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Commentary

Controversies surrounding mercury in vaccines: autism denial as impediment to universal immunisation

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In 2004, the US Center for Disease Control (CDC) published a paper showing that there is no link between the age at which a child is vaccinated with MMR and the vaccinated children's risk of a subsequent diagnosis of autism (1). One of the authors, William Thompson, has now revealed that statistically significant information was deliberately omitted from the paper (2). Thompson first told Dr S Hooker, a researcher on autism, about the manipulation of the data. Hooker analysed the raw data from the CDC study afresh. He confirmed that the risk of autism among African American children vaccinated before the age of 2 years was 340% that of those vaccinated later. Hooker published his findings in the peer-reviewed open-access journal, *Translational Neurodegeneration*. However, within hours of CNN publishing the story of the CDC whistle-blower, Hooker's article was removed from the website of the open-access journal. It was stated that the journal and publisher "believe that its continued availability may not be in the public interest". The full article is now available only on the PubMed website (3).

The MMR vaccine contains no Thimerosal, but the story of Thompson and the paper on MMR serves to illustrate how disputed the areas of vaccine-related injury and autism have become.

Protection from mercury as an equity issue

This issue of the *IJME* features an article by Sykes and colleagues on Thimerosal – a mercury-based preservative used in vaccines (4). The article inveighs against the exemption under the UN Convention on Mercury (Minamata Convention) that allows the use of Thimerosal-containing vaccines in developing countries. The authors, who are from the Coalition for Mercury-free Drugs and the Institute of Chronic Illnesses, argue that developing children and developing nations are the most vulnerable to toxic exposures and the UN's primary aim should be to protect them. They sidestep contentious issues, such as claims about vaccine-related injury, and dwell mainly on the matter of unfair discrimination.

The demand for mercury-free vaccines, however, springs from the perception that the heavy metal added to vaccines is harmful. It is felt that there was a spike in the incidence of autism in the USA when the *Haemophilus influenza b* (Hib) and hepatitis B vaccines were recommended for universal use (5). This commentary attempts to bring together the evidence. We discuss the need for mercury in vaccines and the suggestion that the use of ethyl mercury is safe. It draws extensively on a US House of Representatives report, "Mercury in Medicine Report" (6).

Thimerosal as preservative in vaccines

Thimerosal is an organic mercurial compound made up of equal parts of thiosalicylic acid and ethyl mercury. Ethyl mercury dissociates from Thimerosal and acts as a preservative (7). Thimerosal is used to prevent bacterial contamination of vials which are entered multiple times, ie multi-dose vials of vaccines. Preservatives are not required for single-dose ampoules.

Methyl mercury experience

Thimerosal has been in use since the 1930s in a number of biological and drug products (8). The US Food and Drug

Administration (FDA) did not require manufacturers to submit reports on pre-licensure safety testing until 1938, and efficacy testing until the 1960s, and as such, very few studies explored the toxicity of ethyl mercury (9). More data is available on methyl mercury, which was used for its anti-fungal properties from the 1860s when storing seeds. In the 1950s, methyl mercury toxicity was noticed in the Minamata Bay, Japan, with dead fish being washed ashore, seagulls falling out of the sky, frenzied cats whirling in a mad dance ending in death, and doctors reporting patients with a staggering gait. In 1968, the Japanese government released a statement implicating methyl mercury for the symptoms (10). It is assumed that the toxicity of ethyl mercury would be qualitatively similar to that of methyl mercury, although this has not been proved.

Recommended upper limit of mercury intake

The FDA has proposed 0.4 µg per kg of body weight per day as the acceptable daily intake of methyl mercury, on the basis of the threshold at which paresthesia occurs in adults (11). However, the foetus and infants are particularly susceptible to mercury toxicity, and long-term studies in Iraq have shown language delays among infants exposed to mercury (12). On the basis of the findings of the Iraq studies, the Environmental Protection Agency lowered its reference dose for methyl mercury exposure to 0.1 µg per kg per day.

Mercury in vaccines exceeding recommended intake

In 1999, the concern was raised that children being given the recommended doses of immunisation could be receiving doses of organic mercury, specifically ethyl mercury, which exceeded the specifications in the guidelines for the intake of methyl mercury (13).

