Global Vaccination Recommendations and Thimerosal

AUTHORS: Walter A. Orenstein, MD,[a,b] Jerome A. Paulson, MD, FAAP,[c,d] Michael T. Brady, MD, FAAP,[e] Louis Z. Cooper, MD,[f] and Katherine Seib, MSPH[g]

[a]*Departments of Medicine, Pediatrics and Global Health, School of Medicine and Rollins School of Public Health,* [b]*Emory Vaccine Center, and* [g]*Hubert Department of Global Health, Emory University, Atlanta, Georgia;* [c]*Department of Pediatrics, School of Medicine & Health Sciences, School of Public Health & Health Services, George Washington University, Washington District of Columbia;* [d]*Department of Environmental and Occupational Health Children's National Medical Center, Washington District of Columbia;* [e]*Division of Infectious Diseases, Nationwide Children's Hospital, The Ohio State University, Columbus, Ohio; and* [f]*Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, New York*

KEY WORDS

thimerosal, global vaccine supply, vaccine manufacturing, global immunization

ABBREVIATIONS

UNEP—United Nations Environmental Programme
WHO—World Health Organization

Dr Orenstein conceptualized the ideas presented in the commentary, critically reviewed the manuscript, and approved the final manuscript as submitted; Dr Paulson reviewed and revised the manuscript and approved the final manuscript as submitted; Dr Brady critically reviewed the manuscript and approved the final manuscript as submitted; Dr Cooper conceptualized the ideas presented in the commentary and approved the final manuscript as submitted; and Ms Seib drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Opinions expressed in these commentaries are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees.

www.pediatrics.org/cgi/doi/10.1542/peds.2012-1760

doi:10.1542/peds.2012-1760

Accepted for publication Oct 9, 2012

Address correspondence to Walter A. Orenstein, MD, 1462 Clifton Rd, Suite 446, Atlanta, GA 30322. E-mail: worenst@emory.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

FUNDING: No external funding.

COMPANION PAPERS: Companions to this article can be found on pages 152 and 154, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2012-1823 and www.pediatrics.org/cgi/doi/10.1542/peds.2012-2976.

Vaccines remain one of the most effective ways to prevent infectious disease and deaths globally.[1] Universal childhood immunization provides herd immunity against many infectious agents and is a policy that has achieved dramatic reductions in common childhood illnesses. Thimerosal, which contains ethyl mercury, has been used as a preservative in vaccines to prevent contamination of multidose vials from bacteria and fungi since the 1930s.[2] Although there are clear neurotoxic effects of methyl mercury absorption, ethyl mercury has not been associated with those consequences. Nevertheless, before data were available on risks of thimerosal in vaccines, in 1999 the American Academy of Pediatrics and the US Public Health Service recommended moving toward removing thimerosal use in preservatives as a precautionary measure.[3] Thus, thimerosal as a preservative has been removed from most vaccines in the United States, generally resulting in distribution of vaccines in single-dose rather than multidose vials. US vaccines routinely recommended for children that still contain thimerosal as a preservative are seasonal influenza vaccines including the multi-dose presentation Afluria (CSL Limited) and multidose formulations (Fluzone (Sanofi Pasteur) and Fluvirin (Novartis).[4] Thimerosal remains an important vaccine preservative in resource-poor countries. Thimerosal allows the use of multiuse vials, which reduce vaccine cost and the demand on already constrained cold-chain systems. Even in the United States, thimerosal could be critical for dealing with emergencies and the need to rapidly increase vaccine supply and delivery, such as during a serious pandemic of influenza.[5]

Overwhelmingly, the evidence collected over the past 15 years has failed to yield any evidence of significant harm, including serious neurodevelopmental disorders, from use of thimerosal in vaccines. Dozens of studies from countries around the world have supported the safety of thimerosal-containing vaccines. Specifically, the Institute of Medicine, and others have concluded that the evidence favors rejection of a link between thimerosal and autism.[6–12] Careful studies of the risk of other serious neurodevelopmental disorders have failed to support a causal link with thimerosal.[13–17] In May 2002, the American Academy of Pediatrics retired its 1999 statement on thimerosal after evaluating new studies.[3,18] The original decision is explained in an accompanying commentary in this issue by Dr Louis Z. Cooper and Dr Samuel Katz.[19] Had the evidence that is available now been available in 1999, the policy reducing thimerosal use would likely have not been implemented. Furthermore, in 2008 the World Health Organization (WHO) endorsed the use of thimerosal in vaccines.[20]

