

Pertussis vaccines

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References

Afari EA, Kamiya Y, Nkrumah FK, Dunyo SK, Akpedonu P, Kamiya H, Fukai F. Randomized controlled trial of acellular diphtheria, pertussis and tetanus vaccines in southern Ghana. *Ann Trop Paediatr.* 1996 Mar;16(1):39-48.

A randomized controlled trial of acellular diphtheria/pertussis/tetanus (ADPT) freeze-dried and liquid vaccines in infants was conducted in a peri-urban community (Ashaiman) in southern Ghana. Immunogenicity of the acellular vaccines, persistence of antibodies and adverse reactions were compared with those achieved with a whole-cell diphtheria-pertussis-tetanus (DPT) vaccine. The incidence of pertussis in the vaccine groups and prevalence of pertussis in children under 5 years of age in the study area were also determined. The acellular vaccines produced significantly fewer local and systemic reactions. Local reactions such as swelling and redness were observed in 2% (8/399) to 2.3% (9/385) of the acellular vaccine recipients as against 31% (122/394) in the whole-cell vaccine group. Fever (≥ 37.5 degrees C) occurred in 7.27% (29/399) to 9.8% (38/385) in the acellular vaccine groups compared with 36.6% (145/394) in the whole-cell vaccine group. Geometric mean titres (GMTs), measured by ELISA, to pertussis toxin (PT) and filamentous haemagglutinin (FHA) were significantly higher in the acellular vaccine groups than in the whole-cell DPT (WCDPT) group. There were no significant differences in the GMTs of tetanus and diphtheria antitoxins between the two groups after each vaccination. Twelve months after primary vaccination, GMTs to PT in the freeze-dried, liquid ADPT groups and the WCDPT group have fallen from 56.23, 62.63 and 44.97 ELISA U/ml to 6.08, 6.18 and 11.30 ELISA U/ml, respectively. GMTs to FHA in all the vaccine groups also dropped during the same period from 49.94, 41.73 and 20.74 ELISA U/ml to 7.26, 7.72 and 5.91 ELISA U/ml, respectively. In this comparative controlled trial, the ADPT vaccines were more immunogenic, with less local and systemic reactions, than the WCDPT vaccine but there was a considerable drop in antibody titres in all the vaccine groups 12 months after primary vaccination. However, the levels of titres of anti-PT and anti-FHA antibodies in all the three vaccines that confer protection are not known. Further studies are necessary to provide this information in order to assess the need for subsequent booster doses after primary immunization with both ADPT and WCDPT vaccines.

Anonymous. The prevention of whooping-cough by vaccination. A Medical Research Council investigation. *British Medical Journal*, 1951, 1:1463-1471.

Controlled trials were made to assess the prophylactic value of pertussis vaccine in children. Those between the ages of 6 and 18 months whose parents consented to take part in the study were divided by the method of random sampling into two groups of equal size. The groups proved to be strikingly similar in the average age of the trial children, the average number of children in the families, and the average duration of observation. The close similarity

of the groups was also evident from a comparative history of breast-feeding, infectious diseases other than pertussis, immunization against diphtheria, and vaccination against smallpox. The children in one group (referred to as the vaccinated group) were inoculated with pertussis vaccine and those in the other (referred to as the unvaccinated group) with "anticatarrhal" vaccine containing no *H. pertussis*. Each child was visited at frequent intervals for a period of two to three years by a nurse-investigator. Neither parents nor observers knew to which group a child had been allocated.

Five batches of pertussis vaccine from three manufacturers -Parke Davis & Co., of Detroit, the Michigan Department of Health, and Glaxo Laboratories, Ltd.-were tested. Ten separate field trials were made in five different areas. In all, 7,558 children were inoculated and followed up-3,801 in the vaccinated and 3,757 in the unvaccinated group. With only a few exceptions there were no severe local or general reactions after inoculation. None of the children had convulsions and in none did poliomyelitis develop within two months of inoculation.

In all the trials, 149 vaccinated and 687 unvaccinated children developed pertussis. The corresponding attack rates per 1,000 child-months of observation were 1.45 and 6.72, giving a reduction in the incidence of the disease of 78%. Among children exposed to pertussis in their own homes the attack rates were 18.2% in the vaccinated and 87.3% in the unvaccinated groups. The cases that occurred in the vaccinated were on the average less severe and of shorter duration than those in the unvaccinated children. During the two- to three-year periods of observation there was no evidence of a waning in the degree of protection afforded by the pertussis vaccines. Swabs were taken from 96.4% of all clinical cases, and in 59.8% a bacteriological confirmation was obtained. Each batch of vaccine gave substantial protection, but the two batches supplied by the Michigan Department of Health gave a considerably greater degree of protection than the others. Vaccines prepared in this country according to the method used by the Michigan Department of Health are now being tested in similar field trials. An investigation is also being made in which the immunizing properties of vaccines as indicated by laboratory tests are being compared with their prophylactic value in the field.

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.

3801 children aged 5-11 months were entered into a blind placebo-controlled trial of pertussis vaccine. 954 were randomised to receive placebo (vaccine solvent), 1419 to receive a two-component vaccine containing formaldehyde detoxified lymphocytosis promoting factor (LPF) and filamentous haemagglutinin, and 1428 to receive an LPF-toxoid vaccine. After 7-13 weeks 3724 infants received a second dose. Immediate side-effects were mild. Small local reactions occurred more often in the vaccinated infants than in those who received placebo, especially after the second dose of the two-component vaccine. During 15 months of follow-up from 30 days after the second dose, culture-confirmed whooping cough (cough and a positive culture of *Bordetella pertussis*) occurred in 40 placebo, 27 LPF-toxoid vaccine, and 18 two-component vaccine recipients. The point estimate of protective efficacy was 54% (95% confidence intervals 26-72%) for the LPF-toxoid vaccine and 69% (47-82) for the two-

component vaccine; protection against culture-confirmed whooping cough of over 30 days duration was 80% (59-91%) and 79% (57-90%), respectively.

Anonymous: Centres for Disease Control and Prevention. Prevention of pertussis, tetanus and diphtheria among pregnant and postpartum women and their infants. Morbidity and Mortality Weekly Report 2008; 57 RR-4 1-51.

Anonymous: Centres for Disease Control and Prevention. Pertussis--United States, 1997-2000. Morbidity and Mortality Weekly Report 2002, 51(4):73-6.

Pertussis was a major cause of morbidity and mortality among infants and children in the United States during the prevaccine era (i.e., before the mid-1940s). Following the introduction and widespread use of whole-cell pertussis vaccine combined with diphtheria and tetanus toxoids (DTP) among infants and children in the late 1940s, the incidence of reported pertussis declined to a historic low of 1,010 cases in 1976 (Figure 1). However, since the early 1980s, reported pertussis incidence has increased cyclically with peaks occurring every 3-4 years. In 1996, less reactogenic acellular pertussis vaccines (DTaP) were licensed and recommended for routine use among infants. This report summarizes national surveillance data for pertussis during 1997-2000 and assesses the effectiveness of pertussis vaccination in the United States during this period. The findings indicate that pertussis incidence continues to increase in infants too young to receive 3 doses of pertussis-containing vaccine and in adolescents and adults. Prevention efforts should be directed at maintaining high vaccination rates and managing pertussis cases and outbreaks.

Anonymous: Centres for Disease Control and Prevention. Pertussis--United States, 1997-2000. Morbidity and Mortality Weekly Report, 2002, 51:73-76.

Baptista PN, Magalhães V, Rodrigues LC, Rocha MA, Pimentel AM. Source of infection in household transmission of culture-confirmed pertussis in Brazil. *Pediatr Infect Dis J*. 2005 Nov;24(11):1027-8. (No summary).

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.

BACKGROUND: Advantages to combining childhood vaccines include reducing the number of visits, injections and patient discomfort, increasing compliance, and optimizing prevention. The World Health Organization recommends that routine infant immunization programs include a vaccination against Haemophilus influenza type B (HIB) in the combined diphtheria, tetanus, pertussis (DTP)-hepatitis B (HBV) vaccination. The effectiveness and safety of the combined vaccine should be carefully and systematically assessed to ensure their acceptability by the community. **OBJECTIVES:** To compare the effectiveness of combined DTP-HBV-HIB vaccine with DTP-HBV and HIB vaccinations. **SEARCH STRATEGY:** We

searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 1) which contains the Acute Respiratory Infection Group's Specialized Register; MEDLINE (January 1966 to March 2009) and EMBASE (January 1990 to March 2009). SELECTION CRITERIA: Randomized or quasi-randomized controlled trials comparing vaccination with any combined DTP-HBV-HIB vaccine, with or without three types of inactivated poliovirus (IPV) or concomitant oral polio vaccine (OPV) in any dose, preparation or time schedule, compared with separate vaccines or placebo, administered to infants aged up to two years. DATA COLLECTION AND ANALYSIS: Two review authors independently inspected references identified by the searches and evaluated them against the inclusion criteria, extracted data and assessed the methodological quality of included trials. MAIN RESULTS: Meta-analysis was performed to pool the results of 18 studies. There were no data on clinical outcomes for the primary outcome and all studies used immunogenicity and reactogenicity (adverse events). In two immunological responses the combined vaccine achieved lower responses than the separate vaccines for HIB and HBV. Comparison found little heterogeneity. No significant differences in immunogenicity were found for pertussis, diphtheria, polio and tetanus. Serious adverse events were comparable. Minor adverse events were more common in children given the combined vaccine. AUTHORS' CONCLUSIONS: We could not conclude that the immune responses elicited by the combined vaccine were different from, or equivalent to, the separate vaccines. Data for the primary outcome (prevention of disease) were lacking. There was significantly less immunological response for HIB and HBV, and more local reactions in the combined injections. However, these differences rely mostly on one study each. Studies did not use an intention-to-treat analysis and we were uncertain about the risk of bias in many of the studies. These results are therefore inconclusive. Studies addressing clinical end-points whenever possible, using correct methodology and a large enough sample size should be conducted.

Barkin RM, Samuelson JS, Gotlin LP. DTP reactions and serologic response with a reduced dose schedule. J Pediatr. 1984 Aug;105(2):189-94.

In a double-blind study, infants received standard (0.5 ml) or modified (0.25 ml) doses of DTP vaccine for the primary series of three immunizations administered at 2, 4, and 6 months of age and the booster immunization at 18 months. Side effects and antibody responses were determined in 80 children who completed the primary series and 73 who received the booster. The modified regimen was associated with significantly reduced febrile reactions and behavioral changes after the primary series and booster inoculation: 63.2% of those who received the standard dose had febrile reactions, compared to 42.3% who received the modified dose during the primary series; a similar difference was observed with the booster. Only 47.2% of the reduced dosage recipients demonstrated marked behavioral changes, and 62.4% of the standard vaccine recipients had comparable reactions. An even larger difference (33.3% vs 64.7%) was noted at the time of the booster. The modified vaccine produced a local reaction incidence of 58.5%, compared to 72.6% in the control population during the primary immunization series; no differences were noted in local reactions with the booster dose. All patients had serologic evidence of protective titers against diphtheria and tetanus. After the primary immunization series, 97.6% and 97.3% of the infants given the modified and standard doses, respectively, had pertussis agglutinin titers of greater than or equal to 1:16. One patient who received the standard dosage had a titer of less than 1:16 one month after the booster immunization, whereas all those given the modified dose had titers greater than or equal to 1:16. Geometric mean titers of pertussis agglutinins were higher in the standard vaccine

recipients after the primary series, but were similar in the two study groups before and after the 18-month immunization.

Baron S, Njamkepo E, Grimprel E, Begue P, Desenclos JC, Drucker J, Guiso N. Epidemiology of pertussis in French hospitals in 1993 and 1994: thirty years after a routine use of vaccination. *Pediatr Infect Dis J.* 1998 May;17(5):412-8.

BACKGROUND: Despite widespread vaccination during 30 years, the hypothesis of a resurgence of pertussis in France has been raised by outbreaks and sporadic case reports. No surveillance data were available after 1985. **METHODS:** A survey was undertaken in 1993 and 1994 in a pediatric hospital network able to confirm cases; the network (22 hospitals) represents 19.6% of pediatric admissions in France. Case definition included clinical (\geq 21 days of paroxysmal cough), laboratory-confirmed (culture or serology by immunoblot) or epidemiologically confirmed pertussis (documented contact with a laboratory-confirmed case). The pattern of transmission was studied in the household. Vaccine status was obtained from health records. **RESULTS:** during a 15-month period 560 cases (316 index cases, 244 household contact cases) were reported; 49% of index cases and 20% of contact cases were confirmed by culture and/or serology. Sixty-five percent of index cases were younger than 1 year of age (the incidence in this age group could be estimated to be 95/100000) and 66% were hospitalized for a mean duration of 2 weeks. Infection was acquired from parents (34%) and siblings (46%). Seventy-three percent of index cases were unvaccinated.

CONCLUSIONS: Although pertussis vaccination coverage is very high in France, the organism is still circulating, affecting, within the pediatric population, mostly non- or incompletely vaccinated infants. These results strongly support the importance of adhering to the immunization schedule and suggest introducing booster dose(s) to prolong vaccine immunity and reduce the exposure to *Bordetella pertussis* of infants too young to be immunized.

Bettinger JA, Halperin SA, De Serres G, Scheifele DW, Tam T. The effect of changing from whole-cell to acellular pertussis vaccine on the epidemiology of hospitalized children with pertussis in Canada. *Pediatr Infect Dis J.* 2007 Jan;26(1):31-5.

BACKGROUND: Between July 1997 and April 1998, universal childhood immunization programs in Canada changed from using a whole-cell pertussis to a 5-component acellular pertussis-containing vaccine. To assess effects on pertussis epidemiology of this nationwide change, we analyzed hospitalizations during 1991-2004 using the Canadian Immunization Monitoring Program, Active (IMPACT) pertussis database. **METHODS:** IMPACT is an active surveillance network based in 12 pediatric tertiary-care hospitals across Canada. Characteristics of hospitalized cases of pertussis were compared by type of vaccine received or by birth date (if immunization records were unavailable or the child was unvaccinated). Age-stratified incidence rates were calculated by year and vaccine type. **RESULTS:** Two thousand ninety-six cases of pertussis were admitted to IMPACT centers, 1174 during the whole-cell vaccine program (WCV-P) and 842 during the acellular vaccine program (ACV-P). Pertussis incidence among children $<$ 5 years old decreased significantly during the ACV-P, causing an increase in the residual proportion of cases either too young to be immunized ($<$ 2 months old: ACV-P 39% versus WCV-P 26.1%; $P < 0.0001$) or too young for a second dose (2-3 months old: 42.9% versus 34.2%, respectively; $P < 0.0001$). A significantly smaller proportion of cases (ACV-P 15.1% versus WCV-P 27.3%) occurred in infants who were old

enough (4-11 months of age) to have received 2 or 3 doses of vaccine. **CONCLUSIONS:** With ACV-P, pertussis hospitalizations in children 4-59 months old decreased in frequency, consistent with improved vaccine effectiveness, but remained prominent among very young infants. Improved control strategies are needed to reduce infections among infants too young for pertussis vaccination.

Beutels P, Bonanni P, Tormans G, Canale F, Crovari PC. An economic evaluation of universal pertussis vaccination in Italy. *Vaccine*. 1999 May 14;17(19):2400-9.

An economic evaluation was performed of universal acellular pertussis vaccination in Italy, where until recently the overall coverage of pertussis vaccination was estimated at 50%. Over the last two years coverage seems to have increased rapidly. By means of a mathematical simulation model, the consequences of pertussis vaccination in terms of both health effects and economic costs were calculated for a single birth cohort followed for 6 years. Incremental analyses were performed for each additional 10% increase in coverage from 50-90%. The results indicate that a 50% coverage rate of pertussis vaccination in Italy was not optimal on the basis of cost-effectiveness and cost-benefit considerations. Additional increases in coverage were found to yield extra health gains at modest net costs or even potential net savings to the health care sector. For example, an increase in coverage to 90% would yield direct net savings of US\$42 per extra vaccinee in comparison to a situation of 50% coverage. The total net savings for this strategy would be well over US\$100 per additional vaccinee. In the sensitivity analysis, the positive relationship between incremental coverage and incremental efficiency remained unchanged.

Bigard KM, Rhodes P, Connelly BL, Bi D, Hahn C, Patrick S, Glodé MP, Ehresmann KR. Pertussis vaccine effectiveness among children 6 to 59 months of age in the United States, 1998-2001. *Pediatrics*. 2005 Aug;116(2):e285-94.

BACKGROUND: Despite the dramatic pertussis decrease since the licensure of whole-cell pertussis (diphtheria-tetanus toxoids-pertussis [DTP]) vaccines in the middle 1940s, pertussis remains endemic in the United States and can cause illness among persons at any age; >11000 pertussis cases were reported in 2003. Since July 1996, in addition to 2 DTP vaccines already in use, 5 acellular pertussis (diphtheria-tetanus toxoids-acellular pertussis [DTaP]) vaccines were licensed for use among infants; 3 DTaP vaccines were distributed widely during the study period. Because of the availability of 3 DTaP and 2 DTP vaccines and the likelihood of the vaccines being used interchangeably to vaccinate children with the recommended 5-dose schedule, measuring the effectiveness of the pertussis vaccines was a high priority.

OBJECTIVE: To measure the pertussis vaccine effectiveness (VE) among US children 6 to 59 months of age. **DESIGN:** We conducted a case-control study in the Cincinnati, Ohio, metropolitan area, Colorado, Idaho, and Minnesota. **PARTICIPANTS:** Confirmed pertussis cases among children 6 to 59 months of age at the time of disease onset, with onset in 1998-2001, were included. For each case subject, 5 control children were matched from birth certificate records, according to the date of birth and residence. **OUTCOME MEASURES:** A standardized questionnaire was used to obtain vaccination data from parents and providers. Parents/guardians were asked about demographic characteristics, child care attendance, the number of household members who stayed at the same home as the enrolled child for > or =2

nights per week, and cough illness of $>$ or $=2$ -week duration among these household members in the month before the case patient's cough onset. Pertussis vaccine doses among case children were counted as valid if they were received $>$ or $=14$ days before the cough onset date ("valid period"). The age of the case patient (in days) at the end of the valid period was determined, and doses of vaccine for the matched control subjects were counted as valid if they were received by that age. Conditional logistic regression models were used to estimate the matched odds ratios (ORs) for pertussis according to the number of pertussis vaccine doses. The VE was calculated with the following formula: $(1 - OR) \times 100$. Because the pertussis antigen components or amounts differed according to vaccine, the VE of 3 or 4 doses of DTP and/or DTaP was estimated according to the recorded vaccine manufacturer and vaccine type. RESULTS: All enrolled children (184 case subjects and 893 control subjects) had their vaccine history verified. The proportions of children who received 0, 1 or 2, 3, and $>$ or $=4$ pertussis (DTP and/or DTaP) vaccine doses among case subjects were 26%, 14%, 26%, and 34% and among control subjects were 2%, 8%, 33%, and 57%, respectively. Compared with 0 doses, the unadjusted VE estimate for 1 or 2 pertussis doses was 83.6% (95% confidence interval [CI]: 61.1-93.1%), that for 3 doses was 95.6% (95% CI: 89.7-98.0%), and for $>$ or $=4$ doses was 97.7% (95% CI: 94.7-99.0%). Among children who received 4 pertussis vaccinations, the risk of pertussis was slightly higher among those who received only 1 type of vaccine (either 4 DTP doses or 4 DTaP doses), compared with those who received a combination of DTP for doses 1 to 3 and DTaP for dose 4 (OR: 2.4; 95% CI: 1.1-5.2). Among children who received 3 or 4 DTaP vaccine doses, the risk of pertussis was slightly higher among those who received a DTaP vaccine with 4 pertussis antigen components (a vaccine no longer available), compared with those who received the DTaP vaccine with 2 pertussis antigen components (OR: 2.5; 95% CI: 1.1-5.8). Among children who received 4 doses, the risk of pertussis was 2.7 times higher for children who received dose 4 early (age of $<$ or $=13$ months), compared with children who received dose 4 at an older age (age of $>$ or $=14$ months) (95% CI: 1.1-6.8). For children 6 to 23 months of age, features of household structure were significant risk factors for pertussis. In a multivariate model, compared with living with an older parent ($>$ or $=25$ years of age), not living with an "other" household member (a relative other than a parent or sibling or a nonrelated person), and not living with a sibling 6 to 11 years of age, the risk of pertussis for children 6 to 23 months of age was 6.8 times higher if they lived with a young parent ($<$ or $=24$ years of age) (95% CI: 3.1-15.0), 2.5 times higher if they lived with an "other" household member (95% CI: 1.2-5.4), and 2.2 times higher if they lived with a sibling 6 to 11 years of age (95% CI: 1.2-4.3). Adjusting for these risk factors did not change the VE. Compared with control children, case children were significantly more likely to live with a household member (representing all age groups and relationships) who reported a recent cough illness with duration of $>$ or $=2$ weeks (87 [52%] of 168 case subjects, compared with 79 [8%] of 860 control subjects). CONCLUSIONS: Any combination of $>$ or $=3$ DTP/DTaP vaccine doses for children 6 to 59 months of age was highly protective against pertussis. However, there were differences according to vaccine type (DTaP or DTP) and DTaP manufacturer. Among children who received 4 pertussis vaccine doses, a combination of 3 DTP doses followed by 1 DTaP dose had a slightly higher VE than other combinations; among children who received 3 or 4 DTaP vaccine doses, 1 DTaP vaccine performed less well. The finding that pertussis dose 4 was more effective when given to children at $>$ or $=14$ months of age might be confounded if health care providers were more likely to vaccinate children at 12 months of age because of a perceived risk of undervaccination and if these same children were also at higher risk for pertussis. Household members of any age group and relationship could have been the source of pertussis, and household structure was associated with risk for pertussis for children 6 to 23 months of age. In contrast to control children in the study, 26% of case children had never

been vaccinated against pertussis. Unvaccinated children are at risk for pertussis and, in a community with other unvaccinated children, can lead to community-wide pertussis outbreaks. Parents need to be educated about the morbidity and mortality risks associated with *Bordetella pertussis* infection, and they need to be encouraged to vaccinate their children against pertussis on time and with the recommended number of vaccine doses for optimal protection.

Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, Jha P, Campbell H, Walker CF, Cibulskis R, Eisele T, Liu L, Mathers C; for the Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010 Jun 5;375(9730):1969-87.

BACKGROUND: Up-to-date information on the causes of child deaths is crucial to guide global efforts to improve child survival. We report new estimates for 2008 of the major causes of death in children younger than 5 years. **METHODS:** We used multicausal proportionate mortality models to estimate deaths in neonates aged 0-27 days and children aged 1-59 months, and selected single-cause disease models and analysis of vital registration data when available to estimate causes of child deaths. New data from China and India permitted national data to be used for these countries instead of predictions based on global statistical models, as was done previously. We estimated proportional causes of death for 193 countries, and by application of these proportions to the country-specific mortality rates in children younger than 5 years and birth rates, the numbers of deaths by cause were calculated for countries, regions, and the world. **FINDINGS:** Of the estimated 8.795 million deaths in children younger than 5 years worldwide in 2008, infectious diseases caused 68% (5.970 million), with the largest percentages due to pneumonia (18%, 1.575 million, uncertainty range [UR] 1.046 million-1.874 million), diarrhoea (15%, 1.336 million, 0.822 million-2.004 million), and malaria (8%, 0.732 million, 0.601 million-0.851 million). 41% (3.575 million) of deaths occurred in neonates, and the most important single causes were preterm birth complications (12%, 1.033 million, UR 0.717 million-1.216 million), birth asphyxia (9%, 0.814 million, 0.563 million-0.997 million), sepsis (6%, 0.521 million, 0.356 million-0.735 million), and pneumonia (4%, 0.386 million, 0.264 million-0.545 million). 49% (4.294 million) of child deaths occurred in five countries: India, Nigeria, Democratic Republic of the Congo, Pakistan, and China. **INTERPRETATION:** These country-specific estimates of the major causes of child deaths should help to focus national programmes and donor assistance. Achievement of Millennium Development Goal 4, to reduce child mortality by two-thirds, is only possible if the high numbers of deaths are addressed by maternal, newborn, and child health interventions. **FUNDING:** WHO, UNICEF, and Bill & Melinda Gates Foundation. Copyright © 2010 Elsevier Ltd. All rights reserved.

Black SB, Shinefield HR, Bergen R, Hart C, Kremers R, Lavetter A, Lemesurier J, Morozumi PA, Ray P, Lewis EM, Fireman B, Schwalbe J, Hallam P, Shandling M, Dekker C, Granoff DM, Izu A, Podda A. Safety and immunogenicity of Chiron/Biocine recombinant acellular pertussis-diphtheria-tetanus vaccine in infants and toddlers. Pediatr Infect Dis J. 1997 Jan;16(1):53-8.

OBJECTIVE: To evaluate the safety and immunogenicity of the recombinant acellular pertussis-diphtheria-tetanus (aPDT) vaccine (C-aPDT, Chiron/Biocine).

STUDY DESIGN: This is a randomized blinded trial evaluating the safety and immunogenicity of the recombinant aPDT vaccine (C-aPDT, Chiron/Biocine) in 2000 infant recipients compared with 498 controls who received whole cell diphtheria-pertussis-tetanus (wDPT; Connaught) vaccine at 2, 4 and 6 months of age. In addition the safety and immunogenicity of the same C-aPDT vaccine were evaluated as a booster dose in a subset of the same population when given at 15 to 18 months of age and compared with licensed Lederle aPDT vaccine.

RESULTS: The C-aPDT vaccine was associated with very few local or systemic reactions when compared with wDPT. In toddlers the local and systemic side effects observed were similar after either acellular vaccine. When the immunogenicity of the C-aPDT vaccine was compared with the wDPT (Connaught) in infancy, the vaccines were equivalent for anti-diphtheria response, the wDPT developed higher anti-tetanus response and the C-aPDT vaccine was significantly more immunogenic for all other antigens tested. In toddlers the C-aPDT acellular vaccine exhibited equal or improved immunogenicity for antigens tested as compared with Lederle aPDT except for a higher anti-filamentous hemagglutinin response with the Lederle aPDT vaccine.

CONCLUSION: The Chiron/Biocine aPDT vaccine offers an improved safety profile as well as improved immunogenicity when compared with a licensed wDPT product.

Blackwelder WC, Storsaeter J, Olin P, Hallander HO. Acellular pertussis vaccines. Efficacy and evaluation of clinical case definitions. Am J Dis Child. 1991 Nov;145(11):1285-9.

The efficacy of two acellular pertussis vaccines was estimated for various clinical case definitions, with and without the requirement of culture confirmation, from a randomized trial in Sweden. Efficacy increased with duration of coughing spasms and when the case definition included whoops or whoops plus at least nine coughing spasms a day. After deletion of clinical cases not believed to be caused by pertussis, efficacies were closer to the higher values for culture-confirmed disease. Nonspecificity of the clinical criterion "21 days of coughing spasms with whoops" resulted in estimates of predictive value for pertussis of 85% for placebo recipients and 56% for vaccinees. We conclude that laboratory confirmation of suspected cases is needed in pertussis vaccine trials. A suggested case definition is 21 days or more of coughing spasms with confirmation by culture, serologic study, or household exposure to culture-confirmed pertussis.

Blumberg DA, Mink CM, Cherry JD, Johnson C, Garber R, Plotkin SA, Watson B, Ballanco GA, Daum RS, Sullivan B, et al. Comparison of acellular and whole-cell pertussis-component diphtheria-tetanus-pertussis vaccines in infants. The APDT Vaccine Study Group. J Pediatr. 1991 Aug;119(2):194-204.

In a multicenter, double-blind, randomized, longitudinal study, 252 children received licensed Lederle diphtheria-tetanus toxoids and pertussis vaccine adsorbed (DTP) at 2, 4, and 6 months

of age, and 245 children received a DTP vaccine with the Lederle/Takeda acellular pertussis component (APDT) at the same ages. Both groups of children received APDT vaccine at 18 months of age. After each of the first three immunizations, APDT vaccine recipients had fewer local and systemic reactions than did DTP vaccinees. Reactions after the 18-month APDT vaccination were minimal in severity regardless of the vaccine previously received. Antibody responses to lymphocytosis-promoting factor and agglutinogens were more pronounced in DTP recipients; however, APDT recipients had a better serologic response to filamentous hemagglutinin, and responses to the 69K protein were equivalent. This APDT vaccine produces fewer reactions than the standard whole-cell DTP vaccine. The protective significance of the serologic responses to the APDT vaccine is unknown, but the greater response to filamentous hemagglutinin and equivalent response to the 69K protein compared with those to DTP vaccine seem promising.

Bonmarin I, Bouraoui L, Guiso N, Levy-Bruhl D. [Pertussis: data collection and vaccinal strategy.] *Med Mal Infect.* 2009 May;39(5):271-7.

Renacoq is a pediatric hospital-based surveillance network in France, set up in April 1996 to monitor the trend of pertussis among children and the impact of vaccination strategies.

METHOD: The authors studied the link between data collection and public health policy. Microbiologists from 43 hospitals notify diagnosis of pertussis among children less than 16 years of age. Pediatricians complete a questionnaire for infants less than 6 months of age fulfilling the case definitions. Positive cultures are sent to the National reference laboratory to validate biological results. Data collected from 1996 to 2007 was analyzed, as well as its interaction with changes in pertussis vaccine policy.

RESULTS: The introduction of adolescent and adult boosters was largely supported by Renacoq data but this was not the case for interruption of whole cell vaccine use. The impact of adolescent booster is moderate because of a limited vaccine coverage. There was no observed impact of the adult booster but the coverage is very weak. The introduction and then the sole use of acellular vaccine did not have any impact on Renacoq data.

DISCUSSION: The study illustrates the burden of the disease among infants and the link between surveillance data collection and public health decision. It highlights the difficulty to implement new vaccine strategies and the importance of data collection, stressing the need for a better consideration of hospital practitioners involved in public healthcare surveillance.

Brown NJ, Berkovic SF, Scheffer IE. Vaccination, seizures and 'vaccine damage'. *Curr Opin Neurol.* 2007 Apr;20(2):181-7.

PURPOSE OF REVIEW: Concerns about the safety of vaccination have plagued the community, with reduction in vaccine uptake resulting in increased risk of epidemics. Vaccination has been implicated in the cause of febrile seizures, 'vaccine encephalopathy' and autistic spectrum disorders. Evaluation of alleged associations is complicated by evolution in the vaccination field. This review focuses on the risk of seizures following vaccination and the alleged associations of vaccination with vaccine encephalopathy and also with autism spectrum disorders.

RECENT FINDINGS: Over the last decade the introduction of new vaccines such as the acellular pertussis vaccine has produced a reduction in seizures following vaccination, the outcome of which was benign even with older vaccines. New evidence emerged in 2006 showing that cases of alleged 'vaccine encephalopathy' are due to mutations within a sodium channel gene. The weight of epidemiological evidence does not support a relationship between vaccination and childhood epileptic encephalopathies or autism spectrum disorders.

SUMMARY: Vaccines are safer than ever before, but the challenge remains to convey this message to society in such a way that produces change in attitudes to vaccination and subsequent increase in vaccine coverage.

Bryant KA, Humbaugh K, Brothers K, Wright J, Pascual FB, Moran J, Murphy TV. Measures to control an outbreak of pertussis in a neonatal intermediate care nursery after exposure to a healthcare worker. Infect Control Hosp Epidemiol. 2006 Jun;27(6):541-5.

BACKGROUND: Hospitalized premature infants are particularly vulnerable to morbidity and mortality from pertussis. Effective prevention and investigative and control measures are not well described.

OBJECTIVE: To identify the source of nosocomial pertussis in a 2-month-old premature infant in a neonatal intermediate care nursery (ICN) and to critically review the investigation and outbreak control measures.

SETTING: An ICN and a neonatal intensive care unit.

METHODS: We queried healthcare workers (HCWs) and family members about cough illness and contacted potentially exposed patients to determine whether they had symptoms of pertussis. Culture and polymerase chain reaction (PCR) testing for *Bordetella pertussis* were performed by the hospital laboratory with specimens collected from symptomatic patients and HCWs. Levels of pertussis toxin immunoglobulin G antibodies were measured in HCWs with cough of at least 14 days' duration at a public health laboratory. Extensive control measures were instituted.

RESULTS: Four ICN HCWs met the clinical case definition for presence of pertussis. Serologic test results were positive for 3 of the HCWs. The primary case patient was a 36-year-old HCW with a cough illness of 3-weeks' duration that was accompanied by paroxysms, whoop, posttussive emesis, and pneumothorax. Among the 4 affected HCWs, the duration of cough illness prior to identification of the infant index patient ranged from 11 to 25 days. Outbreak control measures included isolation of the infant case patient, furlough and treatment of symptomatic HCWs, administration of chemoprophylaxis to contacts, and surveillance for additional cases. Seventy-two infant patients and 72 HCWs were exposed and were given antibiotic prophylaxis. One additional case of pertussis, confirmed by PCR and culture, occurred in a resident physician who declined prophylaxis; she had cared for the index patient but had no contact with symptomatic HCWs.

CONCLUSION: HCWs or patients may serve as the source of pertussis in nosocomial outbreaks, which can result in substantial morbidity and outlay of resources for control measures. Our review suggested that a diagnosis of pertussis should be an early consideration

for HCWs with cough illness. Targeted pertussis immunization of HCWs, employee health policies that provide for testing and furlough of HCWs with prolonged cough, and monitoring of HCWs for compliance with infection control measures could reduce the morbidity and costs associated with pertussis outbreaks. These measures will require evaluation of their effectiveness.

Calugar A, Ortega-Sánchez IR, Tiwari T, Oakes L, Jahre JA, Murphy TV. Nosocomial pertussis: costs of an outbreak and benefits of vaccinating health care workers. Clin Infect Dis. 2006 Apr 1;42(7):981-8.

BACKGROUND: In September 2003, 17 symptomatic cases of pertussis among health care workers (HCWs) resulted from a 1-day exposure to an infant who was later confirmed to have pertussis. These HCWs identified 307 close contacts. The hospital implemented extensive infection-control measures. The objective of this study was to determine direct and indirect costs incurred by the hospital and symptomatic HCWs as a result of the September 2003 outbreak and to estimate possible benefits of vaccinating HCWs from the hospital perspective.

METHODS: We determined costs by interviewing infection-control and hospital personnel, reviewing billing records, and surveying symptomatic HCWs. We calculated the benefits and costs of a vaccination program for HCWs, using a probabilistic model to estimate the number of pertussis exposures that would require control measures annually. Sensitivity and threshold analyses were performed.

RESULTS: The outbreak cost to the hospital was 74,870 dollars. The total measured cost of the outbreak was 81,382 dollars, including costs incurred by HCWs (6512 dollars). Our model predicted that vaccinating HCWs against pertussis would prevent >46% of exposures from HCWs with pertussis per year and would provide net savings. The benefit for the hospital was estimated to be 2.38 times the dollar amount invested in vaccinating HCWs. The number of exposures prevented and the benefit-cost ratio were sensitive to the number of exposures identified, the incidence of pertussis among HCWs, and HCW turnover.

CONCLUSIONS: A single nosocomial pertussis outbreak resulted in substantial disruption and costs to the hospital and to HCWs. Our model suggests that cost savings and benefits could be accrued by vaccinating HCWs against pertussis.

Carlsson RM, Trollfors B. Control of pertussis--lessons learnt from a 10-year surveillance programme in Sweden. Vaccine. 2009 Sep 25;27(42):5709-18.

Sweden was the only country in the world without any general pertussis vaccination when acellular pertussis (aP) vaccines were introduced. Since 1996 aP vaccines are given at the ages of 3, 5 and 12 months, with a 99% coverage, and until 2007 without a later booster. The long-term effects of aP vaccines, monitored within an enhanced surveillance project, were discussed at an international workshop in Stockholm in November 2008. The unique Swedish experience demonstrates that aP vaccines are capable of achieving the primary goal of a national vaccination programme, i.e., to significantly reduce the burden of pertussis in pre-school children. Throughout the 10-year surveillance period the highest age-specific incidence was reported in unvaccinated infants or those who had received only one dose, with most hospitalisations in this age group and eight deaths among unvaccinated infants.

Complementary strategies are needed to achieve further reduction in morbidity from circulation of *Bordetella pertussis*.

Caro V, Njamkepo E, Van Amersfoorth SC, Mooi FR, Advani A, Hallander HO, He Q, Mertsola J, Riffelmann M, Vahrenholz C, Von König CH, Guiso N. Pulsed-field gel electrophoresis analysis of *Bordetella pertussis* populations in various European countries with different vaccine policies. *Microbes Infect.* 2005 Jun;7(7-8):976-82.

The increasing incidence of pertussis in a number of countries, despite good vaccination coverage, is a cause for concern. We used pulsed-field gel electrophoresis (PFGE) typing to examine the genetic diversity of 101 clinical isolates of *Bordetella pertussis*, recovered during 1999-2001, and circulating in five different European countries to evaluate temporal and geographical distribution. This DNA fingerprinting approach seems to be a more discriminative epidemiological tool than sequencing of individual genes. Despite differences in vaccination policies in the five countries, these European isolates were found to be very similar and fell into the same major PFGE profile groups, with a predominance of one profile group. There was no evidence of geographic clustering, except that one new profile subgroup was predominantly found in one country. This study provides a baseline for continued surveillance of the *B. pertussis* population in Europe.

Carlsson RM, Trollfors B. Control of pertussis--lessons learnt from a 10-year surveillance programme in Sweden. *Vaccine.* 2009 Sep 25;27(42):5709-18.

Sweden was the only country in the world without any general pertussis vaccination when acellular pertussis (aP) vaccines were introduced. Since 1996 aP vaccines are given at the ages of 3, 5 and 12 months, with a 99% coverage, and until 2007 without a later booster. The long-term effects of aP vaccines, monitored within an enhanced surveillance project, were discussed at an international workshop in Stockholm in November 2008. The unique Swedish experience demonstrates that aP vaccines are capable of achieving the primary goal of a national vaccination programme, i.e., to significantly reduce the burden of pertussis in pre-school children. Throughout the 10-year surveillance period the highest age-specific incidence was reported in unvaccinated infants or those who had received only one dose, with most hospitalisations in this age group and eight deaths among unvaccinated infants. Complementary strategies are needed to achieve further reduction in morbidity from circulation of *Bordetella pertussis*.

Casey JR, Pichichero ME. Acellular pertussis vaccine safety and efficacy in children, adolescents and adults. *Drugs.* 2005;65(10):1367-89.

This review offers a perspective on the acellular pertussis vaccine efficiency trials concluded in the 1990s and presents the main conclusions of a meta-analysis of 52 studies that assessed the safety and efficacy of the diphtheria-tetanus (DT)-whole cell pertussis (DTwP) and DT-acellular pertussis (DTaP) vaccines administered to children. A clear serological correlate of

immunity to pertussis following DTaP vaccination was not identified despite an intensive analysis. It can be speculated that this may be because various combinations of antibody to agglutinogens (pertussis toxin, filamentous haemagglutinin, pertactin and fimbriae) provide protection, or because serum antibody levels and responses do not uniformly reflect mucosal IgA antibody levels. Long-term efficacy following DTaP vaccination is becoming characterised and cell-mediated immunity (T-cell memory) may have importance. DTaP vaccination appears to establish herd immunity after sufficient uptake within communities and countries. As experience with DTaP vaccine safety has accumulated, a 1-2% occurrence of large, local injection reactions with all products has been defined for booster doses. The pathophysiological mechanisms for the reactions are not established but a majority appear likely to be IgE-mediated reactive oedema and a minority to be IgG-mediated reactive Arthus-type reactions. DTwP and DTaP combinations with other vaccines have been studied and licensed; the most controversial combination products are the DTaP/Haemophilus influenzae type B polysaccharide conjugate vaccines. Pertussis epidemiology is changing with a clear increase in occurrence in adolescents and adults. This development has spurred studies and licensure of safer DTaP vaccines for this older population. The economic impact of pertussis and transmission from adults to vulnerable infants provides a cost-benefit justification for widespread use of DTaP vaccines in all age groups with routine boosting every 10 years.

Celentano LP, Massari M, Paramatti D, Salmaso S, Tozzi AE; EUVAC-NET Group. Resurgence of pertussis in Europe. *Pediatr Infect Dis J.* 2005 Sep;24(9):761-5.

