

Pertussis Vaccines

WHO Position Paper, Aug 2015

Abstracts of references provided in the position paper and GRADE tables

- **Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014 Oct 25; 384(9953):1521-1528.**

BACKGROUND: In October, 2012, a pertussis vaccination programme for pregnant women was introduced in response to an outbreak across England. We aimed to assess the vaccine effectiveness and the overall effect of the vaccine programme in preventing pertussis in infants.

METHODS: We undertook an analysis of laboratory-confirmed cases and hospital admissions for pertussis in infants between Jan 1, 2008, and Sept 30, 2013, using data submitted to Public Health England as part of its enhanced surveillance of pertussis in England, to investigate the effect of the vaccination programme. We calculated vaccine effectiveness by comparing vaccination status for mothers in confirmed cases with estimates of vaccine coverage for the national population of pregnant women, based on data from the Clinical Practice Research Datalink. **FINDINGS:** The monthly total of confirmed cases peaked in October, 2012 (1565 cases), and subsequently fell across all age groups. For the first 9 months of 2013 compared with the same period in 2012, the greatest proportionate fall in confirmed cases (328 cases in 2012 vs 72 cases in 2013, -78%, 95% CI -72 to -83) and in hospitalisation admissions (440 admissions in 2012 vs 140 admissions in 2013, -68%, -61 to -74) occurred in infants younger than 3 months, although the incidence remained highest in this age group. Infants younger than 3 months were also the only age group in which there were fewer cases in 2013 than in 2011 (118 cases in 2011 vs 72 cases in 2013), before the resurgence. 26 684 women included in the Clinical Practice Research Datalink had a livebirth between Oct 1, 2012 and Sept 3, 2013; the average vaccine coverage before delivery based on this cohort was 64%. Vaccine effectiveness based on 82 confirmed cases in infants born from Oct 1, 2012, and younger than 3 months at onset was 91% (95% CI 84 to 95). Vaccine effectiveness was 90% (95% CI 82 to 95) when the analysis was restricted to cases in children younger than 2 months. **INTERPRETATION:** Our assessment of the programme of pertussis vaccination in pregnancy in England is consistent with high vaccine effectiveness. This effectiveness probably results from protection of infants by both passive antibodies and reduced maternal exposure, and will provide valuable information to international policy makers. **FUNDING:** Public Health England.

- **Bar-ON ES, Goldberg E, 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 for Systematic Reviews 2012;(4):CD005530.**

BACKGROUND: Advantages to combining childhood vaccines include reducing the number of visits, injections and patient discomfort, increasing compliance and optimising prevention. The World Health Organization (WHO) recommends that routine infant immunisation programmes include a vaccination against Haemophilus influenzae (H. influenzae) type B (HIB) in the combined diphtheria-tetanus-pertussis (DTP)-hepatitis B virus (HBV) vaccination. The effectiveness and safety of the combined vaccine should be carefully and systematically assessed to ensure its acceptability by the community. **OBJECTIVES:** To compare the effectiveness of combined DTP-HBV-HIB vaccines versus combined DTP-HBV and separate HIB vaccinations.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 4), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to week 1, November 2011), EMBASE (January 1990 to November 2011) and www.clinicaltrials.gov (up to April 2011). **SELECTION CRITERIA:** Randomised controlled trials (RCTs) or quasi-RCTs comparing vaccination with any combined DTP-HBV-HIB vaccine, with or without three types of inactivated polio virus (IPV) or concomitant oral polio vaccine (OPV) in any dose, preparation or time schedule, compared with separate vaccines or placebo, administered to infants up to two years old. **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:** Data for the primary outcome (prevention of disease) were lacking. We performed a meta-analysis to pool the results of 20 studies with 5874 participants in an immunogenicity analysis and 5232 participants in the reactogenicity analysis. There were no data on clinical outcomes for the primary outcome (prevention of disease) and all studies used immunogenicity and reactogenicity (adverse events). The number of vaccine doses differed significantly between the studies. Heterogeneous interventions, study location, healthcare environment and combining research across disparate geographical locations, may have lead to bias. The risk of bias was unclear across most of the included studies. Comparisons found little heterogeneity. In two immunological responses the combined vaccine achieved lower responses than the separate vaccines for HIB and tetanus. No significant differences in immunogenicity were found for pertussis, diphtheria, polio and hepatitis B. Serious adverse events were comparable with mainly hospitalisation and acute bronchiolitis cases. Minor adverse events such as pain and redness were more common in children given the combined vaccine. Overall, the direction shown by the results is in favour of the DTPw (diphtheria-tetanus-whole cell pertussis)-HBV-HIB vaccine rather than the DTPa (diphtheria-tetanus-acellular pertussis)-HBV-HIB vaccine when compared to the separate vaccines (size of effect: risk ratio (RR) 1.43; 95% confidence interval (CI) 0.98 to 2.10, for 5269 participants). **AUTHORS' CONCLUSIONS:** We could not conclude that the immune responses elicited by the combined vaccine were different from or equivalent to the separate vaccines. There was significantly less immunological response for HIB and tetanus 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 (ITT) 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.

- **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):2400-2409.**
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.

- **Bisgard KM, Rhodes P, Connelly BL, Bi D, Hahn C, Patrick S, et al. Pertussis vaccine effectiveness among children 6 to 59 months of age in the United States, 1998-2001. *Pediatrics* 2005;116.**

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: $(1 - \text{OR}) \times 100$. 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.

- Brenzel L, Wolfson LJ, Fox-Rushby J, Miller M, Halsey NA. Vaccine preventable diseases. In: Jamison DT, Breman JG, Measham AR et al. eds. *Disease control priorities in developing countries*. 2nd ed. New York, Oxford University Press, 2006:389-412. Available at <http://www.ncbi.nlm.nih.gov/books/NBK11728/> (Accessed August 2015).

DCP2 is a comprehensive, 1440-page resource that provides an updated "checkup" for global health and health care. As part of the "health examination," DCP2 asked: What progress has been made in defining and reducing the global burden of disease? How much have countries accomplished in developing and providing efficient, effective, and equitable health care? How can they set and achieve priorities in health services? Once these countries have identified the priorities, how can they deliver interventions to the targeted population in the most cost-effective manner? How can the efforts of the health and closely related sectors (such as nutrition, agriculture, water and sanitation, and education) be integrated to optimize health improvements?

DCP2's answers contribute substantially to global initiatives to improve the health of all peoples by providing a multidisciplinary understanding of these fundamental issues and challenges, as well as effective interventions for the range of communicable and noncommunicable diseases and conditions and risk factors.

Underlying all medical and economic analyses is the appreciation of the need to strengthen health systems so that they can provide highly cost-effective interventions on a large scale. Applying the information, analysis, and strategies set out in DCP2 requires a careful assessment of the local situation, including patterns of disease, institutional capacity, and resources. Combining insights from DCP2 and knowledge of their local situation, actors at many levels—from parliamentarians and health ministers to hospital administrators, health care workers, and concerned citizens—will be able to set priorities, select appropriate interventions, devise better means of delivery, improve management, and be more effective in mobilizing resources. In this

manner, the benefits of technical progress in improving health can be extended and shared by all.

- **Briand V, Bonmarin I, Levy-Bruhl D. Study of the risk factors for severe childhood pertussis based on hospital surveillance data. Vaccine 2007 Oct 10;25(41):7224-7232.**

We used data collected through the French national hospital-based pertussis surveillance network to investigate the risk factors for severe childhood pertussis and more specifically the impact of the vaccination status. For infants, factors associated with a decreased risk of severe disease (defined as hospitalization in intensive care unit, assisted ventilation or death) were having received the first dose of vaccine, being seen late in the course of the disease and in a local hospital. Data also suggested that protection may increase with the number of doses administered. For older children, factors associated with a decreased risk of severity, measured by the hospitalization, were having received a recent booster injection and identification of the contaminator in the close environment. This study reinforces the need for an early start of the primary course in infants and the administration of booster injections in older children.

- **Brown NJ, Berkovic SF, Scheffer IE. Vaccination, seizures and 'vaccine damage'. Curr Opin Neurol 2007 April;20(2):181-187.**

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 JBSN, Pascual FB, Moran J, et al. Measures to Control an Outbreak of Pertussis in a Neonatal Intermediate Care Nursery After Exposure to a Healthcare Worker. Infection Control & Hospital Epidemiology 2006 June;27(6):541-545.**

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.

- **Campbell H, Amirthalingam G, Andrews N, Fry NK, George RC, Harrison TG, et al. Accelerating control of pertussis in England and Wales. *Emerg Infect Dis* 2012 Jan;18(1):38-47.**

Results of an accelerated pertussis vaccination schedule for infants introduced in 1990 in England and Wales were examined. Earlier scheduling and sustained high vaccine coverage resulted in fewer reported cases of pertussis among infants, reinforcing the World Health Organization drive for on-time completion of the infant vaccination schedule. As determined by using the screening method, the first dose of vaccine was 61.7% effective in infants <6 months of age, and effectiveness increased with subsequent doses. Three doses of a good whole-cell pertussis vaccine were 83.7% effective in children 10–16 years of age; a preschool booster vaccination further reduced pertussis incidence in children <10 years of age. As in other industrialized countries, surveillance data during 1998–2009 showed that pertussis in England and Wales mainly persists in young infants (i.e., <3 months of age), teenagers, and adults. Future vaccine program changes may be beneficial, but additional detail is required to inform such decisions.

