccine-derived mercury exposure was based on a cumulative ethylmercury dose of 187.5μg following immunisation according to WHO/EPI schedule up to 14 weeks of age. Breast milk-derived mercury exposure was calculated as: mean weight × mean daily breast milk consumption (140 mL/kg) × number of days × mean mercury concentration in breast milk (1.5 μg/L); mean weight was calculated using fifth percentile of weight for a female infant (birth weight 2.6kg) for specified ages (4.5kg at 14 weeks, 5.9kg at 6 months and 8.0kg at 1 year of age), i.e. mean weights of 3.6kg at 14 weeks, 4.3kg at 6 months and 5.3kg at 1 year of age.[72] The agencies' methylmercury exposure limits were calculated as dosage/kg bodyweight/week × mean weight × age in weeks (i.e. at a dosage of μg Hg/kg/week): WHO – 1.6;[40] US EPA – 0.7;[41] US FDA – 2.8 (estimate derived from an acceptable daily intake of 30 μg /day) [29.37]; ATSDR – 2.1;[43] Health Canada – 1.4.[66] Percentiles for female weight-by-age from US National Center for Health Statistics, published 30 May 2000 (modified 20 April 2001).[72] **ATSDR** = Agency for Toxic Substances and Disease Registry; **US EPA** = US Environmental Protection Agency; **WHO/EPI** = WHO Expanded Programme on Immunisation.

the WHO/EPI recommended schedule (table II), which corresponds to a cumulative dose of ethylmercury up to 187.5μg. The ratio of cumulative vaccine-derived ethylmercury exposure to agencies' calculated cumulative exposure limits for methylmercury rapidly decreases with age.

Since the exposure limit guidelines are derived from similar scientific data, the differences between agencies reflect varying assumptions and uncertainty factors that are applied in translating scientific data into public policy recommendations. None of the recommended exposure guidelines for mercury incorporates any consideration of offsetting health benefits that would be lost as a result of avoiding certain recognised sources of mercury exposure (e.g. protection against vaccine-preventable disease or reduction in cardiovascular disease risk from eating fish).[13] This reflects the guidelines' intended purpose to minimise *mercury-related* risks to health, not *overall* risks to health. For this reason, sound decision making about reducing health risks to individuals or populations must include all relevant risk information and not rely solely on exposure guidelines that consider only part of the total risk.

5. Other Sources of Mercury Exposure in Infants

Typical dietary consumption of some fish species by pregnant or lactating women, can result in fetal or infant mercury exposure approximating those from thiomersal-containing vaccines.[14,54,69,73-77] Recent estimates of breastfed infants' dietary mercury exposure from breast milk under normal environmental conditions range from <1 μg/L to approximately 3 μg/L.[11,76,78-80] A mean mercury concentration in breast milk of 1.5 μg/L, consumed by an exclusively breastfed,[81,82] fifth percentile female infant (mean bodyweight 4.3 kg), with an average intake of 140 ml/kg bodyweight per day of breast milk,[83] corresponds to a cumulative exposure to 164μg dietary mercury during the first 6 months of life. Thus, an exclusively breastfed infant is potentially exposed to approximately the same cumulative amount of mercury from breast milk in the first 6 months of postnatal life as from all WHO/EPI-recommended childhood vaccinations. Given that the same mercury exposure from vaccines occurs as three or four parenteral boluses, one could expect short-term, peak levels of mercury after vaccination to be higher than from ingesting breast milk. However, in either case no measurable adverse health effect from mercury has been recognised at this level of cumulative dose exposure during infancy.

6. Comparative Cumulative Mean Lifetime Mercury Exposures

Table IV places the relative exposures from vaccines in context with other common sources of exposure. Based on daily mercury exposures depicted, exposure to an average 2.4μg of methylmercury per day from fish consumption over an average lifetime of 65 years would result in a lifetime exposure of 57mg. This exceeds the lifetime vaccine-derived ethylmercury exposure from current recommended WHO/EPI childhood and adult immunisations (312.5μg) by a factor of 182. These comparisons do not mean that we should not try to reduce mercury exposure where possible but they do make clear that a <1% reduction in overall lifetime organic mercury exposure can be achieved by eliminating thiomersal from vaccines.