BACKGROUND: A resurgence of pertussis has been observed in Canada, the United States and Australia since the 1980s, but inconsistent data are currently available for Europe. The objective of this paper is to describe the epidemiology of pertussis in Western European countries to discuss future vaccination strategies. **METHODS:** The European Community funded a network for the epidemiologic surveillance of measles and pertussis in 1998. Sixteen European countries provided national surveillance data for pertussis for the period 1998-2002 in a standard format. Data were pooled and analyzed to describe incidence rates by age group, seasonality, proportion of hospitalized patients and deaths among notified cases. **RESULTS:** Children younger than 1 year had the highest incidence during the entire period. Rates in the older than 14 years age group increased by 115% during the study period. Northern countries showed the highest incidence figures in all age groups. Among children younger than 1 year, 70% were admitted into hospital. Children younger than 6 months of age and those not vaccinated were most likely to be hospitalized. Thirty-two deaths were reported, 87% of which were in children younger than 6 months of age. **CONCLUSIONS:** Pertussis is far from being controlled in Europe. Whereas the incidence in children younger than 1 year was high but remained stable, rates in adults doubled in 5 years.

Cohen P, Scadron SJ. The effects of active immunisation of the mother upon the offspring. *Journal of Pediatrics,* 1946, 29: 609-619. (No summary).

Coudeville L, Van Rie A, Getsios D, Caro JJ, Crépey P, Nguyen VH. Adult vaccination strategies for the control of pertussis in the United States: an economic evaluation including the dynamic population effects. PLoS One. 2009 Jul 16;4(7):e6284.

BACKGROUND: Prior economic evaluations of adult and adolescent vaccination strategies against pertussis have reached disparate conclusions. Using static approaches only, previous studies failed to analytically include the indirect benefits derived from herd immunity as well as the impact of vaccination on the evolution of disease incidence over time. **METHODS:** We assessed the impact of different pertussis vaccination strategies using a dynamic compartmental model able to consider pertussis transmission. We then combined the results with economic data to estimate the relative cost-effectiveness of pertussis immunization strategies for adolescents and adults in the US. The analysis compares combinations of programs targeting adolescents, parents of newborns (i.e. cocoon strategy), or adults of various ages. **RESULTS:** In the absence of adolescent or adult vaccination, pertussis incidence among adults is predicted to more than double in 20 years. Implementing an adult program in addition to childhood and adolescent vaccination either based on 1) a cocoon strategy and a single booster dose or 2) a decennial routine vaccination would maintain a low level of pertussis incidence in the long run for all age groups (respectively 30 and 20 cases per 100,000 person years). These strategies would also result in significant reductions of pertussis costs (between -77% and -80% including additional vaccination costs). The cocoon strategy complemented by a single booster dose is the most cost-effective one, whereas the decennial adult vaccination is slightly more effective in the long run. **CONCLUSIONS:** By providing a high level of disease control, the implementation of an adult vaccination program against pertussis appears to be highly cost-effective and often cost-saving.

Crowcroft NS, Pebody RG. Recent developments in pertussis. Lancet. 2006 Jun 10;367(9526):1926-36.

Pertussis causes nearly 300,000 deaths in children every year. Most deaths take place in developing countries, but the infection remains a priority everywhere. Pertussis vaccination protects infants and children against death and admission to hospital, but breakthrough disease in vaccinated people can happen. In high-mortality countries, the challenge is to improve timeliness and coverage of childhood vaccination and surveillance. In regions with low mortality and highest coverage, pertussis is frequently the least well-controlled disease in childhood vaccination programmes. Some countries have reported a rise in pertussis in adolescents, adults, and pre-vaccination infants, but how much these changes are real or a result of improved recognition and surveillance remains uncertain. In response, several countries have introduced adolescent and adult acellular pertussis vaccine boosters. The effect so far is unknown; assessment is impeded by poor data. Uncertainties still persist about key variables needed to model and design vaccination programmes, such as risk of transmission from adults and adolescents to infants. New vaccination strategies under investigation include vaccination of neonates, family members, and pregnant women.

Crowcroft NS, Stein C, Duclos P, Birmingham M. How best to estimate the global burden of pertussis? Lancet Infect Dis. 2003 Jul;3(7):413-8.

In most countries, pertussis surveillance is inadequate for accurately estimating numbers of cases or deaths. Good estimates are needed to help set priorities for vaccination programmes.

We aimed to develop a simple, reliable, and explicit method for estimating pertussis cases and deaths for children under 15 years to calculate the global disease burden in 1999. We estimated the proportion of susceptible children becoming infected in countries with poor vaccination coverage (<70%) in 1999 at 30% by 1 year, 80% by 5 years, and 100% by 15 years of age and for countries with good coverage (> or =70%) at 10% by 1 year, 60% by 5 years, and 100% by 15 years. Vaccine efficacy was estimated at 80% for preventing infection and 95% for preventing deaths. We used UN population estimates and vaccination coverage reported to WHO (adjusted for specific survey data if available). Case fatality ratios for countries with high and low child mortality were derived from published and unpublished work. For some countries with good vital events registration we used reported deaths adjusted for underascertainment. In 1999 there were an estimated 48.5 million pertussis cases in children worldwide. Deaths from pertussis were estimated at 390000 and at 295000 after adjustment for local data sources. Based on this approach, disability-adjusted life years from pertussis (12.7 million) in 2000 exceeded those of other preventable diseases such as lung cancer (11.4 million) and meningitis (5.8 million). This simple approach yields estimates that can be used for setting vaccination programme priorities. Better data are needed on the public health importance of pertussis in high mortality countries, the benefits of incomplete vaccination, and the harm from delayed vaccination.

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.

OBJECTIVE: To compare the reactogenicity of a licensed conventional whole-cell (WCL) and 13 acellular pertussis vaccines that differed in the source, manufacture, and quantity of included antigens; all vaccines included diphtheria and tetanus toxoids. **METHODS:** Healthy infants were enrolled through six university-based vaccine and treatment evaluation units and were randomized to receive one of the study vaccines at 2, 4, and 6 months of age. Parents recorded the occurrence of fever, redness, swelling, pain, fussiness, drowsiness, anorexia, and use of antipyretics for 2 weeks after each inoculation; nurses interviewed parents on the third day and at each succeeding visit; long-term follow-up information was collected from parents and medical records 1 year after the third immunization. **RESULTS:** Of 2200 vaccinated infants, 2189 contributed reaction data after 6375 vaccinations. For every acellular vaccine, every monitored reaction except vomiting occurred at a significantly lower frequency and severity than was seen with WCL. The groups receiving acellular pertussis vaccines differed significantly with respect to redness, swelling, pain, and vomiting, but not with respect to fussiness, antipyretic use, drowsiness, or anorexia. **CONCLUSION:** Although there were differences among the acellular vaccines, none was consistently the most or least reactogenic; all were associated with substantially fewer and less severe adverse reactions than a standard commercial whole-cell vaccine. Selection of acellular vaccines for further development and for introduction into efficacy trials can give priority to assessments of immunogenicity and purity, with comparative reactogenicity a secondary consideration.

Edmunds WJ, Brisson M, Melegaro A, Gay NJ. The potential cost-effectiveness of acellular pertussis booster vaccination in England and Wales. *Vaccine*. 2002 Jan 31;20(9-10):1316-30.

A cost-effectiveness analysis of the introduction of acellular pertussis booster doses at either 4 or 15 years of age was performed. A transmission dynamic model was used to predict the level of indirect protection in those too young to be vaccinated. Multivariate sensitivity analyses were performed. In England and Wales there are an estimated 35,000 general practitioner (GP) consultations, 5500 inpatient days, and nine deaths annually attributable to pertussis, despite high levels of coverage for the primary course (approximately 95%). Around 80% of the bed-days and 90% of the deaths occur in those too young to be immunised (< 3 months of age). The introduction of acellular booster doses at 4 years is expected to reduce morbidity and mortality in the younger age groups by 40-100%, and at 15 years by 0-100%. From the perspective of the health care provider, roughly 50% of the simulations result in a cost per life-year gained of less than 10,000 pounds for vaccination at 4 years, the corresponding proportion for vaccination at 15 years being only 35%. Apart from the degree of indirect protection the model was most sensitive to the discount rate, the price of the vaccine, and the mortality rate. Significant uncertainty remains regarding the epidemiology of pertussis and the impact of booster doses. Nevertheless, the introduction of acellular boosters, particularly at 4 years, has the potential to be cost-effective in the UK.

Edwards KM et al. Pertussis vaccines. In: Plotkin S, Orenstein W, Offit P, eds. Vaccines, 5th ed. Philadelphia, Saunders, 2008: 467-517.

Edwards KM, Decker MD, Halsey NA, Koblin BA, Townsend T, Auerbach B, Karzon DT. Differences in antibody response to whole-cell pertussis vaccines. Pediatrics. 1991 Nov;88(5):1019-23.

It has been assumed that whole-cell pertussis vaccines (WCVs) commercially distributed in the United States are of comparable immunogenicity, as all must comply with established standards for licensure. However, we have recently noted significant differences in antibody responses between groups of infants receiving the two WCVs commercially available in the United States. In separate studies performed concurrently under similar protocols at Vanderbilt and Johns Hopkins universities, infants were randomized to receive either an acellular pertussis vaccine or WCV. The acellular pertussis vaccine used at the two sites was identical, but the WCVs were from different manufacturers. Antibody responses to acellular pertussis vaccine did not differ between the two studies; responses to WCV differed dramatically, with infants receiving the Lederle WCV producing a 46-fold increase in antibody to pertussis toxin, compared with a 2.4-fold increase for infants receiving the Connaught WCV ($P = .00003$). Evaluation of other comparative data sets that were available provided further support for the conclusion that the two commercially available WCVs consistently differed in their ability to induce antibody to pertussis toxin. These findings have important implications for the design and interpretation of clinical trials comparing acellular and WCV products.

Esposito S, Agliardi T, Giammanco A, Faldella G, Cascio A, Bosis S, Friscia O, Clerici M, Principi N. Long-term pertussis-specific immunity after primary vaccination with a

combined diphtheria, tetanus, tricomponent acellular pertussis, and hepatitis B vaccine in comparison with that after natural infection. Infect Immun. 2001 Jul;69(7):4516-20.

The aim of this study was to compare pertussis-specific humoral and cellular immunity in children 5 years after a primary vaccination with a combined diphtheria, tetanus, tricomponent acellular pertussis, and hepatitis B vaccine (DTaP-HBV; InfanrixHepB; SmithKline Beecham) with immunity after natural infection. The subjects were 38 children aged 5 to 6 years who received DTaP-HBV at 3, 5, and 11 months of life and 21 subjects of similar ages and sex who acquired pertussis in the first year of life. Immunoglobulin G (IgG) antibody titers against Bordetella pertussis antigens, peripheral blood mononuclear cell-specific proliferation, and the secretion of cytokines were evaluated. After 5 years, only a small proportion of vaccinated and infected children had significant specific concentrations of IgG in serum against all three B. pertussis antigens, and T-cell responses persisted in a minority of subjects. A preferential type 1 cytokine response with the secretion of gamma interferon was observed in the pertussis group, whereas a type 2 skewed response was observed in the vaccinated children; however, the quantitative differences in the cytokines produced by DTaP-HBV and natural infection were minimal. In conclusion, our results show that the immune responses induced by primary pertussis vaccination are qualitatively and quantitatively similar to those seen in children who recovered from natural infection and highlight the need for booster immunization with pertussis vaccines in order to maintain adequate levels of a specific immune response to B. pertussis.

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.

BACKGROUND: Concern about both safety and efficacy has made the use of whole-cell pertussis vaccines controversial. In some European countries, including Italy, the rate of vaccination against pertussis is low. **METHODS:** We conducted a double-blind trial in Italy in which infants were randomly assigned to vaccination at two, four, and six months of age with an acellular pertussis vaccine together with diphtheria and tetanus toxoids (DTP); a DTP vaccine containing whole-cell pertussis (manufactured by Connaught Laboratories); or diphtheria and tetanus toxoids without pertussis (DT). The acellular DTP vaccine was either one containing filamentous hemagglutinin, pertactin, and pertussis toxin inactivated with formalin and glutaraldehyde (SmithKline Beecham) or one with filamentous hemagglutinin, pertactin, and genetically detoxified pertussis toxin (Chiron Biocine). Pertussis was defined as 21 days or more of paroxysmal cough, with infection confirmed by culture or serologic testing. **RESULTS:** The efficacy of each vaccine, given in three doses, against pertussis was determined for 14,751 children over an average of 17 months, with cases included in the analysis if cough began 30 days or more after the completion of immunization. For both of the acellular DTP vaccines, the efficacy was 84 percent (95 percent confidence intervals, 76 to 89 percent for Biocine DTP and 76 to 90 percent for SmithKline DTP), whereas the efficacy of the whole-cell DTP vaccine was only 36 percent (95 percent confidence interval, 14 to 52 percent). The antibody responses were greater to the acellular vaccines than to the whole-cell vaccine. Local and systemic adverse events were significantly more frequent after the administration of the whole-cell vaccine. For the acellular vaccines, the frequency of adverse

events was similar to that in the control (DT) group. CONCLUSIONS: The two acellular DTP vaccines we studied were safe, immunogenic, and efficacious against pertussis, whereas the efficacy of the whole-cell DTP vaccine was unexpectedly low.

Griffin MR, Ray WA, Mortimer EA, Fenichel GM, Schaffner W. Risk of seizures and encephalopathy after immunization with the diphtheria-tetanus-pertussis vaccine. JAMA. 1990 Mar 23-30;263(12):1641-5.

We evaluated the risks of seizures and other neurological events following diphtheria-tetanus-pertussis (DTP) immunization for 38,171 Tennessee Medicaid children who received 107,154 DTP immunizations in their first 3 years of life. There were 2 children with encephalitis; both had disease onset more than 2 weeks following DTP immunization. There were 277 children who had febrile seizures, 42 with afebrile seizures, and 37 with seizures associated with other acute neurological illness (acute symptomatic). The risk of febrile seizures in the 0 to 3 days following DTP immunization (n = 6) was 1.5 (95% confidence interval, 0.6 to 3.3) times that of the control period 30 or more days following DTP immunization. There was no evidence that in the 0 to 3 days following DTP immunization the risk of afebrile seizures (n = 1) or acute symptomatic seizures (n = 0) was increased. No child who was previously normal without a prior history of seizures had a seizure in the 0 to 3 days following immunization that marked the onset of either epilepsy or other neurological or developmental abnormality.

Guiso N, Njamkepo E, Vié le Sage F, Zepp F, Meyer CU, Abitbol V, Clyti N, Chevallier S. Long-term humoral and cell-mediated immunity after acellular pertussis vaccination compares favourably with whole-cell vaccines 6 years after booster vaccination in the second year of life. Vaccine. 2007 Feb 9;25(8):1390-7.

Humoral and cell-mediated immune responses (CMI) were evaluated in subjects 3 and 6 years after primary and booster vaccination with either three-component acellular (Pa) or whole-cell (Pw) vaccines. Low anti-pertussis toxin (PT) antibody levels confirmed the absence of pertussis disease, consistent with ongoing protection. Anti-pertactin (PRN) antibodies, remained at higher levels in Pa-vaccinated subjects. At year 6, CMI responses continued to be present and were higher in Pa-vaccinated than Pw-vaccinated subjects. Long-term protection with Pa vaccines can be expected to be at least as good as that provided by efficacious Pw vaccines.

Guris D, Strebel PM, Tachdjian R, Bardenheier B, Wharton M, Hadler SC. Effectiveness of the pertussis vaccination program as determined by use of the screening method: United States, 1992-1994. J Infect Dis. 1997 Aug;176(2):456-63.

The screening method was used to evaluate the effectiveness of the pertussis vaccination program in the United States during 1992-1994. The formula $VE = 1 - [PCV/(1 - PCV)] \cdot [(1 - PPV)/PPV]$ was used (VE = vaccine effectiveness; PCV = proportion of cases vaccinated; PPV = proportion of population vaccinated). Data from the national Supplementary Pertussis Surveillance System and the National Health Interview Survey were used to determine PCV

and PPV, respectively. Among children aged 7-18 months, VE for 3 doses of pertussis vaccine was 79% (95% confidence interval, 74%-83%) for preventing culture-confirmed pertussis. Between the ages of 19 and 47 months, VE for > or = 4 doses was 90% (95% confidence interval, 88%-92%). VE estimates appeared lower in epidemic (1993) than non-epidemic years (1992, 1994). VE estimates determined using the screening method were consistent with the previous estimates from the United States. This method will continue to be useful for assessing the effectiveness of the pertussis vaccination program in the United States, where acellular pertussis vaccines are recommended for infants.

Gustafsson L, Hessel L, Storsaeter J, Olin P. Long-term follow-up of Swedish children vaccinated with acellular pertussis vaccines at 3, 5, and 12 months of age indicates the need for a booster dose at 5 to 7 years of age. *Pediatrics*. 2006 Sep;118(3):978-84.

OBJECTIVES: The purpose of this work was to evaluate the long-term effectiveness of vaccination with acellular pertussis vaccines at 3, 5, and 12 months of age. **METHODS:** Clinical follow-up of reported culture- and polymerase chain reaction-confirmed cases of pertussis was initiated during October 1997 in most of Sweden (except Gothenburg and environs). The study population included 90% of Swedish children born during 1996 or later (ie, who received diphtheria-tetanus-acellular pertussis vaccines at 3, 5, and 12 months of age) and children who had participated in a large pertussis vaccine trial in 1993-1996. Age-specific incidences were estimated using reported culture- or polymerase chain reaction-confirmed pertussis from October 1997 to September 2004 in areas covered by enhanced surveillance. In addition, annual overall and age-specific incidences of pertussis throughout Sweden before and after introduction of acellular pertussis vaccines were estimated. **RESULTS:** The overall incidence of notified culture- and polymerase chain reaction-confirmed pertussis dropped from 113 to 150 per 100,000 during 1992-1995 to 11 to 16 per 100,000 during 2001-2004. In areas of enhanced surveillance, the incidence of pertussis was 31 per 100,000 person-years after 2 doses and 19 per 100,000 person-years after the third dose at 12 months of age. The age-specific incidence remained low for approximately 5 years after the third dose but increased in children aged 6 to 8 years, becoming 32 and 48 per 100,000 person-years, respectively. The highest incidence occurred among infants who were unvaccinated or had received only 1 dose of diphtheria-tetanus-acellular pertussis vaccine. **CONCLUSIONS:** The increased incidence among 7- to 8-year-olds (ie, mainly acellular pertussis vaccine-vaccinated children) suggests waning of vaccine-induced protection from pertussis. Along with a concomitant increase in incidence among infants, most likely infected by older siblings, these data suggest a booster dose of acellular pertussis vaccine is warranted from 5 to 7 years of age.

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.

BACKGROUND: Because of concern about safety and efficacy, no pertussis vaccine has been included in the vaccination program in Sweden since 1979. To provide data that might permit the reintroduction of a pertussis vaccine, we conducted a placebo-controlled trial of two acellular and one whole-cell pertussis vaccines. **METHODS:** After informed consent was obtained, 9829 children born in 1992 were randomly assigned to receive one of four vaccines: a two-component acellular diphtheria-tetanus-pertussis (DTP) vaccine (2566 children), a five-

component acellular DTP vaccine (2587 children), a whole-cell DTP vaccine licensed in the United States (2102 children), or (as a control) a vaccine containing diphtheria and tetanus toxoids (DT) alone (2574 children). The vaccines were given at 2, 4, and 6 months of age, and the children were then followed for signs of pertussis for an additional 2 years (to a mean age of 21/2 years). RESULTS: The whole-cell vaccine was associated with significantly higher rates of protracted crying, cyanosis, fever, and local reactions than the other three vaccines. The rates of adverse events were similar for the acellular vaccines and the control DT vaccine. After three doses, the efficacy of the vaccines with respect to pertussis linked to a laboratory-confirmed case of pertussis or contact with an infected household member with paroxysmal cough for \geq 21 days was 58.9 percent for the two-component vaccine (95 percent confidence interval, 50.9 to 65.9 percent), 85.2 percent for the five-component vaccine (95 percent confidence interval, 80.6 to 88.8 percent), and 48.3 percent for the whole-cell vaccine (95 percent confidence interval, 37.0 to 57.6 percent). CONCLUSIONS: The five-component acellular pertussis vaccine we evaluated can be recommended for general use, since it has a favorable safety profile and confers sustained protection against pertussis. The two-component acellular vaccine and the whole-cell vaccine were less efficacious.

Hallander HO, Advani A, Donnelly D, Gustafsson L, Carlsson RM. Shifts of *Bordetella pertussis* variants in Sweden from 1970 to 2003, during three periods marked by different vaccination programs. *J Clin Microbiol.* 2005 Jun;43(6):2856-65.

