References for Diphtheria Vaccine: WHO Position Paper, August 2017
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Priorities among the infectious diseases affecting the three billion people in the less developed world have been based on prevalence, morbidity, mortality and feasibility of control. With these priorities in mind a program of selective primary health care is compared with other approaches and suggested as the most cost-effective form of medical intervention in the least developed countries. A flexible program delivered by either fixed or mobile units might include measles and diphtheria-pertussis-tetanus vaccination, treatment for febrile malaria and oral rehydration for diarrhea in children, and tetanus toxoid and encouragement of breast feeding in mothers. Other interventions might be added on the basis of regional needs and new developments. For major diseases for which control measures are inadequate, research is an inexpensive approach on the basis of cost per infected person per year.

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WHO/UNICEF. Joint Reporting Form. Available at http://www.who.int/immunization/monitoring_surveillance/routine/reporting/reporting/en/, accessed April 2017.
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Dittmann S et al. Successful control of epidemic diphtheria in the states of the former Union of Soviet Socialist Republics: Lessons learned. J Infect Dis. 2000;181(1):pp.S10-S22
Epidemic diphtheria reemerged in the Russian Federation in 1990 and spread to all Newly Independent States (NIS) and Baltic States by the end of 1994. Factors contributing to the epidemic included increased susceptibility of both children and adults, socioeconomic instability, population movement, deteriorating health infrastructure, initial shortages of vaccine, and delays in implementing control measures. In 1995, aggressive control strategies were implemented, and since then, all affected countries have reported decreases of diphtheria; however, continued efforts by national health authorities and international assistance are still needed. The legacy of this epidemic includes a reexamination of the global diphtheria control strategy, new laboratory techniques for diphtheria diagnosis and analysis, and a model for future public health emergencies in the successful collaboration of multiple international partners. The reemergence of diphtheria warns of an immediate threat of other epidemics in the NIS and Baltic States and a longer-term potential for the reemergence of vaccine-preventable diseases elsewhere. Continued investment in improved vaccines, control strategies, training, and laboratory techniques is needed.

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Galazka A. The Changing Epidemiology of Diphtheria in the Vaccine Era. J Infect Dis 2000; 181(Suppl 1): 52-59.
The epidemic of diphtheria in the Newly Independent States (NIS) of the former Soviet Union has drawn attention to our incomplete understanding of the epidemiology of diphtheria. Many unanswered questions remain concerning the reasons for a resurgence of diphtheria and for the shift in the age of patients and concerning the mechanisms for acquisition of immunity in adults through natural infection under unfavorable living conditions. Other unanswered questions relate to the precise role of socioeconomic factors and hygiene conditions in the initiation, buildup, and spread of the epidemic. Important characteristics of the NIS epidemic can be used to help predict the spread of future diphtheria epidemics. These characteristics include a high proportion of infected adults, a progressive spread of disease from urban centers to rural areas, and transition from initial amplification of disease in groups with high rates of close contacts in focalized, well-distinguished outbreaks to a more generalized epidemic.

Dhanashekar R et al. Milk-borne infections. An analysis of their potential effect on the milk industry. Germs. 2012;2:101–109.

In developed countries such as the United States of America, foodborne illnesses account for 48 million infections per year. Developing countries such as India face greater simultaneous challenges particularly since incorrect processing or storage of dairy products can represent a transmission hazard for a large number of pathogens and can be responsible for outbreaks of brucellosis, listeriosis, tuberculosis, etc.

It is important to recognize the types of germs which can be transmitted through insufficient thermal preparation of milk or milk products or through post-pasteurization contamination, in order to successfully avoid transmission of milk-borne infections.

Leggett BA et al. Toxigenic *Corynebacterium diphtheriae* isolated from a wound in a horse. Vet Rec. 2010;166:656-7.
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WHO, Scheifele DW and Ochnio JJ. Immunological basis for vaccination series. Diphtheria Update 2009. Available at http://apps.who.int/iris/bitstream/10665/44094/1/9789241597869_eng.pdf, accessed April 2017.
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WHO. List of prequalified vaccines. Available at https://extranet.who.int/gavi/PQ_Web/, accessed April 2016.
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Cherian T et al. Safety and immunogenicity of Haemophilus influenzae type B vaccine given in combination with DTwP at 6, 10 and 14 weeks of age. Indian Pediatr. 2002;39(5):427-36.

OBJECTIVE:
To assess the immunogenicity and reactogenicity of a tetanus conjugate Haemophilus influenzae type b vaccine (Act-Hib) when extemporaneously mixed and administered as a DTwP-Hib combination using an Indian DTwP vaccine (BE DTwP) in comparison with a licensed DTwP-Hib combination vaccine.

METHODS:
378 healthy infants were enrolled and randomly allocated to receive either three doses, at 6, 10 and 14 weeks of age, of Act-Hib in combination with BE DTwP (Group A, n = 160), TetrAct-Hib (Group B, n = 160), or BE DTwP and Act-Hib as separate injections (Group C, n = 58). Sera collected before the first dose and one month after the third dose were tested for antibodies to vaccine antigens. Safety was determined using parental diary cards.

RESULTS:
Anti-Hib antibody concentrations indicative of short-term protection (> 0.15 g/ml) were elicited in all but one subject in Group A (99.3%), and all subjects in Groups B and C. The concentration of 1 g/ml, considered to provide long-term protection, was achieved in 96.7%, 100% and 98.2% of the infants in Groups A, B and C, respectively. All children displayed satisfactory responses to the three DTwP component antigens, TetrAct-Hib eliciting higher titers against diphtheria and tetanus than BE DTwP. No vaccine-associated serious adverse events occurred. The BE DTwP vaccine was associated with more reports of fever than TetrAct-Hib, but most symptoms were regarded as mild and all resolved without sequelae.

