Thiomersal and vaccines

Thiomersal (also known as thimerosal and mercurothiolate) is a mercury-based substance that is added to some vaccines to prevent them from being contaminated by bacteria and fungi. Recently, concerns have been raised over the safety of thiomersal in vaccines.

This factsheet addresses these concerns by looking at the scientific evidence for the safety of thiomersal in vaccines. It also answers parents' questions around the immunisation of their children with thiomersal-containing vaccines.

Introduction

This factsheet covers the following topics on thiomersal:

- what thiomersal is and why it is added to vaccines,
- which vaccines contain thiomersal,
- the safety of thiomersal, and
- the background to the recent concerns over the use of thiomersal-containing vaccines in the UK childhood immunisation programme.

What is thiomersal and why is it added to vaccines?

Thiomersal is a mercury-based substance that has been used widely in vaccines for over 60 years. Thiomersal is added to vaccines as a preservative to prevent bacterial and fungal contamination, particularly in multi-dose vials where repeated doses are withdrawn once the vial is opened. The use of this preservative has prevented many deaths or illnesses from contamination of vaccines. Thiomersal is also used as an inactivating agent in the very early stages of production of some killed vaccines. Only minuscule amounts of thiomersal used for this purpose remain after the manufacture is completed.

Once in the body, thiomersal is broken down to form ethylmercury and thiosalicylate. Ethylmercury, which binds to blood cells or other tissues, is rapidly converted to inorganic mercury. Ethylmercury is primarily excreted in the faeces and bile (mainly as inorganic mercury).

KEY POINT

- thiomersal is a mercury-containing material present in some vaccines to prevent contamination.

Which vaccines contain thiomersal?

The vaccines currently used in the routine childhood programme that contain thiomersal are shown in Table 1.*

Table 1 Vaccines used in the routine childhood immunisation programme that contain thiomersal.

Vaccine currently in use	Vaccine name and manufacturer(s)	Use
Hib-DTwP** (whole-cell)	• Act-Hib DTP	• Routine primary immunisation
DT	• Adsorbed Diphtheria and Tetanus vaccine (Chiron Behring)	• Routine primary immunisation and pre-school booster when pertussis component contraindicated
Td	• Diftavax vaccine	• School leaving booster
Not currently used but have been available in the last year		
DTwP (whole-cell)	• DTP vaccine Behring	Last issued Dec 2002
Td	• Low dose Diphtheria and Tetanus vaccine (Generic)	Last issued May 2003
DT	• Adsorbed Diphtheria and Tetanus vaccine (Aventis Pasteur MSD)	Last issued May 2003

* As part of the routine programme children have either Hib-DTwP, DTaP and Hib separately or DT and Hib separately.
** The Hib component of this vaccine does not contain thiomersal.

Other vaccines (not routinely used in the childhood programme) which may contain thiomersal include:

- some single hepatitis B vaccines
- some hepatitis A and B combination products and
- some influenza vaccines.

KEY POINT

- some of the routinely recommended childhood vaccines do contain thiomersal.

Which vaccines do not contain thiomersal?

Thiomersal is not added to MMR, Hib, polio, Men C or BCG vaccines used in the UK and is not used in the production of these vaccines.

Details of the brand names of the vaccines currently being used that do not contain thiomersal are summarised in Table 2 below.

Table 2. Vaccines used in the childhood immunisation programme that DO NOT contain thiomersal.

Vaccine currently in use	Vaccine name and manufacturer(s)	Use
Polio vaccine	• Poliomyelitis Vaccine, Live (Oral) • IMOVAX POLIO	• Routine primary immunisation, pre-school, booster and school leaving booster
MMR	• MMR-II • Priorix	• Routine primary immunisation
DTaP	• Infanrix	• Pre-school booster • Routine primary immunisation when DTwP contraindicated
Hib	• Hiberix	• Routine primary immunisation or Hib catch-up campaign
BCG	• BCG vaccine SSI (Statens Serum Institute) (available since December 2002)	• Routine immunisation (10-14 yrs) • At-risk neonates
Men C	• Menjugate • Meningitec • NeisVac-C	• Routine primary immunisation
Tuberculin PPD	• Tuberculin PPD 10 units/1ml (Evans Vaccines) • Tuberculin PPD 100 units/1ml (Evans Vaccines) • Tuberculin PPD 1000 units/1ml (Evans Vaccines) • Tuberculin PPD 100,000 units/1ml (Evans Vaccines)	• Mantoux test • Mantoux test • Mantoux test • Heaf test
Not currently used but have been available in the last year		
DTaP-Hib	• Infanrix-Hib	Last issued August 2002
Hib	• Act-Hib	Last issued April 2002
BCG	• Intradermal BCG (Evans Vaccines) • Percutaneous BCG (Evans Vaccines)	Withdrawn August 2002