The Swedish population of *Bordetella pertussis* strains was characterized from 1,247 isolates covering a whole-cell vaccine program up to 1979, a 17-year period without vaccination (1979 to 1996), and a period after the introduction of general vaccination among newborns with acellular pertussis vaccines (1997 to 2003). Strains were characterized by serotyping and genotyping of pertactin and *ptxA* and by means of pulsed-field gel electrophoresis (PFGE). With emphasis on vaccine-related markers, the vast majority of circulating strains were of nonvaccine type. There were shifts of serotype connected with shifts of vaccination program. Serotype Fim3 was most frequent during the periods with general vaccination schedules, whereas serotype Fim2 was predominant during the 17-year vaccine-free period. Pertactin 1 was predominant during the pertussis whole-cell (Pw) vaccine period but was thereafter replaced by *prn2* and has not reappeared after the introduction of acellular pertussis (Pa) vaccines. *ptxA* (1) was predominant over all three decades. There was a significant difference in the distribution of serotypes between vaccinated and unvaccinated individuals, but not for pertactin. A few PFGE profiles were predominant over the years: BpSR25 (serotype Fim3 *prn1/7*) and BpSR18 (serotype Fim3 *prn2*) during the Pw period, BpSR1 (serotype Fim2 *prn2*) during the 17 years without general vaccination, and BpSR11 (serotype Fim3 *prn2*) after the reintroduction of general vaccination in 1996. Despite differences between the pertactin and toxin types of Pa vaccines and circulating strains, there is no evidence that there is a threat, i.e., the vaccination program so far has been effective against whooping cough, and there seems to be no impact on the effectiveness of the vaccination program from the bacterial polymorphism.

Halperin, SA. 2007. The Control of Pertussis – 2007 and Beyond. *NEJM* 2007; 356(2):110-3. (No abstract)

Halperin SA, Wang EE, Law B, Mills E, Morris R, Déry P, Lebel M, MacDonald N, Jadavji T, Vaudry W, Scheifele D, Delage G, Duclos P. Epidemiological features of

pertussis in hospitalized patients in Canada, 1991-1997: report of the Immunization Monitoring Program--Active (IMPACT). Clin Infect Dis. 1999 Jun;28(6):1238-43.

To assess the morbidity associated with the continued high levels of pertussis, we studied all children <2 years of age who were admitted to the 11 Immunization Monitoring Program--Active (IMPACT) centers, which constitute 85% of Canada's tertiary care pediatric beds. In the 7 years preceding implementation of acellular pertussis vaccine, a total of 1,082 pertussis cases were reported, of which 49.1% were culture-confirmed. The median age of the patients was 12.4 weeks; 78.9% of cases were in children <6 months of age. Complications of pertussis were common: pneumonia was reported in 9.4% of cases, new seizures in 2.3%, and encephalopathy in 0.5%. There were 10 deaths (0.9%), all in children < or =6 months of age. Duration of hospitalization was longer (9.3 days vs. 4.9 days; P = .001) and intensive care was required more frequently (19.2% vs. 4.9%; P = .001) in infants under <6 months of age than in those > or =6 months. Pertussis continues to cause significant morbidity and occasional mortality in Canada, particularly in young infants.

Halperin SA, Bortolussi R, Langley JM, Miller B, Eastwood BJ. Seven days of erythromycin estolate is as effective as fourteen days for the treatment of Bordetella pertussis infections. Pediatrics. 1997 Jul;100(1):65-71.

OBJECTIVE AND METHODS: Although 14 days of erythromycin is recommended for the treatment of Bordetella pertussis infection, there have been no prospective controlled studies to support the contention that this long course of therapy is required to eradicate the microorganism from the nasopharynx or to prevent bacteriological relapse. We randomly allocated children and adults with culture-positive community-acquired pertussis to either 7 or 14 days of erythromycin estolate treatment (40 mg/kg/d; maximum dose 1 g/d). Nasopharyngeal aspirate cultures were obtained by study nurses during home visits before and at the end of treatment, and 1 week after the completion of treatment. B pertussis-specific antibodies were measured before treatment and 1 month later. Information about clinical symptoms, adverse reactions, and compliance were collected at each scheduled contact.

RESULTS AND CONCLUSIONS: A total of 168 participants were eligible for analysis (74 treated for 7 days and 94 treated for 14 days). Bacteriological persistence (positive end of therapy culture) occurred once in each group, and bacteriological relapse (positive culture 1 week after completion of treatment) occurred in one participant treated for 7 days. The overall failure rate (persistence plus relapse) of 2.70% in the 7-day group was not different than the rate of 1.06% in the 14-day group. The study had a power of 99.99% at the 5% level to detect a difference in failure rates of 10% and a power of 80% to detect a difference of 5%. We conclude that 7 days of erythromycin estolate is as effective as 14 days for the eradication of B pertussis.

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Halperin SA, Mills E, Barreto L, Pim C, Eastwood BJ. Acellular pertussis vaccine as a booster dose for seventeen- to nineteen-month-old children immunized with either whole cell or acellular pertussis vaccine at two, four and six months of age. Pediatr Infect Dis J. 1995 Sep;14(9):792-7.

The safety and immunogenicity of two formulations of an acellular pertussis vaccine as a booster at 17 to 19 months of age were assessed in children immunized at 2, 4 and 6 months of age with acellular or whole cell pertussis vaccine. In Study I 86 children primed with a

five-component acellular vaccine combined with diphtheria and tetanus toxoids or with a whole cell pertussis-diphtheria-tetanus vaccine were boosted with the same vaccine. Local reactions (64% vs. 93%; relative risk, 0.7; 95% confidence interval, 0.5 to 0.9) and systemic reactions (68% vs. 97%; relative risk, 0.7; 95% confidence interval, 0.5 to 0.9) were less common after the fourth dose of acellular vaccine than after the fourth dose of whole cell vaccine. In Study II 96 children primed with either an acellular or whole cell pertussis vaccine were boosted with an acellular vaccine. Local adverse reactions after booster immunization with acellular vaccine were more common in children primed with acellular vaccine than those primed with whole cell vaccine (68% vs. 33%; relative risk, 2.1; 95% confidence interval, 1.3 to 3.3). Antibody response to pertussis toxin, filamentous hemagglutinin and fimbriae were higher before and 1 month after the booster dose in children primed with the acellular vaccine. We conclude that the acellular pertussis vaccine is safe and immunogenic when used for the booster dose in children primed with either whole cell or acellular vaccine but is associated with local reactions.

Happe LE, Lunacsek OE, Kruzikas DT, Marshall GS. Impact of a pentavalent combination vaccine on immunization timeliness in a state Medicaid population. *Pediatr Infect Dis J.* 2009 Feb;28(2):98-101.

BACKGROUND: Use of combination vaccines has been associated with improved coverage rates, but their effect on timeliness remains to be explored. This study assessed the effect of diphtheria-tetanus-acellular pertussis/hepatitis B/inactivated polio vaccine (DTaP/HepB/IPV) on the timeliness of vaccine administration. **METHODS:** This retrospective cohort study used administrative claims data from the Georgia Medicaid program. Children with 24 months of continuous enrollment and at least 4 vaccine-related office visits were stratified into 2 cohorts: those with at least 3 DTaP/HepB/IPV doses (DTaP/HepB/IPV cohort) and those with at least 3 doses of DTaP but no doses of DTaP/HepB/IPV (reference cohort). Children who received any dose of HepB/Hib were excluded to isolate the effect of the study vaccine. Timeliness was measured as the percentage of children who received their vaccines on time and the cumulative days undervaccinated. **RESULTS:** There were 2880 children in the DTaP/HepB/IPV cohort and 2672 in the reference cohort. After controlling for covariates, receipt of DTaP/HepB/IPV was associated with significantly improved timeliness for 3 doses of DTaP (on-time rates: 66.3% vs. 60.8%, $P < 0.0001$; cumulative days undervaccinated: 29.5 vs. 70.4 days, $P < 0.0001$). Significantly improved timeliness was also observed in the DTaP/HepB/IPV cohort for IPV, HepB, Hib, 4 DTaPs, and the combination series assessed ($P < 0.001$ for all comparisons). **CONCLUSIONS:** Use of DTaP/HepB/IPV in this Medicaid population was associated with improved on-time vaccination and fewer undervaccinated days. These findings, along with previous research associating combination vaccines with improved coverage rates, provide quantitative data to support the ACIP, AAP, and AAFP preference for combination vaccines.

Heininger U, Klich K, Stehr K, Cherry JD. Clinical findings in *Bordetella pertussis* infections: results of a prospective multicenter surveillance study. *Pediatrics.* 1997 Dec;100(6):E10.

OBJECTIVE: To study the clinical presentation of culture-confirmed pertussis in children and their contacts with cough illnesses in an outpatient setting. **METHODOLOGY:** In conjunction with a large pertussis vaccine efficacy trial in Germany, a central laboratory to isolate *Bordetella* species from nasopharyngeal specimens was established in Erlangen in October 1990. Pediatricians in private practices in southern Germany, the Saar region, and Berlin were encouraged to obtain nasopharyngeal specimens and clinical characteristics from patients with cough illnesses ≥ 7 days' duration. *Bordetella* species were isolated by use of calcium alginate swabs, Regan-Lowe agar, and modified Stainer-Scholte broth. Clinical characteristics were determined by initial and follow-up questionnaires. **RESULTS:** From October 1990 to September 1996, 20 972 specimens were submitted, and *B. pertussis* was isolated in 2592 instances (12.4%). Of the culture-proven cases, 50.7% were female, and the age range was 6 days to 41 years, with a mean and median of 4.3 years and 4.1 years, respectively. The following characteristics were noted. Only 4% of the patients had received pertussis vaccine. Of unvaccinated patients, 90.2% had paroxysmal cough, 78.9% demonstrated whooping, and 53.3% presented with posttussive vomiting; 5.7% had fever ≥ 38 degrees C. The duration of cough was ≤ 4 weeks in 37.9% and ≤ 3 weeks in 17.4%. Leukocytosis and lymphocytosis (values above the age-specific mean) were observed in 71.9% and 75.9% of unvaccinated patients, respectively. The overall complication rate was 5.8%, and pneumonia (29%) was the most frequent complication. In infants < 6 months of age, the rate of complications was 23.8%. One death in a 7-month-old infant occurred. **CONCLUSIONS:** Typical symptoms of pertussis were observed in the great majority of patients regardless of age group. However, the duration of cough was surprisingly short in one sixth of the patients. These short illness cases would not be classified as pertussis according to the World Health Organization clinical case definition, which requires ≥ 21 days of spasmodic cough.

Hellenbrand W, Beier D, Jensen E, Littmann M, Meyer C, Oppermann H, Wirsing von König CH, Reiter S. The epidemiology of pertussis in Germany: past and present. BMC Infect Dis. 2009 Feb 25;9:22.

BACKGROUND: Current and past pertussis epidemiology in the two parts of Germany is compared in the context of different histories of vaccination recommendations and coverage to better understand patterns of disease transmission. **METHODS:** Available regional pertussis surveillance and vaccination coverage data, supplemented by a literature search for published surveys as well as official national hospital and mortality statistics, were analyzed in the context of respective vaccination recommendations from 1964 onwards. **RESULTS:** Routine childhood pertussis vaccination was recommended in the German Democratic Republic (GDR) from 1964 and in former West German states (FWG) from 1969, but withdrawn from 1974-1991 in FWG. Pertussis incidence declined to < 1 case/100,000 inhabitants in GDR prior to reunification in 1991, while in FWG, where pertussis was not notifiable after 1961, incidence was estimated at 160-180 cases/100,000 inhabitants in the 1970s-1980s. Despite recommendations for universal childhood immunization in 1991, vaccination coverage decreased in former East German States (FEG) and increased only slowly in FWG. After introduction of acellular pertussis vaccines in 1995, vaccination coverage increased markedly among younger children, but remains low in adolescents, especially in FWG, despite introduction of a booster vaccination for 9-17 year olds in 2000. Reported pertussis incidence increased in FEG to 39.3 cases/100,000 inhabitants in 2007, with the proportion of adults increasing from 20% in 1995 to 68% in 2007. From 2004-2007, incidence was highest among 5-14 year-old children, with a high proportion fully vaccinated

according to official recommendations, which did not include a preschool booster until 2006. Hospital discharge statistics revealed a ~2-fold higher pertussis morbidity among infants in FWG than FEG. CONCLUSION: The shift in pertussis morbidity to older age groups observed in FEG is similar to reports from other countries with longstanding vaccination programs and suggests that additional booster vaccination may be necessary beyond adolescence. The high proportion of fully vaccinated cases in older children in FEG suggests waning immunity 5-10 years after primary immunisation in infancy. The higher incidence of pertussis hospitalisations in infants suggests a stronger force of infection in FWG than FEG. Nationwide pertussis reporting is required for better evaluation of transmission patterns and vaccination policy in both parts of Germany.

Hendriks LH, Berbers GA, Veenhoven RH, Sanders EA, Buisman AM. IgG responses after booster vaccination with different pertussis vaccines in Dutch children 4 years of age: effect of vaccine antigen content. *Vaccine*. 2009 Nov 5;27(47):6530-6.

Since whooping cough is reemerging in the Netherlands from 1996 onwards, several changes in the national immunization program have been implemented regarding the pertussis vaccinations. The aim of this study is to investigate IgG responses in whole cell (wP) and acellular (aP) pertussis vaccine primed children following revaccination with different pertussis booster vaccines at 4 years of age. IgG levels to pertussis toxin (Pt), filamentous haemagglutinin (FHA), pertactin (Prn) and fimbriae type 2 and 3 (Fim2/3) and avidities of Pt and Prn antibodies were measured using a multiplex immunoassay. Before and after the booster we found significantly higher IgG levels to Pt, FHA and Prn in aP compared to wP primed children. In all children a booster vaccination with a pertussis vaccine containing a high antigen dose (Infanrix) induced higher IgG responses compared to a low antigen dose containing vaccine (Triaxis). Avidities of Pt- and Prn-antibodies before and after booster vaccination were significantly higher in aP than in wP primed children. This study shows that a booster vaccine with high pertussis antigen concentrations induces higher antibody levels than a low antigen containing vaccine. In children primed with the Dutch DTwP-IPV-Hib vaccine we suggest to administer a booster vaccine containing high pertussis antigens to optimize IgG responses. The pertussis vaccination history has to be taken into account in decisions on changes in pertussis vaccination policy.

Howson CP, Fineberg HV. Adverse events following pertussis and rubella vaccines. Summary of a report of the Institute of Medicine. *JAMA*. 1992 Jan 15;267(3):392-6.

In August 1991, the Institute of Medicine released a report entitled Adverse Effects of Pertussis and Rubella Vaccines, which examined 18 adverse events in relation to diphtheria-tetanus-pertussis (DTP) vaccine and four adverse events in relation to the currently used rubella vaccine strain, RA 27/3. The committee spent 20 months reviewing a wide range of information sources, including case series and individual case reports, both published and unpublished, epidemiologic studies, studies in animals, and other laboratory studies. The committee found that the evidence indicates a causal relation between DTP vaccine and anaphylaxis and between the pertussis component of DTP vaccine and extended periods of inconsolable crying or screaming. The committee also reported that the evidence indicates a causal relation between the rubella vaccine and acute arthritis in adult women. The committee found the available evidence weaker but still consistent with a causal relation between DTP vaccine and two conditions--acute encephalopathy and hypotonic, hyporesponsive episodes--

and between rubella vaccine and chronic arthritis in adult women. Estimated incidence rates of these adverse events following vaccination are provided, where possible. The committee found that the evidence does not indicate a causal relation between the DTP vaccine and infantile spasms, hypsarrhythmia, Reye's syndrome, and sudden infant death syndrome. The committee found insufficient evidence to indicate either the presence or absence of a causal relation between DTP vaccine and chronic neurologic damage, aseptic meningitis, erythema multiforme or other rash, Guillain-Barré syndrome, hemolytic anemia, juvenile diabetes, learning disabilities and attention-deficit disorder, peripheral mononeuropathy, or thrombocytopenia, and between rubella vaccine and radiculoneuritis and other neuropathies or thrombocytopenic purpura. The committee's evaluative methods are briefly described and a summary of research needs is provided.

Hviid A, Stellfeld M, Andersen PH, Wohlfahrt J, Melbye M. Vaccine. 2004 Sep 9;22(27-28):3530-4. Impact of routine vaccination with a pertussis toxoid vaccine in Denmark.

In many countries, acellular pertussis vaccines have replaced whole-cell vaccines. We evaluated the impact of a pertussis toxoid vaccine on pertussis in Denmark. We calculated incidence rates for pertussis before and after pertussis toxoid vaccine was introduced, and estimated vaccination effectiveness (VE). We found that routine vaccination with pertussis toxoid vaccine was effective against both hospitalisation with pertussis (VE, 93% for three doses) and non-hospitalised pertussis (VE, 78% for three doses). However, after the introduction we found an increase in pertussis among the youngest infants, a direct result of the new schedule (ages 3, 5 and 12 months) where the youngest infants are unvaccinated for a longer time-period compared with the prior schedule (ages 5, 9 weeks and 10 months).

Jacquet JM, Bégué P, Grimpel E, Reinert P, Sandbu S, Silfverdal SA, Faldella G, Nolan T, Lambert S, Richmond P, Marshall H, Robertson D, Schuerman L. Safety and immunogenicity of a combined DTPa-IPV vaccine administered as a booster from 4 years of age: a review. Vaccine. 2006 Mar 20;24(13):2440-8.

A combined DTPa-IPV booster vaccine was administered as a 4th or 5th dose after DTPa or DTPw priming. Over 99% vaccines developed antibody levels considered to be protective to diphtheria, tetanus and poliovirus, and >95% mounted a response to acellular pertussis antigens. Rectal temperature >39.5 degrees C was observed in at most 3.2% of vaccinees. Swelling >50 mm occurred in 24% of DTPa-primed compared to 5.5% of DTPw-primed children. Large swelling involving the entire upper arm (extending to involve the elbow joint) was reported for up to 1.2% of DTPa-primed subjects, which is consistent with literature reports for other DTPa vaccines.

Jardine A, Conaty SJ, Lowbridge C, Staff M, Vally H. Who gives pertussis to infants? Source of infection for laboratory confirmed cases less than 12 months of age during an epidemic, Sydney, 2009. Commun Dis Intell. 2010 Jun;34(2):116-21.

An important approach to protecting infants against pertussis is to provide a booster vaccination to close contacts, however this strategy requires a good understanding of infection sources to be effective. The objective of this study was to identify the most important sources of transmission of pertussis infection to infants, regardless of hospitalisation status. Standardised interviews were conducted during routine follow-up calls with the parent or guardian of laboratory confirmed pertussis cases less than 12 months of age notified to 3 Sydney metropolitan public health units during a pertussis outbreak from January to May 2009. All contacts with a coughing illness or laboratory confirmed pertussis during the 3 weeks prior to onset of illness in the index case, were recorded. A source of infection could not be identified for 29 infants (31%) and a total of 86 known or suspected sources were identified for the other 66 infants. The most frequently identified sources were siblings (36%) and parents (24%), followed by other family members (21%), friends (13%), and settings outside the home such as medical centres (6%). Of 20 siblings aged 3 or 4 years, 16 (80%) were sources of infection, compared with 14 of the 44 (32%) other siblings less than 18 years of age. During this epidemic siblings were more important sources of infant infection than parents. Siblings aged 3 and 4 years of age were particularly important transmitters of pertussis infection to infants. Minimising pertussis infection in 3 and 4 year olds may be an important measure to prevent infant infection.

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.

OBJECTIVE: To assess the efficacy and safety of whole-cell and acellular pertussis vaccines administered to children singly or within diphtheria, tetanus and pertussis (DTP) vaccines. **DATA SOURCES:** We searched the Cochrane Library, MEDLINE, EMBASE, Biological Abstracts and Science Citation Index to December 2001. Specialised websites and bibliographies of retrieved articles and reviews were assessed. Vaccine manufacturers and investigators were contacted for additional data. **REVIEW METHODS:** We included randomised and cohort studies comparing efficacy and/or safety of pertussis vaccines with placebo, DT, no intervention or each other. **RESULTS:** We included 52 studies (49 randomised controlled trials (RCTs), 3 cohort studies). All tested whole-cell and acellular vaccines were significantly more effective than placebo against pertussis. Absolute efficacy of whole-cell DTP varied from 37 to 92%. One- and two-component acellular vaccines had lower absolute efficacy (67-70%), than vaccines with ≥ 3 components (80-84%). Whole-cell 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 >2 h (OR 4.72, 95% CI 2.94-7.59) than placebo or DT. Differences in incidence of hypotonic hyporesponsive episodes (HHE) and convulsions 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. **CONCLUSION:** All tested pertussis vaccines were efficacious. Whole-cell vaccines show variable efficacy, making interpretation of direct comparisons unreliable. Acellular vaccines with ≥ 3 antigenic components showed higher efficacy than one- and two-component vaccines. The adverse event profile of acellular vaccines was similar to that of placebo and considerably better than that of whole-cell vaccines.

