10 May 2006

WHO Position Paper on tetanus vaccines: Selected references

Epidemiology

Bytchenko B. Geographical distribution of tetanus in the world. Bull World Health Organization 34: 71-104, 1966. (Abstract not available)**.**

Galazka A, Gasse F. The present status of tetanus and tetanus vaccination. Curr Top Microbiol Immunol. 1995;195:31-53. (Abstract not available).

Pedalino B, Cotter B, Ciofi degli Atti M, Mandolini D, Parroccini S, Salmaso S. Epidemiology of tetanus in Italy in years 1971-2000. Euro Surveill. 2002 Jul;7(7):103-10.

The incidence of reported tetanus in Italy decreased from 0.5/100,000 in the 1970s to 0.2/100,000 in the 1990 s. During this period of time, the case-fatality ratio decreased from 68% to 39%. Italy has the highest reported number of tetanus cases in European countries. Elderly women are the most affected: the proportion of women aged over 64 years among cases has increased from 60% in the 1970s to 76% in the 1990s. Vaccination campaigns need to be conducted to target this group, and the surveillance of tetanus has to be improved to identify additional groups of population at risk.

Clinical features of tetanus

Bleck TP. Tetanus: pathophysiology, management, and prophylaxis. Dis Mon. 1991 Sep;37(9):545-603.

As tetanus has become a rare disease in the developed world, physicians have become less comfortable with its diagnosis and management. The extent of adequate antitetanus immunity in the adult population, especially the elderly, is waning, in great measure because primary care physicians have not made prophylaxis a priority in their routine encounters with patients. Furthermore, as the population of immunocompromised hosts grows, an increasing percentage of our patients may not respond to standard active immunization routines. Unless these trends are reversed, we face a substantial increase in the incidence of this dread disorder. Tetanus is also of interest as a relatively simple model of disordered motor control that can instruct us in the management of the many more common causes of neurogenic muscular rigidity. The toxin produced by Clostridium tetani finds increasing use in laboratories investigating brain function as well. Clinical tetanus is divided into four symptomatic types: generalized tetanus, local tetanus, cephalic tetanus, and neonatal tetanus. This monograph discusses the diagnostic aspects of each type of tetanus, its pathophysiology, diagnosis, differential diagnosis, and treatment. Preventing tetanus should be a high priority for all primary care physicians. Active immunization with

tetanus toxoid is remarkably effective and safe. Passive immunization with human tetanus immune globulin is indicated in certain circumstances, which are discussed below.

**Thwaites CL, Yen LM, Nga NT, Parry J, Binh NT, Loan HT, Thuy TT, Bethell D, Parry CM, White NJ, Day NP, Farrar JJ. Impact of improved vaccination programme and intensive care facilities on incidence and outcome of tetanus in southern Vietnam, 1993-2002. Trans R Soc Trop Med Hyg. 2004 Nov;98(11):
671-7.**

Unvaccinated individuals throughout the world are vulnerable to tetanus, but there are few data regarding the impact of focused vaccination programmes and modern intensive care facilities on the disease, particularly in the developing world. The Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam admitted 2422 patients with tetanus aged > or =1 year between April 1993 and December 2002, during which time vaccine coverage and treatment facilities improved. The proportion of children < or =10 years old admitted with tetanus fell from 11.1 to 5.6% over the 10 year period (P = 0.002). The proportion of women aged 20-40 years fell from 10.1 to 1.2% (P < 0.001). Mortality rates fell from a maximum of 27.81% in 1994 to 10.04% in 2002 (P < 0.001). Thus, a marked reduction in tetanus incidence has occurred in age groups specifically targeted by the national vaccination programme. However, tetanus continues to be a major cause of morbidity and mortality in individuals outside the target population. Improved intensive care facilities, such as mechanical ventilation and low-cost infection control procedures are associated with a significant reduction in mortality.

**Farrar JJ, Yen LM, Cook T, Fairweather N, Binh N, Parry J, Parry CM. Tetanus.
J Neurol Neurosurg Psychiatry. 2000 Sep;69(3):292-301.**

Galazka A, Stroh G. Guidelines on the community-based survey on neonatal tetanus mortality. Geneva: World Health Organization, 1986: WHO/EPI/GEN/86/8.

The vaccine: Methods for measuring toxoid and antitoxin

Hendriksen C, Winsnes R. Serological methods for potency testing of tetanus toxoid vaccines for human use. Dev Biol (Basel). 2002;111:131-40.

