References Tetanus vaccines: WHO position paper – February 2017

(References with abstracts cited in the position paper in the order of appearance.)

Guidance for the development of evidence-based vaccine-related recommendations. http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf; accessed Jan 2017.

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WEEKLY EPIDEMIOLOGICAL RECORD, NO. 20, 19 MAY 2006. Tetanus vaccine. WHO position paper.

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Roper MH, Vandelaer JH, Gasse FL. Maternal and neonatal tetanus. The Lancet. 2007;370(9603):1947–59.

Maternal and neonatal tetanus are important causes of maternal and neonatal mortality, claiming about 180 000 lives worldwide every year, almost exclusively in developing countries. Although easily prevented by maternal immunisation with tetanus toxoid vaccine, and aseptic obstetric and postnatal umbilical-cord care practices, maternal and neonatal tetanus persist as public-health problems in 48 countries, mainly in Asia and Africa. Survival of tetanus patients has improved substantially for those treated in hospitals with modern intensive-care facilities; however, such facilities are often unavailable where the tetanus burden is highest. The Maternal and Neonatal Tetanus Elimination Initiative assists countries in which maternal and neonatal tetanus has not been eliminated to provide immunisation with tetanus toxoid to women of childbearing age. The ultimate goal of this initiative is the worldwide elimination of maternal and neonatal tetanus. Since tetanus spores cannot be removed from the environment, sustaining elimination will require improvements to presently inadequate immunisation and health-service infrastructures, and universal access to those services. The renewed worldwide commitment to the reduction of maternal and child mortality, if translated into effective action, could help to provide the systemic changes needed for long-term elimination of maternal and neonatal tetanus.

Roper MH, Wassilak SGF, Tiwari TSP, Orenstein WA. Tetanus toxoid. In: Plotkin S, Orenstein W, Offit P, eds. Vaccines, 6th ed. Philadelphia, Sauders, 2013:447-492.

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Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. The Lancet. 2016;388(10063):3027–35.

BACKGROUND: Despite remarkable progress in the improvement of child survival between 1990 and 2015, the Millennium Development Goal (MDG) 4 target of a two-thirds reduction of under-5 mortality rate (U5MR) was not achieved globally. In this paper, we updated our annual estimates of child mortality by cause to 2000-15 to reflect on progress toward the MDG 4 and consider implications for the Sustainable Development Goals (SDG) target for child survival.

METHODS: We increased the estimation input data for causes of deaths by 43% among neonates and 23% among 1-59-month-olds, respectively. We used adequate vital registration (VR) data where available, and modelled cause-specific mortality fractions applying multinomial logistic regressions using adequate VR for low U5MR countries and verbal autopsy data for high U5MR countries. We updated the estimation to use Plasmodium falciparum parasite rate in place of malaria index in the modelling of malaria deaths; to use adjusted empirical estimates instead of modelled estimates for China; and to consider the effects of pneumococcal conjugate vaccine and rotavirus vaccine in the estimation.

FINDINGS: In 2015, among the 5·9 million under-5 deaths, 2·7 million occurred in the neonatal period. The leading under-5 causes were preterm birth complications (1·055 million [95% uncertainty range (UR) 0·935-1·179]), pneumonia (0·921 million [0·812 -1·117]), and intrapartum-related events (0·691 million [0·598 -0·778]). In the two MDG regions with the most under-5 deaths, the leading cause was pneumonia in sub-Saharan Africa and preterm birth complications in southern Asia. Reductions in mortality rates for pneumonia, diarrhoea, neonatal intrapartum-related events, malaria, and measles were responsible for 61% of the total reduction of 35 per 1000 livebirths in U5MR in 2000-15. Stratified by U5MR, pneumonia was the leading cause in countries with very high U5MR. Preterm birth complications and pneumonia were both important in high, medium high, and medium child mortality countries; whereas congenital abnormalities was the most important cause in countries with low and very low U5MR.

INTERPRETATION: In the SDG era, countries are advised to prioritise child survival policy and programmes based on their child cause-of-death composition. Continued and enhanced efforts to scale up proven life-saving interventions are needed to achieve the SDG child survival target.

WHO. Global Vaccine Action Plan 2011-2020. Available at http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/; accessed Nov 2016.

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WHO vaccine-preventable diseases: monitoring system 2016 global summary. Available at http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencettetanus.html; accessed Nov 2016.

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CDC. Tetanus surveillance — United States, 2001-2008. MMWR 2011;60:365-96.

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Chatchatee P, Chatproedprai S, Warinsathien P, et al: Seroprevalence of tetanus antibody in the Thai population: a national survey. Asian Pac J Allergy Immunol 2007; 25: 219-223.

Tetanus is a disease with high mortality and the most important measure for effective prevention is vaccination. Tetanus immunization has been introduced to Thailand's national immunization program for 30 years. Yet, the coverage and seroprevalence of tetanus antibody in vast parts of the population has not been assessed. This study has been performed on 1,277 subjects aged between 6 months and 60 years or above from four geographically distinct provinces of Thailand. Tetanus antibody levels were measured using a commercially available ELISA kit. Most of the Thai population had immunity against tetanus. The level of antibodies to tetanus, as demonstrated by the geometric mean titer of antibody (GMT) (and 95% confidence interval) was 2.62 (2.34-2.91) IU/ml. The highest and lowest GMT was found in subjects aged between 5 and 9 years, and above 60 years of age with GMT (and 95% confidence intervals) of 3.64 (3.34-3.96) and 1.24 (0.67-2.29) IU/ml respectively. The minimum protective level of antitoxin (>0.01 IU/ml) was detected in 99.7 % of subjects. More than 90% of subjects displayed durable antibody protection levels (DAPL) (> or = 1.0 IU/ml), except for subjects above the age of 60 years (82%). According to this study, the majority of the population expresses tetanus antibody levels that can confer long term protection. Yet, considering the lowest GMT and the highest incidence of tetanus cases found in subjects aged above 60 years, re-immunization should be targeted at this age group especially if they had sustained any tetanus-prone injury.

Gouveia PA da C, Silva CEF, Miranda Filho D de B, Bernardino SN, Escarião AG, Ximenes RA de A. Mortality trend due to accidental tetanus from 1981 to 2004 in Pernambuco and analysis of the impact on intensive care unit attendance. Rev Soc Bras Med Trop. 2009;42(1):54–7.