Jenkinson D. Duration of effectiveness of pertussis vaccine: evidence from a 10 year community study. Br Med J (Clin Res Ed). 1988 Feb 27;296(6622):612-4.

A 10 year study of whooping cough in a discrete general practice community was performed to assess longitudinally the efficacy of pertussis vaccine from one to seven years after immunisation. Of the 436 cases of whooping cough over 10 years, 326 occurred in children aged 1-7 years. The rate of immunisation was known for each cohort of children born during each year, and the attack rate of whooping cough was thus calculated for those immunised and unimmunized. The attack rates were highest in those cohorts exposed to the epidemics of 1977-9, 1981-3, and 1985-7. The efficacy of the vaccine was calculated as a percentage as (attack rate in unimmunized group--attack rate in immunised group) x 100/attack rate in unimmunized group. It fell from 100% in the first year to 46% in the seventh, being 84% in the fourth and only 52% in the fifth. Thus the pertussis vaccine or its schedule of use does not seem to provide sufficient herd immunity to prevent outbreaks of whooping cough. Matters might be improved if vaccination against pertussis were included in the preschool immunisation programme.

Kalies H, Grote V, Verstraeten T, Hessel L, Schmitt HJ, von Kries R. The use of combination vaccines has improved timeliness of vaccination in children. Pediatr Infect Dis J. 2006 Jun;25(6):507-12.

BACKGROUND: In Germany, Haemophilus influenzae type b (Hib), polio and hepatitis B (HBV) vaccines have been combined with diphtheria, tetanus and acellular pertussis vaccines. We examined whether the use of combination vaccines has improved the timing of these vaccinations. **METHODS:** Vaccination information was obtained from representative nationwide telephone interviews about 2701 children born from 1996 through 2003 in Germany. We assessed up-to-date vaccination as the percentage of children vaccinated by 3, 5 and 15 months for the first dose, full primary series and full immunization, respectively. We compared results over periods when different combination vaccines were used. We also compared median age at first dose, full priming and full immunization for children receiving different types of combination vaccines. **RESULTS:** During the study period, monovalent vaccines were replaced by higher-valent combination vaccines. With the change from mono- to 4-, 5- and 6-valent vaccines, up-to-date vaccination increased for Hib, polio and HBV. Median age at immunization improved by 0.5 month for Hib, 0.4 month for polio and 0.9 month for HBV at the first dose and 2.2 months for Hib, 3.2 months for polio and 1.4 months for HBV at full immunization when comparing hexavalent with monovalent vaccines. Median age for 4-5-valent vaccines was intermediate. The difference between monovalent and 6-valent vaccines remained significant after stratifying/adjusting for the effect of birth cohorts. **CONCLUSION:** Combination vaccines are usually advocated for reducing the number of injections. In Germany, however, the use of combination vaccines has also significantly improved timeliness of immunizations.

Kenyon TA, Izurieta H, Shulman ST, Rosenfeld E, Miller M, Daum R, Strebel PM. Large outbreak of pertussis among young children in Chicago, 1993: investigation of potential contributing factors and estimation of vaccine effectiveness. Pediatr Infect Dis J. 1996 Aug;15(8):655-61.

BACKGROUND: An outbreak of pertussis from July, 1993, to April, 1994, in Chicago was investigated to identify potential contributing factors. **METHODS:** Surveillance was enhanced to identify cases. Information from a vaccination coverage survey was used to define a retrospective cohort to estimate vaccine effectiveness of three or more doses of pertussis vaccine. **RESULTS:** The median age of 218 reported cases was 8 months, 46% had Hispanic surnames and cases were clustered geographically. Vaccination status was known for 173 of 191 (91%) children younger than 6 years of age. Of these 173, 90 (52%) were younger than 7 months, and 35 (20%) children at least 7 months of age had received fewer than 3 doses of pertussis vaccine. Pertussis vaccine effectiveness was 76% (95% confidence interval, 29 to 92). **CONCLUSIONS:** The limited ability of the current pertussis vaccination schedule to protect young infants accounted for 52% of cases, primary vaccine failure accounted for 28% of cases and failure to vaccinate children on time accounted for 20% of cases in young children. Low vaccine effectiveness did not appear to be a contributing factor.

Langley JM, Halperin SA, Boucher FD, Smith B; Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC). Azithromycin is as effective as and better tolerated than erythromycin estolate for the treatment of pertussis. Pediatrics. 2004 Jul;114(1):e96-101.

OBJECTIVE: Although universal immunization against *Bordetella pertussis* (whooping cough) infection has resulted in dramatic reductions in the incidence of pertussis, outbreaks continue to occur in countries with excellent vaccine coverage. Treatment of infection may ameliorate symptom severity during the catarrhal phase of pertussis but has no effect on established paroxysms, emesis, or apnea if given during the paroxysmal or convalescent phases. Erythromycin, recommended for treatment of pertussis to prevent transmission of infection, is poorly tolerated because of gastrointestinal side effects. We compared the safety and efficacy of erythromycin with azithromycin for treatment of pertussis in a large, randomized, controlled trial that enrolled children from primary care practices in 1 American and 11 Canadian urban centers.

METHODS: Children who were 6 months to 16 years of age and had cough illness that was suspected to be or was culture confirmed as pertussis were randomized to azithromycin (10 mg/kg on day 1 and 5 mg/kg on days 2-5 as a single dose) or erythromycin estolate (40 mg/kg/day in 3 divided doses for 10 days) with stratification by center. The primary outcome measure was bacteriologic cure of infection as determined by cultures of nasopharyngeal aspirates. Culture-positive participants had a second aspirate collected at the end of therapy (days 5-7 for azithromycin, days 10-12 for erythromycin) and 1 week after therapy. Bacteriologic cure was defined as negative cultures at the end of therapy. Bacteriologic relapse was defined as a positive culture 1 week after completion of therapy and after a negative end-of-therapy culture. Secondary outcomes were pertussis diagnosed by serology and polymerase chain reaction (PCR), treatment-associated adverse events, compliance, and presence of clinical symptoms at the end of the treatment course. Serology was performed using standard enzyme-linked immunosorbent assay methods. A participant was considered to have pertussis when the PCR was positive or a 4-fold increase in pertussis toxin antibody between baseline and follow-up visits was observed. PCR was performed using a 1046-bp *Cla*I DNA fragment from *B pertussis*. Adverse events (nausea, vomiting, diarrhea, any gastrointestinal complaint, or other) were determined by a parent-completed diary that was reviewed with study personnel during study visits. Compliance was measured by review of

the parent medication diary during study visits and observation of medication containers by the pharmacist at study completion. Symptoms were determined by history collected by study personnel at enrollment and subsequently from the diary. The design of the study was an equivalence trial, aimed at demonstrating that the bacteriologic failure rates with the 2 therapies did not differ by >8%. For the safety analysis, all participants who received at least 1 dose of study drug were included. In the per-protocol efficacy analysis, all culture-positive participants with end-of-treatment cultures were considered.

RESULTS: A total of 477 children were enrolled and randomly assigned to either azithromycin (n = 239) or erythromycin (n = 238). Of these children, 114 (24%) grew B pertussis from nasopharyngeal specimens (azithromycin group: 58 of 239 [24%]; erythromycin group: 56 of 238 [23%]); these children composed the efficacy cohort for the per-protocol and intention-to-treat analyses. Serology and PCR added 52 children to the number considered to have pertussis for a total of 35% (166 of 477) of all children who presented with cough illness. In the safety analysis (antibiotic side effects, compliance) and comparison of cough symptoms after treatment, all randomized children are reported in their assigned treatment group. At end of therapy, bacterial eradication was demonstrated in all 53 patients in the azithromycin group and all 53 patients in the erythromycin group with follow-up cultures available (eradication 100%; 95% confidence interval [CI]: 93.3-100). No bacterial recurrence was demonstrated in children with 1 week posttreatment nasopharyngeal cultures available (51 and 53 participants in the azithromycin and erythromycin arms, respectively [0%, 95% CI: 0-7.0; and 0%, 95% CI: 0-6.7]). No serious adverse events attributable to study drug were observed. Gastrointestinal adverse events were reported less frequently in azithromycin (18.8%; 45 of 239) than in erythromycin estolate (41.2%; 98 of 238) recipients (90% CI on difference: -29.0% to -15.7%) as a result of less nausea (2.9% vs 8.4%; 95% CI: -8.9% to -2.0%), less vomiting (5.0% vs 13.0%; 95% CI: -4.9% to -1.4%), and less diarrhea (7.1% vs 11.8%; 95% CI: -9.0% to -0.3%). Children who were randomized to azithromycin were much more likely to have complied with antimicrobial therapy over the treatment period. In the azithromycin group, 90% of children took 100% of prescribed doses, whereas only 55% of children in the erythromycin group took 100% of prescribed doses.

CONCLUSIONS: In this large, multicenter, randomized trial, we found that azithromycin is as effective as erythromycin estolate for the treatment of pertussis in children. Gastrointestinal adverse events were much more common with erythromycin treatment than azithromycin. Compliance with therapy was markedly better with azithromycin than with erythromycin in this study.

Liese JG, Meschievitz CK, Harzer E, Froeschle J, Hosbach P, Hoppe JE, Porter F, Stojanov S, Niinivaara K, Walker AM, Belohradsky BH. Efficacy of a two-component acellular pertussis vaccine in infants. *Pediatr Infect Dis J.* 1997 Nov;16(11):1038-44.

OBJECTIVE: This case-control study investigated the protective efficacy against pertussis of three doses of a two-component acellular pertussis vaccine (manufactured by Biken in Japan) combined with diphtheria and tetanus toxoids (manufactured by Connaught Laboratories in the US) in infants. **METHODS:** A case-control study was performed in 63 pediatric practices in Germany. Prospective recruitment of 16,780 infants ages 6 to 17 weeks took place between February, 1993, and July, 1994. According to parental choice infants received either Biken acellular pertussis vaccine combined with diphtheria and tetanus toxoids (DTacP) (74.6%) at approximately 2, 4 and 6 months of age, or a licensed German diphtheria-tetanus toxoids-

whole cell pertussis vaccine (10.9%), diphtheria-tetanus toxoids vaccine (12.5%) or no vaccine (2.0%). Prospective surveillance of pertussis cases between February, 1993, and May, 1995, was accomplished by culturing all infants \leq 2 years of age presenting with cough \geq 7 days. A pertussis case was defined as any cough of 21 days or longer plus a positive *Bordetella pertussis* culture or household contact exposure. RESULTS: We identified 241 pertussis cases prospectively by 11,017 *B. pertussis* cultures and 949 controls matched for age were selected from the same pediatric practices. Medical history and demographic and vaccine status data were collected from each case and for four controls. Data were analyzed through conditional logistic regression taking into account individual matching and adjusting for potential confounding variables. DTaP combined with diphtheria and tetanus toxoids vaccine was 82% protective (95% confidence interval, 68 to 90), diphtheria-tetanus toxoids-whole cell pertussis vaccine was 96% protective (95% confidence interval, 78 to 99). Protection against typical *B. pertussis* infection characterized by paroxysmal cough lasting \geq 21 days was 96% (95% confidence interval, 87 to 99) for DTaP and was 97% (95% confidence interval, 79 to 100) for diphtheria-tetanus toxoids-whole cell pertussis vaccine. Adjustment for potentially confounding variables did not change the results significantly. CONCLUSIONS: Three doses of the two-component acellular pertussis vaccine protected infants against pertussis disease during the period before the recommended booster vaccination. For typical pertussis disease as defined by the WHO efficacy was high and similar to that of a licensed German diphtheria-tetanus toxoids-whole cell pertussis vaccine.

McIntyre PB, Burgess MA, Egan A, Schuerman L, Hoet B. Booster vaccination of adults with reduced-antigen-content diphtheria, Tetanus and pertussis vaccine: immunogenicity 5 years post-vaccination. Vaccine. 2009 Feb 11;27(7):1062-6. Epub 2008 Dec 16.

At 60 months post-vaccination, adults (mean age 45.6 years) randomised to receive combined reduced-antigen-content diphtheria-tetanus and acellular pertussis vaccine (dTpa) versus tetanus-diphtheria (Td)+monovalent acellular pertussis (pa) were seroprotected against diphtheria (\geq or $=$ 0.016IU/mL Vero cell assay) and tetanus (\geq or $=$ 0.1IU/mL ELISA assay) in 94.4% and 96.2%, respectively (dTpa), compared with 93.7% and 90.6% (Td+pa). Anti-FHA, anti-PT and anti-PRN antibodies (\geq or $=$ 5EL.U/mL) were maintained in 100%, 89.5% and 95.0% of dTpa versus 100%, 85.5% and 90.6% of pa vaccine recipients. At 5 years post boosting, antibody levels to diphtheria and tetanus are similar amongst adults receiving a dTpa or dT, and pertussis antibodies remain above pre-booster levels in at least 85%.

McVernon J, Andrews N, Slack MP, Ramsay ME. Risk of vaccine failure after Haemophilus influenzae type b (Hib) combination vaccines with acellular pertussis. Lancet. 2003 May 3;361(9368):1521-3.

An increase in invasive Hib disease incidence in the UK has coincided with the distribution of combination vaccines that contain acellular pertussis (DTaP-Hib). These vaccines have been associated with reduced immunogenicity of the Hib component, although there is little agreement on the clinical relevance of this finding. We retrospectively compared vaccine formulations given to fully vaccinated Hib cases with those administered to fully immunised age-matched controls using conditional logistic regression. More cases than controls received

all three doses of their infant primary course as DTaP-Hib, compared with two or three doses of another Hib vaccine (conditional odds ratio 6.77 [95% CI 3.26-14.07]).

Miller DC, Wadsworth MJ, Ross EM. Pertussis vaccine and severe acute neurological illnesses. Response to a recent review by members of the NCES team. Vaccine. 1989 Dec;7(6):487-9.

Dr. A. H. Griffith's article on this subject raises some important issues which require comment. We, like him, regret the controversy over the safety and efficacy of whole cell pertussis vaccines over the last 15 years. It does indeed represent a sorry saga whose principal victims are children, many of whom have not been vaccinated against this unpleasant and sometimes dangerous illness because of fears over safety of the vaccine. The National Childhood Encephalopathy Study (NCES), was set up in 1976 as an independent scientific enquiry into severe acute neurological illnesses associated with pertussis vaccine in an attempt to help resolve the matter. The report on the results concluded that these suggested, but did not prove, that the vaccine may very rarely cause the development of potentially damaging severe acute neurological illnesses in children who were previously apparently neurologically normal. Unfortunately the number of cases in the NCES was too small to allow any firm conclusions on whether or not the vaccine can cause permanent damage. The NCES has since been subject to intense scrutiny and criticism both by those who consider the vaccine can cause permanent neurological damage and by those, such as Dr Griffith, who consider it does not. Regrettably, the controversy continues.

Miller D, Madge N, Diamond J, Wadsworth J, Ross E. Pertussis immunisation and serious acute neurological illnesses in children. BMJ. 1993 Nov 6;307(6913):1171-6.

OBJECTIVE: To determine long term outcome in children who had a severe acute neurological illness in early childhood associated with pertussis immunisation. **DESIGN:** Follow up study of cases and matched controls. **SETTING:** Assessment of children at home and at school throughout Britain. **SUBJECTS:** Children recruited into the national childhood encephalopathy study in 1976-9 were followed up, with one of their two original matched controls, in 1986-9. **MAIN OUTCOME MEASURES:** Performance in educational attainment tests; behaviour problems reported by teachers and parents; continuing convulsions; evidence of other neurological or physical dysfunction. **RESULTS:** Over 80% of cases and controls were traced. Case children were significantly more likely than controls to have died or to have some form of educational, behavioural, neurological, or physical dysfunction a decade after their illness. The prevalence of one or more of these adverse outcomes in case children who had been immunised with diphtheria, tetanus, and pertussis vaccine within seven days before onset of their original illness was similar to that in case children who had not been immunised recently. The relative risk for recent diphtheria, tetanus, and pertussis immunisation in children who had died or had any dysfunction in comparison with controls was 5.5 (95% confidence interval 1.6 to 23.7). However, the number of cases associated with vaccine (12) was extremely small and statistically vulnerable, and other possible agents or predisposing factors could not be excluded. **CONCLUSIONS:** Diphtheria, tetanus, and pertussis vaccine

may on rare occasions be associated with the development of severe acute neurological illnesses that can have serious sequelae. Some cases may occur by chance or have other causes. The role of pertussis vaccine as a prime or concomitant factor in the aetiology of these illnesses cannot be determined in any individual case. The balance of possible risk against known benefits from pertussis immunisation supports continued use of the vaccine.

Mooi FR, He Q, Guiso N Phylogeny, evolution, and epidemiology of Bordetellae. In: Locht C, editor. *Bordetella* molecular microbiology, 1st ed. Norfolk (UK): Horizon Bioscience; 2007. p. 17–45.

Njamkepo E, Rimlinger F, Thiberge S, Guiso N. Thirty-five years' experience with the whole-cell pertussis vaccine in France: vaccine strains analysis and immunogenicity. *Vaccine*. 2002 Jan 31;20(9-10):1290-4.

A resurgence in infant and adult pertussis cases has been observed in many countries around 25 years after the introduction of generalised vaccination. An antigenic differences between circulating isolates and vaccinal strains, due to changes in vaccine procedures, could be due to this resurgence. In this study, we analysed the genome and antigenic expression of vaccinal strains of the Aventis Pasteur whole-cell pertussis vaccine from multiple lots stored since 1984. Despite lyophilisation having been performed on these strains for over 30 years, their genome remain conserved, and they still express the major toxins and adhesins. A study in mice confirmed that vaccine lots were highly immunogenic. In conclusion, there is no evidence to suggest that many years of production have resulted in alteration in the French vaccinal strains which quality has remained consistent since its introduction, this can explain its continued efficacy, effectiveness and the lack of epidemics in France.

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.

BACKGROUND: Trials in Italy and Sweden showed high efficacy for three-component and five-component pertussis vaccines, and poor efficacy for a whole-cell vaccine licensed in the USA and a two-component vaccine. We compared the efficacy of three acellular vaccines with a UK whole-cell vaccine. **METHODS:** We enrolled 82,892 babies aged 2-3 months. Babies were vaccinated at age 3 months, 5 months, and 12 months, or age 2 months, 4 months, and 6 months. They were randomly assigned a two-component acellular diphtheria-tetanus-pertussis (DTP) vaccine (n = 20,697), a three-component acellular DTP vaccine (n = 20,728), a five-component acellular DTP vaccine (n = 20,747), or a UK whole-cell DTP vaccine (n = 20,720). We collected data for all reported cases of culture-confirmed pertussis during 3 years of follow-up. The treatment status of the two-component-vaccine group had to be made known midway through the trial for boosting because of poor efficacy. We included data for the two-component vaccine in the analysis of safety and immunogenicity, and data up

its unmasking in secondary analyses of relative efficacy. Analyses were by intention to treat. FINDINGS: During follow-up from the third dose (mean 22 months), in the 3 months, 5 months, 12 months schedule, there were 15 cases of culture-confirmed pertussis with at least 21 days of paroxysmal cough in the whole-cell group, relative risk 1.00, compared with 13 in the five-component group (0.85 [95% CI 0.41-1.79]), and 21 in the three-component group (1.38 [0.71-2.69]). For culture-confirmed pertussis, with or without cough, there were 19 cases in the whole-cell group (1.00), 27 in the five-component group (1.40 [0.78-2.52]), and 49 in the three-component group (2.55 [1.50-4.33]). In the intention-to-treat analyses, from the first dose in the 3 months, 5 months, 12 months schedule the whole-cell vaccine was significantly more protective than the three-component vaccine against typical pertussis. Between the second and the third doses, culture-confirmed pertussis with any cough and with at least 21 days of paroxysmal cough was significantly more frequent in the two-component group than in the three-component group, and in the three-component group than in the five-component and the whole-cell groups, respectively. The serological response of the acellular vaccines in the 2 months, 4 months, 6 months schedule were similar to those previously reported. The whole-cell vaccine was highly immunogenic for fimbriae, pertactin, and filamentous haemagglutinin, but had a low antipertussis toxin response. Hypotonic hyporesponsiveness occurred significantly more frequently in the whole-cell group ($p < 0.05$) and was more frequent in the acellular groups than previously reported. High fever and seizures occurred more frequently after whole-cell vaccine than after any of the acellular vaccines ($p < 0.001$). INTERPRETATIONS: The efficacy of the UK whole-cell vaccine and the five-component and three-component vaccines was similar against culture-confirmed pertussis with at least 21 days of paroxysmal cough. The lower efficacy of the three-component vaccine against mild disease suggests that fimbriae have a role in protection against infection. The efficacy of acellular vaccines depends on the number of components, and different whole-cell vaccines have variable efficacies.

