

# ATAGI advice regarding the use of influenza vaccines containing thiomersal

## Summary of Advice

The following advice applies to both seasonal and (H1N1) monovalent influenza vaccines:

- Influenza vaccines are safe and reduce the likelihood of illness from influenza;
- The pandemic (H1N1) influenza vaccine is recommended for use in pregnant women to confer protection to themselves and also possibly to their infants (up to 6 months of age);
- ATAGI considers that influenza vaccines containing thiomersal are safe in infants, children, adolescents and adults (including pregnant women);
- This is based on consistent safety data from several laboratory and clinical studies and the conclusions of independent systematic reviews that have examined data on the use of thiomersal-containing vaccines, including influenza vaccines, in all these groups; and,
- ATAGI notes that use of thiomersal-containing vaccines (including influenza vaccines) is endorsed by the World Health Organization and by several countries comparable to Australia.

## Background

Thiomersal, (also known as thimerosal, mercuriothiolate or sodium 2-ethylmercuriothio-benzoate), is a mercury-containing organic compound with 49.6% ethyl mercury by weight. Thiomersal is a preservative and retards bacterial and fungal growth. It has not been shown to inhibit the growth of viruses. Thiomersal has been in use since the 1930s in medications including vaccines. In vaccines, it has been included as an excipient in both single and multi-dose vials to prevent contamination, and it has also been used during the manufacturing process.<sup>1, 2</sup> Vaccines presented in single use presentations (either single dose vials or pre-filled syringes) no longer require the addition of thiomersal as a preservative. However, vaccine presented in single dose pre-filled syringes and/or vials requires more time and expense to produce, and may be less convenient to use in a large scale immunisation program such as may be required during a disease outbreak.<sup>1, 2</sup> To expedite the rapid rollout of a targeted vaccine in response to the current outbreak of pandemic (H1N1) influenza, the Australian Government has purchased pandemic (H1N1) influenza presented in multi-dose vials.

## Mercury

The two organic forms of mercury, methyl mercury and ethyl mercury are closely related but have important differences. Thiomersal contains only ethyl mercury (49.6% w/w). Once in the body, thiomersal is metabolised to ethyl mercury and thiosalicylate and actively excreted into the intestinal tract. There, ethyl mercury is rapidly converted to inorganic mercury (that is less toxic to the brain than ethyl or methyl mercury) and is excreted in the faeces with minimal accumulation in body tissues.<sup>1, 3-5</sup> In addition, the time taken for elimination (known as the "half-life") of ethyl mercury (6 days; 95% CI: 3-10 days) is substantially shorter than the half-life of methyl mercury (59 days; 95% CI 32-86 days). Methyl mercury is more potent and accumulates in the body tissues to a much greater extent than ethyl mercury.<sup>1, 3-5</sup>

Mercury can have harmful effects on the central nervous system, skin, kidneys and other organs, such as the liver or pancreas. Most reports of mercury toxicity relate to methyl mercury, not the ethyl form found in thiomersal.<sup>2-6</sup> Mercury accumulation, and therefore toxicity, is a function of the amount of mercury consumed, body weight and time. Because of their low body weight, infants and young children are at greater risk from exposure to a fixed quantity of mercury than adults. Studies describing the harmful effects of mercury, particularly those undertaken in pregnant women and their offspring, have generally pertained to the ingestion of foods containing high levels of methyl mercury, such as fish. Recommendations to limit the oral ingestion of foods potentially high in methyl mercury specify an "upper dietary intake" or the "provisional tolerable weekly intake" (PTWI) for the general population of between 0.7µg/kg body weight/week and 3.3µg/kg of body weight/week.<sup>3, 4, 7</sup> The PTWI is the amount of a substance that can be consumed weekly over an entire lifetime without