Despite reductions in the incidence of accidental tetanus cases in Brazil, there has not been any significant decrease in its mortality. In this case series, the mortality rates before and after establishing standard management practices for tetanus patients in the intensive care unit at the Oswaldo Cruz University Hospital are compared over the period from 1981 to 2004. Over these 24 years, 1.971 patients were admitted. Before establishing the intensive care unit management, the mortality rate was 35%. The Intensive care unit for attending to tetanus patients was established in 1997. From 1998 to 2004, the mortality rate fell to 12.6%: OR = 0.27 (95% CI = 0.18-0.39); $p < 0.001$. This trend was seen in all age groups and both sexes. The centralization of attendance for these patients into a single specialized service with early treatment in an intensive care unit has therefore been decisive in reducing the mortality rate. This service can count on the medical team's vast experience of tetanus management, with better treatment of symptoms that forestalls the serious complications from this disease.

Dalal S, Samuelson J, Reed J, Yakubu A, Ncube B, Baggaley R. Tetanus disease and deaths in men reveal need for vaccination. Bull World Health Organ. 2016;94(8):613–21.

With efforts focused on the elimination of maternal and neonatal tetanus, less attention has been given to tetanus incidence and mortality among men. Since 2007 voluntary medical male circumcision has been scaled-up in 14 sub-Saharan African countries as an effective intervention to reduce the risk of human immunodeficiency virus (HIV) acquisition among men. As part of a review of adverse events from these programmes, we identified 13 cases of tetanus from five countries reported to the World Health Organization (WHO) up to March 2016. Eight patients died and only

one patient had a known history of tetanus vaccination. Tetanus after voluntary medical male circumcision was rare among more than 11 million procedures conducted. Nevertheless, the cases prompted a review of the evidence on tetanus vaccination coverage and case notifications in sub-Saharan Africa, supplemented by a literature review of non-neonatal tetanus in Africa over the years 2003-2014. The WHO African Region reported the highest number of non-neonatal tetanus cases per million population and lowest historic coverage of tetanus-toxoid-containing vaccine. Coverage of the third dose of diphtheria-tetanus-polio vaccine ranged from 65% to 98% across the 14 countries in 2013. In hospital-based studies, non-neonatal tetanus comprised 0.3-10.7% of admissions, and a median of 71% of patients were men. The identification of tetanus cases following voluntary medical male circumcision highlights a gender gap in tetanus morbidity disproportionately affecting men. Incorporating tetanus vaccination for boys and men into national programmes should be a priority to align with the goal of universal health coverage.

Tetanus and voluntary medical male circumcision: risk according to circumcision method and risk mitigation. Report of the WHO Technical Advisory Group on Innovations in Male Circumcision – consultative review of additional information, 12 August 2016. WHO 2016. Available at http://apps.who.int/iris/bitstream/10665/250146/1/WHO-HIV-2016.19-eng.pdf; accessed Dec 2016.

(No abstract available.)

Scobie HM, Patel M, Martin D, Mkocha H, Njenga SM, Odiere MR, et al. Tetanus immunity gaps in children 5 − 14 Years and men ⩾ 15 years of age revealed by integrated disease serosurveillance in Kenya, Tanzania, and Mozambique. Am J Trop Med Hyg. 2016;16 − 0452.

Recent tetanus cases associated with male circumcision in Eastern and Southern Africa (ESA) prompted an examination of tetanus immunity by age and sex using multiplex serologic data from community surveys in three ESA countries during 2012-2013. Tetanus seroprotection was lower among children 5-14 years versus 1-4 years of age in Kenya (66% versus 90%) and Tanzania (66% versus 89%), but not in Mozambique (91% versus 88%), where children receive two booster doses in school. Among males ≥ 15 years of age, tetanus seroprotection was lower than females in Kenya (45% versus 96%), Tanzania (28% versus 94%), and Mozambique (64% versus 90%). Tetanus immunity from infant vaccination doses wanes over time, and only women of reproductive age routinely receive booster doses. To prevent immunity gaps in older children, adolescents, and adult men, a life-course vaccination strategy is needed to provide the three recommended tetanus booster doses.

Schiavo G, Matteoli M, and Montecucco C. Neurotoxins affecting neuroexocytosis. Physiol Rev 2000; 80:717-766.

Nerve terminals are specific sites of action of a very large number of toxins produced by many different organisms. The mechanism of action of three groups of presynaptic neurotoxins that interfere directly with the process of neurotransmitter release is reviewed, whereas presynaptic neurotoxins acting on ion channels are not dealt with here. These neurotoxins can be grouped in three large families: 1) the clostridial neurotoxins that act inside nerves and block neurotransmitter release via their metalloproteolytic activity directed specifically on SNARE proteins; 2) the snake presynaptic neurotoxins with phospholipase A(2) activity, whose site of action is still undefined and

which induce the release of acethylcholine followed by impairment of synaptic functions; and 3) the excitatory latrotoxin-like neurotoxins that induce a massive release of neurotransmitter at peripheral and central synapses. Their modes of binding, sites of action, and biochemical activities are discussed in relation to the symptoms of the diseases they cause. The use of these toxins in cell biology and neuroscience is considered as well as the therapeutic utilization of the botulinum neurotoxins in human diseases characterized by hyperfunction of cholinergic terminals.

Srivastava P., Brown K., Chen J., et al: Trends in tetanus epidemiology in the United States, 1972–2001. In (eds): . DC: Washington, 2005.

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Millard AH. Local Tetanus. The Lancet. 1954;264(6843):844–6.

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Jagoda A, Riggio S, Burguieres T. Cephalic tetanus: A case report and review of the literature. The American Journal of Emergency Medicine. 1988;6(2):128–30.

Cephalic tetanus is a rare form of tetanus defined as trismus plus paralysis of one or more cranial nerves. The most frequently involved cranial nerve is the seventh. It accounts for 1 to 3% of the total number of reported cases of tetanus and has a mortality of 15 to 30%. The incubation period is 1 to 14 days, and approximately two thirds of cases progress to generalized tetanus. The mechanism of the paralysis is not completely understood. Treatment involves debridement of wounds, administration of penicillin and tetanus immune-globulin, aggressive supportive care, and initiation of active immunization.

WHO. WHO-recommended standards for surveillance of selected vaccine-preventable diseases. Geneva: World Health Organization, 2003. Available at http://apps.who.int/iris/bitstream/10665/68334/1/WHO_V-B_03.01_eng.pdf; accessed Nov 2016.

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WHO, Department of Reproductive Health and Research. Managing newborn problems: A guide for doctors, nurses and midwives. 2003. Available at http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9241546220/en/; accessed Nov 2016.