Prior to the approval of the Hepatitis B recombinant vaccine, the only vaccine containing Thimerosal that was routinely given to infants was the DPT. This contained 25 µg of ethyl mercury, and was administered thrice in the first 6 months of life (75 mg of ethyl mercury) and a total of 4 times in 2 years (100 µg). After licensing of the Hepatitis B vaccine (administered within hours of birth and a total of 3 times in the first 6 months), which contained 12.5 µg of ethyl mercury, and the *Haemophilus influenza b* vaccine (administered 3 times in the first 6 months), which contained 25 µg of ethyl mercury, the cumulative quantity of ethyl mercury administered in the first 6 months went up from 75 µg to 187.5 µg. Using the EPA threshold of 0.1 µg per kg, the threshold would be 0.5 µg for a baby weighing 5 kg. The cumulative dose administered to babies receiving 187.5 µg would thus be higher than the threshold (14). It was feared that autism might result from the administration of high doses of Thimerosal to genetically susceptible children.

The autism epidemic

According to the US House of Representatives report, autism was once considered a rare disease that affected an estimated 1 in 10,000 individuals in the USA. In 2000, federal agencies estimated that autism affected 1 in 500 children and by 2002, the National Institute of Health had reported a rate of 1 in 250. The Autism Society estimates that the number of autistic children is growing by 10% to 17% each year (15). It found that 1 in 149 children between 3 and 10 years of age was autistic, and the proportion of autistic children was 10 times higher than that reported by studies conducted in the 1980s. As for children whose condition met all the diagnostic criteria for autistic disorder, the prevalence was 4 per 1000, while the prevalence of pervasive developmental disorder and Asperger disorder was 2.7 per 1000. The study stated that the increase was real and could not be explained by changes in diagnostic criteria or better diagnosis (6).

A study from the University of California showed that the number of autistic people in the state grew by 273% between 1987 and 1998 (16). This study did not include people with pervasive developmental disorder, Asperger syndrome or any milder autism spectrum disorder (ASD), but only those who received a professional diagnosis of level one autistic disorder (using the DSM IV criteria) – the most severe form of autism.

The Autism Research Institute, on analysing its databank of 30,000 cases of autism from around the world, found that before the 1980s, most parents reported that their children first showed abnormal behaviour from birth itself or in the first year of life. However, after the mid-1980s, the numbers who reported that their babies developed normally in the first year-and-a-half and then suddenly became autistic doubled. Further, children among whom the onset of autism was at 18 months came to outnumber those among whom the onset was at birth by a ratio of 2 to 1. The cause for the increase in cases of autism and the reason for the rapid growth in late-onset autism are not known (6). The fact that the increase in the prevalence of autism coincided with the addition of new Thimerosal-containing vaccines gave rise to the suspicion that mercury was causing the increase.

Ethyl mercury-specific studies

Experts have disputed the validity of the norms laid down for the use of ethyl mercury as these were originally developed in the context of methyl mercury poisoning. According to a recent WHO review, there is "no scientific evidence of toxicity from Thiomersal-containing vaccines" (17). Some of the studies that specifically examine ethyl mercury toxicity are discussed below.

Use of Thimerosal in meningitis

In 1931, in the pre-antibiotic era when meningitis was a killer disease, Powell and Jamieson wrote about 22 meningitis patients injected with 1% Thimerosal. The only adverse event, observed in two patients, was sloughing of the skin after local infiltration. The treatment was not successful and all the patients died of meningitis. The patients did not live long enough for it to be possible to examine long-term toxicity and injury (18). However, this study is often quoted as evidence that intravenous administration of Thimerosal is safe.

Comparison of methyl and ethyl mercury in murine model

The neurotoxicity and renal toxicity of ethyl mercury and methyl mercury were compared in rats given the compounds orally by Magos and colleagues. Greater weight loss and renal damage were observed in the rats treated with ethyl mercury than those given methyl mercury. Damage to the granular layer in the cerebellum was widespread in the latter. There was a higher concentration of inorganic mercury in the brains of the rats treated with ethyl mercury than in the brains of those treated with methyl mercury. Both damage and mercury deposits were more widespread in the case of the former (19).

Thimerosal excretion in infants

A study of the use of a Thimerosal-containing vaccine in 40 two- and six-month-old babies was reported in the *Lancet*. These babies were compared with 21 controls who were given Thimerosal-free vaccines. Samples of blood, urine and stool were collected between 3 and 28 days after the vaccination to determine how much mercury remained in the blood and how much was expelled in urine and stool. Of the 40 who received Thimerosal, blood was tested in 36, urine in 27 and stool in only 22 cases (20). The level of mercury in the blood of the two-month-olds exposed to Thimerosal ranged from less than 3.75 nmol/L to 20.55 nmol/L (parts per billion); in the six-month-olds, all the values were lower than 7.50 nmol/L. After the vaccination, the concentrations of mercury in urine were low, but they were high in the stools (mean 82 ng/g dry weight in the two-month-olds and 58 ng/g in the six-month-olds). The authors concluded that the administration of vaccines with Thimerosal to infants does not seem to raise blood concentrations above the safe values, and that ethyl mercury is eliminated from the blood rapidly via stools after parenteral administration of Thimerosal in vaccines.

