Maternal and neonatal tetanus

Martha H Roper[a], *Jos H Vandelaer*[b], *Fran çois L Gasse*[c]

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[a] M.H. Roper : Weybridge, VT, USA

[b] J.H Vandelaer: WHO Expanded Programme on Immunization, Department of Immunization, Vaccines, and Biologicals, Geneva, Switzerland; and UNICEF, Health Section, Programme Division, New York, NY, USA

[c] F L Gasse : UNICEF, Health Section, Programme Division, New York, NY, USA

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.

Tetanus in the first 28 days of life (neonatal tetanus) was long recognised by clinicians in resource-poor settings as an important cause of neonatal death. However, since babies affected by this disease usually are born at home and die there without registration of either event, the true burden was unknown. In the 1970s and 1980s, community-based surveys about neonatal tetanus from more than 40 countries showed that fewer than 10% of tetanus-related cases and deaths were routinely reported in most countries: in some regions, the reporting fraction was as low as 2–5%.[1,2] Estimates based on the results of these surveys, and tetanus data routinely reported to WHO suggested that, in the 1980s, more than 1 million deaths every year were attributable to tetanus, with an estimated 787 000 deaths in 1988 from neonatal tetanus alone.[1,3] In 1989, the worldwide public-health community made a commitment to the elimination of neonatal tetanus (defined as fewer than one case of neonatal tetanus per 1000 livebirths in all districts) by 1995.[3,4]

Maternal tetanus is defined as tetanus during pregnancy, or within 6 weeks of the end of pregnancy (whether pregnancy ended with birth, miscarriage, or abortion), and has the same risk factors and means of prevention as neonatal tetanus. In the early 1990s it was estimated to account for about 5% of maternal mortality, or 15 000–30 000 deaths every year.[5,6] In 1999, the elimination of maternal tetanus was added to the goals of the elimination programme for neonatal tetanus, and the initiative was renamed the Maternal and Neonatal Tetanus Elimination Program.[6]

Good progress has been made in the 15 years since the neonatal tetanus elimination programme began (figure 1). Worldwide mortality from neonatal tetanus was estimated at 180 000 in 2002, which represents a 78% reduction since the late 1980s.[13] This disease now accounts for 5–7% of worldwide neonatal mortality, compared with 14% in 1993.[14,15] Estimates of present incidence and mortality of maternal tetanus are unavailable; however, the number of deaths worldwide from this disease has probably undergone a commensurate reduction. In developed countries, tetanus is now little more than a medical curiosity; maternal and neonatal tetanus are exceedingly rare.[16,17] However, tetanus as a whole continues to cause about 213 000–293 000 deaths worldwide each year,[14,18,19] predominantly in low-income and middle-income countries. Deaths from maternal or neonatal tetanus are concentrated in 48 countries, mostly in Asia and Africa (figure 2).[20]

In this Seminar, we review general tetanus pathophysiology, clinical presentation, immunology, and the epidemiology, prevention, and control of maternal and neonatal tetanus, focusing on developing countries, where most cases and deaths take place.

Microbiology and pathophysiology

Tetanus is caused by a neurotoxin produced by *Clostridium tetani,* a gram-positive, obligate anaerobic rod-shaped bacterium that forms spores. *C tetani* spores worldwide as constituents of soil and in the gastrointestinal tracts of animals (including human beings), and can contaminate many surfaces and substances. The spores are extremely hardy; destruction requires autoclaving or prolonged exposure to iodine, hydrogen peroxide, formalin or gluteraldehyde.[21,22] Infection begins when tetanus spores are introduced into damaged tissue. Maternal and neonatal tetanus are caused by unhygienic methods of delivery, abortion, or umbilical-cord care. For germination and vegetative growth, the bacillus needs low tissue oxygen-reduction (redox) potential, such as that associated with necrosis; proliferation is enhanced by the presence of blood, foreign bodies, and chemicals such as lactic acid, calcium salts, and quinine.[21,23]

Tetanus toxin, the endotoxin responsible for tetanus, is one of the most potent toxins ever identified, with a minimum lethal dose of less than 2·5 ng/kg in human beings.[21,24] This high potency is caused by the toxin's absolute neurospecificity and enzymatic action.[25] Tetanus toxin is synthesised as an inactive polypeptide chain during the bacterial growth phase. The genes for the neurotoxin and its transcriptional regulator, ToxR, which is needed for toxin production, are located in an intracellular plasmid. At autolysis, after death of the bacterium, the toxin molecule is released and transformed by bacterial or tissue proteases into its active form: a 100 kDa heavy chain and a 50 kDa light chain. The heavy chain is necessary for binding to and entry into the neuron. The light chain is responsible for the toxic properties.[26–31]

