Thursday, October 06, 2011

Mr. Fernando Lugris
Chair, Intergovernmental Negotiating Committee
United Nations Environment Programme
Ministro Consejero
Embajada de Uruguay
Budapest Street No. 32
10787 Berlin
Germany

Dear Honorable Chair Lugris,

Recognizing the harms of some types of mercury, we commend the United Nations Environment Programme for supporting the work to prepare a legally binding instrument on mercury. However, as organizations committed to protecting the health of people worldwide, we have grave concerns about language in the draft treaty that would limit the availability of vaccines containing mercury-added products. As you are likely aware, vaccines are one of the most cost-effective and important medical interventions to prevent infectious diseases worldwide. As we strive to expand access to safe and effective vaccines, it is critical that any policies that may limit access accurately reflect the relevant science.

We understand that this treaty could include a ban on thiomersal, a preservative included in vaccines that protect more than 80 million infants from deadly diseases each year. Thiomersal is an ethylmercury-containing antimicrobial compound used to prevent bacterial and fungal growth in some vaccine vials. Some anti-thiomersal activists have confused ethylmercury with methylmercury. Methylmercury is a known neurotoxin that can cause serious health problems. There is no evidence that suggests the amount of ethylmercury found in thiomersal-containing vaccines is harmful to human health.

Over the past ten years, reputable scientific bodies have evaluated the safety of thiomersal. The World Health Organization's (WHO's) Global Advisory Committee on Vaccine Safety concludes that existing thiomersal-containing vaccines are safe and that any risks are unproven. Similar conclusions have been drawn by the US Institute of Medicine, the American Academy of Pediatrics, the UK Committee on Safety of Medicines, and the European Medicines Agency.

The implications of restricting the manufacture, distribution, or use of thiomersal could significantly limit access to several lifesaving vaccines in poor countries. According to WHO, making vaccines thiomersal free would require either using an alternative preservative (which would require costly and time-consuming clinical studies, thereby driving up the cost of the vaccines) or using preservative-free single-dose vaccines exclusively (which would considerably increase costs and require twice the storage and transport capacity, an impossibility for most countries). Neither of these scenarios is desirable, particularly given that there is no evidence to suggest that removing thiomersal from vaccines would result in a positive health impact.
We urge the Intergovernmental Negotiating Committee to consider the scientific evidence provided by WHO as it negotiates the treaty on mercury.

We invite you to contact Erin Fry at efry@path.org with any questions.

Enclosure: United Nations Environment Programme. Intergovernmental negotiating committee to prepare a global legally binding instrument on mercury, third session. Annex 1: *Mercury in human vaccine preservatives* (submitted by WHO). Nairobi, Kenya; 2011. Available at: http://www.unep.org/hazardoussubstances/Portals/9/Mercury/Documents/INC3/3_6_health_advance.pdf.

Sincerely,

Professional Associations and Research Programs

American Academy of Pediatrics (US)

International Pediatric Association (Global)

Pediatric Infectious Diseases Society (US)

American Society of Tropical Medicine (US)

National Association of City and County Health Officials (US)

Infectious Diseases Society of America (US)

Sabin Vaccine Institute (Global)

Aeras (Global)

International AIDS Vaccine Initiative (Global)

Global Implementing and Advocacy Organizations

PATH (Global)

Agence de Médecine Préventive (Global)

World Vision (Global)

United Nations Foundation Shot@Life (Global)

American Red Cross (US)

ONE (Global)

International Vaccine Access Center (Global)

John Snow, Inc. (Global)

Management Sciences for Health (Global)

Global Alliance to Prevent Prematurity and Stillbirth (Global)

Global Health Visions (Global)

Results (US)

Results United Kingdom (UK)

Results Canada (Canada)

Regional, Country and Local Organizations

ADVocacy for IMmunization (Western Africa)

Réseau International Epivac (Francophone Africa)

Health and Rights Education Program (Malawi)

Kenya AIDS NGOs Consortium (Kenya)

National Meningitis Association (US)