Okada K, Ohashi Y, Matsuo F, Uno S, Soh M, Nishima S. Effectiveness of an acellular pertussis vaccine in Japanese children during a non-epidemic period: a matched case-control study. *Epidemiol Infect.* 2009 Jan;137(1):124-30.

The number of pertussis cases in Japan has decreased dramatically following the nationwide use of an acellular pertussis vaccine combined with diphtheria-tetanus toxoids (DTaP vaccines) which began in 1981. However, the effectiveness of the DTaP vaccine has not been systematically evaluated using appropriate epidemiological methods during a non-epidemic period in Japan. We evaluated the vaccine effectiveness (VE) of the Kaketsuken DTaP vaccine which contains two-component pertussis antigens in Japanese children from 1999 to 2001 using a matched case-control design and data from the Basic Resident Registration and Maternal and Child Health Handbooks. The DTaP vaccination history of 15 children with pertussis and 59 controls was obtained. The VE of 3 or 4 pertussis vaccinations compared with non-vaccination (baseline) was 96.9% for coughing attacks that lasted 7 days, 96.4% for those lasting 14 days, and 95.9% for those lasting 21 days. These findings suggest that DTaP vaccination effectively prevented pertussis during a non-epidemic period in Japan.

Onorato IM, Wassilak SG, Meade B. Efficacy of whole-cell pertussis vaccine in preschool children in the United States. *JAMA.* 1992 May 27;267(20):2745-9.

OBJECTIVE: To evaluate the efficacy of currently used whole-cell pertussis vaccines. **DESIGN:** Active surveillance to detect pertussis cases in Baltimore, Md, Denver, Colo, and Milwaukee, Wis, and investigation of secondary attack rates in 347 household contacts, aged 1 through 4 years, to estimate vaccine efficacy. **OUTCOME MEASURE:** Vaccine efficacy was estimated using different case definitions for pertussis. **RESULTS:** Vaccine efficacy was 64%, 81%, and 95% for case definitions of mild cough, paroxysmal cough, and severe clinical illness, respectively. Requiring laboratory confirmation increased efficacy to 95% to 98% for culture-positive children and to 77% to 95% for culture- or serology-confirmed cases, depending on disease severity. Vaccine efficacy for typical paroxysmal cough increased from 44% for one diphtheria, tetanus, and pertussis vaccine dose to 80% for four or more doses. **CONCLUSIONS:** The trend toward increasing vaccine efficacy with different case definitions may be due to improved efficacy in preventing severe illness and to case definitions that are more specific for pertussis. Whole-cell pertussis vaccine was highly effective in preventing pertussis in preschool children exposed to infection within their households. Direct side-by-side efficacy studies of whole-cell vaccine and the recently licensed acellular vaccine will be necessary to assure that comparable protection is afforded by the new vaccines if they are to be used for immunization of infants.

Pichichero ME, Deloria MA, Rennels MB, Anderson EL, Edwards KM, Decker MD, Englund JA, Steinhoff MC, Deforest A, Meade BD. A safety and immunogenicity comparison of 12 acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fourth dose in 15- to 20-month-old children. *Pediatrics*. 1997 Nov;100(5):772-88.

OBJECTIVE: To compare the safety and immunogenicity of 12 different acellular pertussis vaccines combined with diphtheria and tetanus toxoids (DTaP) with one licensed diphtheria, tetanus, and whole-cell pertussis vaccine (DTwP) as a fourth-dose booster in children who had previously received DTaP or DTwP primary vaccinations. **METHODS:** Healthy 15- to 20-month-old children were enrolled at six National Institutes of Health Vaccine Treatment and Evaluation Units. All had been randomly assigned to receive three primary doses of DTaP or DTwP at 2, 4, and 6 months of age as part of an earlier National Institutes of Health multicenter trial of DTaP vaccines in the same Vaccine Treatment and Evaluation Units. Parents recorded the occurrence and magnitude of fever; irritability; and injection site redness, swelling, and pain for 3 days after vaccination. Sera obtained before and 1 month after the booster vaccination were analyzed for antibody to pertussis toxin (PT), filamentous hemagglutinin (FHA), fimbriae (FIM), and pertactin (PRN). Diphtheria and tetanus toxoid as well as PT neutralizing (Chinese hamster ovary cell) and whole-cell agglutinating antibodies were measured on a subset of sera. **RESULTS:** A total of 1293 children contributed fourth-dose reaction data. Reactions were less frequent after DTaP than after DTwP. For children vaccinated with a fourth dose of DTaP, which was the same DTaP as received in the primary series, fever and injection site redness, swelling, and pain increased in prevalence compared with the third dose in the primary series. For children receiving DTaP as a fourth dose, injection site redness and swelling occurred more frequently in DTaP-primed than in DTwP-primed children. Variation in the occurrence of reactions among DTaP vaccines was observed. A total of 1160 paired pre- and postvaccination sera were available for analysis. Serum antibody concentrations before boosting were lower than those obtained 1 month after the primary immunization. After the fourth dose, significant increases in antibodies directed against the included antigens were observed for all vaccines; postbooster vaccination antibody

titers differed significantly among the DTaP vaccines. For children primed and boosted with the same DTaP, antibody levels were not directly related to the quantity of antigen included for PT, FHA, and FIM; for PRN, there was a closer relationship. Some DTaP vaccines given as fourth-dose boosters elicited antibody to PRN or FIM in some vaccinees, although the DTaP vaccines were not reported to contain these antigens; these responses were observed more frequently in DTwP-primed children. Agglutinin antibody rises were observed in all groups immunized with four doses of a DTaP vaccine containing FHA or PRN, regardless of whether the vaccine included FIM. Diphtheria and tetanus antibody levels exceeded the presumed protective concentration (0.1 IU/mL for diphtheria and 0.01 IU/mL for tetanus) after the fourth dose for all vaccinees. **CONCLUSION:** Although differences were observed in reaction rates among the DTaP vaccines given as a fourth dose, the DTaP vaccines were, in general, associated with fewer adverse events than a US-licensed DTwP. For DTaP vaccines, fever; irritability; and injection site pain, redness, and swelling occurred more frequently after the fourth dose than after the third dose of the same vaccine in the primary series. No DTaP was consistently most or least reactogenic or immunogenic. Although serologic correlates of pertussis immunity are not defined, it is clear that most DTaP vaccines can stimulate comparable or higher serum antibody responses than DTwP for those antigens contained in the vaccine.

Préziosi MP, Halloran ME. Effects of pertussis vaccination on disease: vaccine efficacy in reducing clinical severity. Clin Infect Dis. 2003 Sep 15;37(6):772-9.

We estimated the effectiveness of pertussis vaccination in reducing the clinical severity of breakthrough disease among vaccinated individuals from a comprehensive follow-up study of a community of 30,000 residents of Niakhar, Senegal, in 1993. A physician examined all children with potential pertussis (cough of >7 days' duration). Samples were collected from 97% of these children for culture or serologic testing as part of the active surveillance for a pertussis vaccine trial. Cases of pertussis were defined by confirmation through culture or serologic testing or by a history of contact with a person with culture-confirmed pertussis. Among children with confirmed cases, severity of illness was assessed according to a scale that combined clinical signs and symptoms. The efficacy of the vaccine in reducing disease severity was 48% (95% confidence interval, 39%-55%) among children vaccinated with 3 doses of whole-cell (67%) or acellular (32%) vaccine. Primary cases were more severe than secondary cases in residential compounds. Pertussis vaccination is effective in reducing the severity of illness.

Préziosi MP, Yam A, Wassilak SG, Chabirand L, Simaga A, Ndiaye M, Dia M, Dabis F, Simondon F. Epidemiology of pertussis in a West African community before and after introduction of a widespread vaccination program. Am J Epidemiol. 2002 May 15;155(10):891-6.

The control of pertussis remains a worldwide concern. Little has been documented about its epidemiology in Africa. The authors have studied pertussis in a prospective cohort of children in a rural West African community over a 13-year period comprising time before and after introduction of a vaccination program. Children under age 15 years who were residents of the Niakhar study area in Senegal were followed prospectively between January 1984 and

December 1996 for the occurrence of pertussis. Morbidity and mortality rates were extremely high before the launch of immunization. Crude incidence was 183 per 1,000 child-years at risk under age 5 years, with a 2.8% case-fatality rate. After the introduction of the vaccination program, overall incidence dropped rapidly and dramatically-by 27% after 3 years and 46% after 6 years. The decline in incidence involved all age groups but was most substantial in the group under age 5 years and was particularly pronounced in unvaccinated infants. The median age of acquisition of the disease rose steadily with population vaccine coverage. This study shows the tremendous magnitude of the disease burden in children and the rapid decline after vaccination, and it suggests a strong herd-immunity effect.

Quinn HE, McIntyre PB. Pertussis epidemiology in Australia over the decade 1995-2005--trends by region and age group. *Commun Dis Intell.* 2007 Jun;31(2):205-15.

Important changes have occurred in the National Immunisation Program for pertussis during the decade 1995-2005, including the introduction of acellular pertussis vaccine for all doses, removal from the schedule of the booster dose at 18 months, and the introduction of a booster dose for adolescents. In addition, the coverage of pertussis vaccine at 12 and 24 months has substantially increased as recorded by Australian Bureau of Statistics surveys and the Australian Childhood Immunisation Register. There were 75,458 notifications nationally between 1995 and 2005, with little change in the annual number of notifications at the national level but with periodic and dramatic changes in the age distribution of notified cases. Pertussis is well controlled in the 1-4 and 5-9 year age groups, and the highest annual notification rates continue to be in infants under 6 months of age. Adolescents aged 10-19 years had high notification rates in all states and territories, over this period, but 63% of notifications are now in the 20-59 year age range. Following the introduction of a fifth dose for adolescents, the current focus should be on protecting infants too young to be vaccinated and further defining the true morbidity of the disease in the elderly population.

Ray P, Hayward J, Michelson D, Lewis E, Schwalbe J, Black S, Shinefield H, Marcy M, Huff K, Ward J, Mullooly J, Chen R, Davis R; Vaccine Safety Datalink Group. Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study. *Pediatr Infect Dis J.* 2006 Sep;25(9):768-73.

BACKGROUND: Whole-cell pertussis (wP) and measles vaccines are effective in preventing disease but have also been suspected of increasing the risk of encephalopathy or encephalitis. Although many countries now use acellular pertussis vaccines, wP vaccine is still widely used in the developing world. It is therefore important to evaluate whether wP vaccine increases the risk of neurologic disorders.

METHODS: A retrospective case-control study was performed at 4 health maintenance organizations. Records from January 1, 1981, through December 31, 1995, were examined to identify children aged 0 to 6 years old hospitalized with encephalopathy or related conditions. The cause of the encephalopathy was categorized as known, unknown or suspected but unconfirmed. Up to 3 controls were matched to each case. Conditional logistic regression was used to analyze the relative risk of encephalopathy after vaccination with diphtheria-tetanus-

pertussis (DTP) or measles-mumps-rubella (MMR) vaccines in the 90 days before disease onset as defined by chart review compared with an equivalent period among controls indexed by matching on case onset date.

RESULTS: Four-hundred fifty-two cases were identified. Cases were no more likely than controls to have received either vaccine during the 90 days before disease onset. When encephalopathies of known etiology were excluded, the odds ratio for case children having received DTP within 7 days before onset of disease was 1.22 (95% confidence interval [CI] = 0.45-3.31, P = 0.693) compared with control children. For MMR in the 90 days before onset of encephalopathy, the odds ratio was 1.23 (95% confidence interval = 0.51-2.98, P = 0.647).

CONCLUSIONS: In this study of more than 2 million children, DTP and MMR vaccines were not associated with an increased risk of encephalopathy after vaccination.

Rendi-Wagner P, Kundi M, Mikolasek A, Vécsei A, Frühwirth M, Kollaritsch H. Hospital-based active surveillance of childhood pertussis in Austria from 1996 to 2003: estimates of incidence and vaccine effectiveness of whole-cell and acellular vaccine. Vaccine. 2006 Aug 14;24(33-34):5960-5.

BACKGROUND: This study was undertaken to analyse the epidemiology of pertussis disease among hospitalised children during the transition period from whole-cell to acellular pertussis vaccine in order to compare the respective estimates of vaccine effectiveness. **METHODS:** Surveillance was conducted between 1 January 1996 and 31 December 2003. The data originated from a voluntary hospital-based surveillance network including all 44 nationwide paediatric departments. **RESULTS:** The mean annual hospitalisation incidence for children decreased over time, from 27.9 per 100,000 population in 1996 to 6.8 cases per 100,000 population in 2003. The mean age of reported hospitalised pertussis cases was 4.7 years (+/- 5.5 S.D.), increasing from 4.06 years (+/- 4.6 S.D.) in 1996 to 5.5 years (+/- 8.6 S.D.) in 2003. Estimated vaccine effectiveness (after three vaccine doses) was 79% for the whole-cell versus 92% for the acellular pertussis vaccine. A significantly higher proportion (19%) of fully immunised children among hospitalised patients was observed for the years where only acellular pertussis vaccine was used compared to whole-cell vaccine era (2%) which was, however, mainly due to children above 2 years of age. **CONCLUSIONS:** Our results imply that despite high vaccination coverage rate, pertussis is still a considerable cause of hospital admissions in children in Austria where it remains to be shown that the novel vaccination strategy of additional booster doses in adolescents and adults will control disease in the long term.

Rennels MB, Black S, Woo EJ, Campbell S, Edwards KM. Safety of a fifth dose of diphtheria and tetanus toxoid and acellular pertussis vaccine in children experiencing extensive, local reactions to the fourth dose. Pediatr Infect Dis J. 2008 May;27(5):464-5.

Extensive local reactions have been reported after booster doses of diphtheria and tetanus toxoid and acellular pertussis vaccine, but few data are available on revaccination after these reactions. Of 20 children with extensive local reactions after dose 4, only 4 experienced entire upper arm swelling and 7 had swelling >5 cm after dose 5. These reactions were well tolerated and support revaccination.

Rennels MB. Extensive swelling reactions occurring after booster doses of diphtheria-tetanus-acellular pertussis vaccines. *Semin Pediatr Infect Dis.* 2003 Jul;14(3):196-8.

Extensive local reactions are recognized to occur after administration of the fourth and fifth booster doses of diphtheria-tetanus-acellular pertussis (DTaP) vaccines. The incidence of these reactions is being delineated by prospective studies. Retrospective evaluations suggest that entire proximal limb swelling occurs in 2 to 6 percent of children given booster doses of DTaP vaccines. The reactions subside without sequelae, but they may be misdiagnosed as cellulitis and lead to unnecessary medical intervention. The pathogenesis of these reactions probably is multifactorial. Evidence suggests that both antigen content and prevaccination immunity have roles. Important, unanswered questions are the safety of revaccinating a child who previously has had an extensive local reaction and the safety of introducing further DTaP boosters into the adolescent and adult populations.

Ray P, Hayward J, Michelson D, Lewis E, Schwalbe J, Black S, Shinefield H, Marcy M, Huff K, Ward J, Mullooly J, Chen R, Davis R; Vaccine Safety Datalink Group. Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study. *Pediatr Infect Dis J.* 2006 Sep;25(9):768-73.

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METHODS: A retrospective case-control study was performed at 4 health maintenance organizations. Records from January 1, 1981, through December 31, 1995, were examined to identify children aged 0 to 6 years old hospitalized with encephalopathy or related conditions. The cause of the encephalopathy was categorized as known, unknown or suspected but unconfirmed. Up to 3 controls were matched to each case. Conditional logistic regression was used to analyze the relative risk of encephalopathy after vaccination with diphtheria-tetanus-pertussis (DTP) or measles-mumps-rubella (MMR) vaccines in the 90 days before disease onset as defined by chart review compared with an equivalent period among controls indexed by matching on case onset date.

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CONCLUSIONS: In this study of more than 2 million children, DTP and MMR vaccines were not associated with an increased risk of encephalopathy after vaccination.

Riffelmann M, Wirsing von König CH, Caro V, Guiso N; Pertussis PCR Consensus Group. Nucleic Acid amplification tests for diagnosis of Bordetella infections. J Clin Microbiol. 2005 Oct;43(10):4925-9. (No summary).

Salmaso S, Mastrantonio P, Tozzi AE, Stefanelli P, Anemona A, Ciofi degli Atti ML, Giammanco A; Stage III Working Group. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: the Italian experience. Pediatrics. 2001 Nov;108(5):E81.

BACKGROUND: In 1992-1993, a randomized, double-blind, placebo-controlled clinical trial of two 3-component acellular pertussis vaccines was started in 4 of Italy's 20 regions. During the trial, the children had been randomized to receive 3 doses of 1 of 2 acellular pertussis vaccines combined with diphtheria and tetanus toxoids (DT) or of a DT vaccine only, at 2, 4, and 6 months of age. Both diphtheria-tetanus-acellular pertussis (DTaP) vaccines, 1 manufactured by SmithKline Beecham (DTaP SB; Infanrix) and 1 manufactured by Chiron Biocine (DTaP CB; Triacelluvax), contain pertussis toxin (PT), filamentous hemagglutinin, and pertactin. The results of the first period of follow-up, which ended in 1994 (stage 1), showed that both vaccines had a protective efficacy of 84% in the first 2 years of life; when the trial's follow-up was extended under partial blinding until the participating children had reached 33 months of age (stage 2 of the follow-up), these high levels of efficacy had persisted. Therefore, the objective of this study was to estimate the persistence of protection from 3 to 6 years of age of the 2 3-component DTaP vaccines administered as primary immunization in infancy. **METHODS:** An unblinded prospective longitudinal study of vaccinated and unvaccinated children in 4 Italian regions, with active surveillance of cough, was conducted by study nurses, and Bordetella pertussis infections were confirmed laboratory. The present study (stage 3) included those children who completed stage 2 of the follow-up and were still under active surveillance as of October 1, 1995, accounting for 4217 children who had received DTaP SB (representing 94% of the vaccine's recipients in the initial phase of the trial), 4215 who had received DTaP CB (95% of the original recipients), and 266 who had received DT only (18% of the original recipients). Because the parents of most of the original DT placebo group accepted pertussis vaccination during stage 2 in 1995, an additional 856 children were recruited in the DT group at the initiation of stage 3. These additional children were identified from the census list of children born in the same period and living in the same areas as the trial participants but who had been vaccinated in infancy with DT only. Eligible children were included in stage 3 if they had no history of either pertussis or pertussis vaccination and if a serum sample obtained at the time of enrollment had undetectable immunoglobulin G (IgG) against PT. Parental consent to participate in the study was obtained. Active surveillance for pertussis was conducted in the field by 72 study nurses through monthly contact with each family in the study. A cough episode that lasted ≥ 7 days was considered to be a laboratory-confirmed infection by Bordetella pertussis if at least 1 of the following 5 criteria (listed in hierarchic order) was met: 1) B pertussis was obtained from nasopharyngeal culture (culture-confirmed infection); 2) the enzyme-linked immunosorbent assay (ELISA) IgG or IgA titer against PT in the convalescent-phase serum sample increased by at least 100% compared with the acute-phase sample; 3) the PT-neutralizing titers in Chinese hamster ovary assay in the convalescent-phase sample increased by at least 4-fold compared with the acute-phase sample; 4) the ELISA IgG or IgA titer against filamentous

hemagglutinin in the convalescent-phase sample increased by at least 100% and the culture or the polymerase chain reaction assay on the nasopharyngeal aspirate was negative for B parapertussis; and 5) the ELISA IgG PT titer in 1 of the 2 serum samples exceeded the geometric mean titer computed on convalescent sera of the children with a culture-confirmed B pertussis infection in each study group. Incidence of laboratory-confirmed B pertussis infection, using case definitions that varied in terms of duration and type of cough, was computed and the proportion of cases prevented among DTaP recipients in comparison with DT recipients was calculated. RESULTS: A total of 391 laboratory-confirmed infections were identified in the 3-year follow-up period (138 DTaP SB, 126 DTaP CB, 127 DT recipients, respectively). The mean duration of cough in children with laboratory-confirmed infection was 48, 47, and 70 days for the DTaP SB, DTaP CB, and DT recipients, respectively; the mean duration of spasmodic cough was 15, 13, and 23 days, respectively. When using the primary case definition (ie, laboratory-confirmed B pertussis infection and ≥ 14 days of spasmodic cough or ≥ 21 days of any cough), the efficacy was 78% for the DTaP SB vaccine (95% confidence interval [CI]: 71%-83%) and 81% for the DTaP CB vaccine (95% CI: 74%-85%). When using the case definition based on a more severe clinical presentation (≥ 21 days of spasmodic cough), the vaccine efficacy was 86% (95% CI: 79%-91%) for both vaccines. When using the case definition based on milder clinical presentation (any cough for ≥ 7 days), the efficacy was 76% (95% CI: 69%-81%) for the DTaP SB vaccine and 78% (95% CI: 72%-83%) for the DTaP CB vaccine. CONCLUSIONS: The persistence of protection through 6 years of age suggests that the fourth DTaP dose could be postponed until preschool age in children who received 3-component acellular pertussis vaccines in infancy, provided that immunity to diphtheria and tetanus is maintained. Additional booster doses could be administered at older ages to reduce reactogenicity induced by multiple administrations and to optimize the control of pertussis in adolescents and young adults.