Because of the well-known neurotoxic effects of methyl mercury and the conversion of mercury to methyl mercury in aquatic organisms, the United Nations Environmental Program (UNEP) is working admirably to

develop an international treaty that would lead to the elimination of controllable mercury pollution and exposure throughout the world; we support their efforts to do so. However, as part of this effort, in addition to removing mercury from thermometers, sphygmomanometers, and other medical uses of mercury, the UNEP is considering recommending the removal of thimerosal (ethyl mercury), which has no recognized serious toxic effects as currently used, from vaccines worldwide. Federal agencies based safety limits for ethyl mercury on limits established for methyl mercury. These limits were based on methyl mercury's accumulation in the body due to its long half-life, which is ~7 times greater than that of ethyl mercury.[21]

Global removal of thimerosal has the potential to adversely affect the worldwide vaccine supply. In recent reports given to WHO, estimates were presented by acknowledged experts on the impact of global removal of thimerosal; some estimates were based on expert opinion but had the advantage of input from other experts within the context of 3 WHO technical consultations or expert advisory meetings. The increases in manufacturing cost vary greatly from country to country, ranging from 200% to >500%.[22–25] Single-dose vials would reduce manufacturing capacity and increase the amount of transportation and storage space required more than threefold. The resulting cold-chain requirements would be untenable in many areas of the world because of programmatic challenges and increased workload.[22,24,25] Furthermore, single-dose packaging produces more waste (both vaccine and CO_2 emissions).[22,24,26] The continued benefits of thimerosal use in vaccine manufacturing clearly outweigh any perceived risks.

WHO's Strategic Advisory Group of Experts on Immunization[27] recently recommended that this part of the ban be removed from the UNEP treaty[28] and we concur.[29]

This is an exciting time for global immunization programs. Global immunization efforts are being supported worldwide by many organizations, including the US government as both humanitarian and protective measures.[30] As advocates for the health of all children, we strongly support these efforts also. Immunization prevents ~2.5 million deaths a year globally. Millions more deaths could be prevented if global immunization efforts are bolstered.[31] The preponderance of available evidence has failed to demonstrate serious harm associated with thimerosal in vaccines. As such, we extend our strongest support to the recent Strategic Advisory Group of Experts recommendations to retain the use of thimerosal in the global vaccine supply.

ACKNOWLEDGMENTS

The authors thank the following individuals who reviewed versions of the commentary and provided useful comments to the authors: Henry Bernstein, Carrie Byington, Herbert Davies, Mary Anne Jackson, Harry Keyserling, Yvonne Maldonado, Marie McCormick, Dennis Murray, Gordon Schutze, Rodney Willoughby, and Theoklis Zaoutis.

REFERENCES

1. Bunker JP, Frazier HS, Mosteller F. Improving health: measuring effects of medical care. *Milbank Q*. 1994;72(2):225–258
2. US Food and Drug Administration. Vaccines, blood & biologics: thimerosal in vaccines questions and answers. US Department of Health and Human Services. Available at www.fda.gov/BiologicsBloodVaccines/vaccines/questionsaboutvaccines/ucm070430. Accessed November 15, 2012
3. American Academy of Pediatrics and United States Public Health Service. Joint statement of the American Academy of Pediatrics (AAP) and the United States Public Health Service (USPHS). *Pediatrics*. 1999;104(3 pt 1):568–569
4. US Food and Drug Administration. Thimerosal in vaccines. Available at: www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM096228#t1. Accessed November 16, 2012
5. Schubert C. Pandemic blows lid off laws limiting mercury in vaccines. *Nat Med*. 2010;16(1):9
6. Institute of Medicine. *Immunization Safety Review: Vaccines and Autism*. Washington, DC: National Academy of Sciences; 2004
7. DeStefano F. Vaccines and autism: evidence does not support a causal association. *Clin Pharmacol Ther*. 2007;82(6):756–759
8. Doja A, Roberts W. Immunizations and autism: a review of the literature. *Can J Neurol Sci*. 2006;33(4):341–346
9. Gerber JS, Offit PA. Vaccines and autism: a tale of shifting hypotheses. *Clin Infect Dis*. 2009;48(4):456–461
10. Hurley AM, Tadrous M, Miller ES. Thimerosal-containing vaccines and autism: a review of recent epidemiologic studies. *J Pediatr Pharmacol Ther*. 2010;15(3):173–181
11. Miller L, Reynolds J. Autism and vaccination—the current evidence. *J Spec Pediatr Nurs*. 2009;14(3):166–172
12. Parker SK, Schwartz B, Todd J, Pickering LK. Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data. *Pediatrics*. 2004;114(3):793–804
13. Thompson WW, Price C, Goodson B, et al; Vaccine Safety Datalink Team. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. *N Engl J Med*. 2007;357(13):1281–1292
14. Offit PA, Davis RL, Gust D. Vaccine Safety. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*. Philadelphia, PA: Saunders Elsevier; 2008
15. Pichichero ME. Safety profile of thimerosal and the safety of alternative preservatives. the Strategic Advisory Group of Experts Meeting, Session: Information on Vaccines for an Intergovernmental Negotiating Committee on Mercury; April 2012; Geneva, Switzerland. Available at: www.who.int/immunization/sage/meetings/2012/april/Pichichero_Update_on_safety.pdf. Accessed November 15, 2012