KEY POINT

- many of the routine vaccines, including MMR, do not contain thiomersal.

How much thiomersal is added to vaccines?

A 0.5ml dose of vaccine that has thiomersal contains 50 micrograms (µg) of thiomersal, with the mercury content being approximately 25 micrograms (µg). Vaccines that involve the use of thiomersal in the early stages of production may contain only trace amounts of thiomersal because every molecule cannot be removed.

KEY POINT

- there are 25µg of mercury in each dose of thiomersal-containing vaccine.

What are safe levels of mercury exposure?

This depends on the form that the mercury is in (elemental mercury, inorganic mercury, or an organo-mercury compound). In the case of thiomersal, we are dealing with an organo-mercury compound. The key concern about organo-mercury compounds relates to neurotoxicity – the possible damage to the nervous system. There is evidence that the unborn child and very young infants are more sensitive than adults. But it is important to realise that the available guidelines on safe levels of exposure to such compounds are based on the organo-mercury compound methylmercury and *not* ethylmercury. Methylmercury is the form that may be in fish such as tuna and is ingested from the environment. The mercury in thiomersal is ethylmercury, a different chemical.

The World Health Organisation set a tolerable exposure level to methylmercury that is equivalent to 0.47 micrograms/kg body weight/day, but noted that the level might be lower for pregnant women. The United States Environmental Protection Agency (EPA) has set a reference dose of 0.1 micrograms/kg body weight/day based on subtle neurological effects seen in children exposed to methylmercury in the womb (Center for Biologics Evaluation and Research (CBER), (CBER 2003).[1] In 2002, the UK Committee on Toxicity (COT) concluded that the WHO guideline of 0.47 micrograms/kg body weight/day is sufficiently protective for the general population but that the EPA reference dose of 0.1 micrograms/kg body weight/day is more appropriate for women who are pregnant, or who may become pregnant within the following year, or for breast-feeding mothers. This is because of the potential risk to the developing foetus or neonate (COT, 2002).[2] The levels are deliberately set much lower than the levels at which harm might occur – the EPA level is ten times below the lowest calculated level for harm, so has a big margin of safety built in.

However, thiomersal breaks down in the body to ethylmercury not methylmercury and there are important differences between these forms of mercury. There is good evidence from studies that both thiomersal and ethylmercury are less toxic than methylmercury, and are eliminated out of the body much faster than methylmercury, which can accumulate. This means that the safety levels for methylmercury are likely to give even more protection if it is ethylmercury that is being considered (Magos, 2001).[3]

A recent paper has shown that mercury is cleared more quickly from infants than from adults. This paper provides reassurance that infants do not readily accumulate mercury (Magos, 2003).[4]

KEY POINTS

- vaccines with thiomersal have ethylmercury in them. The mercury that may be toxic in the diet or the environment is methylmercury. Ethyl- and methylmercury are handled quite differently by the body. Ethylmercury is excreted quickly and does not accumulate.
- there are very large safety factors built in to the estimated levels recommended, and the mercury in UK vaccines does not exceed these safety levels.

Are the levels of thiomersal in vaccines used in the UK safe?

