

APPENDIX 4

THIOMERSAL

In June 2000, a joint statement on thimerosal* in vaccines was prepared by the American Academy of Family Physicians (AAFP), the American Academy of Pediatrics (AAP), the Advisory Committee on Immunization Practices (ACIP), and the Public Health Service (PHS) in response to 1) the progress in achieving the national goal declared in July 1999 to remove thimerosal from vaccines in the recommended childhood vaccination schedule, and 2) results of recent studies that examined potential associations between exposure to mercury in thimerosal-containing vaccines and health effects. In this statement, AAFP, AAP, ACIP, and PHS recommend continuation of the current policy of moving rapidly to vaccines that are free of thimerosal as a preservative. Until adequate supplies are available, use of vaccines that contain thimerosal as a preservative is acceptable.

A joint statement issued by AAP and PHS in July 1999 and agreed to by the AAFP later in 1999 established the goal of removing thimerosal as soon as possible from vaccines routinely recommended for infants. The goal was established as a precautionary measure. No evidence existed of any harm caused by low levels of thimerosal in vaccines. Public concern had been expressed about the health effects of mercury exposure of any sort, and the elimination of mercury from vaccines

was considered a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources of exposure are more difficult or impossible to eliminate (e.g. certain foods).

Since July 1999, substantial progress has been made in removing thimerosal from vaccines. As of March 2000, all U.S. children had access to hepatitis B vaccines that do not contain thimerosal as a preservative. Beginning July 2000, only single-dose thimerosal-free Haemophilus influenzae type b vaccine will be produced in the United States; previously manufactured multidose vials containing thimerosal still may be in distribution. One diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) that does not contain thimerosal is available, and it is projected that additional DTaP vaccines without thimerosal as a preservative will become available in early 2001. On the basis of this progress, the most likely maximum amount of ethylmercury that an infant may be exposed to from the routine vaccination schedule has been reduced by 60%, from 187.5 μg to 75 μg . Measles-mumps-rubella, varicella, inactivated polio, and pneumococcal conjugate vaccines have never contained thimerosal.

Research on the potential health effects of exposure to thimerosal is continuing, and findings will be monitored closely by PHS to determine whether any changes in policy are needed. AAFP, AAP, and PHS, in consultation with the ACIP, reaffirm the goal set in July 1999 to remove

or greatly reduce thimerosal from vaccines as soon as possible. On the basis of information from the Food and Drug Administration and manufacturers, PHS projects that the United States will complete its transition to a secure routine paediatric vaccine supply free of thimerosal as a preservative by the first quarter of 2001.

The vaccination of children in much of the world will continue to require the use of multidose vials because of cost, production, and storage capacity. Multidose vials require a preservative to prevent microbial contamination after the vial is opened. For multidose vials, manufacturers are encouraged to seek alternatives to thimerosal.

* Thimerosal is a derivative of ethylmercury and has been used as an additive to biologics and vaccines since the 1930s because it is effective in killing bacteria and in preventing bacterial contamination, particularly in opened, multidose containers. The full text of this statement is available on the World-Wide Web at <http://www.aafp.org/policy/camp/20.html>, <http://www.aap.org/policy/jointthim.html> and http://www.cdc.gov/nip/vacsafe/concerns/thimerosal/joint_statement_00.htm. References to sites of non-CDC organizations on the World-Wide Web are provided as a service to MMWR readers and do not constitute or imply endorsement of these organizations or their programs by CDC or the U.S. Department of Health and Human Services. CDC is not responsible for the content of pages found at these sites.

Pertussis: Immunization Beyond Childhood

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Paediatric immunizations have had a significant impact on reducing the prevalence of once-common paediatric infections, such as diphtheria and pertussis. However, maladies like these are still far from being eradicated, as evidenced by recent outbreaks of such diseases. One example is the recently reported outbreak of diphtheria in countries that were part of the former Soviet Union.[1]

Although paediatric rates of immunization against diseases such as pertussis are generally high, significant concern has been raised because of the existence of "disease reservoirs" among adults who may not be immune or whose immunity has decreased. Contact of infected adults with nonimmune or partially immunized infants is a potential cause for the development of disease in paediatric populations.[2]

Adult immunization against pertussis was not recommended during the time in which the whole-cell pertussis vaccine was widely used because of concerns about potential side effects if it was administered to persons older than 7 years. However, with the advent of acellular

pertussis vaccines for infants and young children, the use of this type of vaccine in adolescents and adults has been suggested as an alternative to induce active immunity and, thus, decrease the rates of adult disease and limit its spread to infants and children.