CONCLUSIONS:
Combining Act-Hib and a local DTwP vaccine did not affect the anti-Hib response. In countries where DTwP vaccine available for use in the EPI program is manufactured by a local or other developing country manufacturer, mixing it with lyophilised Act-Hib is a reasonable option though the immunogenicity may have to be documented before routine use. However, use of TetrAct-Hib combination vaccine would be preferable in view of its lower reactogenicity and superior immunogenicity with respect to diphtheria and tetanus.

Vesikari T et al. Randomized, Controlled, Multicenter Study of the Immunogenicity and Safety of a Fully Liquid Combination Diphtheria–Tetanus Toxoid–Five-Component Acellular Pertussis (DTaP5), Inactivated Poliovirus (IPV), and Haemophilus influenzae type b (Hib) Vaccine Compared with a DTaP3-IPV/Hib Vaccine Administered at 3, 5, and 12 Months of Age. Clin Vaccine Immunol. 2013;20(10):1647-1653.

This study compared the levels of immunogenicity and safety of diphtheria-tetanus toxoid-five-component acellular pertussis (DTaP(5)), inactivated poliovirus (IPV), and Haemophilus influenzae type b (Hib) (DTaP(5)-IPV-Hib) and DTaP(3)-IPV/Hib vaccines for study participants 3, 5, and 12 months of age. Post-dose 3 noninferiority criteria comparing DTaP(5)-IPV-Hib to DTaP(3)-IPV/Hib using rates of seroprotection were demonstrated against diphtheria, tetanus, and polio types 1 to 3, but not for polyribosylribitol phosphate (PRP). While PRP did not meet

noninferiority criteria, the seroprotection rate and geometric mean concentration (GMC) were high, indicating a clinically robust immune response. GMCs or titers for other antigens (including pertussis) and the safety profiles were generally similar between groups. Fully liquid DTaP(5)-IPV-Hib can be administered using the 3-, 5-, and 12-month vaccination schedule.

Bar On ES et al. 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) (Review). Cochrane Database of Systematic Reviews. 2012; Issue 4. Art. No.: 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-HIBvaccine, 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 (diptheria-tetanus-whole cell pertussis)-HBV-HIB vaccine rather than the DTPa (diptheria-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.

Myers MG et al. Primary immunization with tetanus and diphtheria toxoids: reaction rates and immunogenicity in older children and adults. JAMA.1982;248:2478-80.
No abstract available.

Das R, et al. The Effect of Prophylactic Antipyretic Administration on Post-Vaccination Adverse Reactions and Antibody Response in Children: A Systematic Review. Plose One. 2014. Available at https://doi.org/10.1371/journal.pone.0106629, accessed July 2017.

Background

Prophylactic antipyretic administration decreases the post-vaccination adverse reactions. Recent study finds that they may also decrease the antibody responses to several vaccine antigens. This systematic review aimed to assess the evidence for a relationship between prophylactic antipyretic administration, post-vaccination adverse events, and antibody response in children.

Methods

A systematic search of major databases including MEDLINE and EMBASE was carried out till March 2014. Randomized controlled trials (RCTs) comparing prophylactic antipyretic treatment versus placebo post-vaccination in children ≤6 years of age were included. Two reviewers independently applied eligibility criteria, assessed the studies for methodological quality, and extracted data [PROSPERO registration: CRD42014009717].

Results

Of 2579 citations retrieved, a total of 13 RCTs including 5077 children were included in the review. Prophylactic antipyretic administration significantly reduced the febrile reactions (≥38.0°C) after primary and booster vaccinations. Though there were statistically significant differences in the antibody responses between the two groups, the prophylactic PCM group had what would be considered protective levels of antibodies to all of the antigens given after the primary and booster vaccinations. No

significant difference in the nasopharyngeal carriage rates (short-term and long-term) of *H. influenzae* or *S. pneumoniae* serotypes was found between the prophylactic and no prophylactic PCM group. There was a significant reduction in the local and systemic symptoms after primary, but not booster vaccinations.

Conclusions

Though prophylactic antipyretic administration leads to relief of the local and systemic symptoms after primary vaccinations, there is a reduction in antibody responses to some vaccine antigens without any effect on the nasopharyngeal carriage rates of *S. pneumoniae* & *H. influenza* serotypes. Future trials and surveillance programs should also aim at assessing the effectiveness of programs where prophylactic administration of PCM is given. The timing of administration of antipyretics should be discussed with the parents after explaining the benefits & risks.

Wheeler SM et al. Epidemiological observations in the Halifax epidemic. Am J Public Health. 1942;32:947-956.
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Stuart G. A note on diphtheria incidence in certain European countries. Br Med J 1945;2:613-615.
No abstract available.

Miller LW et al. Diphtheria immunization: effect on carriers and the control of outbreaks. Am J Dis Child. 1972;123:197-199.
A diphtheria epidemic in a small central Texas community centered in the elementary school. Epidemiological investigation at the school included throat cultures and immunization histories of 306 of the 310 students and staff. Of these, 104 (34%) had culture-proven diphtheria infections; 15 were symptomatic cases and 89 were carriers. There was no statistical difference in the risk of diphtheria infection among those with full, lapsed, inadequate, or no previous diphtheria immunizations. However, the risk of symptomatic diphtheria was 30 times as great for those with none, and 11.5 times as great for those with inadequate immunizations as for those fully immunized. Diphtheria toxoid helps prevent symptomatic disease but does not prevent the carrier state nor stop the spread of infection. Identifying, isolating, and treating carriers are very important aspects in the control of diphtheria outbreaks.