Two recent independent population-based studies involving over 100,000 children have examined this issue (Committee on Safety of Medicines (CSM), 2003).[5] These two studies specifically set out to assess the safety of thiomersal in vaccines used according to the UK childhood immunisation schedule. Both studies produced very reassuring results. Neither found any link between thiomersal exposure from the UK childhood immunisation programme and developmental and behavioural disorders, including autism. These new studies reinforce CSM advice from 2001 that there is no evidence of neurological adverse effects caused by thiomersal in vaccines according to the routine UK immunisation schedule. There is also animal data that shows how different ethyl- and methylmercury are, and confirms that ethylmercury is cleared out of the blood and tissues much more effectively than methylmercury. The balance of benefits and risks of thiomersal-containing vaccines, therefore, remains overwhelmingly positive.

A recent study in the US has looked specifically at whether the low levels of thiomersal present in routine childhood vaccines cause significant changes in the level of mercury in infants' blood and also examined how ethylmercury is broken down (Pichichero, 2002).[6] This study found that the levels of thiomersal did not raise blood concentrations of mercury above the safe values (as defined as those thought to be safe in cord blood – 29nmol) in infants. Furthermore, it showed that infants rapidly eliminated ethylmercury from their body following immunisation with thiomersal-containing vaccines.

A recent review of the available information by the UK Committee on Safety of Medicines concluded that there was no evidence that thiomersal-containing vaccines caused neurological problems (CSM, 2003).[5] Since then, a study in Denmark looking at nearly 500,000 children, found that the risk of autism and other autistic-spectrum disorders did not differ significantly between children vaccinated with thiomersal-containing vaccine and those vaccinated with thiomersal-free vaccine (Hviid *et al*, 2003).[7]

In the recent past in the United States, the addition of thiomersal-containing vaccines (Hib and hepatitis B) to the childhood immunisation programme increased the exposure of children (aged 6 months) to mercury and this has been suggested as an explanation for the reported rise in autism there. The United States Center for Disease Control has conducted a study and found no association between autism and thiomersal (CDC).[8]

KEY POINTS

- studies on babies in the UK found no link between the thiomersal they got in their vaccines and their subsequent development, including autism. US and Danish studies have found the same
- studies on clearing mercury from the body in children and animals have found that ethylmercury is cleared quickly and does not build up.

What types of reactions may be seen following thiomersal-containing vaccines?

The only evidence of harm due to thiomersal in vaccines is a small risk of hypersensitivity reactions (that typically include skin rashes or local swelling at the site of injection).
There is no evidence of long-term adverse effects due to the exposure levels of thiomersal in vaccines.

KEY POINT

- the only well-recognised reaction after thiomersal is an allergic skin reaction.

Additional questions

What is mercury and where does it come from?

Mercury is a heavy metal naturally found in the environment in rocks, soil and plants and is found as a contaminant in air, water and food. It is present either in inorganic form (e.g. mercury chloride) or organic form (e.g. methylmercury or ethylmercury). For most people, the main source of mercury exposure is the diet, where the predominant form of mercury is the organic form methylmercury, found mainly in fish such as tuna.

All forms of mercury entering the aquatic environment, as a result of man's activities or from geological sources, are converted into methylmercury by microorganisms and subsequently concentrated in fish and other aquatic species. Fish may concentrate the methylmercury either directly from the water or through consuming other marine creatures. Methylmercury accumulates in fish and so large older fish, particularly predatory species, will have accumulated considerably more mercury than small younger fish.

Exposure to mercury in humans can be from a range of sources but is most likely through diet. Individuals who eat large quantities of fish or seafood may be exposed to high levels of mercury (see below) (Mahaffey *et al.*, 1997).[9]

Should pregnant women avoid exposure to mercury?

The UK Food Standards Agency advises that women who are pregnant, intending to become pregnant or breastfeeding should avoid eating shark, marlin and swordfish and may need to limit their consumption of tuna (FSA press release, 2003).[10] This is because of their high mercury content and the possibility that mothers may expose their unborn child or young infant to high levels of mercury. This may be through maternal transfer or breastfeeding.

It is known that organic mercury crosses the placenta easily and that mercury present in the mother's blood is passed through the umbilical cord to the foetus. Babies, therefore, can be exposed to mercury (in the form of methylmercury) prior to birth. The level of exposure will depend on the mother's diet. Babies of women who eat large quantities of certain types of fish will be exposed to higher levels of methylmercury than babies of women who eat small quantities of fish or no fish at all.