Sato Y, Kimura M, Fukumi H. Development of a pertussis component vaccine in Japan. Lancet. 1984 Jan 21;1(8369):122-6.

Antibodies against two physicochemically purified haemagglutinins (HAs) of *Bordetella pertussis* (filamentous HA and leucocytosis-promoting-factor HA) protect laboratory animals from pertussis. A vaccine containing these two HAs was prepared and tested in trials involving about 5000 children. Culture supernatant of *Bordetella pertussis*, phase I, was treated with ammonium sulphate, and a crude extract of the HAs was extracted from the precipitate by the use of concentrated sodium chloride. This crude extract was fractionated by sucrose density gradient centrifugation to obtain an HA preparation practically free of endotoxin. The HA preparation was treated with formalin to destroy its ability to induce leucocytosis and to cause histamine sensitisation. Aluminium hydroxide was added to the preparation as an adjuvant. The component vaccine is not only potent as judged by the mouse test but is also less than one-tenth as toxic as whole-cell vaccine as judged by leucocytosis promotion, histamine sensitisation, and endotoxicity tests. Field trials showed that component vaccine was as effective as and produced less side-effects than did conventional whole-cell vaccine. The vaccine has been used for mass immunisation in Japan since the autumn of 1981.

Schmitt HJ, Beutel K, Schuind A, Knuf M, Wagner S, Müschenborn S, Bogaerts H, Bock HL, Clemens R. Reactogenicity and immunogenicity of a booster dose of a

combined diphtheria, tetanus, and tricomponent acellular pertussis vaccine at fourteen to twenty-eight months of age. J Pediatr. 1997 Apr;130(4):616-23.

OBJECTIVES: The primary objective was to assess the nature and incidence of adverse events after a fourth dose of a tricomponent acellular pertussis-diphtheriatetanus vaccine given in the second year of life after primary vaccination with the same vaccine at 3, 4, and 5 months of age. A secondary objective was to analyze the immunogenicity of the booster vaccination.

DESIGN: Of the 5361 children enrolled (aged 14 to 28 months), adverse reactions were specifically solicited from the first 1863 enrollees for the first 4 days after vaccination and then were unsolicited for the remainder of the 4 weeks of follow-up (group 1). In the next 3498 subjects, safety and reactogenicity were entirely unsolicited for this 4-week period (group 2). Immunogenicity was analyzed by means of prebooster and postbooster serum antibody titers for all vaccine components in a random subgroup of 197 children from group 1.

RESULTS: Soliciting symptoms elicited reports of at least one symptom in 1314 of 1809 children in group 1 (72.6%), including 993 (54.9%) with local and 885 (48.9%) with general symptoms during the first 4 days after vaccination. When symptoms were gathered in an unsolicited fashion, only 580 of 3498 children in group 2 (16.6%) had a reported symptom during this time, consisting of 344 (9.8%) local and 319 (9.1%) general symptoms, respectively. An unsolicited symptom, areactive edematous swelling of the whole thigh, occurred in 62 children (1.1%), with 45 and 17 reports in groups 1 and 2, respectively. The vast majority of all reported symptoms were mild to moderate, and all children recovered without sequelae. Fourteen serious adverse events were reported, but none was considered to be related to the vaccination. Immunogenicity analysis showed a vaccine response to pertussis toxin in 99.5% of subjects, to filamentous hemagglutinin in 98.5%, and to pertactin (69 kd outer membrane protein) in 99%. All subjects had postvaccination antibody titers of 0.1 IU/ml or greater against diphtheria and tetanus toxoids.

Schmitt HJ, von König CH, Neiss A, Bogaerts H, Bock HL, Schulte-Wissermann H, Gahr M, Schult R, Folkens JU, Rauh W, Clemens R. Efficacy of acellular pertussis vaccine in early childhood after household exposure. JAMA. 1996 Jan 3;275(1):37-41.

OBJECTIVE: To evaluate the efficacy of a three-dose primary vaccination with a diphtheria-tetanus tricomponent acellular pertussis vaccine against "typical" pertussis, defined as a spasmodic cough of 21 days or longer with confirmation of *Bordetella pertussis* infection by culture or serology. **DESIGN:** Passive monitoring for suspected first household (index) cases of typical pertussis in six areas in Germany comprising 22,505 children vaccinated with study vaccine at 3, 4, and 5 months of age. Blinded, prospective follow-up of household contacts of index cases for incidence and progression of pertussis. **SETTING:** Six areas in Germany with a high incidence of pertussis. **SUBJECTS:** Four hundred fifty-three households with index cases comprising 360 evaluable contacts eligible for analysis of vaccine efficacy. **MAIN OUTCOME MEASURE:** Vaccine efficacy from attack rates of pertussis in household contacts classified by vaccination status. **RESULTS:** Of the 173 nonvaccinated household contacts, 96 developed typical pertussis, compared with seven of 112 contacts vaccinated with acellular pertussis vaccine. Vaccine efficacy was consequently calculated to be 88.7% (95%

confidence interval, 76.6% to 94.6%). Protection did not wane until at least the time recommended for booster vaccination. None of the analyzed potential confounding factors--age, socioeconomic status, erythromycin treatment, household composition, center effect, and selection bias--influenced study results in favor of the vaccine. **CONCLUSIONS:** Under conditions of intense household exposure, primary vaccination with acellular vaccine protected against pertussis until at least the time recommended for booster vaccination. The vaccine can be expected to be equally or more effective in settings with lower infectious pressure.

Simondon F, Preziosi MP, Yam A, Kane CT, Chabirand L, Iteman I, Sanden G, Mboup S, Hoffenbach A, Knudsen K, Guiso N, Wassilak S, Cadoz M. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. *Vaccine*. 1997 Oct;15(15):1606-12.

A randomized, double-blind trial comparing a diphtheria-tetanus-acellular pertussis vaccine (DTaP) (pertussis toxoid and filamentous hemagglutinin) with a whole-cell vaccine (DTwP) was conducted. A case-contact study was nested in the trial to estimate absolute efficacy. From 1990 through 1994, 4181 children were randomized to receive one of the vaccines at 2, 4, and 6 months. Severe adverse events were monitored weekly during two visits after vaccination. Fewer serious adverse events were observed after DTaP. Surveillance for cough illnesses persisting more than 7 days, in children under 15 years of age, was made by weekly home visits. Examining physicians, blind to vaccination status, took samples for culture and serologic testing. Pertussis was defined as 21 or more days of cough confirmed by culture, serology, or contact with a culture-confirmed person. Beginning 28 days after the third vaccine dose, the overall ratio of pertussis incidence in the DTaP group relative to the DTwP group (RR ac/wc) was 1.54 (95% CI, 1.23-1.93). In children younger than 18 months of age, RR ac/wc was 1.16 (95% CI, 0.77-1.73) and 1.76 (95% CI, 1.33-2.33) in children older than 18 months, which suggests a shorter duration of protection with the acellular vaccine ($P = 0.090$). Absolute efficacy estimates derived from the case-contact study confirmed the lower protection afforded by the acellular vaccine compared with the whole-cell vaccine: 31% (95% CI, 7-49) versus 55% against the protocol case definition, and 85% (95% CI, 66-93) versus 96% for the more severe WHO case definition. Although vaccination with DTaP provided a lower degree of protection than the highly effective DTwP, this difference was less prominent before 18 months of age, the customary age for a fourth dose. The safer DTaP vaccine may prove a valuable substitute for whole-cell vaccines when used in a schedule that includes a booster-dose.

Southern J, McVernon J, Gelb D, Andrews N, Morris R, Crowley-Luke A, Goldblatt D, Miller E. Immunogenicity of a fourth dose of Haemophilus influenzae type b (Hib) conjugate vaccine and antibody persistence in young children from the United Kingdom who were primed with acellular or whole-cell pertussis component-containing Hib combinations in infancy. *Clin Vaccine Immunol*. 2007 Oct;14(10):1328-33.

In response to the rising incidence of Haemophilus influenzae type b (Hib) disease in the United Kingdom, a national campaign to give a booster dose of single-antigen Hib conjugate vaccine to children aged 6 months to 4 years was undertaken in 2003. Children ($n = 386$)

eligible for Hib vaccine in the campaign were recruited. Hib antibody concentrations were measured before boost and at 1 month, 6 months, 1 year, and 2 years after boost and were analyzed according to children's ages at booster dose and whether a Hib combination vaccine containing acellular pertussis (aP) or whole-cell pertussis (wP) components was given in infancy. The geometric mean antibody concentrations (GMCs) before the booster declined as the time since primary immunization increased ($P < 0.001$), and GMCs were threefold higher in recipients of wP-Hib than aP-Hib combination vaccines ($P < 0.001$). GMCs 1 month after the booster increased with age ($P < 0.001$) as follows: 6 to 11 months, 30 microg/ml (95% confidence interval [CI], 22 to 40); 12 to 17 months, 68 microg/ml (95% CI, 38 to 124); and 2 to 4 years, 182 microg/ml (151 to 220), with no difference according to the type of priming vaccine received. Antibody levels declined after the booster, but 2 years later, GMCs were more than 1.0 microg/ml for all age groups. By extrapolating data for the decline in antibody levels, we found the GMCs 4 years after boosting were predicted to be 0.6, 1.4, and 2.6 microg/ml for those boosted at 6 to 11 months, 12 to 17 months, and 2 to 4 years, respectively, with levels of at least 0.15 microg/ml in about 90% of individuals. A booster dose of Hib vaccine given after the first year of life should provide long-lasting protection.

Stehr K, Cherry JD, Heininger U, Schmitt-Grohé S, Überall M, Laussucq S, Eckhardt T, Meyer M, Engelhardt R, Christenson P. A comparative efficacy trial in Germany in infants who received either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP vaccine, or DT vaccine. *Pediatrics*. 1998 Jan;101(1 Pt 1):1-11.

BACKGROUND: The goal of the trial was to determine the efficacy of a multicomponent acellular pertussis vaccine against *Bordetella* illnesses in comparison with a whole-cell product and DT. **DESIGN:** In a randomized, double-blind fashion, 2- to 4-month-old infants received 4 doses of either DTP or DTaP vaccine at 3, 4.5, 6, and 15 to 18 months of age. The controls received 3 doses (3, 4.5, 15 to 18 months of age) of DT vaccine. The DTP vaccine was Lederle adsorbed vaccine (licensed in the United States) and DTaP was Lederle/Takeda adsorbed vaccine. Follow-up for vaccine efficacy started 2 weeks after the third dose (DTP/DTaP) and at the same age (6.5 months) in DT recipients. Reactogenicity of all doses of all three vaccines was documented by standardized parent diary cards. In addition, all subjects were monitored for respiratory illnesses and serious adverse events by biweekly phone calls. **RESULTS:** From May 1991 to January 1993, a total of 10 271 infants were enrolled: 8532 received either DTP or DTaP and 1739 received DT. Specific efficacy against B pertussis infections with cough ≥ 7 days duration was 83% (95% confidence interval [CI]: 76-88) and 72% (95% CI: 62-79) for DTP and DTaP, respectively; results for DTP and DTaP based on ≥ 21 days of cough with either paroxysms, whoop or posttussive vomiting (PWV) were 93% (95% CI: 89-96) and 83% (95% CI: 76-88), respectively. For DTaP vaccine, efficacy was higher after the fourth dose as compared with its efficacy after the third dose (78% vs 62% for cough ≥ 7 days and 85% vs 76% for cough ≥ 21 days with PWV). For DTP vaccine, efficacy was less varied after the third and fourth dose (78% vs 85% for cough ≥ 7 days and 93% vs 93% for cough ≥ 21 days with PWV). In contrast with DTP, the DTaP vaccine had some efficacy against B parapertussis infection (point estimate for cough ≥ 7 days: 31% [95% CI: -10-56]). All vaccines were generally well-tolerated. However, side reactions were significantly less after DTaP compared with DTP. **CONCLUSIONS:** Like other multicomponent acellular pertussis vaccines, the Lederle/Takeda DTaP vaccine demonstrated good efficacy against mild and typical pertussis due to B pertussis infections. Interestingly, it

also may have some efficacy against B parapertussis. Based on the results of this trial, the vaccine was licensed in the United States in December 1996 for all 5 doses of the currently recommended immunization schedule in this country.

Stevenson M, Beard S, Finn A, Brennan A. Estimating the potential health gain and cost consequences of introducing a pre-school DTPa pertussis booster into the UK child vaccination schedule. Vaccine. 2002 Mar 15;20(13-14):1778-86.

This work estimates the health and cost impacts of a pre-school booster vaccination for Bordetella pertussis, when added to existing UK primary vaccination. A transition state simulation model of pertussis infection in a closed population was constructed comprising of susceptible, infected and immune population sub-groups, across eight age bands. Epidemiological, service use and cost data were sourced from routine statistics, published literature and clinician estimates. The introduction of a pre-school booster is predicted to reduce the number of hospitalisations by approximately 1400 and pertussis cases suffered by up to 28,000 at a net investment of under 13 million pounds over a 5-year period.

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

OBJECTIVES: Routine use of whole cell pertussis vaccines was suspended in some countries in the late 1970s and early 1980s, leading to a resurgence of whooping cough. Acellular pertussis vaccines containing purified or recombinant Bordetella pertussis antigens were developed in the hope that they would be as effective but less toxic than the whole cell vaccines. The objective of this review was to assess the effects of acellular pertussis vaccines in children. **SEARCH STRATEGY:** The Cochrane Controlled Trials Register and Medline were searched up to January 1998. **SELECTION CRITERIA:** Double-blind randomised efficacy and safety trials of acellular pertussis vaccines in children, with active follow-up of participants and laboratory verification of pertussis cases. **DATA COLLECTION AND ANALYSIS:** One reviewer assessed trial quality and extracted data. **MAIN RESULTS:** Six efficacy trials and 45 safety trials were included. Acellular pertussis vaccines with three or more pertussis vaccines were more effective than those with one or two antigens. They were also more effective than one type of whole cell pertussis vaccine, but less effective than two other types of whole cell vaccines. Differences in trial design precluded pooling of the efficacy data and results should be interpreted with caution. Most systemic and local adverse events were significantly less common with acellular than with whole cell pertussis vaccines. **REVIEWER'S CONCLUSIONS:** Multi-component acellular pertussis vaccines are effective, and show less adverse effects than whole cell pertussis vaccines. However in areas where whooping cough is more likely to be fatal, the higher toxicity of some whole cell vaccines may be offset by their increased effectiveness.

Tiwari T, Murphy TV, Moran J; National Immunization Program, CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. MMWR Recomm Rep. 2005 Dec 9;54(RR-14):1-16.

The recommendations in this report were developed to broaden the spectrum of antimicrobial agents that are available for treatment and postexposure prophylaxis of pertussis. They include updated information on macrolide agents other than erythromycin (azithromycin and clarithromycin) and their dosing schedule by age group.

Torvaldsen S, Simpson JM, McIntyre PB. Effectiveness of pertussis vaccination in New South Wales, Australia, 1996-1998. *Eur J Epidemiol.* 2003;18(1):63-9.

Pertussis notifications have increased over the past decade in Australia and other industrialised countries. This study estimates the effectiveness of pertussis vaccination in one Australian State (New South Wales, NSW) among children aged less than 14 years, during a period when an Australian whole-cell pertussis vaccine was in routine use. Cases notified with pertussis between 1996 and 1998 and pertussis vaccine coverage estimates from the Australian Childhood Immunisation Register were used. Vaccine effectiveness (VE) was calculated using the screening method, with adjustment for age group, year of disease onset and area of residence. VE was highest (91%) in the youngest age group (8-23 months) and lowest (78%) in the oldest age group (9-13 years). Pertussis vaccination is highly effective at preventing pertussis in NSW children, as measured by notified cases. Ongoing monitoring will be important to evaluate VE following Australia's change to an acellular vaccine based program.

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.

BACKGROUND: Although many whole-cell vaccines have been effective in preventing pertussis, these vaccines are difficult to standardize and can produce side effects. In Sweden, pertussis became endemic during the 1970s despite vaccination. Because of its limited efficacy, the Swedish-made whole-cell vaccine was withdrawn in 1979. **METHODS:** To evaluate the efficacy of an acellular vaccine consisting of pertussis toxin inactivated by hydrogen peroxide (pertussis toxoid), we conducted a randomized, double-blind, placebo-controlled trial in Sweden. Infants were vaccinated with either diphtheria and tetanus toxoids alone (DT toxoids, 1726 infants) or diphtheria, tetanus, and pertussis toxoids (DTP toxoids, 1724 infants) at 3, 5, and 12 months of age. **RESULTS:** There were no serious reactions. With the pertussis vaccine there were slightly more local reactions than with the DT toxoids alone, but the rates of postvaccination fever were the same. The main period of surveillance, which began 30 days after the third vaccination, continued for a median of 17.5 months. There were 312 cases of pertussis (72 in the DTP-toxoids group and 240 in the DT-toxoids group) that met the clinical criterion (paroxysmal cough lasting \geq 21 days) and laboratory criteria for pertussis as defined by the World Health Organization. The efficacy of this acellular vaccine was 71 percent (95 percent confidence interval, 63 to 78 percent). The recipients of DTP toxoids who had pertussis had cough of shorter duration than the recipients of DT toxoids, and fewer had whooping and vomiting. The vaccine efficacy after two doses was 55 percent (95 percent confidence interval, 12 to 78 percent), on the basis of 14 cases in the DTP-toxoids group and 31 in the DT-toxoids group that met the definition of the World Health

Organization. CONCLUSIONS: A pharmacologically inert, acellular pertussis-toxoid vaccine that is easily standardized is safe and confers substantial protection against pertussis.

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.

Severe adverse events were evaluated in a comparative efficacy trial in Germany in infants who received either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP (DTP) or DT vaccine. Vaccinees received four doses (at three, four-and-a half, six and 15-18 months of age) of either DTP or DTaP vaccine or three doses at three, four-and-a half and 15-18 months of age) of DT vaccine. The analysis included 4,273 DTaP recipients, 4,259 DTP recipients and 1,739 DT vaccinees. Convulsions within three days of vaccination occurred in 1/15,912 doses in DTaP recipients and 1/3,926 doses in DTP vaccinees ($p = 0.22$). Persistent inconsolable crying was more common in DTP vaccinees (1/113 doses) compared with DTaP (1/497 doses, $p < 0.001$) and DT (1/359 doses, $p < 0.001$) recipients. High fever (≤ 40.5 degrees C) was less frequent in DTaP vaccinees (1/16,239 doses) compared with DTP (1/5,359) and DT recipients (1/4,665). One hypotonic-hyporesponsive episode was observed.

van Amersfoorth SC, Schouls LM, van der Heide HG, Advani A, Hallander HO, Bondeson K, von König CH, Riffelmann M, Vahrenholz C, Guiso N, Caro V, Njamkepo E, He Q, Mertsola J, Mooi FR. Analysis of Bordetella pertussis populations in European countries with different vaccination policies. J Clin Microbiol. 2005 Jun;43(6):2837-43.