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WHO. Current recommendations for treatment of tetanus during humanitarian emergencies. Technical Note 2010. Available at http://www.who.int/diseasecontrol_emergencies/publications/who_hse_gar_dce_2010.2/en/; accessed October 2016.

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Apte NM, Karnad DR. Short report: the spatula test: a simple bedside test to diagnose tetanus. Am J Trop Med Hyg. 1995;53(4):386–7.

Four hundred patients with suspected tetanus were studied to determine the value of the spatula test to diagnose tetanus. A positive test result (reflex spasm of the masseters on touching the posterior pharyngeal wall) was seen in 359 (94%) of 380 patients with tetanus and in no patient without tetanus. Thirty-three of 400 patients (13 with tetanus and 20 with other diagnoses) had a negative test result (a gag reflex with attempted expulsion of the spatula). Thus, the test performed on presentation had a high specificity (100%) and sensitivity (94%) for diagnosing tetanus.

Rodrigo C, Fernando D, Rajapakse S. Pharmacological management of tetanus: an evidence-based review. Crit Care. 2014;18(2):217.

Tetanus is becoming rarer in both industrialized and developing nations due to an effective vaccination program. In 2010, the World Health Organization estimated there was a 93% reduction in newborns dying from tetanus worldwide, compared to the situation in the late 1980s. Due to its rarity, many diagnostic delays occur as physicians may not consider the diagnosis until the manifestations become overt. Without timely diagnosis and proper treatment, severe tetanus is fatal (mortality is also influenced by the comorbidities of the patient). The principles of treating tetanus are: reducing muscle spasms, rigidity and autonomic instability (with ventilatory support when necessary); neutralization of tetanus toxin with human antitetanus immunoglobulin or equine antitetanus sera; wound debridement; and administration of antibiotics to eradicate locally proliferating bacteria at the wound site. It is difficult to conduct trials on different treatment modalities in tetanus due to both logistical and ethical reasons. However, it is imperative that physicians are aware of the best evidence-based treatment strategies currently available to improve the outcome of patients. This review concentrates on analyzing the current evidence on the pharmacological management of tetanus.

WHO. Department of Violence and Injury Prevention and Disability. Prevention and management of wound infection. Guidance from WHO's Department of Violence and Injury Prevention and Disability and the Department of Essential Health Technologies. Available at http://www.who.int/hac/techguidance/tools/guidelines_prevention_and_management_wound_infection.pdf?ua=1; accessed Nov 2016.

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WHO Expert Committee on Biological Standardization. Sixty-third report. Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 980). See Annex 6, Recommendations to assure the quality, safety and efficacy of DT-based combined vaccines, pp.335-406. (Also avai¬lable from http://www.who.int/biologicals/vaccines/Combined_Vaccines_TRS_980_Annex_6.pdf?ua=1.) See http://www.who.int/biologicals/vaccines/tetanus/en/; accessed Oct 2016.

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WHO Information Sheet: Observed rate of vaccine reactions – Diphtheria, pertussis, tetanus vaccines, 2014. Available at http://www.who.int/vaccine_safety/initiative/tools/DTP_vaccine_rates_information_sheet.pdf?ua=1; accessed October 2016.

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Borrow R., Balmer P., and Roper M.H.: The immunologic basis for immunization: module 3: tetanus. Geneva: World Health Organization, 2007. http://apps.who.int/iris/bitstream/10665/43687/1/9789241595551_eng.pdf; accessed Oct 2016.

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Myers MG, Beckman CW, Vosdingh RA, Hankins WA. Primary immunization with tetanus and diphtheria toxoids: Reaction rates and immunogenicity in older children and adults. JAMA. 1982;248(19):2478–80.

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Schofield FD, Tucker VM, Westbrook GR. Neonatal Tetanus in New Guinea. British Medical Journal. 1961;2(5255):785.

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Demicheli V, Barale A, Rivetti A. Vaccines for women for preventing neonatal tetanus. In: Cochrane Database of Systematic Reviews [Internet]. John Wiley & Sons, Ltd; 2015 [cited 2016 Oct 14]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002959.pub4/abstract;jsessionid=3E06435AA61D55B24A43CD96131EEEC0.f04t01

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**.**

Blencowe H, Lawn J, Vandelaer J, Roper M, Cousens S. Tetanus toxoid immunization to reduce mortality from neonatal tetanus. Int J Epidemiol.;39 Suppl 1:i102–9.

BACKGROUND: Neonatal tetanus remains an important and preventable cause of neonatal mortality globally. Large reductions in neonatal tetanus deaths have been reported following major increases in the coverage of tetanus toxoid immunization, yet the level of evidence for the mortality effect of tetanus toxoid immunization is surprisingly weak with only two trials considered in a Cochrane review.

OBJECTIVE: To review the evidence for and estimate the effect on neonatal tetanus mortality of immunization with tetanus toxoid of pregnant women, or women of childbearing age.

METHODS: We conducted a systematic review of multiple databases. Standardized abstraction forms were used. Individual study quality and the overall quality of evidence were assessed using an adaptation of the GRADE approach. Meta-analyses were performed.

RESULTS: Only one randomised controlled trial (RCT) and one well-controlled cohort study were identified, which met inclusion criteria for meta-analysis. Immunization of pregnant women or women of childbearing age with at least two doses of tetanus toxoid is estimated to reduce mortality from neonatal tetanus by 94% [95% confidence interval (CI) 80-98%]. Additionally, another RCT with a case definition based on day of death, 3 case-control studies and 1 before-and-after study gave consistent results. Based on the consistency of the mortality data, the very large effect size and that the data are all from low/middle-income countries, the overall quality of the evidence was judged to be moderate.

CONCLUSION: This review uses a standard approach to provide a transparent estimate of the high impact of tetanus toxoid immunization on neonatal tetanus.

Dietz V, Galazka A, van Loon F, Cochi S. Factors affecting the immunogenicity and potency of tetanus toxoid: implications for the elimination of neonatal and non-neonatal tetanus as public health problems. Bull World Health Organ. 1997;75(1):81–93.