Several clinical trials have already been performed to evaluate the safety and immunogenicity of acellular pertussis vaccines in healthy adolescents and adults. In an attempt to maximize compliance and ease of administration, adult combination vaccines that include pertussis components have been developed.[3] They include a 5-component pertussis vaccine combined either with diphtheria and tetanus toxoids (TdaP) or with inactivated poliovirus vaccine and diphtheria and tetanus toxoids (TdaP-IPV).

A recent study performed in Canada with TdaP-IPV evaluated its safety and immunogenicity in 1207 individuals, including adolescents and adults. Adults were divided into 3 groups and received either TdaP-IPV, Td followed by aP administered during a different visit, or TdaP and IPV. Adolescents included in the study received either Td-IPV followed by aP given at a different visit or TdaP-IPV. In the adolescent group, side effects, which included fever, chills, and headache, were reported less commonly after administration of aP vaccine alone than after the administration of TdaP-IPV. However, there was no difference in reported side effects between TdaP-IPV and Td-IPV. The authors

suggested that the increased number of side effects in the TdaP-IPV group was likely the result of the presence of vaccine components other than aP. No differences in antibody responses were observed among any of the different groups in this study. The authors concluded that the TdaP-IPV vaccine used in this study is safe and immunogenic and should be considered as a candidate for adult immunizations.[4]

Additional clinical trials will be needed to assess the effectiveness of this immunization approach in adult populations. In addition to the challenges offered by ensuring that these vaccine formulations are safe, immunogenic, and effective in adults, compliance with future adult immunization endeavours will have to be ensured. In order to meet the challenges of availability and administration of these vaccinations for adult immunization programs, the National Vaccine Advisory Committee has stated the need to study the possibility of implementing immunization programs for adults in nontraditional settings, such as pharmacies and churches.[5] If effective, this approach would have the potential to improve immunization rates in adults.

Although the administration of acellular pertussis vaccine to adults is not yet widely approved, it will certainly require further study and consideration. Benefits of implementing such regimens would include a decrease in adult disease and adult co-immunization with vaccines against other infectious diseases, such as tetanus, diphtheria, polio,

Streptococcus pneumoniae infection, and influenza. This prophylactic approach could have a potentially significant impact on vaccine-preventable paediatric infections by decreasing their rates even further.

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2. Orenstein W. (1999) Pertussis in adults: epidemiology, signs, symptoms and implications for vaccination. *Clin. Infect. Dis.* 28 (suppl 2), S147-S150.
3. Rothstein EP, Anderson EL, Decker MD, *et. al.* (1999) An acellular pertussis vaccine in healthy adults: safety and immunogenicity. *Vaccine.* 17, 2999-3006.
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The Declaration of Geneva of the World Medical Association
International Code of Medical Ethics

- The European Guidelines for Good Clinical Practice for Trials on Medicinal Products in the European Community. CPMP WORKING PARTY (1991). Document 111/3976/88-EN (Final)
- Vaccine research and trials are generally carried out with the pharmaceutical company involved in developing the clinical product acting as the sponsor: the sponsor will select an investigator(s) who will conduct the trial (usually in conjunction with a local study group (and a co-ordinator). The third key individual(s) involved in the trial is a monitor whose principal responsibility is to ensure that the trial is being conducted correctly - usually by ensuring adherence to the SOPs in the trial protocol.
- In the UK-based phase III conjugate meningococcal C study mentioned previously, an important issue for the insurers was to ensure that any potential litigation by non-UK nationals recruited to the trial would be subject to UK law only.
- A more comprehensive description of this trial is available on the website address <http://www.healthnet.org/programs/procaare-hma/procaare.199706/msg00047.html>
- The Tuskegee syphilis study was carried out between 1932 and 1972 by the Public Health Service in Macon County, USA.. In order to study the natural history of syphilis disease, treatment was withheld from 400 infected Black male subjects even after

penicillin had been developed as a safe effective cure.

- Project LinCS investigators at the University of North Carolina Center for Health Promotion and Disease Prevention and the Durham, NC Project LinCS Community Advisory Board. (website reference address <http://www.cdc.gov/hiv/pubs/brochure/unc3bro.htm> - date 8th May, 2000).
- Langley JM (1998) *et. al.* Parental willingness to enter a child in a controlled vaccine trial. *Clin. Invest. Med.* 21(1), 12-16.
- A further advantage is that such units working in collaboration with national governments and the pharmaceutical industry facilitate the development of an organised programme of vaccine research.
- Based in the Department of Epidemiology and Health Sciences at the Manchester University Medical School.
- Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989.