- **Carlsson RM, Trollfors B. Control of pertussis--lessons learnt from a 10-year surveillance programme in Sweden. *Vaccine* 2009 Sep 25;27(42):5709-5718.**

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*.

- **Crowcroft NS, Pebody RG. Recent developments in pertussis. Lancet 2006 Jun 10;367(9526):1926-1936.**

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.

- **Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. Clin Infect Dis 2015 Feb 2015;60(3):333-337.**

BACKGROUND: Infants with pertussis infection are at risk of severe clinical illness and death. Several countries, including the United Kingdom, have introduced maternal pertussis vaccination during pregnancy to protect infants from infection following national increases in pertussis notifications. The objective of this study was to estimate the effectiveness of maternal pertussis vaccination in protecting infants against laboratory-confirmed pertussis infection. **METHODS:** A case-control study was undertaken in England and Wales between October 2012 and July 2013. Cases were infants aged <8 weeks at onset with pertussis infection tested by real-time polymerase chain reaction or culture. Family doctors of each case were asked to identify healthy infants born consecutively after the case in each practice, to act as controls. Fifty-eight cases and 55 controls were included in this study. Odds ratios (ORs) were calculated for the association between maternal vaccination and infant pertussis infection. The vaccine effectiveness (VE) was calculated as $1 - \text{OR}$. This was adjusted for sex, geographical region, and birth period. **RESULTS:** Mothers of 10 cases (17%) and 39 controls (71%) received pertussis vaccine in pregnancy. This gave an unadjusted VE of 91% (95% confidence interval [CI], 77%-97%). Adjusted VE was 93% (95% CI, 81%-97%). **CONCLUSIONS:** Maternal pertussis vaccination is effective in preventing pertussis infection in infants aged <8 weeks and may be considered in other countries experiencing high levels of pertussis notifications.

- **Dolan S, Wallace A, Burnett E, Ehlman D, Sui W, Garon J, Patel M, Hampton L, Kay A, Chmielewski E, and Hyde T. Summary of evidence on the administration of multiple injectable vaccines in infants during a single visit: safety, immunogenicity, and vaccine administration practices: Prepared for the April 2015 SAGE Meeting . Available at http://www.who.int/immunization/sage/meetings/2015/april/5_Summary_of_Evidence_3-25-2015.pdf?ua=1 (Accessed August 2015).**

As new vaccines are introduced into national immunization programmes, there is an increasing need to provide clear and sound guidance to countries on how to handle the administration of multiple injectable vaccines to infants during the same immunization visit. In view of perceived hesitancy of health care workers or caretakers about accepting the administration of multiple injectable vaccines during the same visit, some national programmes are choosing various alternatives: delaying scheduled vaccinations, creating additional visits, administering doses during other visits that are not within the recommended interval between doses, or

administering injections via different routes to avoid giving more than one injection in the same limb or visit. Even in the case that national programmes do not alter the schedule, apparent hesitancy by vaccinators to administer multiple injectable vaccines can pose a risk to the success of immunization programmes and may result in parents declining scheduled vaccines.

Prior to PCV being recommended for the routine childhood immunization schedule, there were few examples of EPI programs that required more than 1 vaccine in a visit. However, countries using PCV, pentavalent (DTPSHepBSHib) and IPV vaccines are now faced with the possibility of administering multiple injectable vaccines in one visit. This issue has become more prominent in the context of the Inactivated Polio Vaccine (IPV) introduction as part of the Polio Eradication and Endgame Strategic Plan 2013-2018. Although many country EPI programmes have been administering two injectable vaccines at a visit (mainly pentavalent and PCV vaccines), the addition of the injectable IPV at 14 weeks can lead to recommendations that three injectable vaccines be administered at a single visit, which has caused concern in some countries.

Although there are no specific SAGE recommendations on multiple injections in the context of administering pentavalent, PCV, and IPV in one visit, WHO has provisionally provided the following recommendations:

- IPV (non-Adjuvanted) can be given intramuscularly (IM) or subcutaneously (SC), but because of reduced reactogenicity and easier administration, the WHO recommends the IM route.
- For IM injections in infants below 15 months of age, the deltoid injection site (upper arm) should not be used due to its inadequate muscle mass.
- When three IM injections are scheduled simultaneously in children under 15 months of age, it is safe and acceptable to give 2 injections in the same thigh.
- For this, the WHO recommendation is: One thigh: PCV+IPV, separated by 2.5 cm; the other thigh: DTPSHepBSHib.

We present the evidence from both the peer-reviewed and grey literature that pertains to the recommendations on multiple injections at a single visit. Information in this document focuses on the administration of IPV, PCV, and DTPSHepBSHib vaccines as these will be the vaccines most commonly administered simultaneously during the same visit, once all countries have introduced IPV. Acellular pertussis containing vaccines were not the focus of this summary as they are not often used in developing countries. However, they were included in some of our findings on adverse events following simultaneous administration of vaccinations because the studies provided relevant information for our review when such information was lacking for whole cell pertussis vaccines. We organized our findings based on four topic areas: 1. Biological Issues: Is there evidence that giving immunizations simultaneously at the same visit has the same biologic effect as when they are given alone? 2. Safety Issues: Is it safe to administer multiple injectable vaccines simultaneously? Are there any cumulative enhanced adverse effects from administering multiple injectable vaccines simultaneously? 3. Methods of Administration: What is the recommended method for administering multiple injections in a single visit? 4. Programmatic: What is the recommended practice for preparing for an immunization session at which multiple injectable vaccines will be administered?

- **Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. BMJ 2014 July 12;349:g4219.**

OBJECTIVE: To examine the safety of pertussis vaccination in pregnancy. **DESIGN:** Observational cohort study. **SETTING:** The UK Clinical Practice Research Datalink. **PARTICIPANTS:** 20,074 pregnant women with a median age of 30 who received the pertussis vaccine and a matched historical unvaccinated control group. **MAIN OUTCOME MEASURE:** Adverse events identified from clinical diagnoses during pregnancy, with additional data from the matched child record identified through mother-child linkage. The primary event of interest was stillbirth (intrauterine death after 24 weeks' gestation). **RESULTS:** There was no evidence of an increased risk of stillbirth in the 14 days immediately after vaccination (incidence rate ratio 0.69, 95% confidence

interval 0.23 to 1.62) or later in pregnancy (0.85, 0.44 to 1.61) compared with historical national rates. Compared with a matched historical cohort of unvaccinated pregnant women, there was no evidence that vaccination accelerated the time to delivery (hazard ratio 1.00, 0.97 to 1.02). Furthermore, there was no evidence of an increased risk of stillbirth, maternal or neonatal death, pre-eclampsia or eclampsia, haemorrhage, fetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, low birth weight, or neonatal renal failure, all serious events that can occur naturally in pregnancy. **CONCLUSION:** In women given pertussis vaccination in the third trimester, there is no evidence of an increased risk of any of an extensive predefined list of adverse events related to pregnancy. In particular, there was no evidence of an increased risk of stillbirth. Given the recent increases in the rate of pertussis infection and morbidity and mortality in neonates, these early data provide initial evidence for evaluating the safety of the vaccine in pregnancy for health professionals and the public and can help to inform vaccination policy making.

- **Edwards KM, Decker MD. Pertussis vaccines. In: Plotkin S, Orenstein W, Offit P, eds. Vaccines, 6th ed. Philadelphia, Saunders, 2013:447–492.**
No abstract available.
- **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):1316-1330.**
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.
- **Gambhir M, Clark TA, Cauchemez S, Tartof SY, Swerdlow DL, Ferguson NM. A change in vaccine efficacy and duration of protection explains recent rises in pertussis incidence in the United States. PLoS Comput Biol 2015 Apr;11(4):e1004138.**
Over the past ten years the incidence of pertussis in the United States (U.S.) has risen steadily, with 2012 seeing the highest case number since 1955. There has also been a shift over the same time period in the age group reporting the largest number of cases (aside from infants), from adolescents to 7-11 year olds. We use epidemiological modelling and a large case incidence dataset to explain the upsurge. We investigate several hypotheses for the upsurge in pertussis cases by fitting a suite of dynamic epidemiological models to incidence data from the National Notifiable Disease Surveillance System (NNDSS) between 1990-2009, as well as incidence data from a variety of sources from 1950-1989. We find that: the best-fitting model is one in which vaccine efficacy and duration of protection of the acellular pertussis (aP) vaccine is lower than that of the whole-cell (wP) vaccine, (efficacy of the first three doses 80% [95% CI: 78%, 82%]

versus 90% [95% CI: 87%, 94%]), increasing the rate at which disease is reported to NNDSS is not sufficient to explain the upsurge and 3) 2010-2012 disease incidence is predicted well. In this study, we use all available U.S. surveillance data to: 1) fit a set of mathematical models and determine which best explains these data and 2) determine the epidemiological and vaccine-related parameter values of this model. We find evidence of a difference in efficacy and duration of protection between the two vaccine types, wP and aP (aP efficacy and duration lower than wP). Future refinement of the model presented here will allow for an exploration of alternative vaccination strategies such as different age-spacings, further booster doses, and cocooning.

- **Global Health Observatory Data Repository . World Health Organization. 2015. Available at <http://apps.who.int/gho/data/node.main.ChildMortREG100?lang=en> (Accessed August 2015).** No abstract available.
- **Greco D, Salmaso S, Mastrantonio P, Giuliano M, Tozzi AE, Anemona A, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group. New England Journal of Medicine 1996 Feb; 334(6):341-348.**
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.
- **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 February 8;334(6):349-355.**
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 ≥ 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.