16. Mitkus R. A review of thimerosal in vaccines. Presented at the Strategic Advisory Group of Experts Meeting, Session: Information on Vaccines for an Intergovernmental Negotiating Committee on Mercury; April 2012; Geneva, Switzerland. Available at www.who.int/immunization/sage/meetings/2012/april/WHO_meeting_slides_Mitkus_040312.pdf. Accessed November 15, 2012
17. Pichichero ME. *Perspective—Report to WHO: No New Concerns About Thimerosal Elsevier Global Medical News*. MedConnect; May 10, 2012. Available at www.medconnect.com.sg/tabid/92/ct1/c45477/Perspective-Report-to-WHO-No-New-Concerns-About-Thimerosal-/Default.aspx. Accessed November 15, 2012
18. American Academy of Pediatrics. Policy Statement—AAP Publications Reaffirmed and Retired. *Pediatrics*. 2011;127(3). Available at: www.pediatrics.org/cgi/content/full/127/3/e857
19. Cooper LZ, Katz SL. Ban on thimerosal in draft treaty on mercury: why the AAP's position in 2012 is so important. *Pediatrics*. 2013;131(1):152–153
20. World Health Organization. Meeting of Global Advisory Committee on Vaccine Safety, June 18–19, 2008. *Wkly Epidemiol Rec*. 2008;83(32):287–292
21. World Health Organization. Statement on thiomersal. Global Advisory Committee on Vaccine Safety. Available at: www.who.int/vaccine_safety/topics/thiomersal/statement_jul2006/en/index.html. Accessed November 15, 2012
22. World Health Organization. SAGE meeting of 10-April 12, 2012. www.who.int/immunization/sage/meetings/2012/april/en/index.html. Accessed November 15, 2012
23. Goverment of Chile. Timerosal: problems, costs and solutions. Presented at the Strategic Advisory Group of Experts Meeting, Session: Information on Vaccines for an Intergovernmental Negotiating Committee on Mercury; April 2012; Geneva, Switzerland. Available at www.who.int/immunization/sage/meetings/2012/april/timerosol_problems_costs_solution_de_chile.pdf. Accessed November 15, 2012
24. Deschamps I. Manufacturer perspectives on alternatives to thiomersal. Presented at the Strategic Advisory Group of Experts Meeting, Session: Information on Vaccines for an Intergovernmental Negotiating Committee on Mercury; April 2012; Geneva, Switzerland. Available at www.who.int/immunization/sage/meetings/2012/april/Alternatives_Thiomersal_novartis_sanofi_pasteur.pdf. Accessed November 15, 2012
25. Battersby A, Garnett A. Indicative operational, financial and environmental impact of thiomersal-free vaccines. Presented at the Strategic Advisory Group of Experts Meeting, Session: Information on Vaccines for an Intergovernmental Negotiating Committee on Mercury; April 2012; Geneva, Switzerland. Available at www.who.int/immunization/sage/meetings/2012/april/assessing_impact_battersby.pdf. Accessed November 15, 2012
26. Jadhav S. Thiomersal in vaccines: DCVMN perspective. Presented at the Strategic Advisory Group of Experts Meeting, Session: Information on Vaccines for an Intergovernmental Negotiating Committee on Mercury; April 2012; Geneva, Switzerland. Available at www.who.int/immunization/sage/meetings/2012/april/3_S_Jadhav_Thiomersalpresentation_SAGE_Final.pdf. Accessed November 15, 2012
27. World Health Organization. Strategic Advisory Group of Experts (SAGE) on Immunization. Available at: www.who.int/immunization/sage/en. Accessed November 15, 2012
28. World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, April 2012—conclusions and recommendations. *Wkly Epidemiol Rec*. 2012;87(21):201–216
29. American Academy of Pediatrics. Ban on all mercury-based products would risk global immunization efforts, says AAP, WHO. *AAP News*. Available at http://aapnews.aappublications.org/content/early/2012/06/01/aapnews.20120601-1.full?rss=1. Accessed November 15, 2012
30. US Department of Health & Human Services. 2010 national vaccine plan. Available at: www.hhs.gov/nvpo/vacc_plan/2010%20Plan/nationalvaccineplan.pdf. Accessed November 15, 2012
31. Liu L, Johnson HL, Cousens S, et al; Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet*. 2012;379(9832):2151–2161

Global Vaccination Recommendations and Thimerosal

Walter A. Orenstein, Jerome A. Paulson, Michael T. Brady, Louis Z. Cooper and Katherine Seib

Pediatrics originally published online December 17, 2012;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Global Vaccination Recommendations and Thimerosal

Walter A. Orenstein, Jerome A. Paulson, Michael T. Brady, Louis Z. Cooper and Katherine Seib

Pediatrics originally published online December 17, 2012;

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™