The Director of the Environmental Toxicology Programme of the Institute of Environmental Health Sciences in the USA, Dr Christopher Portier, told the US House of Representatives Committee that given the small sample size and failure to measure mercury at the peak levels (the blood levels were checked somewhere between 3 and 27 days, whereas the peak levels would be within the first day of vaccination), as well as the study's inability to measure the ethyl mercury present in the bodies of the subjects, it was difficult to understand how the authors came to the conclusion that Thimerosal, as a part of routine vaccines, poses very little risk to full-term infants (6).

Vaccine Safety Datalink studies

Using the database of the Vaccine Safety Datalink established by the CDC, Thomas Verstraeten and colleagues carried out a two-phase study. In phase I, 124,170 infants were screened to look for associations between neuro-developmental disorders (NDs) and exposure to Thimerosal. In phase II, the disorders found to be associated most commonly with exposure to Thimerosal in phase I were re-evaluated in a much smaller sample of 16,717 children. The relative risks of NDs were calculated per 12.5 µg-increase in the estimated cumulative exposure to mercury from Thimerosal-containing vaccines in the first, third and seventh months of life.

In phase I, a significant positive association was found between exposure to Thimerosal and tics (relative risk [RR]: 1.89; 95% confidence interval [CI]: 1.05–3.38). The risks of language delay were increased in the case of cumulative exposure at 3 months (RR: 1.13; 95% CI: 1.01–1.27) and 7 months (RR: 1.07; 95% CI: 1.01–1.13). In phase II, no significant associations were found. There was no increased risk of autism or attention-deficit disorder (21).

Geier and Geier published details of a meeting of the CDC and other government organisations, as well as members of the vaccine manufacturers, prior to the publication of the data of Verstraeten and colleagues. The authors obtained these details under the Freedom of Information Act. This transcript reveals that the study initially found a statistically significant dose–response relationship between increasing doses of mercury from childhood vaccines containing Thimerosal and various types of NDs. The transcript documents that the data were real and statistically significant for many types of NDs, but that the participants of the meeting felt that the data had to be "handled". However, some participants expressed the concern that the work which had already been done would be obtained by others through the Freedom of Information Act. In this event, even if professional bodies expressed the opinion that there was no association between Thimerosal and NDs, it would already be too late to do anything. In addition, other participants pointed out that the manufacturers of the vaccine were barely in a position to defend lawsuits alleging that there was a relationship between Thimerosal and NDs, since given the available data, no one would say that there was no relationship between the two (22).

Autism rates after elimination of thimerosal

A study of autism in Denmark and Sweden reported that autism rates continued to increase in 2002, even though Thimerosal began to be phased out in 1992 (23). However, the recent 2013 Denmark study (24) has established that phasing out of the Thimerosal-preserved vaccines from the Danish vaccination programme resulted in a significant decline in the percentage of ASD cases in Danish children from 1.5% in 1994–1995 birth cohort to 1.0% in 2002–2004 birth cohort.

An ecological study was undertaken to evaluate the NDs (autism, mental retardation and speech disorders) reported to the Vaccine Adverse Event Reporting System (VAERS) from 1991 through 2004. There was a peak in the proportion of reports received in 2001–2002 and in the proportion of reports, by date of administration of the vaccine, in 1998. There was a significant reduction in the proportion of NDs reported to the VAERS as Thimerosal began to be removed from childhood vaccines in the US from mid-1999 onwards (25).

Dose–response data

Using the Vaccine Safety Datalink (VDS), a dose–response relationship between exposure to organic mercury from

Thimerosal-containing vaccines and NDs was found and these data were published recently. Using the VSD portion available to the researchers, a case-control study found that, on a "per µg of organic Hg" exposure basis, pervasive development disorder (odds ratio (OR) = 1.054), specific developmental delay (OR = 1.035), tic disorder (OR = 1.034) and hyperkinetic syndrome of childhood (OR = 1.05) were significantly more likely to occur among those exposed to organic Hg than among the controls (26).