Jones EE et al. Diphtheria: a possible foodborne outbreak in Hodeida, Yemen Arab Republic. Bull World Health Organ. 1985;63:287-293.

Between 29 August 1981 and 16 January 1982, an epidemic of diphtheria produced 149 cases in Hodeida, Yemen Arab Republic. The overall attack rate was 11.8 per 10 000; the most frequent victims were males under 5 years of age, with an attack rate of 55.7 per 10 000. Severity of the illness varied inversely with age and the number of previous doses of DPT. A case—control study showed that vaccination with DPT was protective ($P = 0.03$) with an efficacy of 87.3% (95% confidence interval, 32.2-99.5%) among those who had received 3 or more doses. Risk factors for the development of disease were previous contact with a case ($P = 0.002$), previous contact with a person having skin disease ($P = 0.04$), obtaining drinking-water from a wheeled carrier ($P = 0.008$), and consumption of factory-made yoghurt ($P = 0.003$). The secondary attack rate among household contacts under 15 years of age was at least 1.3%.

Chen RT et al. Ukraine, 1992: first assessment of diphtheria vaccine effectiveness during the recent resurgence of diphtheria in the former Soviet Union. J Infect Dis. 2000;181(Suppl.1): 178-183.
A case-control study in Ukraine provided the first data on the field effectiveness of Russian-produced vaccine during the 1990 diphtheria resurgence in the former Soviet Union. For each of 262 diphtheria cases <15 years of age who were reported from January through October 1992, 2 controls, matched by age and clinic, were selected. The effectiveness of three doses of diphtheria vaccine was 98.2% (95% confidence interval: 90.3-99.9). Among controls, 84% had received three or more vaccinations by 2 years of age. These results suggest that the following five hypothesized causes of the outbreak appeared unlikely: appearance of a new "mutant" diphtheria strain, low potency of the Russian-produced diphtheria vaccine, inadequate cold chain, poor host immunogenicity due to radiation exposure from Chernobyl, and low routine childhood vaccination coverage. It is concluded that initial priority for scarce resources for controlling this outbreak should be placed on vaccination of persons susceptible to diphtheria (e.g., adults) rather than revaccination of children.

Bisgard KM et al. Diphtheria toxoid vaccine effectiveness: a case-control study in Russia. J Infect Dis. 2000; 181(Suppl.1): 184-187.
Prior to the completion of this and other studies, low effectiveness of diphtheria toxoid-containing vaccine was suspected to be a major contributing factor to the diphtheria epidemic that began in the Russian Federation in 1990. A vaccine effectiveness study was done in Moscow by enrolling physician-diagnosed cases and 10 control subjects per case. Controls were matched to cases by age (+/-3 months) and clinic registration. Vaccination history was abstracted from a standardized form for case-patients and from clinic vaccination records for control subjects. Two hundred seventeen case-patients and 2169 matched controls were included in the study. Most controls (92%) had received three or more doses of a diphtheria toxoid vaccine, compared with 72% of case-patients. The vaccine effectiveness for three or more doses was 97% (95% confidence interval: 94.3-98.4). Low vaccine effectiveness was not a contributing factor to the diphtheria epidemic in the Russian Federation. To control and prevent diphtheria epidemics, it is necessary to achieve and maintain high vaccination coverage with three or more doses of diphtheria toxoid among adults and children.

WHO. Comparative efficacy/effectiveness of schedules in infant immunisation against pertussis, diphtheria and tetanus: Systematic review and meta-analysis. Available at http://www.who.int/immunization/sage/meetings/2015/april/5_Report_D_T_140812.pdf?ua=1, accessed April 2017.
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WHO. Diphtheria vaccine. Review of evidence on vaccine effectiveness and immunogenicity to assess the duration of protection ≥10 years after the last booster dose. Available at http://www.who.int/immunization/sage/meetings/2017/april/2_Review_Diphtheria_results_April2017_final_clean.pdf?ua=1, accessed April 2017.

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Swart EM et al. Long-Term Protection against Diphtheria in the Netherlands after 50 Years of Vaccination: Results from a Seroepidemiological Study. PLoS ONE 11(2):e0148605.

Background and Aims

To evaluate the National Immunisation Programme (NIP) a population-based cross-sectional seroepidemiological study was performed in the Netherlands. We assessed diphtheria antitoxin levels in the general Dutch population and in low vaccination coverage (LVC) areas where a relatively high proportion of orthodox Protestants live who decline vaccination based on religious grounds. Results were compared with a nationwide seroepidemiological study performed 11 years earlier.

Methods

In 2006/2007 a national serum bank was established. Blood samples were tested for diphtheria antitoxin IgG concentrations using a multiplex immunoassay for 6383 participants from the national sample (NS) and 1518 participants from LVC municipalities. A cut-off above 0.01 international units per ml (IU/ml) was used as minimum protective level.