The complex mechanisms for binding of tetanus toxin to peripheral neurons and its absorption into these cells, transport to the CNS, and toxic activity have been reviewed in detail elsewhere.[21,25,28,31–33] After its release, tetanus toxin diffuses to adjacent muscle tissue, where it binds to specific glycoproteins in lipid-raft microdomains of the plasma membrane of α motorneurons, and is absorbed by endocytosis. The lipid-raft constituents needed for the effective binding of tetanus toxin are not fully understood.[28,34] Free tetanus toxin also enters the lymphatic system and the bloodstream, disseminating widely before entering motor neurons at disparate sites. Inside motor neurons, tetanus toxin is transported to the CNS at 3–13 mm/h by a specific retrograde axonal transport system.[25,28,35] At the spinal cord and brainstem, the toxin diffuses across synaptic spaces to enter glycinergic and gabinergic inhibitory interneurons.[33,35]

Inside inhibitory interneurons, the disulphide bond connecting the heavy and light chains of the toxin is broken. The freed light chain is a zinc-endopeptidase that cleaves synaptobrevin proteins in synaptic vesicle membranes. Synaptobrevin is essential for the fusion of synaptic vesicles with the presynaptic nerve membrane; when this process is disrupted, synaptic vesicles accumulate at the nerve ending and are unable to release neurotransmitter into the adjacent synaptic space. The action of inhibitory neurons is thereby impeded, leaving α motorneuron excitation unopposed, and resulting in the muscle rigidity and longlasting painful spasms which are characteristic of tetanus.[21,29–33] In addition to its action on the motor system, tetanus toxin can have profound and life-threatening effects on the autonomic nervous system by interrupting spinal inhibitory sympathetic reflexes, resulting in a hyperadrenergic state.[21,33] The action of tetanus toxin within neurons persists for several weeks; the mechanism of functional recovery remains unclear.[21,33]

Clinical manifestations

Tetanus is characterised by muscle rigidity and painful muscle spasms caused by tetanus toxin's blockade of inhibitory neurons that normally oppose and modulate the action of excitatory motor neurons. Maternal and neonatal tetanus are both forms of generalised tetanus (the most common manifestation of the disease), and have similar courses. The time from inoculation of tetanus spores into damaged tissue to the appearance of the first symptom, or incubation period, is usually 3–21 days[36,37] (median 8 days[38,39]), although cases have been reported with incubation periods as short as 1 day, or longer than a month.[32,40] The average incubation period for neonatal tetanus (age at first symptom) is shorter than that of non-neonatal tetanus. About 90% of neonates with tetanus develop symptoms in the first 3–14 days of life, mostly on days 6–8, distinguishing neonatal tetanus from other causes of neonatal mortality which typically occur in the first two days of life.[37,41,42]

Tetanus muscle rigidity usually begins in the masseter muscles, resulting in trismus (lockjaw). Dysphagia and neck, shoulder, back, or abdominal muscle stiffness and pain are other common early symptoms. Risus sardonicus, a flat-lipped grimace resulting from tightened facial muscles is a pathognomonic finding, but can be subtle.[33,43] In neonatal tetanus, trismus and lip muscle rigidity interfere with normal sucking and feeding, which is the hallmark of disease onset.[44] As disease severity increases, muscle rigidity extends throughout

the body and muscle spasms begin, first in response to sensory stimuli but later progressing to spontaneous longlasting excruciating spasms of many muscle groups (figure 3). The onset period, or time from first symptom to first spasm, is typically 1–3 days, ranging from hours to 5 days.[37–39] In severe tetanus, sudden generalised tonic contractions of all muscle groups, or tetanospasms, result in opisthotonos, adduction of the shoulders, flexion of the elbows and wrists, and extension of the legs, usually accompanied by temperature rises of several degrees.[36] Consciousness is preserved, making tetanus a truly dreadful disease. Onset and disease progression are more rapid in neonatal tetanus than in non-neonatal tetanus, often taking hours instead of days, perhaps because axonal length, and thus the time for transport of toxin to the CNS, is shorter in young infants than in older children and adults.