appreciable risk to health and is also an end-point used for ingestion of food contaminants (such as heavy metals like methyl mercury with cumulative properties). As Table 1 demonstrates there are different reference levels adopted in various countries.<sup>8</sup> For example, the USA EPA level is stated to be 10 times below the lowest level thought to cause harm, so there is a large “built-in” safety margin.<sup>4</sup> All these guidelines refer to methyl mercury, not ethyl mercury, which, given the later substance’s properties, provides a further safety margin. In 2003, the WHO and the Food and Agricultural Organization of the United Nations established a new PTWI for pregnant women, (where the margin is set to protect the fetus) of 1.6µg methyl mercury/kg body weight/week.<sup>5</sup> All regulatory recommendations, including those issued by Food Standards Australia New Zealand, apply to a sustained level (or steady state) of methyl mercury associated with ongoing dietary intake, with the half-life of methyl mercury taken into consideration.<sup>5,7-11</sup> This level was derived from an analysis of maternal/neonatal methyl mercury levels from extensive studies in both the Faroe and the Seychelles Islands where oral intake of methyl mercury was high.<sup>12-14</sup>

Table 1: Various reference levels adopted for use in various countries (adapted from reference<sup>8</sup>)

Country/Organisation	Reference Level (µg methyl mercury/kg of body weight/week	Year level adopted
Australia <sup>7</sup>	1.6	2004
Canada <sup>9</sup>	1.4 <sup>†</sup>	1997
Japan <sup>10</sup>	2.0	2005
Netherlands <sup>11</sup>	0.7	2000
United States <sup>4</sup>	0.7 <sup>‡</sup>	2001
JECFA <sup>5</sup>	1.6 <sup>†</sup>	2003

\* Level for Australian women of childbearing age (16-44). For the remainder of population the level is 3.3 µg methyl mercury/kg body weight/week

† For pregnant women, women of childbearing age and young children. The reference level for the general population of 3.3 µg methyl mercury/kg body weight/week was established in 1972

‡ Originally expressed in terms of µg methyl mercury/kg body weight/day

### Thiomersal use in vaccines

The WHO Global Advisory Committee on Vaccine Safety (GACSV) reviews the safety of thimerosal-containing vaccines on a regular basis and has concluded that there is currently no evidence of mercury toxicity in infants, children, adolescents or adults (including pregnant women) exposed to thiomersal in vaccines.<sup>15</sup>

Thiomersal-containing vaccines were in general use in Australia (and many other countries) until 2000 when a precautionary ATAGI recommendation was made to only provide vaccines to Australian children containing no or only trace amounts of thiomersal. This recommendation was made for four reasons. First at that time there was increasing public concern about the presence of thiomersal in vaccines which whilst unfounded, had the potential to undermine public confidence in the childhood vaccination program. Second, thiomersal was no longer needed in the single dose, ready to administer vaccines which were then in general use in Australia. Third, to further limit the exposure to mercury in infants with low body weight (eg premature infants) in whom there was a theoretical risk that mercury levels after repeated doses of thiomersal-containing vaccines could be transiently high.<sup>9, 16-18</sup> Fourth, to reduce the total intake of mercury, which inevitably occurs to some extent from other sources, such as the diet and other environmental exposures.<sup>10, 11, 15</sup> However, it is necessary that thiomersal remains present as a preservative for the prevention of microbial contamination when inactivated vaccines are packaged in MDVs.<sup>16</sup> Vaccines presented in MDVs are currently used in many other countries in the world, including annual seasonal influenza vaccine and several other vaccines in the USA, some annual seasonal influenza vaccines, hepatitis B vaccine and quadrivalent meningococcal polysaccharide vaccines in Canada; diphtheria, tetanus and pertussis (DTP), hepatitis B, diphtheria and tetanus toxoids and *Haemophilus influenzae* type b in many countries via the WHO Expanded Programme on Immunization.<sup>2, 20</sup>

In adults and adolescents levels of mercury resulting from administration of thiomersal-containing vaccines are so low that removal of thiomersal is not deemed necessary.