- Halasa NB, O'Shea A, Shi JR, LaFleur BJ, Edwards KM. Poor Immune Responses to a Birth Dose of Diphtheria, Tetanus, and Acellular Pertussis Vaccine. J Pediatr 2008 Sept;153(3):327-332.e1.**

OBJECTIVES: To evaluate the safety and immunogenicity of an additional birth dose of diphtheria, tetanus, and acellular pertussis vaccine (DTaP). **STUDY DESIGN:** Fifty infants between 2 to 14 days of age were randomly assigned to receive either DTaP and hepatitis B vaccines (experimental) or hepatitis B alone (control) at birth. At 2, 4, 6, and 17 months of age, DTaP and routine vaccines were administered to both groups. Safety data were collected after each dose, and sera were obtained at birth, 6, 7, 17, and 18 months. Immune responses to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae were measured by enzyme-linked immunosorbent assay; responses to other vaccines were assessed. **RESULTS:** No differences were seen between the 2 groups in either local or systemic reactions; all vaccines were well tolerated. Compared with the control group, infants in the experimental group demonstrated significantly lower geometric mean antibody concentrations for pertussis toxin and pertactin 6, 7, and 18 months, for fimbriae at 6, 7, 17, and 18 months, and for FHA at 18 months, and lower geometric mean antibody concentrations for diphtheria at 7 months. Immune responses to all other vaccine antigens were comparable. **CONCLUSION:** Administration of an additional dose of DTaP at birth was safe but was associated with a significantly lower response to diphtheria and 3 of 4 pertussis antigens compared with controls.
- Hardy-Fairbanks AJ, Pan SJ, Decker MD, Johnson DR, Greenberg DP, Kirkland KB, et al. Immune responses in infants whose mothers received Tdap vaccine during pregnancy. Pediatr Infect Dis J 2013 Nov;32(11):1257-1260.**

BACKGROUND: The effect of maternal Tdap vaccination on infant immunologic responses to routine pediatric vaccines is unknown. **METHODS:** This was a cohort study of infants whose mothers received or did not receive Tdap vaccine during pregnancy. Maternal and cord blood samples were collected at delivery; infant blood samples were collected before and after primary series and booster dose of diphtheria, tetanus, and acellular pertussis (DTaP) and other vaccines. Geometric mean antibody concentrations or titers to pertussis, hepatitis B, tetanus, diphtheria, Haemophilus influenzae type b and polio antigens were measured. Mean maternal-to-cord blood antibody ratios were calculated. **RESULTS:** At delivery, maternal and cord antibody concentrations to pertussis antigens were higher in the Tdap group (n=16) than control group (n=54; maternal: 1.9- to 20.4-fold greater; cord: 2.7- to 35.5-fold greater). Increased antibody concentrations persisted for infants at first DTaP (3.2- to 22.8-fold greater). After primary series, antibody concentrations to pertussis antigens were lower in Tdap group (0.7- to 0.8-fold lower), except for fimbriae types 2 and 3 (FIM) (1.5-fold greater). Antibody concentrations to pertussis

antigens before and after booster dose were comparable (prebooster: Tdap group 1.0- to 1.2-fold higher than controls; postbooster: 0.9- to 1.0-fold lower). Differences in FIM values at these time points are difficult to interpret, due to varying FIM content among DTaP vaccines administered to infants in both groups. **CONCLUSIONS:** Maternal Tdap immunization resulted in higher pertussis antibody concentrations during the period between birth and the first vaccine dose. Although slightly decreased immune responses following the primary series were seen compared with controls, differences did not persist following the booster.

- Healy CM, Rench MA, Wootton SH, Castagnini LA. Evaluation of the impact of a pertussis cocooning program on infant pertussis infection. *Pediatr Infect Dis J* 2015 Jan;34(1):22-26.**

BACKGROUND: Tetanus, diphtheria and acellular pertussis immunization of infant contacts (cocooning) is recommended by the Centers for Disease Control and Prevention to prevent infant pertussis. We determined whether implementing a cocooning program at Ben Taub General Hospital, Houston, reduced severe pertussis in young infants.

METHODS: Infants ≤ 6 months of age, diagnosed with pertussis (determined by International Classification of Diseases, Ninth Revision codes and microbiology records) at 4 hospitals, and born at times when only postpartum women (January 2008 through May 2009) and all infant contacts (June 2009 through August 2011) were offered tetanus, diphtheria and acellular pertussis vaccine at Ben Taub General Hospital were compared with infants born preintervention (May 2004 through December 2007).

RESULTS: One hundred ninety-six (49%) infants with pertussis were born preintervention, 140 (35%) during maternal postpartum (PP) and 64 (16%) during cocooning (C) periods. Infants were similar in age at diagnosis (81.2 vs. 71.3 [PP] vs. 72.5 [C] days; $P = 0.07$), sex (male 59% vs. 51% [PP] vs. 48% [C]; $P = 0.17$), hospitalization (68% vs. 71% [PP] vs. 78% [C]; $P = 0.27$) and outcome (2 deaths in the PP period; $P = 0.15$), but more were admitted to intensive care units during cocooning (24% vs. 35% [PP] vs. 68% [C]; $P < 0.001$). Similar proportions of infants were born at Ben Taub General Hospital throughout the study (8% vs. 9% [PP] vs. 5% [C]; $P = 0.53$).

CONCLUSIONS: Postpartum immunization and cocooning did not reduce pertussis illness in infants ≤ 6 months of age. Efforts should be directed toward increasing tetanus, diphtheria and acellular pertussis immunization during pregnancy, combined with cocooning, to reduce life-threatening young infant pertussis.
- Hegerle N, Dore G, Guiso N. Pertactin deficient *Bordetella pertussis* present a better fitness in mice immunized with an acellular pertussis vaccine. *Vaccine* 2014 Nov 20;32(49):6597-6600.**

Bordetella pertussis is the etiologic agent of whooping cough and has been the target of vaccination for over fifty years. The latest strategies include the use of acellular pertussis vaccines that induce specific immunity against few virulence factors amongst which pertactin is included in three and five component acellular pertussis vaccines. Recently, it has been reported that *B. pertussis* clinical isolates loose the production of this adhesin in regions reaching high vaccine coverage with vaccines targeting this virulence factor. We here demonstrate that isolates not producing pertactin are capable of sustaining longer infection as compared to pertactin producing isolates in an in vivo model of acellular pertussis immunization. Loosing pertactin production might thus provide a selective advantage to these isolates in this background, which could account for the upraise in prevalence of these pertactin deficient isolates in the population.
- Hegerle N, Guiso N. *Bordetella pertussis* and pertactin-deficient clinical isolates: lessons for pertussis vaccines. *Expert review of vaccines* 2014 Sept;13(9):1135-1146.**

Bordetella pertussis causes whooping cough in humans, a highly transmissible respiratory disease life threatening for unvaccinated infants. Vaccination strategies were thus introduced worldwide with great success in developed countries reaching high vaccine coverage with efficacious vaccines. In the late 20th/early 21st century, acellular pertussis vaccines replaced

whole cell pertussis vaccines but *B. pertussis* still circulates and evolves in humans, its only known reservoir. The latest transformation of this pathogen, and of its close relative *Bordetella parapertussis*, is the loss of pertactin production, a virulence factor included in different acellular pertussis vaccines. The real impact of this evolution on acellular pertussis vaccines efficacy and effectiveness should be assessed through standardized surveillance and isolation of *B. pertussis* and *B. parapertussis* worldwide.

- **Hegerle N, Guiso N. Epidemiology of whooping cough & typing of *Bordetella pertussis*.(Report). *Future Microbiology* 2013 Nov;8(11):1391-1403.**

Bordetella pertussis is a Gram-negative human-restricted bacterium that evolved from the broad-range mammalian pathogen, *Bordetella bronchiseptica*. It causes whooping cough or pertussis in humans, which is the most prevalent vaccine-preventable disease worldwide. The introduction of the pertussis whole-cell vaccination for young children, followed by the introduction of the pertussis acellular vaccination (along with booster vaccination) for older age groups, has affected the bacterial population and epidemiology of the disease. *B. pertussis* is relatively monomorphic worldwide, but nevertheless, different countries are facing different epidemiological evolutions of the disease. Although it is tempting to link vaccine-driven phenotypic and genotypic evolution of the bacterium to epidemiology, many other factors should be considered and surveillance needs to continue, in addition to studies investigating the impact of current clinical isolates on vaccine efficacy.

- **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.**
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.

- **Hong Choi Y, Campbell H, Amirthalingam G, Miller E. Modelling pertussis transmission in England and Wales: investigating the cause of the recent resurgence and impact of additional vaccination strategies.**

In 2012 England and Wales experienced a resurgence of pertussis and an increase in infant deaths. This occurred eight years after acellular pertussis (aP) vaccine replaced whole cell (wP)

vaccine and despite continued high coverage for the primary series and pre-school aP booster. We developed a mathematical model to describe pertussis transmission dynamics in England and Wales since the 1950s and used it to investigate the cause of the resurgence and the potential impact of additional vaccination strategies.

- **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. BMJ 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.

- **Juretzko P, von Kries R, Hermann M, von Konig WCH, Weil J, Giani G. Effectiveness of Acellular Pertussis Vaccine Assessed by Hospital-Based Active Surveillance in Germany. Clinical Infectious Diseases 2002 July 15;35(2):162-167.**

We assessed the effectiveness of complete and partial pertussis vaccination in Germany--a country where acellular vaccine is predominantly used--for the prevention of cases of pertussis requiring hospitalization. Vaccine effectiveness was estimated by means of a screening method.