Tetanus symptoms typically progress after the patient presents for medical care, despite aggressive treatment, because tetanus toxin being transported inside neurons is shielded from neutralising antibodies. In moderate and severe tetanus, respiratory compromise develops because of chest wall muscle rigidity and spasm, diaphragmatic dysfunction, airway obstruction from laryngeal or glottal spasm, or aspiration pneumonia.[45,46] Episodes of cyanosis and apnoea are common in uncontrolled severe disease. Before mechanical ventilation and effective agents to control muscle spasm were available, tetanus mortality was mainly caused by respiratory failure.[33,47]

Autonomic dysfunction leading to severe sustained or labile hypertension, hypotension, tachycardia, bradycardia, and arrhythmias can result in life-threatening haemodynamic instability and cardiac arrest. This sympathetic overactivity and catecholamine excess develops later in the disease course and has become an important cause of death in patients whose muscle spasms and respiratory function have been stabilised.[38,47–49]

In newborn babies, sepsis can accompany tetanus, exacerbating the severity of illness.[50–52] The hospital course of tetanus patients who survive is often protracted and complicated by pneumonia or other nosocomial infections. Other complications such as pulmonary embolism, decubitus ulcers, and contractures can result

from the lengthy debilitation and catabolic state that accompanies the disease.

Historically, survivors of neonatal tetanus have been few, and little attention has been paid to the long-term consequences of the disease. Although several studies assessing long-term sequelae of neonatal tetanus did not detect any abnormalities,[42,53,54] other studies identified neurological damage, ranging from cerebral palsy and severe psychomotor retardation to subtle intellectual and behavioural abnormalities.[55–60] These findings are plausible in view of the repeated hypoxic insults sustained during tetanus, especially in settings where drugs and equipment to control spasms and ventilation are scarce. The available case series and small studies describe neurological abnormalities or cognitive impairment in 4–50% of patients; severe disabilities are identified in 10–20%. The frequency of such complications might vary substantially in relation to availability and quality of medical facilities.

The prognosis of generalised tetanus is strongly predicted by the incubation and onset periods. Short incubation and onset periods correlate with increased disease severity and higher mortality.[33,37,38,40,42] Autonomic dysfunction also predicts high mortality, especially if it manifests early in the disease course.[38,61] The risk of death is highest for very young and very old patients. Neonatal tetanus mortality approached 100% in community-based surveys in the 1980s,[2,37] but is now 10–60% with hospital care.[62–64] Low birthweight might compound the risk of death.[65] Several classification systems,[32,33,66] based on incubation and onset, portal of entry of infection, disease severity at presentation, and other factors, predict prognosis in non-neonatal tetanus better than any one factor, and have been used for therapeutic decisionmaking.[32,33,66] Their true clinical utility is unclear; however, they provide a valuable objective approach to grouping patients participating in clinical tetanus research.

Overall case fatality rates for patients admitted to hospital with non-neonatal tetanus in developing countries are 8–50%; mortality increases with age.[38,39,67–72] Maternal tetanus has been associated with higher mortality in some series than has adult tetanus associated with other types of wounds.[37,39,71] Women with tetanus after abortion seem to have especially high mortality, perhaps because they might delay seeking medical care until later in their disease.[5] A history of previous tetanus immunisation, even if distant or incomplete, is associated with longer incubation periods, milder disease and decreased mortality than with no previous immunisation.[16,64,73]

The diagnosis of tetanus is made strictly on clinical grounds. Cultures of tetanus patients' wounds frequently fail to detect growth of *C tetani ;* moreover, the organism occasionally grows in cultures from patients without tetanus. Negligible serum tetanus antibody concentrations can support but cannot prove the diagnosis. The minimum tetanus antibody concentration conferring protection against disease or death in human beings has not been convincingly established.[74] Tetanus antibody concentrations in the conventionally accepted protective range (greater than 0·01 IU/mL by in vivo neutralisation assay or 0·10–0·16 IU/mL by ELISA) do not exclude the diagnosis; many tetanus cases, some fatal, have been reported in patients whose tetanus antibody levels were well above the protective threshold.[75–79] The differential diagnosis of tetanus includes other causes of trismus such as dental infections, tonsillitis, parotitis,

temporomandibular joint disease; strychnine poisoning, phenothiazine toxicity, stiff man syndrome, hypocalcaemia, CNS infections, and psychogenic tetanus. In neonates, tetanus must be differentiated from neonatal seizures, meningitis, and metabolic disorders such as hypoglycaemia and hypocalcaemia.