In 2001, in response to increasing public concerns about childhood exposure to thiomersal in vaccines, the Institute of Medicine, an independent expert body in the United States, examined the evidence available at that time.<sup>21</sup> The IOM at that time concluded that "the evidence is inadequate to accept or reject a causal relationship between thiomersal exposures from childhood vaccines and neuro-developmental disorders."<sup>21</sup> The IOM undertook a second extensive review of all studies of both thiomersal-containing and non-thiomersal containing vaccines in 2004, and concluded that "the evidence favors rejection of a causal relationship between thiomersal-containing vaccines and autism."<sup>22</sup> The IOM reviewers noted that the epidemiologic studies suggesting a link came from only one pair of authors and "have significant design flaws that invalidate their conclusions."<sup>21</sup> The Global Advisory Committee on Vaccine Safety (GACVS) of the WHO has concluded that "there is currently no evidence of mercury toxicity in infants, children or adults exposed to thiomersal-containing vaccines" and that "there is no reason to change current immunisation practices with thiomersal-containing vaccines on the grounds of safety."<sup>18</sup>

### **Influenza vaccines, Thiomersal and Pregnancy or Breastfeeding**

In Australia, trivalent inactivated influenza vaccine (TIV) is the only vaccine currently recommended for administration during pregnancy.<sup>23</sup> The use of influenza vaccine in pregnancy has also been recommended in the USA and Canada for many years.<sup>24-27</sup> In the United States, the Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynaecologists both recommend that every pregnant woman, regardless of trimester, should receive TIV, and when available pandemic H1N1 influenza vaccine.<sup>26-28</sup> In Canada, the National Advisory Committee on Immunization (NACI) have made similar recommendations.<sup>25</sup> The Australian and other international influenza vaccine recommendations are supported by data regarding the immunogenicity, efficacy and safety of influenza vaccines (most of which contained thiomersal) obtained from over 7000 pregnant women.<sup>29-37</sup> Recent data from a study conducted in Bangladesh suggested that there may be additional benefits to their offspring derived by immunising pregnant women in the third trimester.<sup>37</sup> Zaman et al. found there was a 63% reduction in laboratory confirmed influenza during the first 6 months of life among infants whose mothers had received influenza vaccine.<sup>37</sup> This potential benefit is particularly relevant because the TIV is currently not registered or recommended for use in infants < 6 months of age.

In addition, breastfeeding does not affect the immune response adversely and is not a contraindication for vaccination. Unless contraindicated because of other medical conditions, women who are breastfeeding can receive seasonal TIV or the H1N1 influenza vaccine.<sup>19, 23-26</sup> There is no evidence of risk to the breastfeeding baby if the mother is vaccinated with either seasonal TIV or the H1N1 influenza vaccines. Breastfeeding does not adversely affect immunisation and is not a contraindication for the administration of any vaccine to the baby.

Adverse events following immunisation (AEFI) with seasonal influenza vaccine have not differed among pregnant and non-pregnant vaccinees. The CDC USA Immunization Safety Office reported in 2006 that the VAERS database (a passive surveillance system in the USA that collects spontaneously reported AEFI) indicated that there were no unexpected adverse events following TIV in approximately 2 million pregnant women vaccinated between 2000 and 2003.<sup>38</sup> The vaccines reported on by VAERS would, in the US context, have contained thiomersal.

Pregnant or breastfeeding women require only one dose of the pandemic influenza vaccine, which, if drawn from a multi-dose vial, will contain 50µg of thiomersal (approximately 25µg of ethyl mercury).<sup>39,40</sup> For a pregnant woman weighing 60 kg, this would translate to 0.42µg per kg of ethyl mercury, well below the most conservative upper limit for weekly consumption of methyl mercury of 0.7µg per kg (see Table 1). As discussed above, ethyl mercury is rapidly excreted and weekly levels will thus fall well short of the provisional tolerable weekly intake level recommended for consumption of the more harmful methyl mercury.<sup>20</sup> On this basis, any exposure of the unborn fetus or breastfed infant to mercury would also be miniscule and would be expected to be well below that encountered from maternal exposure to dietary and