Despite the widespread use of pertussis vaccines during the last decades, pertussis has remained an endemic disease with frequent epidemic outbreaks. Currently two types of vaccines are used: whole-cell vaccines (WCVs) and recently developed acellular vaccines (ACVs). The long-term aim of our studies is to assess the effect of different vaccination policies on the population structure of *Bordetella pertussis* and ultimately on the disease burden in Europe. In the present study, a total of 102 *B. pertussis* isolates from the period 1998 to 2001 from five European countries (Finland, Sweden, Germany, The Netherlands, and France) were characterized. The isolates were analyzed by typing based on variable number of tandem repeats (VNTR); by sequencing of polymorphic genes encoding the surface proteins pertussis toxin S1 and S3 subunits (ptxA and ptxC), pertactin (prn), and tracheal colonization factor (tcfA); and by fimbrial serotyping. The results reveal a relationship between geographic location and VNTR types, the frequency of the ptxC alleles, and serotypes. We have not observed a relationship between the strain characteristics we studied and vaccination programs. Our results provide a baseline which can be used to reveal changes in the *B. pertussis* population in Europe in the coming years.

Visser HK. [Health Council of the Netherlands advisory report 'Vaccination against pertussis'--time for a new vaccine] Ned Tijdschr Geneeskd. 2004 May 8;148(19):916-8.

An advisory report on vaccination against pertussis by the National Vaccination Programme Review Committee of the Health Council of the Netherlands makes recommendations on improving pertussis vaccination in the Netherlands. Since 1996, between 4000 and 8000 cases of pertussis have been reported each year, mainly in young children who have already been vaccinated. The main cause of this increase, apart from decreasing immunity in older children and adults, seems to be diminished vaccine effectiveness due to the occurrence of non-vaccine related strains of the pertussis bacterium in the Netherlands. The cellular vaccine used in the Netherlands contains low levels of the major antigens pertussis toxin and pertactin. The Health Council recommends the fastest possible transition to the use of an acellular combination vaccine. Such a vaccine will be effective and will have considerably fewer side effects than the one currently in use. The Committee recommends that research is done into the sources of pertussis infections in young infants.

Wei SC, Tatti K, Cushing K, Rosen J, Brown K, Cassiday P, Clark T, Olans R, Pawloski L, Martin M, Tondella ML, Martin SW. Effectiveness of adolescent and adult tetanus, reduced-dose diphtheria, and acellular pertussis vaccine against pertussis. Clin Infect Dis. 2010 Aug 1;51(3):315-21.

BACKGROUND: Pertussis is among the most poorly controlled bacterial vaccine-preventable diseases in the United States. In 2006, a tetanus, reduced-dose diphtheria, and acellular pertussis (Tdap) booster was recommended for adolescents and adults. Tdap vaccines were licensed on the basis of antibody response without vaccine effectiveness data.

METHODS: From 30 September 2007 through 19 December 2007, a pertussis outbreak occurred at a nursery through twelfth grade school on St. Croix, US Virgin Islands. We screened all students for cough and collected clinical history, including Tdap receipt. Coughing students were offered diagnostic testing. We defined clinical case patients as students with cough 14 days in duration plus either whoop, paroxysms, or post-tussive vomiting, and we defined confirmed case patients as students with any cough with isolation of *Bordetella pertussis* or those with clinical cases and polymerase chain reaction or serological evidence of pertussis; other clinical cases were classified as probable.

RESULTS: There were 51 confirmed or probable cases among 499 students (attack rate, 10%). Disease clustered in grades 6-12, with a peak attack rate of 38% among 10th graders. Of 266 students aged 11 years with complete data, 31 (12%) had received Tdap. Forty-one unvaccinated students (18%) had confirmed or probable pertussis, compared with 2 (6%) of the vaccinated students (relative risk, 2.9); vaccine effectiveness was 65.6% (95% confidence interval, -35.8% to 91.3%; [Formula: see text]).

CONCLUSIONS: This first evaluation of Tdap vaccine effectiveness in the outbreak setting suggests that Tdap provides protection against pertussis. Increased coverage is needed to realize the full benefit of the vaccine program. Serological testing was an important tool for case identification and should be considered for inclusion in the Council of State and Territorial Epidemiologists case definition.

Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of immunity against pertussis after natural infection or vaccination. *Pediatr Infect Dis J.* 2005 May;24(5 Suppl):S58-61.

Despite decades of high vaccination coverage, pertussis has remained endemic and reemerged as a public health problem in many countries in the past 2 decades. Waning of vaccine-induced immunity has been cited as one of the reasons for the observed epidemiologic trend. A review of the published data on duration of immunity reveals estimates that infection-acquired immunity against pertussis disease wanes after 4-20 years and protective immunity after vaccination wanes after 4-12 years. Further research into the rate of waning of vaccine-acquired immunity will help determine the optimal timing and frequency of booster immunizations and their role in pertussis control.

Wendelboe AM, Njamkepo E, Bourillon A, Floret DD, Gaudelus J, Gerber M, Grimprel E, Greenberg D, Halperin S, Liese J, Muñoz-Rivas F, Teyssou R, Guiso N, Van Rie A; Infant Pertussis Study Group. Transmission of *Bordetella pertussis* to young infants. *Pediatr Infect Dis J.* 2007 Apr;26(4):293-9.

BACKGROUND: Pertussis vaccination has reduced the number of notified cases in industrialized countries from peak years by more than 95%. The effect of recently recommended adult and adolescent vaccination strategies on infant pertussis depends, in part, on the proportion of infants infected by adults and adolescents. This proportion, however, remains unclear, because studies have not been able to determine the source case for 47%-60% of infant cases. **METHODS:** A prospective international multicenter study was conducted of laboratory confirmed infant pertussis cases (aged \leq 6 months) and their household and nonhousehold contacts. Comprehensive diagnostic evaluation (including PCR and serology) was performed on all participants independent of symptoms. Source cases were identified and described by relationship to the infant, age and household status. **RESULTS:** The study population comprised 95 index cases and 404 contacts. The source of pertussis was identified for 48% of infants in the primary analysis and up to 78% in sensitivity analyses. In the primary analysis, parents accounted for 55% of source cases, followed by siblings (16%), aunts/uncles (10%), friends/cousins (10%), grandparents (6%) and part-time caretakers (2%). The distribution of source cases was robust to sensitivity analyses. **CONCLUSIONS:** This study provides solid evidence that among infants for whom a source case was identified, household members were responsible for 76%-83% of transmission of *Bordetella pertussis* to this high-risk group. Vaccination of adolescents and adults in close contact with young infants may thus eliminate a substantial proportion of infant pertussis if high coverage rates can be achieved.

Wendelboe AM, Hudgens MG, Poole C, Van Rie A. Estimating the role of casual contact from the community in transmission of *Bordetella pertussis* to young infants. *Emerg Themes Epidemiol.* 2007 Oct 19;4:15.

ABSTRACT: The proportion of infant pertussis cases due to transmission from casual contact in the community has not been estimated since before the introduction of pertussis vaccines in

the 1950s. This study aimed to estimate the proportion of pertussis transmission due to casual contact using demographic and clinical data from a study of 95 infant pertussis cases and their close contacts enrolled at 14 hospitals in France, Germany, Canada, and the U.S. between February 2003 and September 2004. A complete case analysis was conducted as well as multiple imputation (MI) to account for missing data for participants and close contacts who did not participate. By considering all possible close contacts, the MI analysis estimated 66% of source cases were close contacts, implying the minimum attributable proportion of infant cases due to transmission from casual contact with community members was 34% (95% CI = 24%, 44%). Estimates from the complete case analysis were comparable but less precise. Results were sensitive to changes in the operational definition of a source case, which broadened the range of MI point estimates of transmission from casual community contact to 20%-47%. We conclude that casual contact appears to be responsible for a substantial proportion of pertussis transmission to young infants. Medical subject headings (MeSH): multiple imputation, pertussis, transmission, casual contact, sensitivity analysis, missing data, community.

Wharton M. Vaccine safety: current systems and recent findings. *Curr Opin Pediatr.* 2010 Feb;22(1):88-93.

PURPOSE OF REVIEW: An understanding of vaccine safety is important for all immunization providers, who have responsibilities to identify, report, and prevent adverse events.

RECENT FINDINGS: New analytic methods can provide more rapid information on adverse events compared with traditional observational studies. Some adverse events following vaccination are preventable. Syncope is increasingly recognized postvaccination and may be associated with severe injury or death. Both human and system factors should be addressed to prevent vaccine administration errors. Ongoing basic science and clinical research is critical to improved understanding of vaccine safety. A recent study suggests that many cases of encephalopathy following whole-cell pertussis vaccine were due to severe myoclonic epilepsy of infancy, a severe seizure disorder associated with mutations of the sodium channel gene SCN1A.

SUMMARY: Vaccine safety requires prelicensure evaluation, postlicensure surveillance and investigation, addressing preventable adverse events, reconsideration of vaccine policy as understanding of risks and benefits changes, and ongoing research to better understand the response to vaccination and the pathogenesis of adverse events.

Wood N, McIntyre P, Marshall H, Robertson D. Acellular pertussis vaccine at birth and one month induces antibody responses by two months of age. *Pediatr Infect Dis J.* 2010 Mar;29(3):209-15.

BACKGROUND: Infants less than 3 months of age are at highest risk of hospitalization and death from pertussis. Several studies have examined antibody responses to pertussis vaccines at birth but no previous study has evaluated 2 doses of monovalent acellular pertussis vaccine (aPV) before 2 months of age.

METHODS: Seventy-six newborns were randomized at birth to 3 groups-aPV at birth and 1 month, aPV at birth, and control. All infants received hepatitis B vaccine (HBV) at birth followed at 2, 4, and 6 months by a combination vaccine including aPV, diphtheria, tetanus, Haemophilus influenzae type b (Hib), hepatitis B, polio antigens and 7 valent conjugate pneumococcal vaccine. IgG antibody responses to pertussis toxoid (PT), filamentous hemagglutinin (FHA), and pertactin (PRN) were measured in maternal serum and in infants at 2, 4, 6, and 8 months of age. Antibody responses to hepatitis B, diphtheria, tetanus, and Hib were measured at 8 months only. A parental diary and active telephone follow-up occurred for 7 days after each vaccination.

RESULTS: The aPV birth dose was well tolerated. By 2 months of age, 22 of 25 (88%) of 2 dose recipients had detectable IgG antibody to PT (IgG PT) compared with 9 of 21 (43%) who received a birth dose only and 3 of 20 (15%) of controls. Infants in the 2 dose group had a geometric mean concentration (GMC) of IgG PT of 16 ELISA units per mL (EU/mL), 95% CI: 11 to 25, significantly higher than birth dose only (5 EU/mL, 95% CI: 3-8) and controls (3 EU/mL, 95% CI: 2-5). At 8 months of age, following 5, 4, and 3 doses of aP-containing vaccine, respectively, IgG PT had plateaued but IgG to FHA and PRN increased with successive doses. There was a trend to lower antibody responses for hepatitis B and Hib with higher numbers of Pa doses.

CONCLUSION: These data suggest that aPV at birth and 1 month induces significantly higher IgG antibody against pertussis antigens by 2 months of age without reducing subsequent pertussis antibody responses. Larger and more detailed studies of aPV from birth are needed to evaluate other antibody responses and the potential of this approach to reduce death and morbidity from Bordetella pertussis infection in the first 3 months of life.

Wright SW, Edwards KM, Decker MD, Zeldin MH. Pertussis infection in adults with persistent cough. JAMA. 1995 Apr 5;273(13):1044-6.

OBJECTIVE: To determine the prevalence of Bordetella pertussis infection in adult patients with persistent cough.

DESIGN: Prospective case series.

SETTING: Urban university hospital emergency department.

PATIENTS: Convenience sample of 75 patients aged 18 years or older with a cough lasting 2 weeks or longer. Serum specimens from 67 patients without respiratory complaints were used to develop reference values.

INTERVENTIONS: In patients with cough, nasopharyngeal culture and direct fluorescent antibody testing for B pertussis were performed and serum samples were obtained at the first visit and 1 month later. Serum specimens were assayed for antibody to pertussis toxin (PT) and filamentous hemagglutinin (FHA).

MAIN OUTCOME MEASURES: A subject with one or more of the following was defined as having a pertussis infection: a positive B pertussis culture result, a four-fold change in PT or FHA titer, and/or a single PT or FHA titer at least 2 SDs greater than the geometric mean of the control group.

RESULTS: No subject tested culture positive for *B pertussis*. Sixteen (21%) (95% confidence interval [CI], 13% to 32%) of 75 subjects met the serologic criteria for pertussis infection; for 13 (81%; 95% CI, 54% to 96%) of the 16, the criteria were met by the initial serum specimen. In contrast, the geometric mean levels of antibody to PT and FHA for the remaining 59 subjects with cough did not differ from those of the control group. Clinical symptoms and the lymphocyte count did not differentiate patients with pertussis from those without the disease.

CONCLUSION: Pertussis is a common cause of persistent cough in adults and should be considered in the differential diagnosis. Clinical symptoms, pertussis culture, direct fluorescent antibody testing, and lymphocytosis are of limited value in making the diagnosis.

Zackrisson G, Taranger J, Trollfors B. History of whooping cough in nonvaccinated Swedish children, related to serum antibodies to pertussis toxin and filamentous hemagglutinin. *J Pediatr.* 1990 Feb;116(2):190-4.

The aim of this study was to examine whether there is a correlation between parental information on the child's history of whooping cough and the presence or absence of serum antibodies against two antigens of *Bordetella pertussis*, pertussis toxin and filamentous hemagglutinin, in nonvaccinated Swedish children. The parents of 266 Swedish children aged 1 to 4 years answered a questionnaire regarding the child's history of whooping cough, and a serum sample was obtained from the child for determination of IgG, IgM, and IgA antibodies to pertussis toxin and filamentous hemagglutinin. The study was performed from 1984 to 1986, five to seven years after the cessation of general vaccination against pertussis in Sweden; none of the children had received pertussis vaccine. Antibodies to both toxin and filamentous hemagglutinin increased with age. Of the children aged 4 years, 50% had antibodies to both antigens. Of all 266 children, 100 had antibodies to both antigens, 6 to toxin alone, and 49 to filamentous hemagglutinin alone. There was a good correlation between the presence of antibodies and a history of whooping cough. Of 91 children with a history of whooping cough, 77 had antibodies against both antigens and 13 against one antigen; only one child lacked detectable antibodies against both antigens. Of the 175 children with no history of whooping cough, 110 lacked detectable antibodies to both antigens, 23 had antibodies to both, 2 to toxin alone, and 40 to filamentous hemagglutinin alone. The data indicate that parental information on a previous history of whooping cough in their nonimmunized child is reliable, and that many infections with *B. pertussis* are subclinical or atypical. Exposure to other *Bordetella* species than *B. pertussis*, which is the only toxin-producing species, might be important for the development of FHA antibodies. A follow-up 2 to 4 years after the collection of serum samples of children without a history of whooping cough but with antibodies to one or both antigens indicated that serum antibodies to toxin, but not to filamentous hemagglutinin, may be protective against disease.

Zepp F, Knuf M, Habermehl P, Mannhardt-Laakmann W, Howe B, Friedland LR. Safety of reduced-antigen-content tetanus-diphtheria-acellular pertussis vaccine in adolescents as a sixth consecutive dose of acellular pertussis-containing vaccine. *J Pediatr.* 2006 Nov;149(5):603-610.

OBJECTIVE: The safety of a booster dose of a reduced-antigen-content tetanus-diphtheria-acellular pertussis (Tdap) vaccine was evaluated in adolescents previously vaccinated with

five doses of acellular pertussis-containing vaccine. **STUDY DESIGN:** Adolescents (n = 319) previously vaccinated with either 5 doses of diphtheria-tetanus-acellular pertussis (DTaP) (n = 193) or 4 doses of DTaP plus another acellular pertussis-containing vaccine received one dose each of Tdap and hepatitis A vaccine in a double-blinded, randomized, crossover trial. Rates of adverse events (AEs) after vaccination with Tdap versus hepatitis A and rates of local AEs among adolescents vaccinated with Tdap (sixth acellular pertussis-containing vaccine dose) versus rates in these same individuals after vaccination with their fifth DTaP dose were assessed. **RESULTS:** After Tdap, pain (63.6%), redness (51.7%), and swelling (41.4%) were the most frequently reported AEs. Large injection site swelling (swelling > 100 mm, arm circumference increase > 50 mm or diffuse swelling interfering with daily activities) occurred in three adolescents and resolved without sequelae. After the sixth dose of acellular pertussis-containing vaccine, adolescents reported more pain and less redness and swelling compared with incidences of these AEs reported when these same individuals received their fifth DTaP dose. **CONCLUSIONS:** These results suggest that Tdap is well tolerated as a sixth consecutive dose of acellular pertussis-containing vaccine.

Zhang L, Prietsch SOM, Axelsson I, Halperin SA. Acellular vaccines for preventing whooping cough in children. Cochrane Database of Systematic Reviews, 2008, (2): CD001478.

Background: Routine use of whole-cell pertussis vaccines was suspended in some countries in the 1970s/1980s because of concerns about adverse effects. There was a resurgence of whooping cough. Acellular pertussis vaccines (containing purified or recombinant *Bordetella pertussis* antigens) were developed in the hope that they would be as effective but less reactogenic than the whole-cell vaccines.

Objectives: To assess the efficacy and safety of acellular pertussis vaccines in children.

Search strategy: We searched the Cochrane Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 2) which contains the Acute Respiratory Infections Group's Specialised Register; MEDLINE (1950 to April week 2 2009) and EMBASE (1974 to April 2009).

Selection criteria: Double-blind randomised efficacy and safety trials of acellular pertussis vaccines in children up to six years old, with active follow-up of participants and laboratory verification of pertussis cases.

Data collection and analysis: Two review authors independently performed data extraction and study quality assessment. Differences in trial design precluded pooling of the efficacy data. The safety data from individual trials were pooled using the Cochrane statistical package Review Manager 5.

Main results: Six efficacy trials and 52 safety trials were included. The efficacy of multi-component (≥ 3) vaccines varied from 84% to 85% in preventing typical whooping cough, and from 71% to 78% in preventing mild pertussis disease. In contrast, the efficacy of one- and two-component vaccines varied from 59% to 75% against typical whooping cough, and from 13% to 54% against mild pertussis disease. Multi-component acellular vaccines is more effective than low-efficacy whole-cell vaccines, but may be less effective than the highest-efficacy whole-cell vaccines. Most systemic and local adverse events were significantly less

common with acellular than with whole-cell pertussis vaccines for the primary series as well as for the booster dose.

Authors' conclusions: Multi-component acellular pertussis vaccines are effective, and show less adverse effects than whole-cell pertussis vaccines for the primary series as well as for booster doses.

Zieliński A, Rosińska M, Czarkowski M, Rudowska J. The effectiveness of vaccination with whole-cell pertussis vaccine by age group in Poland 1996-2001. Scand J Infect Dis. 2004;36(2):114-8.

Recurrence of pertussis in highly vaccinated populations has been observed in many countries. Two mechanisms have been proposed to explain it: a shift in incidence towards older age groups in which the protective effect of vaccination is diminished; and vaccine-induced changes in genomic and immunological characteristics of circulating strains of *Bordetella pertussis*, which become different from vaccine strains, thereby reducing vaccine efficacy. Marked increase in the incidence of pertussis has been observed in Poland since 1997, following a decade of stability at a low level. As previously shown, the immunization calendar in Poland does not ensure sufficient protection among children older than 9 y. The decrease in the protective effect becomes noticeable after the age of 5. In this paper we examine changes in the effectiveness of pertussis vaccination in 4 age groups during 1996-2001, using surveillance data. We find that over that period a decrease occurred in the reported effectiveness (in children aged 2 to 5 y, from 97.3% in 1996 to 73.5% in 2001 and in 6 to 9 y-olds, from 84.3%, to 68.8%). We also discuss an alternative hypothesis that the above findings are due to selection or measurement bias resulting from incomplete reporting or imperfect diagnostic procedures.