A collaborative study has been performed to validate two in vitro serological assays, ELISA and ToBI test, as alternatives to the direct challenge procedure for potency testing of tetanus toxoid vaccines for human use (Ph.Eur. monograph Tetanus vaccine (adsorbed) (0452)). In six laboratories, guinea-pigs were immunised with tetanus toxoid vaccines from different manufacturers representing various types of combined products, including one product of borderline quality. Blood samples were taken two to four days before challenge. Parameters that were analysed included: (i) correlation of vaccine potencies obtained by direct challenge test and by serological assays, (ii) prediction of survival based on antibody concentrations, and (iii) correlation of antibody concentrations obtained in ELISA, ToBI test and in vivo Toxin Neutralisation test. In addition, ELISA and ToBI test repeatability and reproducibility were further studied by titration of a total of 28 serum samples in 23 laboratories. This paper provides background information, gives an outline of the experimental design and discusses the study results. It is concluded that ELISA and ToBI test are valid alternatives to the challenge procedure. Implementation of the serological assays as alternatives to the challenge

procedure for batch release of tetanus vaccines for human use will result in a marked refinement as well as a substantial reduction of numbers of laboratory animals.

Simonsen O, Schou C, Heron I. Modification of the ELISA for the estimation of tetanus antitoxin in human sera. J Biol Stand. 1987 Apr;15(2):143-57.

The use of indirect ELISA for the quantitation of tetanus toxin neutralizing antibodies in human sera is limited by marked overestimations in low titered sera. The reasons for the discrepancy between the results obtained by ELISA and by in vivo assay and modifications of the ELISA to overcome the problem were investigated. Catching ELISA and indirect ELISA using trays coated with the contaminant proteins in toxoid preparations indicated that antibodies to contaminants were only partly responsible for the discrepancy and the introduction of these modifications did not solve the problem. In ELISA competition experiments with toxin neutralizing monoclonal antibodies, the human immunoglobulins irrelevant in toxin neutralization, but detectable in indirect ELISA, were found to be difficult to inhibit in their binding to the solid antigen phase. These might represent antitoxins bound bivalently to the solid phase but with affinities in monovalent binding insufficient for toxin neutralization or other coupled antibodies due to conformational changes of the antigen. A competition ELISA with toxin in solution was therefore developed to assess selectively the antitoxin capable of binding the antigen in solution and by this approach the in vivo activities of even low titered sera were accurately predicted. This antigen competition ELISA may be easily introduced into routine tetanus serology and the principle may also be of value for the in vitro detection of functional antibodies to other antigens.

Immune responses and duration of protection

Pasetti M, Eriksson P, Ferrero F, Manghi M. Serum antibodies to diphtheria-tetanus-pertussis vaccine components in Argentine children. Infection. 1997 Nov-Dec;25(6):339-45.

The Argentine vaccination schedule against diphtheria, tetanus and pertussis (DTP) recommends three doses of DTP vaccine at 2, 4 and 6 months of age, two boosters at 18 months and 6 years, a booster dose of tetanus vaccine every 10 years and two doses during pregnancy. To evaluate the effect of this schedule, antibodies against pertussis toxin (PT) and filamentous hemagglutinin (FHA) and against tetanus and diphtheria toxoids were determined by ELISA in serum samples from children (1 month to 6 years) who received different doses of DPT vaccine: 0 dose (n = 50), 1 dose (n = 25), 2 doses (n = 25), 3 doses (n = 55), first and second booster (n = 25); 25 pregnant women and their offspring, and 45 adults. High antibody levels against PT (> 140 EU/ml) and FHA (> 80 EU/ml) were recorded in mothers and in the newborn. Antibody titers against PT increased with the number of doses given and decreased with time. Full protection against tetanus (titers > 0.1 IU/ml) was observed in the group of adults (0.37 IU/ml), in mothers (4.4 IU/ml) and their newborn offspring (5.5 IU/ml), and in children after receiving the second dose of DTP vaccine (1.86 IU/ml). The immune status for diphtheria was far lower, as most of the groups lacked adequate protection. After the third dose of DTP vaccine, only 78% of the children had antibody titers above the protective level (0.1 IU/ml). Since antibody levels considered to provide full protection were only achieved after the first booster dose of DTP vaccine, the primary three-dose schedule seems to be insufficient to confer adequate immunity

in all vaccinees. Because of the high proportion of non-protected adults, a booster dose of Td vaccine should be considered for this group.