An estimated 400,000 deaths occur annually from neonatal tetanus (NT). In 1989 WHO adopted the goal of eliminating NT as a public health problem worldwide. To achieve this, and to control non-neonatal tetanus (non-NT), WHO recommends that newborns be passively protected at birth by the antepartum administration of at least two doses of tetanus toxoid (TT) to their mothers and that all children subsequently receive at least three doses of diphtheria-tetanus-pertussis (DTP) vaccine. For this strategy to be effective, the TT used must be immunogenic. Potential factors that may affect TT immunogenicity need to be evaluated if NT is to be eliminated and if non-NT is to be controlled. Although data are conflicting, concurrent malarial infection may decrease the immune response to TT; however, malarial chemoprophylaxis may enhance the immune response. Malnutrition does not appear to affect immunogenicity; nevertheless, one study suggests that vitamin A deficiency is associated with an impaired immune response. Although it has been postulated that placental transfer of tetanus antibody is impaired in African women, a survey of the published literature suggests that this is not the case. Freezing TT has been shown to decrease its potency, but its impact on immunogenicity needs more evaluation.

PIP: An estimated 400,000 children die annually due to neonatal tetanus (NT). In 1989, the World Health Organization (WHO) adopted the goal of eliminating NT as a public health problem worldwide. To that end, and in order to control non-neonatal tetanus (non-NT), the WHO recommends that newborn infants be passively protected at birth by the antepartum administration of at least 2 doses of tetanus toxoid (TT) to their mothers and that all children subsequently receive at least 3 doses of diphtheria-tetanus-pertussis (DTP) vaccine. However, the TT employed must be immunogenic in order for the strategy to work. Although the data are conflicting, concurrent malarial infection may decrease the immune response to TT, while malarial chemoprophylaxis may enhance immune response. Malnutrition does not appear to affect immunogenicity, although a study suggests that vitamin A deficiency is associated with an impaired immune response. A survey of the published literature suggests that there is no basis for accepting the hypothesis that placental transfer of

tetanus antibody is impaired in African women. Finally, freezing TT has been shown to decrease its potency, but its effect upon immunogenicity remains to be determined.

Collins S, Amirthalingam G, Beeching NJ, Chand MA, Godbole G, Ramsay ME, et al. Current epidemiology of tetanus in England, 2001–2014. Epidemiology & Infection. 2016;144(16):3343–53.

Public Health England conducts enhanced national surveillance of tetanus, a potentially life-threatening vaccine-preventable disease. A standardized questionnaire was used to ascertain clinical and demographic details of individuals reported with clinically suspected tetanus. The 96 cases identified between 2001 and 2014 were analysed. The average annual incidence was 0·13/million (95% confidence interval 0·10-0·16) of which 50·0% were male. Where reported, 70·3% of injuries occurred in the home/garden (45/64). Overall, 40·3% (31/77) cases were in people who inject drugs (PWID), including a cluster of 22 cases during 2003-2004. Where known (n = 68), only 8·8% were age-appropriately immunized. The overall case-fatality rate was 11·0% (9/82). All tetanus-associated deaths occurred in adults aged >45 years, none of whom were fully immunized. Due to the success of the childhood immunization programme, tetanus remains a rare disease in England with the majority of cases occurring in older unimmunized or partially immunized adults. Minor injuries in the home/garden were the most commonly reported likely sources of infection, although cases in PWID increased during this period. It is essential that high routine vaccine coverage is maintained and that susceptible individuals, particularly older adults, are protected through vaccination and are offered timely post-exposure management following a tetanus-prone wound.

de Melker HE, van den Hof S, Berbers GAM, Nagelkerke NJD, Rümke HC, Conyn-van Spaendonck MAE. A population-based study on tetanus antitoxin levels in the Netherlands. Vaccine. 1999;18(1–2):100–8.

We assessed the tetanus immunity of the general Dutch population and of religious groups refusing vaccination by means of population-based study to evaluate the effect of tetanus vaccination. More than 95% of those born after the introduction of routine vaccination had tetanus antitoxin levels above the minimum protective level. After the sixth vaccination, a fall in tetanus antitoxin levels occurred. Nevertheless, immunisation in accordance with the routine programme most likely induces protection for much longer than two decades. Not only many members of religious groups who refuse vaccination, but also many adults born before the introduction of vaccination lack tetanus immunity. These cohorts might benefit most from (re)vaccination.

Mueller J. Part 1. Diphtheria and tetanus vaccines. Comparative efficacy/effectiveness of schedules in infant immunization against pertussis, diphtheria and tetanus: systematic review and meta-analysis. 2014. Available from http://www.who.int/immunization/sage/meetings/2015/april/5_Report_D_T_140812.pdf; accessed Nov 2016.

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Dhillon S. DTPa-HBV-IPV/Hib Vaccine (Infanrix hexaTM): A review of its use as a primary and booster Vaccination. Drugs. 2010 Maz 28;70(8):1021–58.

Infanrix hexa, administered intramuscularly, is a diphtheria, tetanus, acellular pertussis, hepatitis B (HBV), inactivated poliomyelitis and Haemophilus influenzae type b (Hib) conjugate vaccine,

indicated for primary and booster vaccination of infants. Infanrix hexa should be administered as a two- or three-dose primary vaccination course in infants aged <or=6 months, followed by booster vaccination between 11 and 18 months of age, with an interval of at least 6 months between the last dose of primary vaccination and the booster dose. This article reviews the immunogenicity and protective effectiveness, as well as the reactogenicity and safety of Infanrix hexa. Infanrix hexa as primary and booster vaccination was safe and highly immunogenic for all its component toxoids/antigens in infants aged <2 years, regardless of vaccination schedules. Its immunogenicity and safety profiles were generally similar to those of currently available vaccines, the diphtheria, tetanus and acellular pertussis-based pentavalent vaccines plus monovalent HBV or Hib vaccines. In large clinical studies, Infanrix hexa elicited a strong immune response against vaccine toxoids/antigens, as indicated by high seroprotection/seropositivity/vaccine response rates and geometric mean titres. Moreover, antibodies against vaccine toxoids/antigens persisted for up to a mean of approximately 6 years after booster vaccination, and the vaccine induced long-term immune memory against hepatitis B surface antigen and Hib antigen. A strong immune response against Infanrix hexa toxoids/antigens after primary vaccination was also induced in infants who had received a dose of HBV vaccine at birth and in pre-term infants, although the response in the latter group was somewhat lower than that in full-term infants. In addition, when coadministered with other childhood vaccines, the immunogenicity of Infanrix hexa or that of the concomitantly administered vaccine was generally not altered. Hexavalent vaccines, including Infanrix hexa, were protective against invasive Hib disease; Infanrix hexa is also expected to be protective against pertussis. Most solicited local and general symptoms with Infanrix hexa were mild to moderate in intensity and the vaccine was associated with few unsolicited adverse events. Available clinical data from more than 10 years' experience with the vaccine suggest that Infanrix hexa as primary and booster vaccination is a safe and useful option for providing protection against the common childhood diseases of diphtheria, tetanus, poliomyelitis, pertussis, hepatitis B and invasive Hib disease.