Centre for Health Policy and Innovation (South Africa)

National Foundation for Infectious Diseases (US)

SMLS Trust

SMLS Trust of Amalapuram (India)

Parents of Kids with Infectious Diseases (US)

Every Child By Two (US)

The Immunization Partnership (US)

Tulsa Area Immunization Coalition (US)

Hawaii Immunization Coalition (US)

New Jersey Immunization Network (US)

Immunization Action Coalition (US)

California Immunization Coalition (US)

People Welfare Services (Cameroon)

Annex I

Mercury in human vaccine preservatives (submitted by WHO)

Background

1. Thiomersal (also known as thimerosal, mercurothiolate and sodium 2-ethylmercuriothio-benzoate) is an ethyl mercury-containing antimicrobial compound used to prevent bacterial and fungal growth in some vaccines during storage, and especially during use of opened multi-dose vials. It is also used during vaccine production both to inactivate certain organisms and toxins and to maintain a sterile production line. Thiomersal has been used since the 1930s in the manufacture of some vaccines and other medicinal products.

Why do vaccines need preservatives?

2. In many countries, for multi-dose vaccines, other than live vaccines, the presence of a preservative is a regulatory requirement. Preservatives inhibit growth of bacterial and fungal contamination, which may be introduced during repeated puncture of a multi-dose vial septum. While a preservative is needed only for multi-dose presentations, a manufacturer will usually make one bulk formulation, so if the product has both multi-dose and single dose presentations, the single dose presentation would also contain preservative.

3. Opened vials of vaccines without preservatives need to be discarded at six hours from opening or at the end of the immunization session, whichever is earlier. The presence of a suitable preservative means that opened multi-dose vials may be kept for use in subsequent immunization sessions (WHO policy statement, 2000). This minimizes wastage and can have a significant impact on programme costs. Based on known patterns of vaccine administration in different countries WHO estimates that at least 30% of vaccine doses required can be saved through application of this policy to preserved multi-dose vials.

Very small amounts of mercury are used for vaccine preservative

4. Vaccines that contain thiomersal include those against diphtheria, tetanus and pertussis (DTP), hepatitis B, Haemophilus influenzae type b (Hib), rabies, influenza and meningococcal diseases. Usually, these have thiomersal added in varying concentrations (8 to 50 µg per dose) as a preservative. This list is not exhaustive, but highlights vaccines of major global public health importance. Also, some vaccines may contain trace amounts of thiomersal (<0.5 µg per dose), if it has been used in the production process as an inactivating agent, but has not been added to the final product as a preservative.

5. Currently thiomersal-containing vaccines are supplied by the United Nations (UNICEF and WHO Regional Office for the Americas in particular) with multi-dose presentations of thiomersal containing vaccines. These vaccines form the basis of the prevention of at least four major killers of infants and children (diphtheria, tetanus, pertussis, Haemophilus influenzae type b disease and influenza) and one other important disease (hepatitis B). During 2010, UNICEF alone supplied over 300 million doses of vaccines against those diseases either for routine vaccination activities or for response against outbreaks of infectious diseases such as influenza or epidemic meningitis.

6. Data from the European Union, where two large manufacturers of inactivated vaccines are located, reveal that the total quantity of thiomersal utilized by members of European Vaccine Manufacturers (EVM) is less than 0.25 ton per year corresponding to 0.125 ton of mercury. A significant part of this is used for vaccines exported to developing countries. In summary, the quantities of mercury involved with vaccine preservatives are fairly small.

Safety of thiomersal

7. Health risks related to the use of thiomersal in vaccines have been reviewed on numerous occasions. In 1999, concerns were raised in the United States of America regarding exposure to mercury following immunization with thiomersal-containing vaccines. This was based on the calculation that the cumulative amount of mercury in infant immunization schedules potentially exceeds the recommended threshold for methyl mercury set by a USA government agency. However, thiomersal contains ethyl mercury, not methyl mercury. The pharmacokinetics of ethyl and methyl mercury are quite different. In particular, the half-life of ethyl mercury is short (6 days; 95% CI: 3-10 days) compared with 40-50 days for methyl mercury. Ethyl mercury is actively excreted into the intestinal tract and not accumulated in the body.