Vaccine coverage of children born during the period of June 1996 through December 1998 was assessed by a telephone survey. Data from hospitalized children with pertussis in 1997-1998 and from patients with pertussis complications in 1997-2000 were acquired by a nationwide, hospital-based, active surveillance system. Age-adjusted vaccine effectiveness of completed primary vaccination was estimated to be 99.8% (95% confidence interval [95% CI], 98.9-100). After receipt of 1 dose of vaccine, vaccine effectiveness was as high as 68.0% (95% CI, 45.6-81.1), increasing to 91.8% (95% CI, 84.7-95.7) after receipt of the second dose. Vaccine effectiveness was even slightly higher for pertussis with complications. Thus, even after partial vaccination, acellular pertussis vaccine is highly effective in preventing hospitalizations for pertussis.

- **King GE, Hadler SC. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. *Pediatr Infect Dis J* 1994 May;13(5):394-407.**

No abstract available.

- **Knuf M, Schmitt HJ, Wolter J, Schuerman L, Jacquet JM, Kieninger D, et al. Neonatal vaccination with an acellular pertussis vaccine accelerates the acquisition of pertussis antibodies in infants. *J Pediatr* 2008 May; 152(5):655-660e1.**

OBJECTIVES: Because young infants are at highest risk of pertussis complications, this study assessed whether neonatal acellular pertussis (aP) vaccination could provide earlier immunity.

STUDY DESIGN: Neonates (n = 121) were randomly assigned (1:1) to receive either aP or hepatitis B vaccine (HBV) (controls) vaccine at birth, followed by vaccination with DTaP-HBV-IPV/Hib at 2, 4 and 6 months. Immune responses were measured. Reactogenicity was assessed for 7 days after each dose. **RESULTS:** The aP birth dose was followed by few adverse events.

Reactogenicity of subsequent vaccine doses did not differ between groups. Seven serious adverse events were reported from each group; none were related to the study vaccines. At 3 months of age, vaccination with aP at birth had induced significantly higher antibody responses to the 3 pertussis antigens compared with controls. At 7 months, geometric mean/concentrations of antibodies against pertussis antigens were similar in both groups, and all subjects had reached "seroprotective" antibody concentrations against diphtheria, tetanus, and poliovirus types 1, 2, and 3. Geometric mean/concentrations of antibodies to haemophilus influenzae type b (Hib) and HBV were significantly lower in the aP group. **CONCLUSIONS:** Early neonatal immunization with aP was safe, well tolerated, and resulted in earlier antibody responses, seen after the first dose of a DTaP combination vaccine. Birth dose of aP did not induce immunologic tolerance to pertussis antigens but appear to dampen responses to Hib and HBV vaccines.

- **Laboratory manual for the diagnosis of whooping cough caused by *Bordetella pertussis*/*Bordetella parapertussis*. Geneva, World Health Organization, Update 2014 (WHO/IPV/14.03). Also available from http://apps.who.int/iris/bitstream/10665/127891/1/WHO_IVB_14.03_eng.pdf (Accessed August 2015).**

Whooping cough is a worldwide infectious disease caused by the bacteria *Bordetella pertussis* and *Bordetella parapertussis*. It is a respiratory disease occurring after transmission of the bacteria from person- to-person in airborne droplets. The bacteria are highly infectious and unprotected close contacts are liable to become infected. Incidence is highest in children under five, except where infant vaccination programmes have been effective and a shift has occurred to adolescents. Whooping cough is not only a childhood disease. It is dramatic for neonates and infants but can also be very severe for children and adults. For over 40 years, whole-cell pertussis vaccines have been very effective, preventing around 760 000 deaths worldwide every

year. Nevertheless, pertussis disease continues to impose a high burden — there are still 50 million cases of pertussis disease and 300 000 deaths annually, mostly among infants. Even in high-coverage countries, pertussis disease continues to cause severe illness and death among neonates and infants too young to have completed the primary vaccination series. Active primary immunization against *B. pertussis* infection is recommended, with three doses of a vaccine consisting of either a suspension of killed bacteria (whole-cell pertussis (wP) or acellular pertussis (aP) preparations that contain 1–5 different components of *B. pertussis*. These are usually given in combination with diphtheria and tetanus toxoids adsorbed on aluminium salts (DTwP or DTaP). In terms of severe adverse effects aP and wP vaccines appear to have the same high level of safety; reactions are less commonly associated with aP vaccines. Similar high efficacy levels (more than 80%) are obtained with the best aP and wP vaccines, although the level of efficacy may vary within each group. Protection is greater against severe disease and begins to wane after about three years. Acellular pertussis vaccines do not protect against infection by *B. parapertussis*. The need and timing for additional booster doses of diphtheria-tetanus-pertussis (DTP) vaccine, and their efficacy, should be assessed by national programmes. In the United States of America (USA), booster doses are recommended at 15–18 months of age, and either at school entry or at adolescence. Formulations of acellular pertussis vaccine, for use in adults, have been licensed and are available in several jurisdictions.

- **Martin SW, Pawloski L, Williams M, Weening K, DeBolt C, Qin X, et al. Pertactin-negative *Bordetella pertussis* strains: evidence for a possible selective advantage.(Report). *Clinical Infectious Diseases* 2015 Jan 15;60(2):223-227.**

BACKGROUND: A recent increase in *Bordetella pertussis* without the pertactin protein, an acellular vaccine immunogen, has been reported in the United States. Determining whether pertactin-deficient (PRN(-)) *B. pertussis* is evading vaccine-induced immunity or altering the severity of illness is needed. **METHODS:** We retrospectively assessed for associations between pertactin production and both clinical presentation and vaccine history. Cases with isolates collected between May 2011 and February 2013 from 8 states were included. We calculated unadjusted and adjusted odds ratios (ORs) using multivariable logistic regression analysis.

RESULTS: Among 753 isolates, 640 (85%) were PRN(-). The age distribution differed between cases caused by PRN(-) *B. pertussis* and cases caused by *B. pertussis* producing pertactin (PRN(+)) ($P = .01$). The proportion reporting individual pertussis symptoms was similar between the 2 groups, except a higher proportion of PRN(+) case-patients reported apnea ($P = .005$). Twenty-two case-patients were hospitalized; 6% in the PRN(+) group compared to 3% in the PRN(-) group ($P = .11$). Case-patients having received at least 1 pertussis vaccine dose had a higher odds of having PRN(-) *B. pertussis* compared with unvaccinated case-patients (adjusted OR = 2.2; 95% confidence interval [CI], 1.3-4.0). When restricted to case-patients at least 1 year of age and those age-appropriately vaccinated, the adjusted OR increased to 2.7 (95% CI, 1.2-6.1).

CONCLUSIONS: The significant association between vaccination and isolate pertactin production suggests that the likelihood of having reported disease caused by PRN(-) compared with PRN(+) strains is greater in vaccinated persons. Additional studies are needed to assess whether vaccine effectiveness is diminished against PRN(-) strains.

- **McVernon J, Andrews N, Slack M, 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 D, Madge N, Diamond J, Wadsworth J, Ross E. Pertussis immunisation and serious acute neurological illnesses in children. BMJ 1993 Nov 6; 307(6913):1171-1176.**
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.
- **Miller DL, Wadsworth MJH, 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 E, Ashworth LAE, Redhead K, Thornton C, Waight PA, Coleman T. Effect of schedule on reactogenicity and antibody persistence of acellular and whole-cell pertussis vaccines: value of laboratory tests as predictors of clinical performance. Vaccine 1997;15(1):51-60.**

The performance of four acellular pertussis vaccines containing between two and five pertussis antigens combined with diphtheria and tetanus toxoids was compared with that of British whole-cell diphtheria/tetanus/pertussis (DTP) vaccine both in laboratory assays for potency, toxicity and immunogenicity, and for reactogenicity and immunogenicity in infants. Clinical responses were evaluated in double blind randomized Phase II trials using 3/5/9 month and 2/3/4 month schedules. The acellular DTPs had much lower toxicity than whole-cell DTP in laboratory tests and were significantly less pyrogenic than whole-cell DTP under both schedules. Local reactions were not consistently lower in acellular than whole-cell vaccinees and varied with the source of the diphtheria and tetanus antigens used. Differences in endotoxin level and content of active pertussis toxin (PT) between acellular DTP vaccines were not clinically significant. The reactogenicity advantage of the acellular vaccines was substantially reduced under the 2/3/4 month schedule due to the reduced reactogenicity of the whole-cell DTP vaccine when given at a younger age. There was no relationship between antigen content measured in micrograms per dose and ELISA antibody responses to filamentous haemagglutinin (FHA) and PT in infants, nor was murine immunogenicity predictive of immunogenicity in humans. Antibody response to PT was attenuated in the whole-cell group under the 2/3/4 month schedule but was unaffected in the group receiving acellular vaccines with individually purified components; antibody response to pertactin (69 kDa antigen) was similar in recipients of the whole-cell and component acellular vaccines under the 2/3/4 month schedule. PT antibody persistence until 4-5 years of age was significantly better in recipients of the component acellular than either the whole-cell vaccine or the co-purified acellular vaccine under the 3/5/9 month schedule. However, diphtheria antitoxin levels were reduced in acellular vaccine recipients under both schedules. Despite significantly lower tetanus potencies of the acellular vaccines in laboratory tests, no differences were found in tetanus anti-toxin responses in children.