Heininger U, Sanger R, Jacquet JM, Schuerman L. Booster immunization with a hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus vaccine and Haemophilus influenzae type b conjugate combination vaccine in the second year of life: safety, immunogenicity and persistence of antibody responses. Vaccine 2007 Jan 22;25(6):1055-63.

The immunogenicity and reactogenicity of booster vaccination with GSK
Biologicals' hexavalent DTPa-HBV-IPV/Hib vaccine was assessed in toddlers aged 12-18 months previously primed with the same combination (N=341), or with DTPa-IPV/Hib and HBV administered separately (N=102; Trials 217744/059 and 217744/096). Antibody persistence at age 4-6 years was also assessed in children who had received a 4th consecutive dose of DTPa-HBV-IPV/Hib vaccine or separate DTPa-IPV/Hib and HBV vaccines in this study and in another study conducted under similar conditions in Germany. Prior to booster vaccination in
the second year of life, antibody concentrations and seroprotection rates were similar irrespective of the primary vaccine used. One month after boosting with DTPa-HBV-IPV/Hib,
substantial antibody increases were observed against all vaccine antigens indicative of previous immune priming. Seropositivity and booster response rates against all antigens were 97.4-100%. Reactogenicity following booster vaccination with DTPa-HBV-IPV/Hib was similar regardless of the primary regimen used. Three to four years after administration of the 4th DTPa-HBV-IPV/Hib
dose, >90% vaccinees had persistent protective antibody concentrations against diphtheria, hepatitis

B, Hib and the three poliovirus types. Anti-tetanus antibody concentrations were > or = 0.1 IU/ml in 76.4% subjects and seropositivity for pertussis antibodies ranged from 34.5% for PT to 98.9% for FHA. In conclusion, the combined hexavalent DTPa-HBV-IPV/Hib vaccine is immunogenic and safe when used for boosting in the second year of life, regardless of the primary vaccine used, and offers sustained protection during early childhood and beyond.

Zinke M, Disselhoff J, Gartner B, Jacquet JM. Immunological persistence in 4-6 and 7-9 year olds previously vaccinated in infancy with hexavalent DTPa-HBV-IPV/Hib. Hum Vaccin 2010 Feb;6(2):189-93.

BACKGROUND: The combined diphtheria-tetanus-pertussis-hepatitis B-inactivated poliomyelitis-Haemophilus influenzae conjugate vaccine (DTP a-HBV-IPV/Hib, Infanrix Hexa() GlaxoSmithKline Biologicals, Rixensart, Belgium) is the only hexavalent vaccine currently licensed for primary and booster vaccination of infants and provides simultaneous protection against six major diseases of childhood. The persistence of the immune response in children aged 4-6 and 7-9 years of age previously vaccinated with four doses of DTP a-HBV-IPV/Hib vaccine was assessed (www.clinicaltrials.gov.au 106744 NCT00356564 and 106745 NCT00335881).

METHODS: A blood sample was collected from 403 children, all of whom had received 3-dose primary vaccination and a booster dose in the second year of life with DTP a-HBV-IPV/Hib, in previous clinical vaccine trials in Germany.

RESULTS: Mean time from the fourth DTP a-HBV-IPV/Hib dose until serological follow-up ranged between 3.6 and 6.4 years. After the 4th DTP a-HBV-IPV/Hib dose, in subjects who had not received additional booster doses, seroprotective antibody levels persisted up to 9 years of age in >/=90% of subjects for diphtheria, Hib and poliomyelitis, in 77.2% subjects for Hepatitis B and in 64.7% of subjects for tetanus. Anti-pertussis toxin antibodies remained detectable in no more than 38.2% of subjects.

CONCLUSION: With the exception of PT , the combined DTP a-HBV-IPV/Hib induces long lasting immune response against all vaccine antigens. Falling seropositivity against PT over time supports the recommended administration of a pertussis booster dose in 5-6 year old children in Germany.

Capua T, Katz JA, Bocchini JA, Jr. Update on adolescent immunizations: selected review of US recommendations and literature. Curr Opin Pediatr 2013;25(3):397-406.

PURPOSE OF REVIEW: To provide a clinically relevant synopsis of recent research findings as well as updated recommendations from the American Academy of Pediatrics (AAP) and Advisory Committee on Immunization Practices (ACIP) regarding adolescent immunizations.

RECENT FINDINGS: Coverage rates for the adolescent vaccinations continue to lag behind those of the childhood vaccinations, despite their importance. Recent research has focused on the reasons for suboptimal adolescent vaccination rates as well as strategies for improvement. By more fully understanding the barriers to immunization, efforts can be implemented to address these concerns and to ensure that all eligible adolescents receive their vaccinations. In addition, much work has focused on the duration of protection induced by childhood and adolescent vaccinations and the need for booster doses in older adolescents. Because immunity has been found to wane after vaccination, these booster doses can serve to more fully protect adolescents. This article reviews

selected recent publications on human papillomavirus, meningococcal conjugate, and tetanus and diphtheria toxoids and acellular pertussis vaccines.

SUMMARY: Adolescent vaccinations will continue to be studied and this research will serve to shape future recommendations. Through this work, we can learn the best methods to optimize the protection of all adolescents against these very serious diseases.

Bourée P. Immunity and immunization in elderly. Pathologie Biologie. 2003;51(10):581–5.

As the average life expectancy increases, retired people want to travel. Five to 8% of travellers in tropical areas are old persons. Immune system suffers of old age as the other organs. The number and the functions of the T-lymphocytes decrease, but the B-lymphocytes are not altered. So, the response to the vaccinations is slower and lower in the elderly. Influenza is a great cause of death rate in old people. The seroconversion, after vaccine, is 50% from 60 to 70 years old, 31% from 70 to 80 years old, and only 11% after 80 years old. But in public health, the vaccination reduced the morbidity by 25%, admission to hospital by 20%, pneumonia by 50%, and mortality by 70%. Antipoliomyelitis vaccine is useful for travellers, as the vaccines against hepatitis and typhoid fever. Pneumococcal vaccine is effective in 60%. Tetanus is fatal in at last 32% of the people above 80 years, therefore this vaccine is very important.

CDC. Update: vaccine side effects, adverse reactions, contraindications, and precautions. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1996;45(RR-12):1–35.