8. Since August 2000, the WHO Global Advisory Committee on Vaccine Safety (GACVS) has periodically reviewed available information on thiomersal pharmacokinetic studies in humans (including low birthweight infants) and in monkeys and has assessed the validity of animal models in studying associations between thiomersal and neurobehavioural disorders in humans:

- Expert consultation and data presented to the GACVS indicate that the pharmacokinetic profile of ethyl mercury is substantially different from that of methyl mercury. The half-life of ethyl mercury is shorter compared to methyl mercury (see above) making exposure to ethyl mercury in blood comparatively brief and preventing accumulation when vaccines are administered at least four weeks apart. Further, ethyl mercury is actively excreted via the gut unlike methyl mercury that accumulates in the body. This rapid elimination of ethyl mercury has been confirmed in all studies reviewed, even those that looked at low birthweight infants.

- Four independent epidemiological studies investigating associations and frequency of neurobehavioural disorders in relation to vaccination with thiomersal-containing vaccines from the United Kingdom and Denmark did not challenge the safety of existing thiomersal-containing vaccines in infants. In particular analyses in the U.K. of the General Practice Research Database (GPRD) and of the data set of the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) suggest that there is no association between developmental delay, adverse neurological developmental outcomes or behavioural problems, and thiomersal-containing diphtheria–pertussis–tetanus vaccines.

- GACVS also reviewed a series of studies by Geier and Geier alleging reduction of neurodevelopmental disorders in the United States of America following discontinuation of thiomersal-containing vaccines in the national immunization programme. The Committee found a number of limitations, including: inaccessibility to the reader of the data on which the analysis was made; lack of clear case definitions for the conditions referred to in the paper; unclear or insufficient description of applied statistical methods; assumption made by the authors that the toxicity of ethyl-mercury is equivalent to that of methyl-mercury (an assumption that cannot necessarily be made, and against which various authorities have warned); assumption in the paper that the populations under study are similar (there is every possibility in the methods used of selection bias); and a failure to account for changing reporting patterns for diseases attributed to the vaccines over the years of the study. Published outcomes regarding neurodevelopment and heart disease following administration of thiomersal-containing vaccines do not meet the scientific criteria required to suggest causal relationship. The Committee therefore found the conclusions made by these authors unconvincing.

9. On that basis the GACVS considers that pharmacokinetic and developmental studies do not support concerns over the safety of thiomersal in vaccines. The Committee concludes, and advises accordingly, that there is no reason on grounds of safety to change current immunization practices with thiomersal-containing vaccines, as the risks are unproven.

10. Similar conclusions were reached by other respected advisory committees such as those from:

- U.S. Institute of Medicine (2001). *"The hypothesis that thimerosal exposure through the recommended childhood immunization schedule has caused neurodevelopmental disorders is not supported by clinical or experimental evidence."*

- American Academy of Pediatrics (2003). *"No scientific data link thimerosal used as a preservative in vaccines with any pediatric neurologic disorder, including autism."*

- UK Committee on Safety of Medicine (2003). *"There is no evidence of harm caused by doses of thiomersal in vaccines, except for hypersensitivity reactions (such as allergic skin reactions). There is no evidence of a link between hypersensitivity reactions and the development of autism."*

- European Agency for the Evaluation of Medicinal Products (2004). *"Recent Evidence Supports Safety of Thiomersal Containing Vaccines."*

Public health implications of restricting manufacture, distribution or use of thiomersal-containing vaccines

11. Thiomersal-containing vaccines are the most commonly used form of vaccine presentation to protect more than 80 million infants from deadly diseases every year. Making vaccines thiomersal free

would require either using alternative preservatives (2-phenoxyethanol, phenol and benzethonium chloride are preservatives used in a small number of other licensed vaccines) or using preservative-free single dose vaccines exclusively.