Aboud S, Matre R, Lyamuya EF, Kristoffersen EK. Levels and avidity of antibodies to tetanus toxoid in children aged 1-15 years in Dar es Salaam and Bagamoyo, Tanzania. Ann Trop Paediatr. 2000 Dec;20(4):313-22.

A study was undertaken to determine the serological response in children (aged 1-15 years) immunized with diphtheria-pertussis-tetanus vaccine (DPT) alone or with a tetanus toxoid (TT) booster dose under the Expanded Programme on Immunization in Dar es Salaam and Bagamoyo, Tanzania. Using an ELISA technique, serum levels of anti-TT antibody, antibody avidity and anti-TT IgG subclasses were determined in 138 apparently healthy children. Our findings revealed that 94.7% and 98% of children aged 1-5 years in Dar es Salaam and Bagamoyo, respectively, had anti-TT antibody levels above that considered protective (> or = 0.1 IU/ml). Among 6-15-year-old children, 53.3% in Dar es Salaam and 55% in Bagamoyo had anti-TT antibody levels > or = 0.1 IU/ml. The avidity index of anti-TT antibodies was high in most of the younger children, 84.2% in Dar es Salaam and 92% in Bagamoyo. Significantly fewer older children in Dar es Salaam and Bagamoyo (53.3% and 50%, respectively) had high avidity index antibodies. The predominant anti-TT IgG subclasses were IgG1 and IgG3. It is concluded that the current DPT immunization schedule provides adequate tetanus immunity for children under 5. However, about half of the older children had no protection against tetanus.

Christenson B, Bottiger M. Immunity and immunization of children against tetanus in Sweden. Scand J Infect Dis. 1991;23(5):643-7.

Tetanus antitoxin titres were determined in sera of 457 children, 6-, 10- and 16- year-old. Primary vaccination against tetanus had been given as 3 doses of DPT or DT vaccine at intervals of 4-6 weeks beginning in the 2nd or 3rd month of life. A booster dose is offered to schoolchildren at 8-10 years of age. As boosters, the children were given 0.1, 0.25 or 0.5 ml of diphtheria/tetanus toxoid (DT) containing 7.5 Lf/ml tetanus toxoid. The antitoxin titres against tetanus were much higher than those against diphtheria found in previous studies. Blood samples tested from 68 children, 5-year-old, who had been given basic immunization according to a spaced time schedule showed that 97% of the children had levels greater than 0.1 IU/ml. Prior to booster injection of the 6-year-old children, 1% lacked protective titre levels (greater than or equal to 0.01 IU/ml). 53% had antitoxin titre levels of greater than or equal to 0.01 - less than 0.1 IU/ml and 46% had levels of 0.1 IU/ml. The corresponding figures for the 10-year-old were 6, 65 and 29%, and for the 16-year-old 2, 7 and 91% respectively. After a booster injection high antitoxin levels were seen in all children. 95% had levels greater than 1 IU/ml irrespective of vaccine dose.

Ramsay ME, Corbel MJ, Redhead K, Ashworth LA, Begg NT. Persistence of antibody after accelerated immunisation with diphtheria/tetanus/pertussis vaccine. BMJ. 1991 Jun 22;302(6791):1489-91.

OBJECTIVE--To determine the persistence of antibody to diphtheria, tetanus, and pertussis in children receiving an accelerated schedule of primary immunisation. DESIGN--Controlled study of antibody testing of blood samples from children immunised according to various schedules: three doses of triple vaccine completed at 8-13 calendar months, 6-7 calendar months, before 6 calendar months, or three doses

followed by diphtheria/tetanus before age 2. SETTING--Plymouth Health Authority. SUBJECTS--129 children aged 4 years who had received three doses of diphtheria/tetanus/pertussis vaccine with or without a diphtheria/tetanus booster. MAIN OUTCOME MEASURES--Diphtheria and tetanus antitoxin concentrations and antibody titres to pertussis toxin, filamentous haemagglutinin, and agglutinogens 2 and 3. RESULTS--All children had protective concentrations of antitoxin to diphtheria and tetanus (greater than or equal to 0.01 IU/ml). There was no evidence of a significant difference in diphtheria or tetanus antitoxin concentrations and pertussis antibody titres in children immunised with an accelerated course (third dose of triple vaccine before 6 months) compared with those who received a longer course (third dose at 8-13 months) with no booster (geometric mean antitoxin concentration 0.411 (95% confidence interval 0.273 to 0.618) v 0.426 (0.294 to 0.616) for diphtheria and 0.358 (0.231 to 0.556) v 0.299 (0.197 to 0.453) for tetanus; geometric mean antibody titres 903 (500 to 1631) v 1386 (848 to 2266) for pertussis filamentous haemagglutinin, 179 (130 to 248) v 232 (167 to 322) for pertussis toxin, and 2002 (1276 to 3142) v 3591 (2220 to 5809) for agglutinogens 2 and 3). CONCLUSION--Immunisation with three doses of triple vaccine at monthly intervals completed before 6 months of age probably provides adequate protection against diphtheria, tetanus, and whooping cough which will persist until the age of the preschool booster.