Treatment

The mortality and morbidity of tetanus patients admitted to hospital decreased substantially in the 1960s and 1970s, with the advent of mechanical ventilation and the introduction of benzodiazepines, with their high efficacy and wide therapeutic index. Mortality rates of less than 20% are increasingly common for both neonatal and non-neonatal tetanus if patients have the benefits of care in a modern intensive-care unit.[38,39,47,49,62,72] Even in settings with limited resources, if basic medication, experienced medical supervision, and high-quality nursing can be provided, mortality can be reduced to less than 50%.[42,63,80] The greatest impediment to improved survival of tetanus patients in developing countries is the lack of access to appropriate medical care.

The specific objectives of tetanus treatment are to stop the production of toxin at the site of infection with appropriate wound care and antibiotic use; to neutralise circulating toxin with antitetanus immunoglobulin; and to provide effective management of muscle spasm, respiratory failure, autonomic dysfunction, and complications that arise during the course of illness. Therapeutic approaches depend on the resources available in the facility to which the patient presents. Comprehensive reviews of tetanus management should be referred to for details of specific drug use.[32,33,81,82]

Immunology

Although some researchers have suggested that natural immunity against tetanus toxin can be induced by gut carriage of *C tetani,*[83–85] the serological and epidemiological evidence in support of this hypothesis is unconvincing.[22,74] The only reliable immunity against tetanus is that induced by vaccination with tetanus toxoid. Tetanus toxoid vaccine is one of the most effective, safe, stable, and inexpensive vaccines ever developed, and can be given safely during pregnancy and to immunocompromised individuals.[22,74] It is available as single-antigen vaccine and in many multiple-antigen preparations.

When handled and given properly, it provides highly protective, longlasting immunity against tetanus. Although mild local and systemic reactions to tetanus toxoid are common, serious adverse reactions are quite rare.

The duration of protection provided by tetanus toxoid immunisation depends on the total number of doses and the age at which they were received; the potency of the vaccine; and the underlying immune competency of the recipient. Antibody response to the first dose of tetanus toxoid develops slowly, and consists of non-neutralising IgM and small amounts of IgG antibodies; this response is insufficient to provide protection. After a second dose, about 90% of people develop protective antibody concentrations; however, a year after vaccination, the proportion of protected individuals drops to 80% or fewer. A third dose results in protection of at least 98% of recipients; the proportion of individuals protected remains high for several years. Subsequent boosters, even when given many years after a three-dose primary series, result in high quantities of effective antibody (figure 4).[22,74] The length of long-term protection after five or six doses is uncertain, but seems to be at least 20–25 years in populations receiving primary doses in infancy, and boosters in childhood and adolescence.[86–88] Recommended vaccination schedules vary by country. WHO recommends that at least five doses of tetanus toxoid vaccine be given over 12–15 years, starting in infancy; a sixth dose given in early adulthood is encouraged, to ensure longlasting protection.[13]

Newborn babies and young infants born to mothers with antitetanus antibodies are protected against tetanus by acquired maternal antibody. Maternal IgG is actively transported by the placenta into the fetal circulation, in a process mediated by IgG Fc-specific receptors on syncytiotrophoblast cells. Antibody transfer increases with gestational age, reaching maximum efficiency in the third trimester.[89,90] Two doses of tetanus toxoid are needed to ensure protection in previously unimmunised pregnant women and their newborn babies.[91–93] The longer the interval between doses, the greater the antibody response to the second dose; an interval of at least 6 weeks is recommended when feasible.[94] Maternal tetanus antibody transfer peaks at 60 or more days after the second dose, which should be given several weeks before delivery to ensure protective antibody concentrations in newborn babies.[94–96] The attainment of optimum timing of vaccine doses during pregnancy can be difficult in developing countries, where women often do not seek antenatal care until late in their pregnancies.[74,94] In recognition of practical constraints, WHO's five-dose tetanus toxoid schedule for previously unimmunised pregnant women and women of childbearing age provides recommendations for the minimum dosing intervals resulting in acceptable antibody levels (table).[13,97] A modified schedule, taking into account doses of tetanus toxoid received in infancy or childhood, has also been developed.[13,74]