12. However, either of the above changes to products currently formulated with thiomersal would require regulatory approval (WHO - Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines, 2004). There is no guarantee of obtaining a vaccine of equivalent quality, safety and efficacy following replacement of thiomersal as an inactivating agent or replacement or removal of thiomersal as the preservative from an existing licensed product. This could require a new licensing application, including conducting of new manufacturing validation studies; pre-clinical and clinical studies. This is time consuming and costly, could lead to an increase in vaccine cost and could interrupt global supply of the vaccines.

13. Vaccines could be supplied in preservative-free single-dose vials as is the case for the majority of vaccines used in industrialized countries. This option, however, requires a significant increase in manufacturers' filling capacity. This would be time consuming and expensive to implement and it may not be possible to produce sufficient single dose product to ensure uninterrupted global supply. Vaccines supplied in single dose vials are more expensive than a dose of vaccine from a multi-dose vial. In addition, single-dose vials require significantly larger cold storage space as well as increased transport capacity, which is currently not feasible for the majority of countries. Current WHO estimates suggest that the vaccine storage requirements would at least double if single dose presentations only were used (WHO vaccine volume calculator, March 2011). Upgrading the cold chains of those countries is limited by local resources and the additional maintenance requirements that would render many existing systems vulnerable.

WHO position on the use of thiomersal in vaccines

14. The assessment of thiomersal as a preservative for vaccines suggests that the amount of mercury involved with thiomersal use in vaccines is small compared to other sources of mercury.

15. WHO has closely monitored scientific evidence related to the use of thiomersal as a preservative for multi-dose inactivated vaccine presentations for over ten years, in particular through its independent expert advisory group GACVS. Although many alleged risks have been studied in detail in different groups of infants, there is no evidence that suggest a possible health hazard with the amounts of thiomersal currently used, in particular no developmental nor neurological defects have been related to the use of this compound.

16. WHO recommends multi-dose vaccine vials for the routine immunization programs in many countries because they are safe and effective, they limit the required storage capacity and help reduce vaccine costs. There is no likelihood of timely supply of sufficient alternative thiomersal-free presentations of inactivated vaccines. Alternative presentations would incur significantly higher costs in manufacturing procedures and regulatory approval, thereby limiting the ability to offer affordable vaccines against major killer diseases where those products are the most needed.

UNEP DTIE Chemicals Branch and WHO Department of Food Safety, Zoonoses and Foodborne Diseases 2008. Guidance for identifying populations at risk from mercury exposure. http://www.who.int/entity/foodsafety/publications/chem/mercuryexposure.pdf

European Commission Directorate-General Environment 2008. Options for reducing mercury use in products and applications, and the fate of mercury already circulating in society. Final report. http://ec.europa.eu/environment/chemicals/mercury/pdf/study_report2008.pdf

WHO 2000. WHO Policy Statement - The use of opened multi-dose vials of vaccine in subsequent immunization sessions.
http://www.who.int/vaccines-documents/DocsPDF99/www9924.pdf

WHO Global Advisory Committee on Vaccine Safety (2006). Statement on thiomersal
The Global Advisory Committee on Vaccine Safety concludes that there is no evidence of toxicity in infants, children or adults exposed to thiomersal (containing ethyl mercury) in vaccines.
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http://www.who.int/vaccine_safety/topics/thiomersal/questions/en/index.html

WHO Global Advisory Committee on Vaccine Safety. Meeting reports from December 2004, June 2005 and June 2008.
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http://www.who.int/wer/2005/wer8028.pdf
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WHO Expert Committee on Biological Standardization (2004). Fifty-third Report. Annex 4 Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines. PP 95-102.
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Knezevic I, Griffith E, Reigel F, Dobbelaer R (2003). Thiomersal in vaccines: a regulatory perspective (meeting report).
http://www.who.int/biologicals/publications/meetings/areas/vaccines/thiomersal/Thiomersal_WHO_Consult%20April%2015_16_April2002.pdf

WHO. Vaccine volume calculator.
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