Results

In the NS 91% of the population had antibody levels above 0.01 IU/ml compared to 88% in the 1995/1996 serosurvey ($p<0.05$). On average, 82% (vs. 78% in the 1995/1996 serosurvey, $p<0.05$) of individuals from the NS born before introduction of diphtheria vaccination in the NIP and 46% (vs. 37% in the 1995/1996 serosurvey, $p = 0.11$) of orthodox Protestants living in LVC areas had antibody levels above 0.01 IU/ml. Linear regression analysis among fully immunized individuals (six vaccinations) without evidence of revaccination indicated a continuous decline in antibodies in both serosurveys, but geometric mean antibodies remained well above 0.01 IU/ml in all age groups.

Conclusions

The NIP provides long-term protection against diphtheria, although antibody levels decline after vaccination. As a result of natural waning immunity, a substantial proportion of individuals born before introduction of diphtheria vaccination in the NIP lack adequate levels of diphtheria antibodies. Susceptibility due to lack of vaccination is highest among strictly orthodox Protestants. The potential risk of spread of diphtheria within the geographically clustered orthodox Protestant community after introduction in the Netherlands has not disappeared, despite national long-term high vaccination coverage.

GRADE table. Duration of protection. Available at
http://www.who.int/immunization/policy/position_papers/diphtheria_GRAD_duration.pdf
No abstract available.

Goncalves G et al. Levels of diphtheria and tetanus specific IgG of Portuguese adult women, before and after vaccination with adult type Td. Duration of immunity following vaccination. BMC Public Health. 2007;7:109.

Background

The need for tetanus toxoid decennial booster doses has been questioned by some experts. Several counter arguments have been presented, supporting the maintenance of decennial adult booster doses with tetanus and diphtheria toxoids (adult formulation of the vaccine: Td). This study aimed to evaluate the use of Td in Portuguese adult women under routine conditions. For that purpose we selected a group of women 30+ years of age to which vaccination was recommended. We intended to know if pre-vaccination antibody concentrations were associated with factors as age at first and last vaccination, number of doses and time since last revaccination. We also intended to assess the serological efficacy of Td booster.

Methods

Following the Portuguese guidelines 100 women were vaccinated with Td. Antitetanus toxin IgG (ATT IgG) and antidiphtheria toxin IgG (ADT IgG) levels were measured (mIU/ml) in 100 pre-vaccination and 91 post-vaccination sera. Detailed vaccination records were available from 88 participants.

Results

Twenty-two women (Group A) began vaccination with DPT/DT in their early childhood and their pre-vaccination ATT IgG levels increased with the number of doses received ($p = 0.022$) and decreased with time since last vaccination ($p = 0.016$). Among the 66 women who began vaccination in adolescence and adulthood (Group B), with monovalent TT, ATT IgG levels decreased with age at first dose ($p < 0.001$) and with time since last vaccination ($p = 0.041$). In Group A, antidiphtheria toxin IgG kinetics was very similar to that observed for ATT IgG. Among women not vaccinated with diphtheria toxoid, ADT IgG levels decreased with age. Serological response to both components of Td was good but more pronounced for ATT IgG.

Conclusion

Our study suggests that, to protect against tetanus, there is no need to administer decennial boosters to the Portuguese adults who have complied with the childhood/adolescent schedule (6 doses of tetanus toxoid). The adult booster intervals could be wider, probably of 20 years. This also seems to apply to protection against diphtheria, but issues on the herd immunity and on the circulation of toxigenic strains need to be better understood.

Hammarlund E et al. Durability of Vaccine-Induced Immunity Against Tetanus and Diphtheria Toxins: A Crosssectional Analysis. Clinical Infectious Diseases. 2016;62:1111–1118.

BACKGROUND:

Many adult immunization schedules recommend that tetanus and diphtheria vaccination be performed every 10 years. In light of current epidemiological trends of disease incidence and rates of vaccine-associated adverse events, the 10-year revaccination schedule has come into question.

METHODS:
We performed cross-sectional analysis of serum antibody titers in 546 adult subjects stratified by age or sex. All serological results were converted to international units after calibration with international serum standards.

RESULTS:
Approximately 97% of the population was seropositive to tetanus and diphtheria as defined by a protective serum antibody titer of ≥0.01 IU/mL. Mean antibody titers were 3.6 and 0.35 IU/mL against tetanus and diphtheria, respectively. Antibody responses to tetanus declined with an estimated half-life of 14 years (95% confidence interval, 11-17 years), whereas antibody responses to diphtheria were more long-lived and declined with an estimated half-life of 27 years (18-51 years). Mathematical models combining antibody magnitude and duration predict that 95% of the population will remain protected against tetanus and diphtheria for ≥30 years without requiring further booster vaccination.

CONCLUSIONS:
These studies demonstrate that durable levels of protective antitoxin immunity exist in the majority of vaccinated individuals. Together, this suggests that it may no longer be necessary to administer booster vaccinations every 10 years and that the current adult vaccination schedule for tetanus and diphtheria should be revisited.

Wagner K et al. Immunity to tetanus and diphtheria in the UK in 2009. Vaccine. 2012;30:7111-7117.

INTRODUCTION:
This study aimed to estimate the immunity of the UK population to tetanus and diphtheria, including the potential impact of new glycoconjugatate vaccines, and the addition of diphtheria to the school leaver booster in 1994.

METHODS:
Residual sera (n=2697) collected in England in 2009/10 were selected from 18 age groups and tested for tetanus and diphtheria antibody. Results were standardised by testing a panel of sera (n=150) to enable comparison with a previously (1996) published serosurvey. Data were then standardised to the UK population.