Simonsen O, Badsberg JH, Kjeldsen K, Moller-Madsen B, Heron I. The fall-off in serum concentration of tetanus antitoxin after primary and booster vaccination. Acta Pathol Microbiol Immunol Scand [C]. 1986 Apr;94(2):77-82.

In 196 randomly selected persons with documented complete primary vaccination against tetanus 12-30 years earlier, antitoxin concentration in serum relative to time since last vaccination was studied. In the group of non-revaccinated persons an exponential decrease in antitoxin concentration with time since primary vaccination was found. 25-30 years after primary vaccination, 28% were unprotected (antitoxin concentration in serum below 0.01 IU/ml). In the group that received a single revaccination earlier, a similar exponential fall in antitoxin concentration was found, but all those revaccinated up to 23 years earlier were still protected. 82 persons who had not been revaccinated earlier were revaccinated. All those revaccinated less than 20 years after primary vaccination attained very high antitoxin concentrations (above 6 IU/ml) corresponding to a duration of immunity of at least 20 years. It was suggested that a revaccination program consisting of a single revaccination in childhood and thereafter every 20 years is sufficient to maintain immunity.

Shohat T, Marva E, Sivan Y, Lerman I, Mates A, Cohen A. Immunologic response to a single dose of tetanus toxoid in older people. J Am Geriatr Soc. 2000 Aug;48(8):949-51.

OBJECTIVES: Several studies have demonstrated that a large percentage of older people are inadequately immunized against tetanus. The aim of this study was to assess the immunity against tetanus in a group of individuals aged 69 and older and to examine the immune response to a single dose of tetanus toxoid. DESIGN: A convenience sample of 115 residents of a large retirement home, aged 69 and older, was studied. After a blood sample for anti-tetanus antibody titer, a single dose of tetanus toxoid vaccine was administered. Repeat titers were obtained 6 weeks after the vaccination and analyzed by ELISA assay. Antibody levels equal to or greater than 0.1 IU/mL were considered protective. RESULTS: Sixty-seven of 115

(58.3%) individuals had adequate antibody titers. Those individuals who reported having been vaccinated with tetanus toxoid in the past were more likely to be immunized adequately compared with those who reported having never been vaccinated (66.7% vs 39.3%, P = .02). After vaccination, 34 of 46 (73.9%) individuals with inadequate antibody titers became seropositive. Those who remained seronegative had mean prevaccination antibody titers significantly lower than those who seroconverted. Sixteen of 17 (94.1%) persons who reported having been vaccinated in the past and were found to be seronegative developed adequate antibody titers following vaccination, compared with only nine of 16 (56.2%) who reported never having been vaccinated (P = .04). There was no association between seroconversion rate and age, sex, underlying diseases, and army service. CONCLUSIONS: Most individuals will develop an adequate anti-tetanus antibody titer following administration of a single dose of tetanus vaccine. A history of past immunization is a good predictor of becoming adequately immunized. It is important that physicians follow the current recommendations for adult immunization and initiate campaigns to ensure that the older population is protected against tetanus.

Immune responses and duration of protection in pregnant women/women in childbearing ages

Jones TS. The use of tetanus toxoid for the prevention of neonatal tetanus in developing countries. *In* Recent Advances in Immunization: A Bibliographic Review (PACHO Scientific Publ No 451). Washington, DC, Pan American Health Organizatiion, 1983, pp 52-64. (No abstract available)

Newell KW, Duenas Lehmann A, LeBlanc DR, Garces Osorio N.The use of toxoid for the prevention of tetanus neonatorum. Final report of a double-blind controlled field trial. Bull World Health Organ. 1966;35(6):863-71.
(No abstract available)

Schofield FD, Tucker VM, Westbrook GR.Neonatal tetanus in New Guinea. Effect of active immunization in pregnancy. Br Med J. 1961 Sep 23;5255:785-9.
(No abstract available)

Some factors potentially affecting the maternal immune response to tetanus toxoid

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.