## REFERENCES

1. ATSDR (Agency for Toxic Substances and Disease Registry) (1999). Toxicological profile for mercury (Update)(PB/99/142416). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. <http://www.atsdr.cdc.gov/tfacts46.html> (accessed September 2009).
2. WHO Thiomersal and vaccines: questions and answers [http://www.who.int/vaccine\\_safety/topics/thiomersal/questions/en/index.html](http://www.who.int/vaccine_safety/topics/thiomersal/questions/en/index.html) (accessed September 2009).
3. National Research Council (NRC) (2000). *Toxicological Effects of Methylmercury*. National Academy Press, Washington, D.C.
4. USA Environmental Protection Agency Integrated Risk Information Service Methylmercury (MeHg) (CASRN 22967-92-6) <http://www.epa.gov/iris/subst/0073.htm> (accessed September 2009).
5. JECFA (2006) Methylmercury. Summary and conclusions of the 67th Joint FAO/WHO Expert Committee on Food Additives. Geneva, World Health Organization, International Programme on Chemical Safety. WHO Technical Report Series 940 [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_940\\_eng.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_940_eng.pdf) (accessed September 2009).
6. The European Agency for the Evaluation of Medicinal Products: Public statement on thiomersal in vaccines for human use. issued March 2004 <http://www.emea.europa.eu/pdfs/human/press/pus/119404en.pdf> (accessed September 2009).
7. Food Standard Australia new Zealand Mercury in Fish March 2004 <http://www.foodstandards.gov.au/foodmatters/mercuryinfish.cfm> (accessed September 2009).
8. UNEP DTIE Chemicals Branch and WHO Department of Food Safety, Zoonoses and Foodborne Diseases. Guidance for identifying populations at risk from mercury exposure. August 2008. Issued by Geneva, Switzerland.
9. National Advisory Committee on Immunization (NACI). Thimerosal: updated statement. *CCDR* 2007;33(ACS-6): 1–13.
10. The Cabinet Office, Japan .Japan Food Sanitation Law (Japan Food Safety Commission). [http://www.fsc.go.jp/english/topics/methylmercury\\_risk\\_assessment.pdf](http://www.fsc.go.jp/english/topics/methylmercury_risk_assessment.pdf) (accessed September 2009).
11. Smit CE, Wezel AP van, Jager T, Traas TP Secondary poisoning of cadmium, copper and mercury: implications for the Maximum Permissible Concentrations and Negligible Concentrations in water, sediment and soil. [Doorvergiftiging van cadmium, koper en kwik: gevolgen voor de Maximum Toelaatbaar Risiconiveau's en Verwaarloosbaar Risiconiveau's in water, sediment en bodem] June 2000. Netherlands. National Institute for Public Health and the Environment.
12. Grandjean, P., Weihe, P., White, R.F., Debes, F., Araki, S., Yokoyama, K., Murata, K., Sorensen, N., Dahl, R. and Jorgensen, P.J. (1997). Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol.* 1997;19: 417-28.
13. Grandjean, P., Murata, K., Budtz-Jorgensen, E. and Weihe, P. (2004). Cardiac autonomic activity in methylmercury toxicity: 14-year follow-up of a Faroese birth

cohort. *J. Pediatr.* 2004;144: 169-76.