Table IV. Estimated daily intake/retention of elemental and mercuric compounds in a general population not occupationally exposed to mercury[84]

Exposure	Elemental mercury vapour (μg/day)		Inorganic mercury compounds (μg/day)		Methylmercury (μg/day)	
	intake	retention	intake	retention	intake	retention
Air	0.030	0.024	0.002	0.001	0.008	0.0064
Food – fish	0	0	0.600	0.042	2.4	2.3
Food – non-fish	0	0	3.6	0.25	0	0
Drinking water	0	0	0.050	0.0035	0	0
Dental amalgam	3.8–21	3–17	0	0	0	0
Total	**3.9–21**	**3.1–17**	**4.3**	**0.3**	**2.41**	**2.31**

7. Global Burden of Diseases for Which Thiomersal-Containing Vaccines are Available

In 2002, an estimated 500 000 children died of vaccine-preventable pertussis or tetanus,[85] while in 2000, an estimated 37 million children worldwide did not receive the routine immunisations in the first year of life that are recommended by WHO/EPI.[32] Immunisation coverage among infants for three doses of diphtheria-tetanus-pertussis vaccine was only 60% in Africa and approximately 70% in South-East Asia.[86] In 2003, over two dozen countries worldwide, mostly African nations designated as high endemic areas for chronic hepatitis B virus (HBV) infection [i.e. >8% prevalence],[87] had still not introduced HBV vaccine into their national infant immunisation programmes.[88] Among many developing countries that report having implemented HBV immunisation programmes, immunisation coverage is seriously compromised by healthcare system financial constraints.[32,89]

8. Implications of Changing Thiomersal Content on Vaccine Effectiveness and Safety

Although thiomersal is added to vaccines primarily as a preservative, it has also been shown to improve vaccine stability, potency and safety.[26,28] In some production processes, such as the manufacture of whole-cell pertussis vaccine, thiomersal is used in conjunction with heat to inactivate bacterial antigen.[25,90] Thimerosal may also be added to some formulations of bulk vaccine prior to filling into final containers as a substitute to filtration-sterilisation.[90] Traces of organic mercury may also have a stabilising effect on vaccine antigens, such as the semi-synthetically produced HBV surface antigen in recombinant HBV vaccines and in whole-cell pertussis vaccine.[90] Its reduction, elimination or replacement from certain vaccines could therefore adversely affect vaccine quality, safety and efficacy. Extensive characterisation, pre-clinical and clinical testing of replacement products will likely be necessary prior to licensure by regulatory authorities.[25,28,90,91] An extended 28 day shelf life has also been approved by WHO following initial use of thiomersal-containing, multi-dose vaccine vials.[92] This extended shelf life does not necessarily apply for alternative vaccine preservatives such as 2-phenoxyethanol or formaldehyde, which are not as effective as thiomersal in terms of bacteriostatic properties.[91]

9. Cost Implications of Changing Thiomersal Content in Vaccines

A significant concern of WHO is the negative impact of thiomersal removal on vaccine production capacity and cost to developing countries. In 2001, 48 countries (including many in the developing world) had domestic vaccine production facilities.[32] As much as 60% of vaccine production in the developing world is used domestically, mostly manufactured as multi-dose, thiomersal-containing vaccines.[1] Multi-dose vials appear to be most appropriate for less expensive (e.g. WHO/EPI-recommended) vaccines and where cold chain systems are very limited.[93]

Despite economic evaluations indicating that childhood immunisation is highly desirable in developing countries,[94] vaccine population coverage can be highly sensitive to even small price increments.[95] In developing countries, which are the primary focus of the WHO/EPI immunisation programme, the total vaccine programme delivery cost per child for complete immunisation with bacilli Calmette-Guérin, diphtheria-tetanus-pertussis, polio and measles vaccines is about $US17,[96] of which vaccine cost represents probably <$US1.[97] Although vaccine cost of $US1 per child may not seem significant, this should be viewed in the context of total government expenditures on health of <$US10 per capita per year in many developing countries.[85] Use of single dose thiomersal-free vaccine formats could raise the overall expense of vaccination programmes and jeopardise the cost effectiveness of immunisation programmes in developing world settings by increasing infrastructure costs related to storage space, containers, container filling, transportation and maintaining adequate cold chain.[91]