(No abstract available.)

Zhou W, Pool V, Chen R (2004). Reports of brachial neuritis in the vaccine adverse event reporting system (VAERS), United States 1991 – 2003 (Abstract 557). 20th International Conference on Pharmacoepidemiology and Therapeutic Risk management. Bordeaux.

(No abstract available.)

Tuttle J, Chen RT, Rantala H, Cherry JD, Rhodes PH, Hadler S. The risk of Guillain-Barré syndrome after tetanus-toxoid-containing vaccines in adults and children in the United States. Am J Public Health. 1997;87(12):2045–8.

OBJECTIVES: This study examined whether there is a risk that tetanus-toxoid-containing vaccines could cause Guillain-Barré syndrome and, if so, how large the risk is.

METHODS: This study was based on previous active surveillance epidemiological studies of Guillain-Barré syndrome and vaccination history.

RESULTS: A background rate of 0.3 cases of Guillain-Barré syndrome per million person-weeks has been estimated. By chance, 2.2 people with the syndrome would have received tetanus-toxoid-containing vaccine within the 6 weeks before onset, yet only 1 person had done so. Data on children show similar results.

CONCLUSIONS: If an association exists, it must be extremely rare and not of public health significance.

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). In: Cochrane Database of 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 (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.

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 29, 19 JULY 2013. Global Advisory Committee on Vaccine Safety, 12–13 June 2013.

(No abstract available.)

King GE, Hadler SC. 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, 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 Oct 2016.

(No abstract available.)

Gasparini R, Tregnaghi M, Keshavan P, Ypma E, Han L, Smolenov I. Safety and Immunogenicity of a Quadrivalent Meningococcal Conjugate Vaccine and Commonly Administered Vaccines After Coadministration. Pediatr Infect Dis J. 2016;35(1):81–93.

BACKGROUND: Given the broad age range across which the quadrivalent meningococcal conjugate vaccine MenACWY-CRM is used, coadministration with routine vaccines should be evaluated across age groups for possible immunologic interference and impact on vaccine reactogenicity and safety.

METHODS: We summarize data from a large population of infants, adolescents and international travelers from 10 phase 3 or 4 clinical studies to evaluate coadministration of MenACWY-CRM with commonly administered vaccines. Noninferiority analyses of immune responses were performed across studies and age groups for each vaccine. Reactogenicity and safety were also assessed.

RESULTS: In infants, MenACWY-CRM coadministered with routine vaccines did not reduce immune responses to diphtheria, tetanus, poliovirus, hepatitis B, Haemophilus influenzae type b, pneumococcal conjugate, measles-mumps-rubella, varicella or pertussis antigens. Noninferiority criteria were not met for some pneumococcal conjugate serotypes at 7 months of age, but no consistent trends were observed. In adolescents, coadministration did not reduce immune responses to tetanus, diphtheria and human papilloma virus vaccine antigens. Noninferiority criteria for pertussis antigens were not uniformly met in infant and adolescent studies, although the clinical relevance is unclear. In adults, coadministration did not reduce immune responses to hepatitis A/B,

typhoid fever, yellow fever, Japanese encephalitis and rabies antigens. Immune responses to MenACWY-CRM were not impacted by coadministration of commonly administered vaccines. Coadministration did not increase frequencies of postvaccination adverse events in any age group.

CONCLUSIONS: With no clinically relevant vaccine interactions or impact on vaccine reactogenicity or safety, these results support the coadministration of MenACWY-CRM with routine vaccines in all age groups.

Schilling A, Parra MM, Gutierrez M, Restrepo J, Ucros S, Herrera T, et al. Coadministration of a 9-valent Human Papillomavirus Vaccine with Meningococcal and Tdap Vaccines. Pediatrics. 2015;136(3):e563–72.

BACKGROUND: This study in 11- to 15-year-old boys and girls compared the immunogenicity and safety of GARDASIL 9 (9-valent human papillomavirus [9vHPV] vaccine) administered either concomitantly or nonconcomitantly with 2 vaccines routinely administered in this age group (Menactra [MCV4; Neisseria meningitidis serotypes A/C/Y/W-135] or Adacel [Tdap; diphtheria/tetanus/acellular pertussis]).

METHODS: Participants received 9vHPV vaccine at day 1 and months 2 and 6; the concomitant group (n = 621) received MCV4/Tdap concomitantly with 9vHPV vaccine at day 1; the nonconcomitant group (n = 620) received MCV4/Tdap at month 1. Antibodies to HPV-, MCV4-, and Tdap-relevant antigens were determined. Injection-site and systemic adverse events (AEs) were monitored for 15 days after any vaccination; serious AEs were monitored throughout the study.

RESULTS: The geometric mean titers for all HPV types in 9vHPV vaccine 4 weeks after dose 3, proportion of subjects with a fourfold rise or greater in titers for 4 N meningitidis serotypes 4 weeks after injection with MCV4, proportion of subjects with antibody titers to diphtheria and tetanus $\geqslant$ 0.1 IU/mL, and geometric mean titers for pertussis antigens 4 weeks after injection with Tdap were all noninferior in the concomitant group compared with the nonconcomitant group. Injection-site swelling occurred more frequently in the concomitant group. There were no vaccine-related serious AEs.

CONCLUSIONS: Concomitant administration of 9vHPV vaccine with MCV4/Tdap was generally well tolerated and did not interfere with the antibody response to any of these vaccines. This strategy would minimize the number of visits required to deliver each vaccine individually**.**

Borrow R, Tang Y, Yakubu A, Kulkarni PS, LaForce FM. MenAfriVac as an Antitetanus Vaccine. Clin Infect Dis. 2015;61 (Suppl 5):S570-7. https://www.ncbi.nlm.nih.gov/pubmed/26553690

BACKGROUND: The group A meningococcal conjugate vaccine, PsA-TT, uses tetanus toxoid (TT) as a carrier protein (PsA-TT). TT as a carrier protein in other conjugate vaccines is known to be immunogenic and generates a robust anti-TT response.

METHODS: Clinical studies in Africa assessed whether PsA-TT generated tetanus serologic responses when tested in African populations (toddlers to adults). Second, the high acceptance of PsA-TT mass immunization campaigns in the 1- to 29-year age group meant that a sizeable fraction of women of reproductive age received PsA-TT. Incidence data for neonatal tetanus were reviewed for countries with and without PsA-TT campaigns to check whether this had any impact on the incidence.