- **Misegades LK, Winter K, Harriman K, Talarico J, Clark TA, Messonnier NE, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA 2012 Nov 28; 308(20):2126-2132.**

CONTEXT: In 2010, California experienced its largest pertussis epidemic in more than 60 years; a substantial burden of disease was noted in the 7- to 10-year-old age group despite high diphtheria, tetanus, and acellular pertussis vaccine (DTaP) coverage, indicating the possibility of waning protection. **OBJECTIVE:** To evaluate the association between pertussis and receipt of 5 DTaP doses by time since fifth DTaP dose. **DESIGN, SETTING, AND PARTICIPANTS:** Case-control evaluation conducted in 15 California counties. Cases (n = 682) were all suspected, probable, and confirmed pertussis cases among children aged 4 to 10 years reported from January through December 14, 2010; controls (n = 2016) were children in the same age group who received care from the clinicians reporting the cases. Three controls were selected per case. Vaccination histories were obtained from medical records and immunization registries. **MAIN OUTCOME MEASURES:** Primary outcomes were (1) odds ratios (ORs) for the association between pertussis and receipt of the 5-dose DTaP series and (2) ORs for the association between pertussis and time since completion (<12, 12-23, 24-35, 36-47, 48-59, or ≥ 60 months) of the 5-dose DTaP series. Logistic regression was used to calculate ORs, accounting for clustering by county and clinician, and vaccine effectiveness (VE) was estimated as $(1 - \text{OR}) \times 100\%$. **RESULTS:** Among cases and controls, 53 (7.8%) and 19 (0.9%) had not received any pertussis-containing vaccines, respectively. Compared with controls, children with pertussis had a lower odds of having received all 5 doses of DTaP (OR, 0.11; 95% CI, 0.06-0.21 [estimated VE, 88.7%; 95% CI, 79.4%-93.8%]). When children were categorized by time since completion of the DTaP series, using an

unvaccinated reference group, children with pertussis compared with controls were less likely to have received their fifth dose within the prior 12 months (19 [2.8%] vs 354 [17.6%], respectively; OR, 0.02; 95% CI, 0.01-0.04 [estimated VE, 98.1%; 95% CI, 96.1%-99.1%]). This association was evident with longer time since vaccination, with ORs increasing with time since the fifth dose. At 60 months or longer (n = 231 cases [33.9%] and n = 288 controls [14.3%]), the OR was 0.29 (95% CI, 0.15-0.54 [estimated VE, 71.2%; 95% CI, 45.8%-84.8%]). Accordingly, the estimated VE declined each year after receipt of the fifth dose of DTaP. **CONCLUSION:** Among children in 15 California counties, children with pertussis, compared with controls, had lower odds of having received the 5-dose DTaP series; as time since last DTaP dose increased, the odds increased, which is consistent with a progressive decrease in estimated vaccine effectiveness each year after the final dose of pertussis vaccine.

- **Mooi FR, He Q, Guiso N. Phylogeny, evolution and epidemiology of Bordetellae. In: Locht C, ed. Bordetella: molecular microbiology. Norfolk, England, Horizon Biosciences, 2007: 17–46.**
No abstract available.
- **Mueller et al. Review on aP schedules and absolute effect - Figures and Tables Version August 19, 2014. Available at http://www.who.int/immunization/sage/meetings/2015/april/7_aP_Tables_Figures_140819.pdf?ua=1 (Accessed August 2015).**
No abstract available.
- **Mueller J, Koutangni T, Guiso, N, Soares-Weiser K, Fine P, Restrepo AH et al. Comparative efficacy/effectiveness of schedules in infant immunisation against pertussis, diphtheria and tetanus: Systematic review and meta-analysis. Part 2: Whole-cell pertussis vaccine. 2014. Available at http://www.who.int/immunization/sage/meetings/2015/april/6_Report_wp_140813.pdf?ua=1 (Accessed August 2015).**
No abstract available.
- **Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, Walter EB, Jackson LA, Englund JA, Edwards MS, Healy CM, Petrie CR, Ferreira J, Goll JB, Baker CJ. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA. 2014 May 7;311(17):1760-9.**
IMPORTANCE: Maternal immunization with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine could prevent infant pertussis. **OBJECTIVE:** To evaluate the safety and immunogenicity of Tdap immunization during pregnancy and its effect on infant responses to diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. **DESIGN, SETTING, AND PARTICIPANTS:** Phase 1-2, randomized, double-blind, placebo-controlled, clinical trial conducted from 2008 to 2012. Forty-eight pregnant women aged 18 to 45 years received Tdap (n = 33) or placebo (n = 15) at 30 to 32 weeks' gestation, with crossover immunization postpartum. **INTERVENTIONS:** Tdap vaccination at 30 to 32 weeks' gestation or postpartum. **MAIN OUTCOMES AND MEASURES:** Primary outcomes were maternal and infant adverse events, pertussis illness, and infant growth and development until age 13 months. Secondary outcomes were antibody concentrations in pregnant women before and 4 weeks after Tdap immunization or placebo, at delivery and 2 months' postpartum, and in infants at birth, at 2 months, and after the third and fourth doses of DTaP. **RESULTS:** No Tdap-associated serious adverse events occurred in women or infants. Injection site reactions after Tdap immunization were reported in 26 (78.8% [95% CI, 61.1%-91.0%]) and 12 (80% [95% CI, 51.9%-95.7%]) pregnant and postpartum women, respectively (P > .99). Systemic symptoms were reported in 12 (36.4% [95% CI, 20.4%-

54.9%]) and 11 (73.3% [95% CI, 44.9%-92.2%]) pregnant and postpartum women, respectively ($P = .03$). Growth and development were similar in both infant groups. No cases of pertussis occurred. Significantly higher concentrations of pertussis antibodies were measured at delivery in women who received Tdap during pregnancy vs postpartum (eg, pertussis toxin antibodies: 51.0 EU/mL [95% CI, 37.1-70.1] and 9.1 EU/mL [95% CI, 4.6-17.8], respectively; $P < .001$) and in their infants at birth (68.8 EU/mL [95% CI, 52.1-90.8] and 14.0 EU/mL [95% CI, 7.3-26.9], respectively; $P < .001$) and at age 2 months (20.6 EU/mL [95% CI, 14.4-29.6] and 5.3 EU/mL [95% CI, 3.0-9.4], respectively; $P < .001$). Antibody responses in infants born to women receiving Tdap during pregnancy were not different following the fourth dose of DTaP. **CONCLUSIONS AND RELEVANCE:** This preliminary assessment did not find an increased risk of adverse events among women who received Tdap vaccine during pregnancy or their infants. For secondary outcomes, maternal immunization with Tdap resulted in high concentrations of pertussis antibodies in infants during the first 2 months of life and did not substantially alter infant responses to DTaP. Further research is needed to provide definitive evidence of the safety and efficacy of Tdap immunization during pregnancy.

- **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):1290-1294.**

A resurgence in infant and adult pertussis cases has been observed in many countries around 25 years after the introduction of generalised vaccination. 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.

- **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. *Epidemiology and Infection* 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.

- 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 Feb 7; 351(9100):1569–1577.

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 to 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.

- Pertussis Report 8/31/2010. California Department of Public Health. Aug, 2010. Available at <http://www.cdph.ca.gov/programs/immunize/Documents/Pertussis%20report%208-31-2010%20-%20For%20Release.pdf> (Accessed August 2015).
No abstract available.

- **Préziosi MP, Yam A, Wassilak SGF, Chabirand L, Simaga A, Ndiaye M, et al. Epidemiology of pertussis in a West African community before and after introduction of a widespread vaccination program. *American Journal of Epidemiology* 2002 May 15; 155(10):891-896.**

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. *Communicable Diseases Intelligence* 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 epidemics, which varied among states and territories 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. *Commun Dis Intell* 2007;31:205–215.
- **Quinn HE, Snelling TL, Habig A, Chiu C, Spokes PJ, McIntyre PB. Parental Tdap boosters and infant pertussis: a case-control study. *Pediatrics* 2014 Oct;134(4):713-720.**

BACKGROUND: Although recommended for almost a decade, evidence for field effectiveness of vaccinating close adult contacts of newborn infants against pertussis ("cocooning") is lacking. We evaluated the impact of a government-funded cocoon program during a pertussis epidemic in New South Wales, Australia. **METHODS:** We matched all New South Wales laboratory-confirmed pertussis cases aged <4 months with onset between April 1, 2009, to March 30, 2011 to controls from the state birth register by date of birth and area of residence. Parental vaccine receipt was by self-report, with a subset verified. Parents were considered "immunized" if vaccinated ≥ 4 weeks before case symptom onset. The effectiveness of parental immunization (versus neither vaccinated) was quantified as $(1 - \text{odds ratio}) \times 100\%$. **RESULTS:** Case households had fewer immunized mothers (22% vs 32%) or fathers (20% vs 31%) but were more likely to include additional and older children. After adjustment, when both parents met our definition of immunized, risk of pertussis at <4 months of age was reduced by 51% (95% confidence interval

10% to 73%). Maternal vaccination prepregnancy and an immunized father reduced the risk by 51% (95% confidence interval 0% to 76%). **CONCLUSIONS:** Timely parental pertussis boosters provided significant protection. Evidence of protection from maternal vaccination prepregnancy is biologically plausible, and more precise data on the magnitude and duration of this is important for future policy recommendations.

- Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of protection after first dose of acellular pertussis vaccine in infants. *Pediatrics*. 2014 Mar;133(3):5**

OBJECTIVE: Data on the effectiveness of the diphtheria-tetanus-acellular pertussis (DTaP) vaccine in the first 4 years of life are sparse. We evaluated the vaccine effectiveness (VE) of 1 and 2 doses of DTaP before 6 months of age and of 3 doses from 6 months of age in Australia, where, since 2003, a fourth dose is not given until 4 years. **METHODS:** We matched reported pertussis cases aged 2 to 47 months between January 2005 and December 2009 to controls from a population-based immunization register by date of birth and region of residence. VE by number of doses and age group was calculated as $(1 - \text{odds ratio}) \times 100\%$. **RESULTS:** VE against hospitalization increased from 55.3% (95% confidence interval [CI], 42.7%-65.1%) for 1 dose before 4 months of age to 83.0% (95% CI, 70.2%-90.3%) for 2 doses before 6 months. The VE of 3 doses of DTaP against all reported pertussis was 83.5% (95% CI, 79.1%-87.8%) between 6 and 11 months, declining to 70.7% (95% CI, 64.5%-75.8%) between 2 and 3 years of age and 59.2% (95% CI, 51.0%-66.0%) between 3 and 4 years of age. **CONCLUSIONS:** DTaP provided good protection against pertussis in the first year of life from the first dose. Without a booster dose, the effectiveness of 3 doses waned more rapidly from 2 to 4 years of age than previously documented for children >6 years of age who had received 5 doses.
- Ray P, Hayward J, Michelson D, Lewis E, Schwalbe J, Black S, et al. Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study. *Pediatric Infectious Disease Journal* 2006 Sept; 25(9):768-773.**

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.

- **Report from the SAGE Working Group on Pertussis vaccines, 26 - 27 August 2014 meeting, Geneva, Switzerland. Available at http://www.who.int/immunization/sage/meetings/2015/april/1_Pertussis_report_final.pdf?ua=1 (Accessed August 2015).**

In March 2013, in the light of a recent increase in reported pertussis cases from some countries, which was in some instances associated with an increase in infant deaths, SAGE and WHO agreed that a new working group on pertussis vaccines would be established to prepare for a SAGE review of the evidence that would lead to updating as needed the 2010 WHO position paper on the use of pertussis vaccine¹. This also provided an opportunity to review newly available data on effectiveness of various vaccination strategies aimed at reducing infant mortality, as well as the pertussis-related outcomes of the vaccine schedule optimization project. The terms of reference for the SAGE pertussis vaccines working group were to:

1. Review epidemiological data on pertussis from selected countries using acellular pertussis (aP) and/or whole cell pertussis (wP) vaccines and evaluate the evidence for resurgence of pertussis, with an emphasis on severe pertussis in very young infants. In countries where the evidence supports resurgence, evaluate the evidence for the hypothesis that resurgence is due to shorter lived protection from aP relative to wP vaccines;
2. Review the evidence on effectiveness of 1 or 2 doses of pertussis vaccines against severe disease and death in young infants;
3. Review the evidence on effectiveness of three key strategies aimed at reducing severe disease and death from pertussis in very young infants (cocooning, maternal immunization during pregnancy, and immunization of newborns);
4. Review the evidence for optimal primary vaccination scheduling and timing of booster dose(s);
5. Review the evidence that changes in circulating pertussis strains have had an adverse impact on the effectiveness of aP or wP vaccines;
6. Propose updated recommendations for SAGE consideration on the use of pertussis vaccines.

The working group completed its review in relation to points 1, 2, 3, and 5, of its terms of reference in February 2014 and presented to SAGE on those points at the April 2014 SAGE meeting.

The review of the optimal primary immunization schedules as per point 4 of the terms of reference was, at that time ongoing, so the initial plan was that this would be presented at the October 2014 SAGE meeting. This review entailed a 4-component framework (epidemiology of the diseases, systematic review of the effectiveness and safety of the various schedules, operational considerations, and modelling) following the model already applied to pneumococcal conjugate, rotavirus and Haemophilus influenzae type b (Hib) vaccines. The initial intent was that both combined diphtheria, tetanus toxoid and pertussis vaccine (DTP) and tetanus toxoid vaccine (TT) schedules be reviewed by the pertussis working group, in view of the challenges of disentangling the primary vaccination schedule for pertussis from that of diphtheria and tetanus and the interrelation of the TT and DTP schedules. Point 6 of the terms of reference was to be fully completed only after completion of point 4.

As a result of SAGE's review of the evidence in April 2014, a brief revised guidance note on choice of pertussis vaccines was published in July 2014², with a plan to update the full position paper on the use of pertussis vaccines after the review of the evidence for optimal primary vaccination scheduling and timing of booster dose(s) would have been presented to SAGE.

- **Rennels MB. Extensive swelling reactions occurring after booster doses of diphtheria-tetanus-acellular pertussis vaccines. Seminars in Pediatric Infectious Diseases 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.

- **Riffelmann M, Wirsing von König CH, Caro V, Guiso N, for the Pertussis PCR, Consensus Group. Nucleic Acid amplification tests for diagnosis of Bordetella infections. Journal of Clinical Microbiology 2005 Oct; 43(10):4925-9.**

The global epidemiology of pertussis has recently been reviewed (12, 15). *Bordetella pertussis* continues to circulate even in populations where high vaccination coverage of infants and children is achieved (15, 23), because the protection after natural infection wanes after 10 to 15 years and protection after vaccination lasts for 6 to 10 years (15). A significant increase of pertussis cases was observed in the United States, in Europe, and in other countries with high vaccination coverage, making pertussis a reemerging disease. Transmission of the disease in highly vaccinated populations occurs mainly from adolescents and adults to infants or among older vaccinated children, adolescents, and adults (15). Thus, most cases of pertussis are now observed in unvaccinated infants, older schoolchildren, adolescents, and adults. In outbreak situations asymptomatic carriage has been observed in up to ~50% (12).

- **Rivero-Santana A, Cuéllar-Pompa L, Sánchez-Gómez LM, Perestelo-Pérez L, Serrano-Aguilar P. Effectiveness and cost-effectiveness of different immunization strategies against whooping cough to reduce child morbidity and mortality. Health Policy 2014 Mar; 115(1):82-91.**

INTRODUCTION: In the last years there has been a significant increase in reported cases of pertussis in developed countries, in spite of high rates of childhood immunization. Health institutions have recommended different vaccination strategies to reduce child morbidity and mortality: vaccination of adolescents and adults, pregnant women, people in contact with the newborn (cocoon strategy) and health care workers. The aim of this paper is to review the scientific evidence supporting these recommendations. **METHODS:** Systematic review on the effectiveness and cost-effectiveness of the above strategies for the reduction of morbidity and mortality from pertussis in infants under 12 months. The electronic databases Medline, PreMedline, Embase, CRD, Cochrane Central, and Trip Database were consulted from 1990 to October 2012. The evidence was assessed using the GRADE system. **RESULTS:** There were eight studies on the efficacy or safety of the strategies analyzed, and 18 economic evaluations. Direct evidence on the efficacy of these strategies is scarce. Economic evaluations suggest that vaccination of adolescents and adults would be cost-effective, although there is major uncertainty over the parameters used. **CONCLUSIONS:** From the perspective of health technology assessment, there is insufficient evidence to recommend the vaccination strategies evaluated.

- **Salmaso S, Mastrantonio P, Tozzi AE, Stefanelli P, Anemona A, Ciofi dA, et al. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: the Italian experience.(Abstract). Pediatrics 2001;108(5):1195.**

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.

- Scheifele DW. "What else could it be?" When neurologic disorders follow immunization.** Scheifele DW, topic ed. In: Tremblay RE, Boivin M, Peters RDeV, eds. *Encyclopedia on Early Childhood Development* [online]. Montreal, Quebec: Centre of Excellence for Early Childhood Development and Strategic Knowledge Cluster on Early Child Development; 2013; 1-5. Available at: <http://www.child-encyclopedia.com/immunization/according-experts/what-else-could-it-be-when-neurologic-disorders-follow-immunization> (Accessed April 8, 2013). When brain disorders such as seizures or encephalopathy occur after an immunization, people (including many doctors) have a strong natural tendency to blame the vaccine. This is especially so when the interval between immunization and symptom onset was short and the child was considered normal beforehand. Without an obvious alternative cause such as trauma or intercurrent infection, immunization may be considered guilty by default: what else could the cause have been? Studies in recent years using increasingly sophisticated diagnostic tools have revealed a substantial number of alternative causes that may not be evident unless looked for. In fact, alternative causes exist for almost all of the severe neurologic disorders that follow infant vaccinations.
- 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;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.

- **Sheridan SL, Frith K, Snelling TL, Grimwood K, McIntyre PB, Lambert SB. Waning vaccine immunity in teenagers primed with whole cell and acellular pertussis vaccine: recent epidemiology. Expert Review of Vaccines 2014 September;13(9):1081-1106.**

The recent epidemics of pertussis (whooping cough) in parts of the USA and Australia have led to the largest numbers of annual cases reported in over half a century. These epidemics demonstrated a new pattern, with particularly high rates of disease among pre-adolescents and early adolescents. These high rates of pertussis coincided with the first cohorts vaccinated with purely acellular pertussis vaccine, which replaced whole-cell pertussis (wP) vaccine in the later 1990s in the USA and Australia. Studies undertaken during these epidemics provide new evidence of more rapid waning of acellular pertussis-containing vaccines and longer-term protection from effective wP-containing vaccines. There is evidence that receiving wP as at least the first dose of pertussis-containing vaccine provides greater and more long-lived protection, irrespective of the nature of subsequent doses. This evidence will be reviewed together with the immunobiology associated with both vaccines, and the implications for pertussis control discussed.