RESULTS:
In 2009, 83% of the UK population were protected (≥0.1 IU/mL) against tetanus compared to 76% in 1996 (p=0.079), and 75% had at least basic protection against diphtheria (≥0.01 IU/mL) in 2009 compared to 60% in 1996 (p<0.001). Higher antibody levels were observed in those aged 1-3 years in 2009 compared to 1996 for both tetanus and diphtheria. Higher diphtheria immunity was observed in those aged 16-34 years in 2009 compared to 1996 (geometric mean concentration [GMC] 0.15 IU/mL vs. 0.03 IU/mL, p<0.001). Age groups with the largest proportion of susceptible individuals to both tetanus and diphtheria in 2009 were <1 year old (>29% susceptible), 45-69 years (>20% susceptible) and 70+ years (>32% susceptible). Low immunity was observed in those aged 10-11 years (>19% susceptible), between the scheduled preschool and school leaver booster administration.

DISCUSSION:
The current schedule appears to induce protective levels; increases in the proportions protected/GMCs were observed for the ages receiving vaccinations according to UK policy. Glycoconjugate vaccines appear to have increased immunity, in particular for diphtheria, in preschool age groups. Diphtheria immunity in teenagers and young adults has increased as a result of the addition of diphtheria to the

school leaver booster. However, currently older adults remain susceptible, without any further opportunities for immunisations planned according to the present schedule.

Oh HML et al. Seroprevalence of pertussis, and diphtheria and poliovirus antibodies among healthcare personnel in Singapore. Poster presented at: 10th Healthcare Infection Society International Conference Edinburgh, Scotland; 2016

No abstract available.

WHO. Safety from randomized controlled trials and observational studies of pertussis vaccines. Available at http://www.who.int/immunization/sage/meetings/2015/april/8_Safety_DTP_RCTs_obs_studies_draft.pdf?ua=1, accessed April 2017.
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WHO. Information sheet. Diphtheria, Pertussis, Tetanus Vaccines. Available at http://www.who.int/vaccine_safety/initiative/tools/DTP_vaccine_rates_information_sheet.pdf?ua=1, accessed May 2017.
No abstract available.

O Simonsen et al. Revaccination of adults against diphtheria. I: Responses and reactions to different doses of diphtheria toxoid in 30-70-year-old persons with low serum antitoxin levels. Acta Pathol Microbiol Immunol Scand [C]. 1986; 94:213-218.

Studies of diphtheria antitoxin levels in serum from adult populations have indicated high frequencies of unprotected subjects. Serum from 351 randomly selected Danes between 30 and 70 years old has been assessed for antitoxin concentration; 123 persons among these, who had low antibody levels, received one vaccination with 2 Lf, 5 Lf or 12 Lf diphtheria toxoid. Side-reactions were recorded, and antibody levels were studied 4 weeks later. Antitoxin concentration following vaccination increased markedly to above protective level in 83% of those vaccinated. Of subjects, who could document a complete primary vaccination series, only one receiving 2 Lf 31 years after primary vaccination did not attain protective antitoxin level. Minor local reactions only were recorded among subjects who did not respond serologically to vaccination. Frequencies of more pronounced reactions experienced by serologically responding subjects depended on dose and were 15%, 14% and 23% respectively. It was concluded that a single vaccination of the present adult Danish population will induce protective antibody levels so frequently that the effect of herd immunity will secure against epidemics if future diphtheria outbreaks are experienced. To secure individual protection, vaccination history and/or serological assessments have to be explored in order to decide whether a single vaccination is sufficient.

Demicheli V et al. Vaccines for women for preventing neonatal tetanus. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD002959.

BACKGROUND:
Tetanus is an acute, often fatal, disease caused by an exotoxin produced by Clostridium tetani. It occurs in newborn infants born to mothers who do not have sufficient circulating antibodies to protect the infant passively, by transplacental transfer. Prevention may be possible by the vaccination of pregnant

or non-pregnant women, or both, with tetanus toxoid, and the provision of clean delivery services. Tetanus toxoid consists of a formaldehyde-treated toxin that stimulates the production of antitoxin.

OBJECTIVES:
To assess the effectiveness of tetanus toxoid, administered to women of reproductive age or pregnant women, to prevent cases of, and deaths from, neonatal tetanus.

SEARCH METHODS:
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 January 2015), CENTRAL (The Cochrane Library 2015, Issue 1), PubMed (1966 to 28 January 2015), EMBASE (1974 to 28 January 2015) and reference lists of retrieved studies.

SELECTION CRITERIA:
Randomised or quasi-randomised trials evaluating the effects of tetanus toxoid in pregnant women or women of reproductive age on numbers of neonatal tetanus cases and deaths.

DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

MAIN RESULTS:
Two effectiveness trials (9823 infants) and one safety trial (48 mothers) were included. The main outcomes were measured on infants born to a subset of those randomised women who became pregnant during the course of the studies. For our primary outcomes, there was no high-quality evidence according to GRADE assessments.One study (1182 infants) assessed the effectiveness of tetanus toxoid in comparison with influenza vaccine in preventing neonatal tetanus deaths. A single dose did not provide significant protection against neonatal tetanus deaths, (risk ratio (RR) 0.57, 95% confidence interval (CI) 0.26 to 1.24; 494 infants; GRADE: low-quality evidence). However, a two- or three-dose course did provide protection against neonatal deaths, (RR 0.02, 95% CI 0.00 to 0.30; 688 infants; GRADE: moderate-quality evidence). Administration of a two- or three-dose course resulted in significant protection when all causes of death are considered as an outcome (RR 0.31, 95% CI 0.17 to 0.55; 688 infants; GRADE: moderate-quality evidence). No effect was detected on causes of death other than tetanus. Cases of neonatal tetanus after at least one dose of tetanus toxoid were reduced in the tetanus toxoid group, (RR 0.20, 95% CI 0.10 to 0.40; 1182 infants; GRADE: moderate-quality evidence).Another study, involving 8641 children, assessed the effectiveness of tetanus-diphtheria toxoid in comparison with cholera toxoid in preventing neonatal mortality after one or two doses. Neonatal mortality was reduced in the tetanus-diphtheria toxoid group (RR 0.68, 95% CI 0.56 to 0.82). In preventing deaths at four to 14 days, neonatal mortality was reduced again in the tetanus-diphtheria toxoid group (RR 0.38, 95% CI 0.27 to 0.55). The quality of evidence as assessed using GRADE was found to be low.The third small trial assessed that pain at injection site was reported more frequently among pregnant women who received tetanus diphtheria acellular pertussis than placebo (RR 5.68, 95% CI 1.54 to 20.94; GRADE: moderate-quality evidence).

AUTHORS' CONCLUSIONS:
Available evidence supports the implementation of immunisation practices on women of reproductive age or pregnant women in communities with similar, or higher, levels of risk of neonatal tetanus, to the two study sites.

McMillan M et al. Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review. Obstet Gynecol. 2017;129:560-573.

OBJECTIVE:
To assess antenatal, birth, and infant outcomes for pregnant women, fetuses, and infants after antenatal vaccination with any antigen present in combination pertussis vaccines.

DATA SOURCES:
PubMed, EMBASE, Literature in the Health Sciences in Latin America and the Caribbean, ClinicalTrials.gov, Cochrane Library, and World Health Organization (inception to May 5, 2016).

METHODS OF STUDY SELECTION:
Studies reporting outcomes for pregnant women, their fetus, or infant after antenatal exposure to either monovalent or combined tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) or inactivated polio vaccines were considered for inclusion.

RESULTS:
A total of 21 studies were included in this review. Point estimates ranged from 0.47 to 1.50 for preterm birth (less than 37 weeks of gestation), 0.65-1.00 for small for gestational age (birth weight less than the 10th percentile), 0.36-0.85 for stillbirth, 0.16-1.00 for neonatal death, 0.76-1.20 for low birth weight (less than 2,500 g), and 0.20-0.91 for congenital anomalies. All lower 95% confidence intervals (CIs) were less than 1.0. Of three retrospective studies assessing chorioamnionitis after vaccination, one showed a small but statistically significant increase. Point estimates for all anomalies after antenatal tetanus toxoid vaccination ranged from 1.20 to 1.60 and had 95% CIs that crossed 1.0. There was substantial clinical and methodologic heterogeneity from mainly retrospective observational studies with an overall high risk of bias. Objective rates of fever were low, 3% or below, and more common systemic events observed included headache, malaise, and myalgia.

CONCLUSION:
Evidence suggests that antenatal combined Tdap administered during the second or third trimester of pregnancy is not associated with clinically significant harms for the fetus or neonate. Medically attended events in pregnant women are similar between vaccinated and unvaccinated groups.

Ryder RW et al. Safety and immunogenicity of bacille Calmette-Guérin, diphtheria-tetanus-pertussis, and oral polio vaccines in newborn children in Zaire infected with human immunodeficiency virus type 1. J Pediatr. 1993;122(5Pt1):697-702.

OBJECTIVE:
To determine the safety and immunogenicity of childhood vaccines in children with perinatally acquired human immunodeficiency virus type 1 (HIV-1) infection.

DESIGN:
Nonrandomized, prospective cohort study; 12-month follow-up period.

SETTING:
Obstetric wards and outpatient pediatric clinics at two large hospitals in Kinshasa, Zaire.

PATIENTS:
A total of 8108 pregnant women were screened for HIV-1 antibodies. The 474 children born to 466 seropositive women identified during screening and the 616 children born to 606 seronegative, age- and parity-matched women were vaccinated.

INTERVENTION:
The following vaccines were administered at the stated ages: bacille Calmette-Guérin (BCG) vaccine (2 days); trivalent oral Sabin poliomyelitis vaccine (2 days and 6, 10, and 14 weeks); and adsorbed diphtheria-tetanus-pertussis (DTP) vaccine (6, 10, and 14 weeks).

MEASUREMENTS AND MAIN RESULTS:
Protective antibody titers to tetanus and poliovirus types 1, 2, and 3 were achieved in 95% of all children. Among children with HIV-1 infection, 70.8% had protective antibody titers to diphtheria compared with 98.5% of uninfected children ($p < 0.05$). Geometric mean antibody titers to diphtheria and poliovirus types 1, 2, and 3 were significantly lower in children with HIV-1 infection than in uninfected children. Vaccine-associated side effects were similarly low in all children.

CONCLUSIONS:
The low incidence of side effects and the high proportion of children with HIV-1 infection who achieved protective postimmunization antibody titers support the continuing use of BCG, DTP, and oral polio vaccines in childhood immunization programs in HIV-1 endemic areas.

