Pertussis vaccines: WHO position paper - October 1, 2010
Grading of scientific evidence in support of key recommendations

Table II: Safety of pertussis vaccines

Question: What is the scientific evidence that wP and aP vaccines are safe with regard to serious adverse events*?

Settings: Global

Conclusion: The scientific evidence demonstrates that both wP and aP vaccines are safe with regard to serious adverse events. Further research is unlikely to change the estimated effect on health outcomes.

*For definition of serious adverse events, see http://www.who.int/vaccines-documents/DocsPDF05/815.pdf

Quality Assessment						Summary of Findings	Importance
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	
Safety of wP vaccines							
4[1]	RCT	No serious	No serious	No serious	No serious	Further research is unlikely to change the estimated effect on health outcomes	Critical
Safety of aP vaccines							
6[1]	RCT	No serious	No serious	No serious	No serious	Further research is unlikely to change the estimated effect on health outcomes	Critical

[1] *Number refers to RCTs comparing aP and wP, respectively, with appropriate controls (absolute safety). In addition, a large number of RCTs (and observational studies) compare the adverse events of wP and aP vaccines (relative safety).*

The systematic review by *Jefferson et al (2002)* included 4 and 6 studies, respectively, on the safety of wP and aP vaccines. The review also included 19 RCTs that compared wP and aP vaccines with regard to adverse events.

Absolute safety, serious adverse events: As compared to the controls, there was no increased risk of invasive bacterial infections or death among those immunized with AP or wP in the studies by *Greco D et al 1996,* (study population 14.751); *Gustafsson L et al 1996,* (study population 9.829); *Olin P et al 1997,* (study population 82.892); *Trollfors B et al 1995,* (study population 3.450); *Decker MD et al 1995,* (study population 2.200); *Black RE et al 1997,* (study population 2.498); *and Uberall MA et al 1997,* (study population 10.271). Also, investigations by *Greco D et al (1996); Gustafsson L et al (1996); Olin P et al (1997); Trollfors B et al (1995); Uberall MA et al (1997)* did not find any cases of encephalitis or encephalopathia in children within the 3 first days of immunization with aP or wP vaccines.

Absolute safety, less serious/mild adverse events: wP vaccines were associated with significantly higher incidences of swelling and induration (odds ratio (OR) 11.67, 95% confidence interval (CI) 8.83-15.44), fever (OR for fever >39 degrees C 3.36, 95% CI 2.06-5.49) and crying for >2h (OR 4.72, 95% CI 2.94-7.59) than placebo or DT. Differences in incidence of hypotonic hyporesponsive episodes (HHE) and convulsions (febrile and afebrile) were not statistically significant.

Acellular pertussis vaccines did not cause a higher incidence of local signs, fever, convulsions, HHE or prolonged crying than placebo or DT.

Relative safety: Jefferson et al concluded that as compared with wP vaccines, all aP vaccines were associated with a lower incidence of local swelling and induration, and in most cases also with significantly less fever. Similarly, a Cochrane report by *Tinnion ON et* al in 2000 covering 45 RCTs on safety concluded that the adverse event profile of aP vaccines was considerably better than that of wP vaccines. More recently, a Cochrane review by *Bar-On ES et al (2009)* investigated the safety of administering combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines. Nine studies with a total of 4932 participants were reviewed. In terms of serious adverse events there were no significant difference between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 0.91, 95% CI 0.56 to 1.48). However, a significant increase in pain (RR 1.09, 95% CI 1.02 to 1.17) and redness (RR 1.09, 95% CI 1.00 to 1.19) was observed in the patients given the combination vaccine.

References

Anonymous: Placebo-controlled trial of two acellular pertussis vaccines in Sweden--protective efficacy and adverse events. Ad Hoc Group for the Study of Pertussis Vaccines. Lancet. 1988 Apr 30;1(8592):955-60.

Bar-On ES, Goldberg E, Fraser A, Vidal L, Hellmann S, Leibovici L. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB). Cochrane Database Syst Rev. 2009 Jul 8;(3):CD005530.

Black SB, Shinefield HR, Bergen R, Hart C, Kremers R, Lavetter A, et al. Safety and immunogenicity of Chiron/Biocine recombinant acellular pertussis–diphtheria–tetanus vaccine in infants and toddlers. Pediatr Infect Dis J 1997;16(1):53–8.

Decker MD, Edwards KM, Steinhoff MC, Rennels MB, Pichichero ME, Englund JA, Anderson EL, Deloria MA, Reed GF. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics. 1995 Sep;96 (3 Pt 2):557-66.

Greco D, Salmaso S, Mastrantonio P, Giuliano M, Tozzi AE, Anemona A, Ciofi degli Atti ML, Giammanco A, Panei P, Blackwelder WC, Klein DL, Wassilak SG. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group. N Engl J Med. 1996 Feb 8;334(6):341-8.

Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med. 1996 Feb 8;334(6):349-55.

Jefferson T, Rudin M, DiPietrantonj C. Systematic review of the effects of pertussis vaccines in children. Vaccine. 2003 May 16;21(17-18):2003-14.

Olin P, Rasmussen F, Gustafsson L, Hallander HO, Heijbel H. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Ad Hoc Group for the Study of Pertussis Vaccines. Lancet. 1997 Nov 29;350(9091):1569-77.

Tinnion ON, Hanlon M. Acellular vaccines for preventing whooping cough in children. Cochrane Database Syst Rev. 2000;(2):CD001478.

Trollfors B, Taranger J, Lagergård T, Lind L, Sundh V, Zackrisson G, Lowe CU, Blackwelder W, Robbins JB. A placebo-controlled trial of a pertussis-toxoid vaccine. N Engl J Med. 1995 Oct 19;333(16):1045-50.

Uberall MA, Stehr K, Cherry JD, Heininger U, Schmitt-Grohé S, Laussucq S, Eckhardt T. Severe adverse events in a comparative efficacy trial in Germany in infants receiving either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP (DTP) or DT vaccine. The Pertussis Vaccine Study Group. Dev Biol Stand. 1997;89:83-9.