- **Simondon F, Preziosi M, Yam A, Kane CT, Chabirand L, Iteaman I, et al. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. Vaccine 1997 Oct; 15(15):1606–1612.**

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.

- **Stehr K, Cherry JD, Heininger U, Schmitt-Grohé S, Uberall M, Laussucq S, et al. 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; 101:1–11.**

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.

- **Tiwari T, Murphy TV, Moran J. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines. *Morbidity and Mortality Weekly Report. Recommendations and Reports* 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.

- **Warfel JM, Merkel TJ. *Bordetella pertussis* infection induces a mucosal IL-17 response and long-lived Th17 and Th1 immune memory cells in nonhuman primates. *Mucosal Immunol* 2013 Jul;6(4):787–796.**

Despite near universal vaccine coverage, the bacterial pathogen *Bordetella pertussis* has re-emerged as a major public health concern. We recently developed a baboon (*Papio anubis*) model of pertussis that provides an excellent model of human pertussis. Using this model, the immune response to pertussis was characterized by measuring cytokines in the nasopharyngeal mucosa of infected baboons. Notably, we observed mucosal expression of interleukin-17 (IL-17) as well as IL-6, IL-23, and several cytokines and chemokines that are orchestrated by IL-17 immune responses. We also found substantial populations of circulating *B. pertussis*-specific Th17 and Th1 cells in convalescent animals >2 years post-infection consistent with a role in

immunological memory to pertussis. Collectively, these data shed important light on the innate and adaptive immune responses to pertussis in a primate infection model and suggest that Th17 and Th1 immune responses contribute to the immunity conferred by natural pertussis infection.

- **Warfel JM, Merkel TJ. Reply to Domenech de Celles et al.: Infection and transmission of pertussis in the baboon model. Proc Natl Acad Sci USA 2014 Feb 18;111(7):E718.**
No abstract available.
- **Warfel JM, Papin JF, Wolf RF, Zimmerman LI, Merkel TJ. Maternal and neonatal vaccination protects newborn baboons from pertussis infection. J Infect Dis 2014 Aug 15;210(4):604-610.**
BACKGROUND: The United States is experiencing a pertussis resurgence that resulted in a 60-year high of 48 000 cases in 2012. The majority of hospitalizations and deaths occur in infants too young to be vaccinated. Neonatal and maternal vaccination have been proposed to protect newborns until the first vaccination, currently recommended at 2 months of age. These interventions result in elevated anti-Bordetella pertussis titers, but there have been no studies demonstrating that these measures confer protection. **METHODS:** Baboons were vaccinated with acellular pertussis vaccine at 2 days of age or at 2 and 28 days of age. To model maternal vaccination, adult female baboons primed with acellular pertussis vaccine were boosted in the third trimester of pregnancy. Neonatally vaccinated infants, infants born to vaccinated mothers, and naive infants born to unvaccinated mothers were infected with *B. pertussis* at 5 weeks of age. **RESULTS:** Naive infant baboons developed severe disease when challenged with *B. pertussis* at 5 weeks of age. Baboons receiving acellular pertussis vaccine and infants born to mothers vaccinated at the beginning of their third trimester were protected. **CONCLUSIONS:** Our results demonstrate that neonatal vaccination and maternal vaccination confer protection in the baboon model and support further study of these strategies for protection of newborns from pertussis.
- **WHO Expert Committee on Biological Standardization. Fifty-sixth report. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 941). See Annex 6, Recommendations for whole cell pertussis vaccine, pp. 301–333. Available at <http://www.who.int/biologicals/publications/trs/Full%20Text%20TRS941.pdf> (Accessed August 2015).**
This report presents the recommendations of a WHO Expert Committee commissioned to coordinate activities leading to the adoption of international recommendations for the production and control of vaccines and other biologicals and the establishment of international biological reference materials. The report starts with a discussion of general issues brought to the attention of the Committee and provides information on the status and development of reference materials for various antibodies, antigens, blood products and related substances, cytokines, growth factors, and endocrinological substances. The second part of the report, of particular relevance to manufacturers and national regulatory authorities, contains guidelines on quality, safety and efficacy of live attenuated rotavirus vaccines; DNA vaccines; a biosafety risk assessment for production and quality control of human influenza pandemic vaccines; recommendations for inactivated rabies vaccines produced in cell substrates and embryonated eggs; for whole cell pertussis vaccine; and for production, control and regulation of human plasma for fractionation. Also included are a list of recommendations, guidelines and other documents for biological substances used in medicine, and of international standards and reference reagent for biological substances.

- **WHO Expert Committee on Biological Standardization. Sixty-second report. Geneva, World Health Organization, 2013 (WHO Technical Report Series No. 979). See Annex 4, Recommendations to assure the quality, safety and efficacy of acellular pertussis vaccines, pp. 187-260. Available at http://www.who.int/biologicals/vaccines/TRS_979_Annex_4.pdf?ua=1 (Accessed August 2015).**

Pertussis immunization is an integral part of immunization programmes in all regions of the world. It is recommended for all infants and children and in some countries it is also recommended for adults and adolescents. Whole-cell pertussis vaccines, which have been used for more than 50 years, have been shown to provide protection against pertussis and still serve as the foundation of global pertussis control. However, there is an increasing interest in acellular pertussis vaccines which have also been shown to be safe and effective and which have been successfully introduced into many national immunization programmes. A detailed comparison of acellular and whole-cell pertussis vaccines is beyond the scope of this document; however, these issues are discussed in detail in a WHO position paper on pertussis vaccines (1). As a consequence of the increasing demand for acellular pertussis vaccines, new manufacturers are entering the field. The expansion in the number and use of acellular pertussis vaccines, the development of new vaccines and advances in the standardization of quality control methods have prompted WHO to update its current Guidelines for acellular pertussis vaccines (2). These Guidelines were approved in 1996, with the recognition that further improvements in the production and evaluation of these vaccines would follow. Since then, stakeholders have gained additional experience with these vaccines, and limitations in the original Guidelines have been identified (3–7). Acellular pertussis vaccines are almost exclusively administered in combinations with diphtheria and tetanus toxoid vaccines. Moreover, in recent years there has been increased interest in the use of more complex combination vaccines – a trend which increases the challenges of clinical evaluation. Furthermore, the evaluation of the clinical efficacy of any new acellular pertussis vaccine formulations has become increasingly difficult due to the decrease in the prevalence of pertussis cases worldwide and for additional reasons discussed below in Part C. The goal of this revision is to address these issues concerning the Guidelines in the light of new information.

- **WHO Information Sheet: Observed rate of vaccine reactions – Diphtheria, pertussis, tetanus vaccines, May 2014. Available at http://www.who.int/vaccine_safety/initiative/tools/DTP_vaccine_rates_information_sheet.pdf?ua=1 (Accessed August 2015).**
No abstract available.
- **Whole Cell Pertussis Vaccines: Summary of evidence relevant to schedules . Available at http://www.who.int/immunization/sage/meetings/2015/april/2_wp_summary_WG_23Mar2015_submitted.pdf?ua=1 (Accessed August 2015).**
No abstract available.
- **WHO recommended standards for surveillance of selected vaccine-preventable diseases. Geneva, World Health Organization, 2003 (WHO/V&B/03.01). Available at http://apps.who.int/iris/bitstream/10665/68334/1/WHO_V-B_03.01_eng.pdf?ua=1 (Accessed August 2015).**

The purpose of this document is to provide WHO recommendations on surveillance standards for selected vaccine-preventable diseases. The recommendations should be carefully adapted to meet national needs in accordance with each country's disease control priorities, objectives and strategies.

Disease surveillance is the routine ongoing collection, analysis and dissemination of health data. An effective surveillance system has the following functions:

- detection and notification of health events;
- collection and consolidation of pertinent data;
- investigation and confirmation (epidemiological, clinical and/or laboratory) of cases or outbreaks;
- routine analysis and creation of reports;
- feedback of information to persons providing data;
- feed-forward (i.e. the forwarding of data to more central levels).

The rationale for the surveillance of a specific health event should be established and based on clear national priorities, disease control objectives and strategies. Otherwise the data collected may be irrelevant. What data to collect depends on the analyses that are needed to guide decision-making on matters of public health. In order not to overburden health staff at the peripheral levels the surveillance system should be as streamlined as possible, i.e. the minimum necessary amount of data should be collected. The most efficient and appropriate means of collecting, consolidating and transferring such data should be employed. Staff at all levels should be trained and encouraged to analyse and use their data. Data that can be more efficiently collected from other sources (e.g. surveys) should not be included in a surveillance system.

An effective surveillance system is:

- useful;
- efficient;
- flexible;
- representative;
- simple.

These attributes should be assessed when evaluating a surveillance system. At the national level, clear surveillance standards should be established to achieve maximum efficiency and ensure that data are comparable throughout the country concerned. These standards cover:

- case definitions;
- the type of surveillance to be conducted;
- the data elements to be collected;
- the minimum analyses and routine reports to be produced;
- the use of data in decision-making.

To achieve operational surveillance it is necessary to carefully define:

- the process of surveillance;
- the tasks at each level;
- the data/specimen flow;
- the logistics, including staff issues:
- designations of staff;
- o staff training;
- o appropriate tool distribution (e.g. means of communication, transportation, specimen kits).