Moss WJ, Clements CJ, Halsey NA. Immunization of children at risk of infection with human immunodeficiency virus. Bull World Health Organ. 2003;81(1):61-70. Epub 2003 Mar 11.

This paper reviews the English language literature on the safety, immunogenicity and effectiveness in children infected with the human immunodeficiency virus (HIV) of vaccines currently recommended by WHO for use in national immunization programmes. Immunization is generally safe and beneficial for children infected with HIV, although HIV-induced immune suppression reduces the benefit compared with that obtained in HIV-uninfected children. However, serious complications can occur following immunization of severely immunocompromised children with bacillus Calmette-Gu rin (BCG) vaccine. The risk of serious complications attributable to yellow fever vaccine in HIV-infected persons has not been determined. WHO guidelines for immunizing children with HIV infection and infants born to HIV-infected women differ only slightly from the general guidelines. BCG and yellow fever vaccines should be withheld from symptomatic HIV-infected children. Only one serious complication (fatal pneumonia) has been attributed to measles vaccine administered to a severely immunocompromised adult. Although two HIV-infected infants have developed vaccine-associated paralytic poliomyelitis, several million infected children have been vaccinated and the evidence does not suggest that there is an increased risk. The benefits of measles and poliovirus vaccines far outweigh the potential risks in HIV-infected children. The policy of administering routine vaccines to all children, regardless of possible HIV exposure, has been very effective in obtaining high immunization coverage and control of preventable diseases. Any

changes in this policy would have to be carefully examined for a potential negative impact on disease control programmes in many countries.

Immunization schedule and booster policy

Orenstein WA, Weisfeld JS, Halsey NA. Diphtheria and tetanus toxoids and pertussis vaccine, combined. *In* Recent Advances in Immunization: A Bibliographic Review (PACHO Scientific Publ No 451). Washington, DC, Pan American Health Organizatiion, 1983, pp 30-51.

Simonsen O, Bentzon MW, Kjeldsen K, Venborg HA, Heron I. Evaluation of vaccination requirements to secure continuous antitoxin immunity to tetanus. Vaccine. 1987 Jun;5(2):115-22.

To investigate minimal requirements for tetanus revaccination to secure continuous protection, recently recommended by WHO, 637 subjects with documented vaccination history were studied. Antitoxin concentration in serum relative to time corresponded to a steep decline in the first years after vaccination continuing exponentially. By multiple regression analyses duration of immunity after three-dose primary vaccination was calculated to be 5 years (upper 95% confidence limit of estimated risk of serum antitoxin concentration below 0.01 IU ml-1 still less than 0.1%). Serum antitoxin concentration relative to time after revaccination depended upon age at revaccination and interval from primary vaccination. When given in childhood 5 years after primary vaccination revaccination was calculated to offer protection for approximately equal to 21 years, but protection was considerably shorter when given to the elderly. Cross-sectional and longitudinal analyses were compared and statistical approaches were introduced which may be generally applicable for evaluation of vaccination programmes. It was concluded that a vaccination programme consisting of primary vaccination in infancy and one revaccination 5 years later will secure continuous protection to about the age of 25 years. This is considerably simpler than programmes recommended in many countries, in which risk of hyperimmunization is apparent.

WHO documents related to tetanus immunization includes

Maternal and neonatal tetanus elimination by 2005. Strategies for achieving and maintaining elimination. UNFPA/UNICEF/ WHO. Geneva Nov 2000. Unpublished document WHO/V&B/02.09; available from Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland and on the internet at http://www.who.int/vaccines-documents/DocsPDF02/www692.pdf/www9563.pdf

Surgical care at the district-hospital level. WHO 2003-ISBN 92 4 154575 5, WHO 2003.

Field manual for neonatal tetanus elimination. Geneva 1999. Unpublished document WHO/V&B/99.14; available from Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland and on the internet at http://www.who.int/vaccines-documents/DocsPDF/www9563.pdf

Scientific advisory group of experts (SAGE). Replacing tetanus toxoid (TT) and diphtheria-tetanus toxoid (DT) with tetanus diphtheria (Td). GVP-CVI/SAGE.98/WP.04, 1998.

The immunological basis for immunization. Module 3: Tetanus. Geneva, 1993 (unpublished document WHO/EPI/GEN/93.13; available from Vaccines and Biologicals**,** World Health Organization, 1211 Geneva 27, Switzerland and on the internet at http://www.who.int/vaccines-documents/DocsPDF-ibi-e/mod3_e.pdf