Concerns have been raised that maternal malaria could affect neonatal protection by reduction of maternal response to immunisation or placental antibody transfer. In some studies, malaria infection has been seen to

decrease the antibody response to tetanus toxoid in children, although malaria chemoprophylaxis seems to preserve the response.[89,100] A study comparing pregnant women with and without malaria parasitaemia noted no difference in the antibody response to tetanus toxoid; however, all participants received chloroquine prophylaxis.[101] Studies investigating the effects of placental malaria on transplacental tetanus antibody transfer have had conflicting results: one showed reduced tetanus antibody concentrations in newborn babies of mothers with severe placental malaria,[102] yet two others detected no such effect.[103,104]

Most studies of the immune response to tetanus toxoid in H IV-infected patients have been done in children and non-pregnant adults. Infants and adults infected with HIV generally do mount a protective response to tetanus toxoid, but their antibody levels tend to be lower than those of uninfected controls, especially in those whose CD4 lymphocyte counts are less than 300 cells per µL. With disease progression, immune response and serum tetanus antibody concentrations decrease.[105–110] This blunted response suggests that H IV-infected individuals might need more frequent booster doses.[106,107] Placental transfer of tetanus IgG was significantly lower in H IV-infected Brazilian mothers than in uninfected controls,[111] a finding that was not replicated in a subsequent study in Malawi.[103] In both studies, all neonates had protective tetanus antibody concentrations.

Other factors affect transplacental maternal tetanus antibody transfer. Prematurity, severe maternal hypergammaglobulinaemia, and high maternal antitetanus IgG concentrations have been associated with reduced cord-maternal ratios of tetanus antibody, compared with controls,[90,111,112] although these findings have not been consistent.[103,104,111] Malaria, HIV, hypergammaglobulinaemia, and prematurity are factors that coexist in countries with a high burden of neonatal tetanus. Although the studies discussed above suggest that maternal tetanus antibody concentrations or placental transfer, or both, can be reduced in these conditions, in all but two studies[102,112] the relative reductions in tetanus antibody did not result in subprotective antibody concentrations in neonates. Thus, it seems that tetanus toxoid vaccine is usually sufficiently immunogenic to afford protection against maternal or neonatal tetanus, even in the presence of disorders affecting maternal and neonatal tetanus antibodies.

Distribution and risk

Maternal and neonatal tetanus cases are clustered in poor, remote, and disenfranchised communities where unhygienic obstetric and postnatal practices prevail, and access to maternal tetanus toxoid immunisation is poor. Differences in neonatal tetanus incidence and mortality of at least an order of magnitude have been identified between regions and countries, and between urban and rural areas within countries.[1,2,41,113] In industrialised countries, neonatal tetanus ceased to be a substantial problem by the mid-20th century: once tetanus toxoid vaccination became widespread, neonatal tetanus disappeared.[17,22] By contrast, mortality rates as high as 67–110 per 1000 livebirths were identified in rural populations in developing countries in the 1960s and 1970s,[41,92,114,115] with neonatal tetanus accounting for 50% or more of all neonatal deaths and 25% of infant mortality in some countries.[1,2,116] Although this situation has improved in the past 20 years, neonatal tetanus mortality rates of 23 and 82 per 1000 livebirths were detected in remote communities in the late 1990s.[117,118] 48 countries continue to have neonatal tetanus incidence rates of more than 1 per 1000 livebirths in some districts.[13]

Information about the incidence and distribution of maternal tetanus is based on more limited data than that available for neonatal tetanus. Both tetanus and maternal mortality are under-reported. Induced abortion is illegal in many countries, so resulting tetanus cases and deaths are even less likely to be reported than those resulting from childbirth. In studies from several Asian countries from the 1950s and 1960s, maternal tetanus accounted for 3–22% of all tetanus cases, with an overall average of 7%.[113] In a 1993 review of studies addressing maternal tetanus, tetanus-associated maternal mortality rates established in community-based studies ranged from 4–56 per 100 000 livebirths.[5] Tetanus was the cause of 0·2–10% of all maternal deaths, with an overall average of about 5%. Of reported cases of maternal tetanus, 27% took place after induced abortion.[5] In a subsequent community-based study from Bangladesh, where efforts to eliminate neonatal tetanus were underway, 1% of deaths in women aged 10–50 years were due to maternal tetanus, of which 35% were associated with abortion. In a related hospital record review, of women aged 10–50 years who died of tetanus, 55% developed tetanus after induced abortion and 5% after childbirth.[119]