Babies may also be exposed to mercury in breast-milk (in the form of methylmercury) (Sundberg and Oskarsson, 1992[11]; Yoshida *et al.*, 1992[12]). The concentration of mercury in breast-milk is about 5 per cent of the blood mercury concentration of the mother (WHO, 1976).[13]

A number of outbreaks of mercury poisoning have occurred in the past (Harada, 1995[14]; Bakir *et al.*,1973[15]). During these outbreaks it was found that foetuses were more sensitive to the effects of methylmercury than adults. Maternal exposure to high levels of methylmercury resulted in their infants exhibiting severe neurological injury including a condition similar to cerebral palsy. In most cases, the mothers of these children showed little or no symptoms. Sensory and motor dysfunction and developmental delay were observed among some children who were exposed in utero to lower levels of methylmercury.

More recent studies have focussed on effects in children in populations that eat a lot of fish. Effects have been reported in the studies of the children in the Faroe Islands studies, whereas studies in the Seychelles Islands have not shown similar effects at similar levels of exposure to methylmercury. The safety guidelines used by the Food Standards Agency in advising women on fish consumption are based on the precautionary opinion of the UK Committee on Toxicity, which allows a ten-fold margin of safety compared with the exposures in the Faroe Islands.

KEY POINTS

- methylmercury is present in food, especially some fish, and has been linked in high doses to harm in the development of children
- ethylmercury that is in thiomersal is not the same, and has not been linked to harm in the levels in vaccines.

Do the effects of ethylmercury differ from those of methylmercury?

Studies comparing the effects of ethyl-and methylmercury have shown that these compounds have different toxicological properties (Magos *et al.*, 1985[16]; Magos, 2001[3]; Suzuki *et al.*,1963[17]).

Animal studies looking at the distribution of ethyl- and methylmercury in the body have shown that the level of mercury in the brain following injection of the same quantities of ethylmercury is less than for methylmercury (Suzuki *et al.*, 1963[17]; Magos *et al.*, 1985[16]). There is good evidence that ethylmercury does not cross the blood-brain barrier as easily as methylmercury. This is due to the larger size of the compound and because methylmercury is transported across the blood-brain barrier by an active system (Kerper *et al.*, 1992[18]). Ethylmercury is also more rapidly broken down in the body than methylmercury.

KEY POINTS

- ethyl- and methylmercury are not the same. This really matters because the data on harm from methylmercury cannot be applied to the ethylmercury in vaccines
- ethylmercury is cleared quickly even from tiny babies' bodies, and does not build up.

I have read that children in the UK may be getting exposed to toxic levels of thiomersal in vaccines, is this true?

No, this is not true. The levels of thiomersal in vaccines are low. Independent expert advice is that there in no evidence of long-term adverse effects from thiomersal in vaccines in the UK childhood immunisation programme.

In the UK, a child will usually receive a total of 75µg of ethylmercury (3 individual 25µg doses, one month apart) through the routine childhood immunisation programme. Two recent studies looked at whether the level of thiomersal in the UK programme was safe. The results of these studies were very reassuring with neither study finding a link between the levels of thiomersal exposure in the UK childhood programme and developmental and behavioural disorders, including autism.

KEY POINT

- the levels of mercury in vaccines are extremely low, and extensive UK studies have not found evidence of harm, including autism.

How can I know if my child may have been exposed to thiomersal in vaccines? Is my child at risk?

Thiomersal has been used in vaccines for over 60 years. It is likely that you, your children and all other children will have received vaccines containing thiomersal. The evidence does not show that this has put you or your children's health at risk: in fact, thiomersal has played a vital safety role in ensuring that vaccines do not become contaminated.

Does thiomersal cause autism?

The CSM has reviewed the safety, including postulated neurological adverse effects, of thiomersal-containing vaccines on a number of occasions.

CSM has recently reviewed two UK-based epidemiological studies that have provided reassuring results regarding the safety of thiomersal in vaccines, in relation to neurodevelopmental disorders. One of these studies, which used the UK's General Practice Research Database (GPRD), specifically investigated whether there is any link between early thiomersal exposure through immunisation and autism. This study concluded that administration of thiomersal through childhood immunisation in the UK was not associated with an increased risk of developing a neurological developmental disability, including autism.