RESULTS: PsA-TT generated robust tetanus serologic responses in 1- to 29-year-olds, similar to those expected after a booster dose of TT. Neonatal cases of tetanus fell by 25% in countries that completed PsA-TT campaigns in 1- to 29-year-olds.

CONCLUSIONS: Although these data are not yet definitive, they are consistent with the hypothesis that improved community immunity to tetanus as a result of the PsA-TT campaigns may be having an impact on the incidence of neonatal tetanus in sub-Saharan Africa.

Borrow R., and Balmer P.: The immunologic basis for immunization: module 15: meningococcal disease. Geneva: World Health Organization, 2010. http://apps.who.int/iris/bitstream/10665/44376/1/9789241599849_eng.pdf.

(No abstract available.)

Tashani M, Alfelali M, Barasheed O, Alqahtani AS, Heron L, Wong M, et al. Effect of Tdap when administered before, with or after the 13-valent pneumococcal conjugate vaccine (coadministered with the quadrivalent meningococcal conjugate vaccine) in adults: A randomised controlled trial. Vaccine. 2016;34(48):5929–37.

Sequential or co-administration of vaccines has potential to alter the immune response to any of the antigens. Existing literature suggests that prior immunisation of tetanus/diphtheria-containing vaccines can either enhance or suppress immune response to conjugate pneumococcal or meningococcal vaccines. We examined this interaction among adult Australian travellers before attending the Hajj pilgrimage 2014. We also investigated tolerability of these vaccines separately and concomitantly. We randomly assigned each participant to one of three vaccination schedules. Group A received adult tetanus, diphtheria and acellular pertussis vaccine (Tdap) 3-4weeks before receiving CRM197-conjugated 13-valent pneumococcal vaccine (PCV13) and CRM197-conjugated quadrivalent meningococcal vaccine (MCV4). Group B received all three vaccines on one day. Group C received PCV13 and MCV4 3-4weeks before Tdap. Blood samples collected at baseline, each vaccination visit and 3-4weeks after vaccination were tested using the pneumococcal opsonophagocytic assay (OPA) and by ELISA for diphtheria and tetanus antibodies. Funding for meningococcal serology was not available. Participants completed symptom diaries after each vaccination. A total of 111 participants aged 18-64 (median 40) years were recruited. No statistically significant difference was detected across the three groups in achieving OPA titre $\geqslant$1:8 post vaccination. However, compared to other groups, Group A had a statistically significant lower number of subjects achieving $\geqslant$4-fold rise in serotype 3, and also significantly lower geometric mean titres (GMTs) to six (of 13) pneumococcal serotypes (3, 5, 18C, 4, 19A and 9V). Group C (given prior PCV13 and MVC4) had statistically significant higher pre-Tdap geometric mean concentration (GMC) of anti-diphtheria IgG; however, there was no difference across the three groups following Tdap. Anti-tetanus IgG GMCs were similar across the groups before and after Tdap. No serious adverse events were reported. In conclusion, Tdap vaccination 3-4weeks before concomitant administration of PCV13 and MCV4 significantly reduced the antibody response to six of the 13 pneumococcal serotypes in adults. The trial is registered at the Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12613000536763.

Niewiesk S. Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Front Immunol. 2014;5:446.

Neonates have an immature immune system, which cannot adequately protect against infectious diseases. Early in life, immune protection is accomplished by maternal antibodies transferred from mother to offspring. However, decaying maternal antibodies inhibit vaccination as is exemplified by the inhibition of seroconversion after measles vaccination. This phenomenon has been described in both human and veterinary medicine and is independent of the type of vaccine being used. This review will discuss the use of animal models for vaccine research. I will review clinical solutions for inhibition of vaccination by maternal antibodies, and the testing and development of potentially effective vaccines. These are based on new mechanistic insight about the inhibitory mechanism of maternal antibodies. Maternal antibodies inhibit the generation of antibodies whereas the T cell response is usually unaffected. B cell inhibition is mediated through a cross-link between B cell receptor (BCR) with the Fcγ-receptor IIB by a vaccine–antibody complex. In animal experiments, this inhibition can be partially overcome by injection of a vaccine-specific monoclonal IgM antibody. IgM stimulates the B cell directly through cross-linking the BCR via complement protein C3d and antigen to the complement receptor 2 (CR2) signaling complex. In addition, it was shown that interferon alpha binds to the CD21 chain of CR2 as well as the interferon receptor and that this dual receptor usage drives B cell responses in the presence of maternal antibodies. In lieu of immunizing the infant, the concept of maternal immunization as a strategy to protect neonates has been proposed. This approach would still not solve the question of how to immunize in the presence of maternal antibodies but would defer the time of infection to an age where infection might not have such a detrimental outcome as in neonates. I will review successful examples and potential challenges of implementing this concept.

Ladhani SN, Andrews NJ, Southern J, Jones CE, Amirthalingam G, Waight PA, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. Clin Infect Dis. 2015;61(11):1637–44.

INTRODUCTION: In England, antenatal pertussis immunization using a tetanus/low-dose diphtheria/5-component acellular-pertussis/inactivated-polio (TdaP5/IPV) vaccine was introduced in October 2012. We assessed infant responses to antigens in the maternal vaccine and to those conjugated to tetanus (TT) or the diphtheria toxin variant, CRM.

METHODS: Infants of 141 TdaP5/IPV-vaccinated mothers in Southern England immunized with DTaP5/IPV/Haemophilus influenzae b (Hib-TT) vaccine at 2-3-4 months, 13-valent pneumococcal vaccine (PCV13, CRM-conjugated) at 2-4 months and 1 or 2 meningococcal C vaccine (MCC-CRM- or MCC-TT) doses at 3-4 months had blood samples taken at 2 and/or 5 months of age.

RESULTS: Antibody responses to pertussis toxin (PT), filamentous hemagglutinin (FHA), fimbriae 2 + 3 (FIMs), diphtheria, tetanus, Hib, MCC and PCV13 serotypes were compared to responses in a historical cohort of 246 infants born to mothers not vaccinated in pregnancy. Infants had high pertussis antibody concentrations pre-immunization but only PT antibodies increased post-immunization (fold-change, 2.64; 95% confidence interval [CI], 2.12-3.30; P < .001), whereas FHA antibodies fell (fold-change, 0.56; 95% CI, .48-.65; P < .001). Compared with infants of unvaccinated mothers, PT, FHA, and FIMs antibodies were lower post-vaccination, with fold-differences of 0.67 (0.58-0.77; P < .001), 0.62 (0.54-0.71; P < .001) and 0.51 (0.42-0.62; P < .001), respectively.