14. Davidson, P.W., Myers, G.J., Cox, C., Axtell, C., Shamlaye, C., Sloane-Reeves, J., Cernichiari, E., Needham, L., Choi, A., Wang, Y., Berlin, M. and Clarkson, T.W. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopmental outcomes at 66 months of age in the Seychelles Child Development Study. *JAMA* 1998;280: 701-7.
15. WHO Statement on Thiomersal. WHO Global Advisory Committee on Vaccine Safety. Geneva, World Health Organization. 2006  
[http://www.who.int/vaccine\\_safety/topics/thiomersal](http://www.who.int/vaccine_safety/topics/thiomersal) (accessed September 2009).
16. Clements CJ, Ball LK, Ball R, Pratt D. Thiomersal in vaccines. *Lancet* 2000;355: 1279-80.
17. Pichichero ME, Cernichiari E, Lopreiato J, Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. *Lancet* 2002;360: 1737-41.
18. Meeting of Global Advisory Committee on Vaccine Safety, 18–19 June 2008 *WER* 2008;32: 83: 292
19. CDC Vaccine safety. Frequently Asked Questions about Mercury and Thimerosal. 2007. [http://www.cdc.gov/vaccinesafety/updates/thimerosal\\_fags\\_mercury.htm](http://www.cdc.gov/vaccinesafety/updates/thimerosal_fags_mercury.htm) (accessed September 2009).
20. USA Food and Drug Administration (FDA) vaccine, Blood & Biologics. Thimerosal in vaccines. 2007.  
<http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM096228> (accessed September 2009).
21. Institute of Medicine. Immunization safety review: thimerosal-containing vaccines and neurodevelopmental disorders. National Academy Press; 2001.
22. Institute of Medicine. Immunization safety review: vaccines and autism. National Academy Press; 2004.
23. National Health and Medical Research Council. *The Australian Immunisation Handbook*. 9th ed. Canberra: Australian Government Department of Health and Ageing; 2008. Available at:  
<http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-home> (accessed September 2009).
24. CDC Season flu. Thimerosal in Seasonal Influenza Vaccine. Questions & Answers <http://www.cdc.gov/flu/about/qa/thimerosal.htm?ref=klasshop.com> (accessed September 2009).
25. National Advisory Committee on Immunization (NACI) Statement on Influenza Vaccination for the 2007-2008 season. *CCDR* 2008;34,ACS3; 1-46 <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-07.pdf> (accessed September 2009).
26. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008 Prevention and Control of Influenza. *MMWR* August 8, 2008 / 57(RR07); 1-60
27. ACOG Committee on Obstetric Practice. Influenza vaccination and treatment during pregnancy. ACOG Committee Opinion No. 305. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2004;104: 1125-6.
28. Rasmussen S Pandemic Influenza Vaccination and Pregnancy *Amer Journ Pub Health* 2009;99:s2-1-7

29. Heinonen OP, Shapiro S, Monson RR, Hartz SC, Rosenberg L, Slone D. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol* 1973;2: 229-35.
30. Sumaya CV, Gibbs RS. Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: reactogenicity and immunogenicity in mother and infant. *J Infect Dis* 1979;140: 141-6.
31. Murray DL, Imagawa DT, Okada DM, St Geme JW Jr. Antibody response to monovalent A/New Jersey/8/76 influenza vaccine in pregnant women. *J Clin Microbiol* 1979;10: 184-7.
32. Deinard AS, Ogburn P Jr. A/NJ/8/76 influenza vaccination program: effects on maternal health and pregnancy outcome. *Am J Obstet Gynecol* 1981; 140:240-5.
33. Englund JA, Mbawuike IN, Hammill H, Holleman MC, Baxter BD, Glezen WP. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. *J Infect Dis* 1993;168: 647-56.
34. Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D; Vaccine Safety Datalink Workgroup. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. *Am J Perinatol* 2004;21: 333-9.
35. Munoz FM, Greisinger AJ, Wehmanen OA, et al. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol* 2005;192: 1098-106.
36. France EK, Smith-Ray R, McClure D, Hambidge S, Xu S, Yamasaki K, et al. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. *Arch Pediatr Adolesc Med* 2006;160: 1277-83.
37. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med* 2008;359: 1555-64.
38. Pool V, Iskander J. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol* 2006;194: 1200.
39. CSL Limited. Australian Product information PANVAX® August 2009.
40. Response after One Dose of a Monovalent Influenza A (H1N1) 2009 Vaccine- Preliminary Report. Greenberg, M.E., Lai, M.H. Hartel, G.F et al. *N Engl J Med*. 2009 Sep 10. [Epub ahead of print]