Standard performance indicators should be monitored as a part of supervision to identify weaknesses in the system so that corrective action can be taken.

- **WHO SAGE pertussis working group. Background paper. SAGE April 2014. Available at http://www.who.int/immunization/sage/meetings/2014/april/1_Pertussis_background_FINA_L4_web.pdf?ua=1 (Accessed August 2015).**

In the light of the recent increase in reported pertussis cases from some countries, which were in some instances associated with an increase in infant deaths, SAGE and the WHO agreed that a new working group on pertussis would be established. This working group would first prepare for a SAGE review of the data and would then consider updating current pertussis vaccine recommendations as published in the 2010 pertussis vaccine position paper (<http://www.who.int/wer/2010/wer8540.pdf>). This also provided an opportunity to review

newly available data on effectiveness of various vaccination strategies aimed at reducing infant mortality, as well as the pertussis-related outcomes of the vaccine schedule optimization project. The terms of reference for the SAGE pertussis vaccines working group were:

1. Review epidemiological data on pertussis from selected countries using acellular pertussis (aP) and/or whole cell pertussis (wP) vaccines and evaluate the evidence for resurgence of pertussis, with an emphasis on severe pertussis in very young infants. In countries where the evidence supports resurgence, evaluate the evidence for the hypothesis that resurgence is due to shorter lived protection from aP relative to wP vaccines;
2. Review the evidence on effectiveness of 1 or 2 doses of pertussis vaccines against severe disease and death in young infants;
3. Review the evidence on effectiveness of three key strategies aimed at reducing severe disease and death from pertussis in very young infants (cocooning, maternal immunization during pregnancy, and immunization of newborns);
4. Review the evidence for optimal primary vaccination scheduling and timing of booster dose(s);
5. Review the evidence that changes in circulating pertussis strains have had an adverse impact on the effectiveness of aP or wP vaccines;
6. Propose updated recommendations for SAGE consideration on the use of pertussis vaccines.

The working group has completed its review in relation with points 1, 2, 3, 5, of its terms of reference. The review of the optimal primary immunization schedules as per point 4 of the terms of reference is still ongoing and will be completed in the summer of 2014 and presented at the October 2014 SAGE meeting. This review entails a 4-component framework (epidemiology of the diseases, systematic review of the effectiveness and safety of the various schedules, operational considerations, and models & ICEA) following the model already applied to pneumococcal conjugate, rotavirus and Haemophilus influenzae type b (Hib) vaccines. Both combined diphtheria, tetanus toxoid and pertussis vaccine (DTP) and tetanus toxoid vaccine (TT) schedules will be reviewed by the pertussis working group in view of the impossibility of disentangling the primary vaccination schedule for pertussis from that of diphtheria and tetanus and the interrelation of the TT and DTP schedules. Point 6 of the terms of reference will only be fully completed after completion of point 4. The 2010 pertussis position paper will be revisited only after the results of the review are available. In the meantime, a brief update to the position paper will be published, pending the decision made by SAGE at its April meeting.

- **Wiley KE, Zuo Y, Macartney KK, McIntyre PB. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. Vaccine 2013;31:618-625.**

BACKGROUND: The relative contribution of different categories of contact in transmitting pertussis to very young infants, who experience the most severe morbidity, is the most important single factor determining the likely benefit of pertussis vaccination of their close contacts (the "cocooning" strategy). **OBJECTIVE:** To identify, evaluate the quality of and summarise existing data on potential sources of infant pertussis infection in high income countries, focussing on infants under 6 months old. **DATA SOURCES:** Online databases MEDLINE and EMBASE. Additional studies were identified from the reference lists of relevant articles. Study selection and analysis: Study quality was evaluated by standardised criteria, based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Pooled estimates of the proportion of pertussis cases attributable to various contact sources were calculated using data from the highest quality studies. **RESULTS:** Nine studies met the inclusion criteria; seven included data on contacts of hospitalised infants less than 6 months old. Case definitions and methods of contact ascertainment were variable. Most identified sources were from the household, of which 39% (95%CI 33-45%) were mothers, 16% (95%CI 12-21%) fathers, and 5% (95%CI 2-10%) grandparents. Estimates for siblings (16-43%) and non-household contacts (4-22%) were more heterogeneous. For 32-52% of infant cases, no source was identified. Asymptomatic pertussis infection was found in 8-13% of contacts evaluated.

CONCLUSIONS: These data suggest that the greatest potential impact of pertussis vaccination of adults to prevent severe disease in young infants comes from vaccinating mothers, followed by fathers, with grandparents having a minor role. Siblings varied in importance and, given recent data regarding waning immunity in vaccinated children, need further study. Non-household sources are also well documented, highlighting the potential limitations of the cocoon strategy to prevent severe infant disease

- **Wirsing von König CH, Rott H, Bogaerts H, Schmitt HJ. A serologic study of organisms possibly associated with pertussis-like coughing. *Pediatr Infect Dis J* 1998 Jul;17(7):645-649.**
OBJECTIVE. To assess the frequency of serologic evidence for an infection with microorganisms other than *Bordetella pertussis* in children with pertussis-like coughs. **METHODS.** The study was performed within a protective efficacy trial of an acellular pertussis vaccine. Children who coughed for >7 days and had no laboratory evidence of recent infection with *B. pertussis* were eligible for the present study. Antibodies to *Mycoplasma*, *Chlamydia*, respiratory syncytial virus and influenza viruses A and B were measured by complement fixation, and antibodies to adenovirus and parainfluenza viruses 1, 2 and 3 were measured by enzyme-linked immunosorbent assay (ELISA) in acute and convalescent serum samples. Significant titer rises (4-fold titer rise in complement fixation, 100% increase of units in ELISA) and concentrations of antibodies beyond age-specific reference values were regarded as indicative of recent infection. In some children IgM antibodies to Epstein-Barr virus and to cytomegalovirus were also measured by ELISA. **RESULTS.** A total of 149 of 1179 (12.6%) children had no laboratory evidence of *B. pertussis* infection. Serologic evidence for other infections were found in 56% (83 of 149). Adenovirus (33), parainfluenza viruses 1, 2 and 3 (18), *Mycoplasma pneumoniae* (15) and respiratory syncytial virus (14) were most common. Of this group 48% had been vaccinated against pertussis. **CONCLUSION.** We present data that a proportion of pertussis-like coughs in children may be caused by adenovirus, parainfluenza viruses, respiratory syncytial virus and *Mycoplasma*. The differential diagnosis of pertussis-like coughs by laboratory methods should include these infections, especially in vaccinated children.
- **Wirsing von König CH. The immunological basis for immunization series: module 4: pertussis – update 2009. Geneva: World Health Organization.2010 pp50. Available at <http://apps.who.int/iris/handle/10665/44311> (Accessed August 2015).**
This module replaces the publication WHO/EPI/93.14. The main purpose of the modules of the series - which are published as separate/vaccine specific modules - is to give immunization managers and vaccination professionals a brief and easily-understood overview of the scientific basis of vaccination. This module focuses on Pertussis viii, 50 p.
- **World Health Organization. Global and regional immunization profile. [internet]. Geneva, Switzerland. Available at http://www.who.int/immunization/monitoring_surveillance/data/gloprofile.pdf?ua=1 (Accessed August 2015).**
No abstract available.
- **Wright SW, Edwards KM, Decker M, Zeldin MHI. Pertussis infection in adults with persistent cough. *Journal of the American Medical Association* 1995 April 5; 273:1044–1046.**
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 fourfold 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.

- **Zhang L, Prietsch S, Axelsson I, Halperin SA. Acellular vaccines for preventing whooping cough in children. The Cochrane database of systematic reviews 2014;9:CD001478.**

BACKGROUND: Routine use of whole-cell pertussis (wP) vaccines was suspended in some countries in the 1970s and 1980s because of concerns about adverse effects. Following such action, there was a resurgence of whooping cough. Acellular pertussis (aP) vaccines, containing purified or recombinant *Bordetella pertussis* (*B. 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 METHODS:** We searched the Cochrane Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 4) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to December week 4, 2011), EMBASE (1974 to January 2012), Biosis Previews (2009 to January 2012), and CINAHL (2009 to January 2012). **SELECTION CRITERIA:** We selected double-blind randomised efficacy and safety trials of aP 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 extracted data and assessed the risk of bias in the studies. Differences in trial design precluded a meta-analysis of the efficacy data. We pooled the safety data from individual trials using a random-effects meta-analysis model. **MAIN RESULTS:** We included six efficacy trials with a total of 46,283 participants and 52 safety trials with a total of 136,541 participants. Most of the safety trials did not report the methods for random sequence generation, allocation concealment and blinding, which made it difficult to assess the risk of bias in the studies. The efficacy of multi-component (> three) vaccines varied from 84% to 85% in preventing typical whooping cough (characterised by 21 or more consecutive days of paroxysmal cough with confirmation of *B. pertussis* infection by culture, appropriate serology or contact with a household member who has culture-confirmed pertussis), and from 71% to 78% in preventing mild pertussis disease (characterised by seven or more consecutive days of cough with confirmation of *B. pertussis* infection by culture or appropriate serology). 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 are 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 aP vaccines than with wP vaccines for the primary series as well as for the booster dose. **AUTHORS' CONCLUSIONS:** Multi-component (> three) aP vaccines are effective and show less adverse effects than wP vaccines for the primary series as well as for booster doses.