Bonetti T et al. Tetanus and diphtheria antibodies and response to a booster dose in Brazilian HIV-1-infected women. Vaccine. 2004; 22, 27–28:3707–3712.
Tetanus and diphtheria (Td) antibodies were studied in HIV-1-infected women during puerperium. HIV group (*n*=61) was compared with Control group (*n*=101). Twenty-one women from HIV and 13 from Control group who had antibody levels lower than 0.1 IU/mL received a booster with Td vaccine. Antibodies were assessed by double antigen ELISA. Mean tetanus and diphtheria antibody levels from HIV group were lower than those from Control group. Multiple linear regression analysis showed that tetanus and diphtheria antibody levels were decreased by HIV-1-infection, and that was independent of the reduction due to the time interval between last booster and antibody assessment. After a booster dose, both groups had an increase in mean tetanus and diphtheria antibody levels, but in Control group the levels were higher than in HIV group.

King GE et al. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. Pediatr Infect Dis J. 1994;13:394–407.
No abstract available.

Dolan S et al. 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, accessed April 2017
No abstract available.

GlaxoSmithKline Biologicals SA Cervarix. Summary of Product Characteristics. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=179, accessed May 2017
No abstract available.

Merck. Gardasil. Summary of Product Characteristics. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=178, accessed May 2017
No abstract available.

Merck. Gardasil 9. Summary of Product Characteristics. European Medicines Agency. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003852/WC500189111.pdf, accessed May2017
No abstract available.

Adacel, package insert. Toronto, Ontario, Canada: Sanofi Pasteur Limited; Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=315, accessed July 2017.

No abstract available.

Bröker M. Potential protective immunogenicity of tetanus toxoid, diphtheria toxoid and Cross Reacting Material 197 (CRM197) when used as carrier proteins in glycoconjugates. Human Vaccines & Immunotherapeutics 2016;12:664–667.
When tetanus toxoid (TT), diphtheria toxoid (DT) or Cross Reacting Material 197 (CRM197), a non-toxic diphtheria toxin mutant protein, are used as carrier proteins in glycoconjugate vaccines, these carriers induce a protein specific antibody response as measured by in vitro assays. Here, it was evaluated whether or not glycoconjugates based on TT, DT or CRM197 can induce a protective immune response as measured by potency tests according to the European Pharmacopoeia. It could be shown, that the conjugate carriers TT and DT can induce a protective immune response against a lethal challenge by toxins in animals, while glycoconjugates based on CRM197 failed to induce a protective immune response. Opportunities for new applications of glycoconjugates are discussed.

Bröker M et al. Polysaccharide conjugate vaccine protein carriers as a ‘‘neglected valency” – Potential and limitations. Vaccine. 2017;35:3286–3294.

The development of vaccines against polysaccharide-encapsulated pathogens (e.g. Haemophilus influenzae type b, pneumococci, meningococci) is challenging because polysaccharides do not elicit a strong and long-lasting immune response (i.e. T-cell independent). This can be overcome by conjugating the polysaccharide to a protein carrier (e.g. tetanus toxoid, cross-reacting material 197 [CRM]), which vastly improves the immune response and induces memory to the polysaccharide (T-cell dependent). Although it is well documented that protein carriers additionally induce an immune response against themselves, this potential "additional valency" has so far not been recognized. The only exception is for the protein D carrier (derived from non-typeable Haemophilus influenzae [NTHi]) used in a pneumococcal conjugate vaccine, which may have a beneficial impact on NTHi acute otitis media. In this review, we describe the immunogenicity of various protein carriers and discuss their potential dual function: as providers of T-cell helper epitopes and as protective antigens. If this "additional valency" could be proven to be protective, it may be possible to consider its potential effect on the number of required immunizations. We also describe the potential for positive or negative interference between conjugate vaccines using the same protein carriers, the resulting desire for novel carriers, and information on potential new carriers. The range of conjugate vaccines is ever expanding, with different carriers and methods of conjugation. We propose that new conjugate vaccine trials should assess immunogenicity to both the polysaccharide and carrier. Ultimately, this so-far "neglected valency" could be an exploitable characteristic of polysaccharide conjugate vaccines.

Tashani M et al. Tetanus–diphtheria–pertussis vaccine may suppress the immune response to subsequent immunization with pneumococcal CRM197-conjugate vaccine (coadministered with quadrivalent meningococcal TT-conjugate vaccine): a randomized, controlled trial. Journal of Travel Medicine. 2017;24(4).

BACKGROUND:
Due to their antigenic similarities, there is a potential for immunological interaction between tetanus/diphtheria-containing vaccines and carrier proteins presented on conjugate vaccines. The interaction could, unpredictably, result in either enhancement or suppression of the immune response to conjugate vaccines if they are injected soon after or concurrently with diphtheria or tetanus toxoid. We examined this interaction among adult Australian travellers before attending the Hajj pilgrimage of 2015.

METHODS:
We randomly assigned each participant to one of three vaccination schedules. Group A received tetanus, diphtheria and acellular pertussis vaccine (Tdap) 3-4 weeks before receiving CRM197-conjugated 13-valent pneumococcal vaccine (PCV13) coadministered with TT-conjugated quadrivalent meningococcal vaccine (MCV4). Group B received all three vaccines concurrently. Group C received PCV13 and MCV4 3-4 weeks before Tdap. Blood samples collected at baseline, at each vaccination visit and 3-4 weeks after vaccination were tested for the pneumococcal opsonophagocytic assay (OPA).

RESULTS:
A total of 166 participants aged 18-64 (median 42) years were recruited, 159 completed the study. Compared with the other groups, Group A had significantly ($P < 0.05$) lower geometric mean titres (GMTs) post-vaccination in seven serotypes of PCV13 (1, 3, 4, 5, 14, 18C and 9V). Additionally, Group A had lower frequency of serorises (≥ 4-fold rise in OPA titres) in serotype5 (79%, $p = 0.01$) and 18C (73.5%, $p = 0.06$); whereas Groups B and C had significantly lower frequencies of serorises in Serotype 4 (82%) and 6A (73.5%), respectively. No statistically significant difference was detected across the three groups in frequencies achieving OPA titre ≥ 1:8 post-vaccination.