Thimerosal for developing countries: the economic argument

Thimerosal has been removed from most of the vaccines used in developed countries, but it is used in vaccines meant for developing countries. Vaccines are sold to developing countries in multi-dose vials at a lower cost-per-dose. It is assumed that single-dose vials of vaccines, which can be preservative-free, are not economical for developing countries, both in terms of the unit cost of vaccines and cold chain requirements. These assumptions are simplistic and not necessarily accurate. A study by WHO has shown that the overall manufacturing cost of a single-dose vial is 0.257 USD, which is about 2.5 times greater than the cost of one dose (which is 0.105 USD) from a 10-dose vial (27). The cost-per-dose of the single-dose formulation would be higher by a mere 0.15 USD, according to this analysis. On the face of it, multi-dose vials have the added advantage that they occupy less cold-storage space per dose, but this advantage is offset by vaccine wastage. A UNICEF study in India reported vaccine-wastage of up to 60% with the use of multi-dose vials (28). Single-dose vials provide a price advantage over 10-dose vials if the wastage of the latter is greater than 44% (based on the price of the hepatitis B vaccine and varying wastage rates for 10-dose vials) (27). Further, single-dose vials simplify inventory logistics and vaccine tracking. Also, the health worker's reluctance to open multi-dose vials for only a few children leads to missed opportunities and lower coverage rates (27). Thus, under actual usage conditions, it would appear that multi-dose vials do not afford any real economic benefits for developing countries.

The marketing of single-dose vials (which do not need preservatives) is especially inexpensive in India, given the capabilities of the local industry. For example, the marked maximum retail price of a single-dose 2-ml ampoule, with 50 mg ranitidine, from Ranbaxy is Rs 3 (0.05 USD), inclusive of the cost incurred by the manufacturer and his/her profits, dealers' margin, taxes and transport to remote parts of the country. Despite such prices, 33 manufacturers, including the multinational pharmaceutical giant, GSK, are competing to get a market share of this drug (29). In the Indian context, where single-dose ampoules are inexpensive to manufacture, switching to preservative-free single-dose vials may, in fact, save costs.

The Burton Report conclusions

Well before the dose–response data were published (27), the "Mercury in Medicine Report" of the US House of Representatives had pointed out that the lack of conclusive proof does not mean there is no connection between Thimerosal and vaccine-induced autism. It stated, "The lack of conclusive proof indicates that the US FDA has failed in its duties to assure that adequate safety studies were conducted prior to marketing." It further stated that after determining that Thimerosal was no longer "generally recognized as safe" for use in topical ointments, the agency did not extend its evaluation to other applications of Thimerosal, in particular, its use as a vaccine preservative. The report said parents were concerned that there might be an inherent conflict between the multiple roles of the department, eg promoting immunisation, regulating manufacturers, looking out for adverse events, managing the programme for compensation for vaccine injury, and developing new vaccines.

The Burton Report records that the CDC Advisory Committee on Immunization rejected a statement of preference for Thimerosal-free vaccines because of a number of factors. These included a desire to avoid confusion in the public mind and a concern that immunisation rates might fall. However, another factor that was also considered by the Advisory Committee on Immunization, according to the Burton Report, was the financial health of the vaccine industry. There was a desire to reduce the potential for the financial losses they would face due to the inability to sell their existing inventories of Thimerosal-laced vaccines. The report goes on to state, "If there is any doubt about the neurological effects of ethyl mercury – and there were substantial doubts - the prevailing consideration should have been how best to protect children from potential harm. However, it appears that protecting the industries' profits took precedence over protecting children from mercury damage." This indictment applies equally to international organisations like WHO and the drug regulatory authorities in India.

Conclusion

It is biologically plausible that mercury toxicity in genetically susceptible persons may contribute to the numbers with autism and ASD. However there is no clear proof linking the mercury in Thimerosal to the spurt in cases seen in recent years. The apparent linkage of autism to the MMR vaccine (which is Thimerosal free) seems to suggest that mercury exposure through Thimerosal-containing vaccines is not the only factor that may be responsible for the subsequent "autism" and "ASD" diagnoses in developing children.

Historically, there may have been reasons to use Thimerosal with vaccines, but they do not apply any longer as single-dose, Thimerosal-free vaccines vials are cheaper now. The Burton Report documents that the CDC Advisory Committee on Immunization rejected a statement of preference for Thimerosal-free vaccines because it apprehended that immunisation rates might fall if it were to admit that it had been fallible in the past. It is felt that removing Thimerosal now is akin to an admission of guilt. With an eye to preserving the faith of parents in the vaccines, it is mistakenly considered

important to deny the fact that the prevalence of autism is increasing or that autism could be related to the use of mercury. Often, a person who demands vaccine safety is illogically branded an anti-vaccine person. This stance may be counterproductive. Long-term harm may be done to all public health initiatives if international organisations do not act decisively to remove the potential threat posed by the use of Thimerosal in vaccines. As with Thompson's revelations about the paper on MMR (2), if the public comes to perceive institutions such as the CDC as untrustworthy, it is likely to do more harm to the vaccine initiative than unscientific rabble-rousers who protest against vaccination.

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