The CSM has carefully considered the results of a recent study, by Geier and Geier (Geier & Geier, 2003[19]), that suggests an association between thiomersal exposure through the United States childhood immunisation schedule and the development of autism and heart disease. CSM advised that the methodology in this publication had been inadequately described and that the authors' conclusions regarding the association between thiomersal in vaccines and autism, speech disorders and heart disease are not justified. The CSM has advised that, with the exception of allergic reactions such as redness and swelling at the injection site, there is no evidence of harm from thiomersal contained in vaccines. The CSM advised that the benefits of immunisation with thiomersal-containing vaccines outweigh any potential risks of vaccination.

This study has also been reviewed by the American Academy of Pediatrics (AAP Statement, 2003[20]). They felt that the methodology used was inappropriate and the paper contained numerous conceptual and scientific flaws, omissions of fact, inaccuracies and misstatements.

KEY POINTS

- UK and US studies have found no links between thiomersal, mercury in vaccines and autism
- one US study said it had found a link. The study had serious flaws sufficient that independent experts say it should be ignored.

I have read that the US has banned thiomersal in vaccines – why is the UK not doing the same?

Use of thiomersal in vaccines has not been banned in USA and Europe and there is strong evidence to show that thiomersal in vaccines does not cause neurological adverse effects. As part of a global goal to reduce exposure to mercury from avoidable sources in general, European and American regulators recommended in 1999 that vaccine manufacturers phase out use of thiomersal wherever possible as a precautionary measure. The UK's Committee on Safety of Medicines (CSM) endorsed this recommendation in 1999 and the Joint Committee on Vaccination and Immunisation (JCVI) also supports this position.

Manufacturers are actively developing research programmes to eliminate, substitute or reduce thiomersal in vaccines, following the European recommendations. This may take time because manufacturers are required to ensure that the replacement or elimination of thiomersal does not affect the safety and efficacy of the final vaccine. To-date, a number of UK licensed vaccines have had levels of thiomersal reduced or removed completely from the manufacture of the component antigens or from the final vaccine. These developments are regularly reviewed and on 1 April 2003 a letter was sent from the Medicines and Healthcare products Regulatory Agency (MHRA) to UK vaccine Marketing Authorisation Holders asking for an update on progress in reducing or removing thiomersal from vaccines.

KEY POINT

- the European Medicines Evaluation Agency has looked at thiomersal in vaccines and has found no evidence of harm. However, on the basis of good practice of reducing any exposure to mercury, they have advised vaccine manufacturers to try to find ways to reduce or remove thiomersal wherever this is possible.

What is the view of the World Health Organisation (WHO)?

The World Health Organisation's Global Advisory Committee on Vaccine Safety (GACVS) has also kept this issue under review and concluded in November 2002 that there is no evidence of toxicity in infants, children or adults exposed to thiomersal in vaccines.

KEY POINT

- WHO has looked very carefully at all of the data on mercury and vaccines and concluded that there is no evidence of harm from thiomersal.

When will there no longer be any thiomersal in vaccines?

Manufacturers are actively developing research programmes to eliminate, substitute or reduce thiomersal in vaccines. As manufacturers are required to ensure that the replacement or elimination of thiomersal does not affect the safety and efficacy of the final vaccine, these new vaccines must undergo rigorous testing before use. This process takes some time.

KEY POINT

- manufacturers are committed to progressively work towards thiomersal-free or thiomersal-reduced vaccines.

Are there any alternatives to thiomersal?

There are other preservatives available such as phenoxyethanol. Manufacturers are developing alternatives but it will take time to introduce them.

Useful web-site links

Center for Biologics Evaluation and Research
www.fda.gov/cber/index.html

Centers for Disease Control and Prevention
www.cdc.gov

Committee on Safety of Medicines
www.mca.gov.uk/aboutagency/regframework/csm/csmhome.htm

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33782 1p 22k Oct03 (XXX)

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