CONCLUSIONS:
Tdap vaccination 3-4 weeks before administration of PCV13 and MCV4 significantly reduced the GMTs to seven of the 13 pneumococcal serotypes in adults. If multiple vaccination is required before travel, deferring tetanus/diphtheria until after administering the conjugate vaccine is recommended to avoid immune interference.

Findlow H and Borrow R. Interactions of conjugate vaccines and co-administered vaccines . Human Vaccines & Immunotherapeutics 2016; 12: 226—230.

Conjugate vaccines play an important role in the prevention of infectious diseases such as those caused by the bacteria *Haemophilus influenzae* (Hi) type b (Hib), *Neisseria meningitidis*, and *Streptococcus pneumoniae*. Vaccines developed against these 3 pathogens utilize 3 main carrier proteins, non-toxic mutant of diphtheria toxin (CRM_{197}), diphtheria toxoid (DT) and tetanus toxoid (TT). Current pediatric immunisation schedules include the administration of several vaccines simultaneously, therefore increasing the potential for immune interference (both positively and negatively) to the antigens administered. Knowledge of vaccine interactions is principally derived from clinical trials, these are reviewed here to explore immune interference which may result of from carrier-specific T-cell helper interactions, bystander interference and carrier induced epitopic suppression.

Ekwueme DU et al. Economic evaluation of use of diphtheria, tetanus, and acellular pertussis vaccine or diphtheria, tetanus, and whole-cell pertussis vaccine in the United States, 1997. Arch Pediatr Adolesc Med. 2000;154(8):797-803.

OBJECTIVE:
To compare the economic costs and benefits associated with using either diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) or diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTwP) in the United States in 1997.

DESIGN:
Standard cost-benefit analysis, from both the societal and health care system perspectives, was performed for each combination vaccine as well as for the pertussis components singly.

SETTING:
A simulated cohort of 4.1 million children from birth to age 15 years.

MAIN OUTCOME MEASURES:
Net costs (savings) and benefit-cost ratios (BCRs)

RESULTS:
Without a vaccination program, diphtheria, tetanus, and pertussis disease caused more than 3 million cases and more than 28,000 deaths, at a cost of $23.6 billion. From the societal perspective, net savings because of the use of DTaP and DTwP were $22.510 million and $22.623 million, respectively. The net savings from the acellular pertussis component and the whole-cell pertussis component only were $4.362 million and $4.474 million, respectively. Benefit-cost ratios for DTaP from a societal and health care system perspective were 27:1 and 9:1, respectively. Sensitivity analyses of key variables did not result in appreciable changes in results.

CONCLUSIONS:
Compared with no program, vaccination with DTaP or DTwP resulted in substantial savings, regardless of the perspective taken and for all sensitivity analyses conducted. Compared with DTwP, use of DTaP generated a small cost increase that might be offset by the value of other factors, such as increased confidence in pertussis vaccination resulting from reduced adverse events.

Zhou F et al. Economic evaluation of the 7-vaccine routine childhood immunization schedule in the United States, 2001. Arch Pediatr Adolesc Med. 2005;159(12):1136-44.

OBJECTIVE:
To evaluate the economic impact of the routine US childhood immunization schedule: diphtheria and tetanus toxoids and acellular pertussis; tetanus and diphtheria toxoids; Haemophilus influenzae type b conjugate; inactivated poliovirus; measles, mumps, and rubella; hepatitis B; and varicella vaccines.

DESIGN:
Decision tree-based analysis was conducted using population-based vaccination coverage, published vaccine efficacies, historical data on disease incidence before vaccination, and disease incidence reported for 1995-2001. Costs were estimated using the direct cost and societal (direct and indirect costs) perspectives. Program costs included vaccine, administration, vaccine-associated adverse events, and parent travel and time lost. All costs were inflated to 2001 US dollars, and all costs and benefits in the future were discounted at a 3% annual rate.

PARTICIPANTS:
A hypothetical 2001 US birth cohort of 3,803,295 infants was followed up from birth through death.

MAIN OUTCOME MEASURES:
Net present value (net savings) and benefit-cost ratios of routine immunization.

RESULTS:
Routine childhood immunization with the 7 vaccines was cost saving from the direct cost and societal perspectives, with net savings of 9.9 billion dollars and 43.3 billion dollars, respectively. Without routine vaccination, direct and societal costs of diphtheria, tetanus, pertussis, H influenzae type b, poliomyelitis, measles, mumps, rubella, congenital rubella syndrome, hepatitis B, and varicella would be 12.3 billion dollars and 46.6 billion dollars, respectively. Direct and societal costs for the vaccination program were an estimated 2.3 billion dollars and 2.8 billion dollars, respectively. Direct and societal benefit-cost ratios for routine childhood vaccination were 5.3 and 16.5, respectively.

CONCLUSION:
Regardless of the perspective, the current routine childhood immunization schedule results in substantial cost savings.

Evidence to recommendation table. Available at
http://www.who.int/immunization/policy/position_papers/diphtheria_evidence_recommendation_table.pdf

No abstract available.

WHO WER No.6, 2017, 92 pp. 53-76.

No abstract available.

WHO WER No. 39, 2015, pp. 505–510.
No abstract available.