10. Different Strategies for Managing Potential Risks and Benefits of Thiomersal-Containing Vaccines

From the perspective of individual risk, the absence of credible evidence linking thiomersal-containing vaccines to mercury-related effects on health and the demonstrated reduction in risk of vaccine-preventable disease indicate that the 'low risk' choice is to immunise with thiomersal-containing vaccines rather than not to immunise because of fears of mercury-related effects on health. That said, in settings such as more affluent countries, it may be perfectly rational to 'prefer' thiomersal-free vaccines to thiomersal-containing vaccines, both on precautionary grounds and to reduce overall exposure to mercury, particularly during infancy.

However, even in affluent countries, individual choice and access to alternative vaccine products may be constrained by pharmaceutical industry product marketing or government vaccine procurement policies for publicly funded immunisation programmes. Consumer preference can be a powerful force for affecting change and much of the impetus for improvements in consumer products and pharmaceuticals in many countries is driven by consumer demand, both directly and through actions of government agencies.

From the perspective of population-based risk, choices are more complicated when it comes to developing national or regional policies on thiomersal-containing vaccines. By-and-large, affluent countries have opted to move towards thiomersal-free, single-dose formats of vaccine for immunisations routinely recommended for children. This decision reflects a desire to maintain protection against vaccine-preventable disease while avoiding or reducing overall exposure to mercury, regardless of any established proven benefit from such exposure reductions. This choice of vaccine products in affluent countries is made possible by a willingness to absorb higher total vaccine programme costs and by having sufficient vaccine production capacity to transition relatively quickly to thiomersal-free products.[1,32] It also reflects a growing concern among parents, fueled by vocal, activist, anti-vaccination groups, about the safety of vaccines.[98] Failure by public policy makers and health officials to respond to these concerns could result in reduced vaccine uptake in the population and a net increase in the risk of vaccine-preventable disease at a population level.

On the other hand, in developing countries, choice is often more limited and the stakes are higher. As the rates of many vaccine-preventable diseases are higher, the benefits of immunisation are greater, as are the risks of failing to immunise or even deferring immunisation. Unlike more affluent countries, there are significant limitations in health-care resources and vaccine storage, handling and delivery infrastructure. In this setting, immunisation programmes using current thiomersal-containing, multi-dose vaccines are one of the most highly cost-effective – even cost-saving – health strategies. In developing countries, as in more affluent countries, the 'highest risk' option is the failure to immunise.

In light of the relatively greater cost implications and practical difficulties in delivering vaccine programmes in developing countries, thiomersal should probably only be replaced in these countries when suitable safe, effective alternatives that produce equivalent or lower costs for total vaccine programme delivery become available.[28] Over time, thiomersal-free vaccines can be systematically introduced to replace low-cost, multi-dose thiomersal-containing combination vaccines that, when administered according to WHO/EPI recommendations, have proven to be so effective in protecting children.

11. Conclusions

The health risks from vaccine-preventable diseases are well documented and are generally far higher in developing countries than in affluent countries. While the toxicity of mercury at high doses is well established, the risks from low-level exposure to thiomersal-containing vaccines are speculative and inadequately quantified.

Removal of thiomersal from vaccines will reduce exposure to mercury, particularly during infancy. Regulatory requirements mandating mercury exposure reduction, along with concern about potential risks to health, has led to the deployment of thiomersal-free vaccines in many countries that are able to afford higher-priced vaccines. Ideally, immunisa-

tion against vaccine-preventable diseases should be provided without incurring mercury exposure. However, the risks of failing to immunise against vaccine-preventable disease outweigh the possible risk associated with mercury in vaccines, particularly in developing nations. For this reason, thiomersal-containing vaccines are a 'safer' choice than no vaccines at all and these vaccines should continue to be employed, especially in developing countries, until thiomersal-free substitutes become a practical, affordable alternative.

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