The Effects of Maternal Malaria and HIV-1 Infection on the Effort to Eliminate Neonatal Tetanus

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(See the article by Cumberland et al., on pages 550–7.)

Tetanus results from infection with toxigenic strains of Clostridium tetani and has been estimated to have caused 213,000 deaths globally in 2002 [1]. An estimated 180,000 of these deaths occurred in neonates, and an additional 15,000–30,000 deaths occurred in women during the early postpartum period. C. tetani is a spore-forming, anaerobic bacillus capable of producing several toxins, including tetanospsamin, which blocks inhibitory neurotransmitters in the central nervous system, resulting in the typical muscle spasms of tetanus. Maternal tetanus results from the introduction of C. tetani spores during unclean delivery or abortion, and neonatal tetanus results from the use of unclean instruments to cut the umbilical cord or inappropriate cord care. Neonatal tetanus usually begins 3 days to 2 weeks after birth and is characterized by trismus, opisthotonic posturing, and generalized tonic seizures. Early signs include the inability to feed and irritability. The case fatality ratio ranges from as low as 10% with optimal intensive care to as high as 70% in some hospitalized infants. Without proper medical care, neonatal tetanus is almost always fatal.

Fortunately, tetanus can be prevented by neutralizing antibodies to tetanospsamin, achieved through active or passive immunization. Concentrations of neutralizing antitoxin antibodies exceeding 0.01 IU/mL have been shown to be protective, but low concentrations of antibody detected with standard EIAs do not correlate well with neutralizing antibodies, and the World Health Organization (WHO) considers 0.1–0.2 IU/mL to be the proper cutoff for protective antibody concentrations when these assays are used [1]. Protection requires multiple doses of tetanus toxoid (TT), a formaldehyde-denatured toxin that is adsorbed to aluminum or calcium salts to enhance immunogenicity [2]. TT is available as a single-antigen preparation but is commonly administered to children in combination with various preparations of diphtheria toxoid, pertussis vaccines, and other routinely administered childhood vaccines (polio, hepatitis B, and/or Haemophilus influenzae type b). Ideally, everyone should receive 5 doses of TT-containing vaccine during childhood (3 doses during infancy and booster doses at 4–7 and 12–15 years of age) and a sixth dose as a young adult, to provide lifelong protection.

Newborns are protected against neonatal tetanus by transplacentally acquired maternal antibodies. Active transfer of maternal antibodies begins at ~28 weeks of gestation, and antibody levels are lower in premature infants than in full-term infants. All IgG subclasses cross the placenta, but IgG1 is preferentially transported via placental Fc receptors [3]. Antigen-specific IgG levels in the newborn are often equivalent to, and sometimes exceed, maternal antibody levels. High-avidity antibodies may be preferentially transported across the placenta to the newborn [4].

Immunization with TT results in the prevention of ~800,000 deaths each year, but many more deaths could be prevented [5]. In 1989, the World Health Assembly endorsed the elimination of neonatal tetanus as a public health problem by 1995. Elimination is defined as the reduction of the number of cases of neonatal tetanus to <1 case/1000 live births in every district. Tetanus cannot be eradicated because C. tetani is found in the intestinal tract of animals throughout the world and because spores remain viable for many years in soil and dust. The recommended elimination strategies were slow to be implemented. In 1999, the Maternal and Neonatal Tetanus Elimination Initiative was launched.
by the WHO, UNICEF, and the United Nations Population Fund, and the target date for elimination of maternal and neonatal tetanus as a public health problem was extended to 2005. Strategies to achieve this goal included strengthening routine immunization services, promotion of clean deliveries, and the use of immunization campaigns (supplementary immunization activities) to provide 3 doses of TT to all women of childbearing age [6]. Between 1999 and 2005, an estimated 64 million women received at least 2 doses of TT. Despite these efforts, by the end of 2005, 49 of the 57 priority countries had not yet eliminated maternal and neonatal tetanus as a public health problem.

Many countries with limited progress in reaching the elimination target are in sub-Saharan Africa and Asia, regions of the world plagued by malaria and HIV-1. In this issue of the Journal, Cumberland et al. [7] report their findings that malaria and HIV-1 infection may contribute to the difficulties encountered in the effort to eliminate maternal and neonatal tetanus. Tetanus antibody levels were reduced by 52% in the cord blood of HIV-1-infected women and by 48% in the cord blood of mothers with active-chronic or past placental malaria. Scott et al. [8], using the same maternal-cord paired serum samples obtained from pregnant women in Kilifi, Kenya, found that cord blood from HIV-1-infected women had 35% lower levels of measles antibodies than did cord blood from HIV-1-uninfected women but found no association between measles antibody levels and placental malaria. Both studies were nested within a randomized, placebo-controlled trial of intermittent sulphadoxine-pyrimethamine to prevent severe anemia in pregnant women exposed to malaria [9], which reduced the incidence of parasitemia and anemia in the treatment arm. Other studies have demonstrated that maternal malaria [10] and HIV-1 infection [11] were associated with lower levels of measles antibodies in infants [12].

Prior studies have shown either no effect on [10, 13] or a reduction in [14] tetanus antitoxin antibody transfer to newborns associated with placental malaria. One strength of the study by Cumberland et al. was the categorization of placental biopsy samples as acute or chronic on the basis of the presence of malarial parasites and/or pigment. Placental malaria likely interferes with the active transport of IgG through inflammation and thickening of the basement membrane.

HIV-1 infection results in lower maternal antibody concentrations and reduced transfer of antibodies across the placenta. The mechanism for reduced transfer of antibodies has not been identified. Reduced antibody responses to primary immunization in HIV-1–infected children have been well documented [15]. HIV-1–infected adults usually acquire HIV-1 infection years after primary immunization, but HIV-1 infection is associated with accelerated rates of antibody decline [15]. Findings from different studies are inconsistent as to how well HIV-1–infected women respond to booster doses of TT [10, 16].

What are the implications of these findings with respect to efforts to eliminate maternal and neonatal tetanus? More children are at risk of neonatal tetanus than would be the case if HIV-1 infection and malaria were not such enormous public health problems. Increased efforts to control all of these diseases are needed. As noted by Cumberland et al., additional doses of TT-containing vaccines should be administered during childhood. Routine immunization services, including administration of TT-containing vaccines through school-based immunization programs and other supplementary immunization activities, should be strengthened to provide the necessary doses of TT during childhood. Increased efforts to promote neonatal health and clean deliveries, including appropriate care of the umbilical cord, could further contribute to a reduction in maternal and neonatal tetanus. Strategies to prevent malarial infection during pregnancy—such as insecticide-treated bed nets, intermittent presumptive malaria therapy during pregnancy, and increased access to antiretroviral therapy for HIV-1–infected women—can help mitigate the impact of malaria and HIV-1 infection on the placental transfer of protective antibodies to newborns. The global public health community should not lose sight of such an important goal as elimination of maternal and neonatal tetanus as a public health problem, and global efforts to alleviate the burden of malaria and HIV-1 infection can be part of this strategy.

References