Antibodies to diphtheria and some CRM-conjugated antigens were also lower, although most infants achieved protective thresholds; antibodies to tetanus and Hib were higher.

CONCLUSIONS: Antenatal pertussis immunization results in high infant pre-immunization antibody concentrations, but blunts subsequent responses to pertussis vaccine and some CRM-conjugated antigens. In countries with no pertussis booster until school age, continued monitoring of protection against pertussis is essential.

UNICEF Supply Division. Vaccine Price Data. Available at https://www.unicef.org/supply/index_57476.html; accessed Dec 2016.

(No abstract available.)

"Maternal and Neonatal Tetanus Elimination (MNTE) Funding." Presented by Flint Zulu, UNICEF, 30 November 2016 at the MNTE Stakeholders Meeting, UNICEF New York.

(No abstract available.)

Adam T, Lim SS, Mehta S, Bhutta ZA, Fogstad H, Mathai M, et al. Cost effectiveness analysis of strategies for maternal and neonatal health in developing countries. BMJ. 2005;331(7525):1107.

OBJECTIVE: To determine the costs and benefits of interventions for maternal and newborn health to assess the appropriateness of current strategies and guide future plans to attain the millennium development goals.

DESIGN: Cost effectiveness analysis.

SETTING: Two regions classified by the World Health Organization according to their epidemiological grouping: Afr-E, those countries in sub-Saharan Africa with very high adult and high child mortality, and Sear-D, comprising countries in South East Asia with high adult and high child mortality.

DATA SOURCES: Effectiveness data from several sources, including trials, observational studies, and expert opinion. For resource inputs, quantities came from WHO guidelines, literature, and expert opinion, and prices from the WHO choosing interventions that are cost effective database.

MAIN OUTCOME MEASURES: Cost per disability adjusted life year (DALY) averted in year 2000 international dollars.

RESULTS: The most cost effective mix of interventions was similar in Afr-E and Sear-D. These were the community based newborn care package, followed by antenatal care (tetanus toxoid, screening for pre-eclampsia, screening and treatment of asymptomatic bacteriuria and syphilis); skilled attendance at birth, offering first level maternal and neonatal care around childbirth; and emergency obstetric and neonatal care around and after birth. Screening and treatment of maternal syphilis, community based management of neonatal pneumonia, and steroids given during the antenatal period were relatively less cost effective in Sear-D. Scaling up all of the included interventions to 95% coverage would halve neonatal and maternal deaths.

CONCLUSION: Preventive interventions at the community level for newborn babies and at the primary care level for mothers and newborn babies are extremely cost effective, but the millennium

development goals for maternal and child health will not be achieved without universal access to clinical services as well.

Griffiths UK, Wolfson LJ, Quddus A, Younus M, Hafiz RA. Incremental cost-effectiveness of supplementary immunization activities to prevent neonatal tetanus in Pakistan. Bulletin of the World Health Organization. 2004;82(9):643.

OBJECTIVE: This study aimed to estimate the incremental cost-effectiveness of supplementary immunizationactivities to prevent neonatal tetanus in the Loralai district of Pakistan. The supplemental immunization activities were carried out in two phases during 2001-03.

METHODS: A state-transition model was used to estimate the effect of routine vaccination with tetanus toxoid as well as vaccination with tetanus toxoid during supplementary immunization activities. The model follows each woman in the target population from birth until the end of her childbearing years, using age-specific fertility data and vaccination history to determine the number of births at risk for neonatal tetanus. Recently published data on the incidence of neonatal tetanus from Loralai were used to determine the number of cases occurring with and without supplementary immunization activities. Data on the costs of the activities were collected from the UNICEF office in Balochistan and from the Provincial Health Department.

FINDINGS: Using base-case assumptions we estimated that the supplementary immunization activities would prevent 280 cases of neonatal tetanus and 224 deaths from neonatal tetanus between 2001 and 2034. Implementation of the supplementary activities was relatively inexpensive. The cost per tetanus toxoid dose delivered was 0.40 U.S. dollars. In the base-case analysis the cost per death averted was 117.00 U.S. dollars (95% confidence interval (CI) = 78-205 U.S. dollars) and the cost per disability-adjusted life year (DALY) averted was 3.61 U.S. dollars (95% Cl = 2.43-6.39 U.S. dollars).

CONCLUSION: Compared with similar analyses of other interventions, the cost per DALY averted is a favourable cost-effectiveness ratio. However, if routine diphtheria-tetanus-pertussis vaccination coverage in the Loralai district had been higher (at a coverage rate of about 80%) the cost-effectiveness of the intervention would have been even more favourable, at 2.65 U.S. dollars per DALY averted.

Zhou F, Shefer A, Wenger J, Messonnier M, Wang LY, Lopez A, et al. Economic Evaluation of the Routine Childhood Immunization Program in the United States, 2009. PEDIATRICS. 2014;133(4):577–85.

OBJECTIVES: To evaluate the economic impact of the 2009 routine US childhood immunization schedule, including diphtheria and tetanus toxoids and acellular pertussis, Haemophilus influenzae type b conjugate, inactivated poliovirus, measles/mumps/rubella, hepatitis B, varicella, 7-valent pneumococcal conjugate, hepatitis A, and rotavirus vaccines; influenza vaccine was not included.

METHODS: Decision analysis was conducted using population-based vaccination coverage, published vaccine efficacies, historical data on disease incidence before vaccination, and disease incidence

reported during 2005 to 2009. 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 work time lost. All costs were inflated to 2009 dollars, and all costs and benefits in the future were discounted at a 3% annual rate. A hypothetical 2009 US birth cohort of 4,261,494 infants over their lifetime was followed up from birth through death. Net present value (net savings) and benefit-cost ratios of routine childhoodimmunization were calculated.

RESULTS: Analyses showed that routine childhood immunization among members of the 2009 US birth cohort will prevent ~42,000 early deaths and 20 million cases of disease, with net savings of $13.5 billion in direct costs and $68.8 billion in total societal costs, respectively. The direct and societal benefit-cost ratios for routinechildhood vaccination with these 9 vaccines were 3.0 and 10.1.

CONCLUSIONS: From both direct cost and societal perspectives, vaccinating children as recommended with these vaccines results in substantial cost savings.

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 39, 25 SEPTEMBER 2015, 90, pp 505-510. Reducing pain at the time of vaccination: WHO position paper – September 2015

(No abstract available.)