Panel 1 summarises specific risk factors associated with maternal and neonatal tetanus. Many factors often coexist, compounding risk of those diseases. Home deliveries assisted by untrained birth attendants are the norm in many developing countries, especially in rural areas, and bring together many factors that confer a high risk of tetanus to both mother and child.[1,41,117,120–123,126] Postnatal cord treatment with contaminated traditional substances in the first few days of life has been identified with multivariate analysis as a particular hazard in case-control studies;[121,125,126,130,132] the use of such materials has been noted to negate the benefits of hospital deliveries.[140–142] Poverty, lack of maternal and paternal education, rural residence, young maternal age, and cultural restrictions on women's access to health services are all associated with unhygienic practices, low

antenatal care attendance, and inadequate vaccination with tetanus toxoid.[1,41,117,123,124,131,137,138] Lack of access to effective contraception and safe abortions are additional risk factors associated with tetanus from abortions.[5,119,127,143] Adolescents face special abortion-related risks because they frequently are not targeted for contraceptive services and tetanus toxoid vaccination, and might have increased difficulty in obtaining safe abortions because of societal prohibitions and cultural taboos.[143,144]

Prevention

Maternal and neonatal tetanus prevention relies on avoidance of unsafe delivery, abortion, and umbilical cord care practices, and promotion of maternal tetanus immunisation. The powerful effect that puerperal and umbilical stump hygiene have on prevention of neonatal tetanus is evident from the history of developed countries before the availability of tetanus toxoid. In the first half of the 20th century, neonatal tetanus in Denmark and the USA steadily decreased to 0·05 and 0·02 cases per 1000 livebirths, respectively, as health facility deliveries and hygienic obstetric and cord-care practices became widespread.[145,146] Even in rural regions of the developing world where home deliveries are common, concerted efforts to educate health workers and pregnant women about safe deliveries and care of neonates can result in substantial reductions in neonatal tetanus.[115,147,148]

A notable example is a controlled trial in Maasai villages in Kenya and Tanzania where a reduction in annual neonatal tetanus incidence from 80 to 0·75 per 1000 livebirths was achieved with the introduction of a programme promoting clean delivery practices, and the replacement of cow dung for postnatal umbilical-cord care by clean water or milk, both culturally acceptable and safer alternatives. The incidence of neonatal tetanus remained below 1·0 per 1000 per year in the intervention villages throughout a decade of observation, while remaining unchanged in control villages.[118] An analysis of interventions aimed at the improvement of neonatal survival estimated that 75–85% of deaths from neonatal tetanus could be prevented through the effective implementation of a family-based package of interventions that included clean home deliveries and hygienic cord care.[149]

The use of topical antimicrobials to replace traditional substances applied for cord care could have an important effect on neonatal tetanus in communities where high-risk cord care practices persist. Case-control studies in rural Pakistan documented reduced risk of neonatal tetanus in association with topical antibiotic use for cord and circumcision wound care.[125,130,136] Additional indirect suport comes from a randomised trial in Nepal that showed significant reductions in omphalitis and neonatal mortality with the use of chlorhexidine for postnatal cord care.[150] By contrast, clinical trials investigating the role of topical antimicrobials for cord care on neonatal illness and death have not shown any benefit in developed countries where aseptic obstetric and surgical practices prevail.[151,152]

Hygienic deliveries and cord care clearly reduce neonatal tetanus, and have the additional benefit of reducing maternal and neonatal sepsis caused by other bacterial pathogens. As important as these measures are for the improvement of maternal and neonatal survival, progress in developing the necessary infrastructure and behavioural changes needed to ensure safe deliveries and neonatal care has proven difficult to achieve, especially in the areas with the greatest burden of maternal and neonatal tetanus. Vaccination with tetanus toxoid to induce immunity against tetanus in both mother and newborn child is the most reliable way to prevent this disease.

The efficacy of tetanus toxoid for the prevention of neonatal tetanus was initially shown by two clinical trials undertaken in the early 1960s, in places with an annual neonatal tetanus incidence of about 80 cases per 1000 livebirths. In the first trial, three doses of fluid tetanus toxoid (without adjuvant; equivalent to about two doses of aluminium-adsorbed tetanus toxoid) had an efficacy of 94% for the prevention of deaths from neonatal tetanus;[114] in the second trial, no deaths from neonatal tetanus were seen in neonates born to mothers who had received two or three doses of aluminium-adsorbed tetanus toxoid within the previous 5 years.[92] Subsequent observational and case-control studies assessing the effect of tetanus toxoid on neonatal tetanus incidence or mortality have consistently noted vaccine effectiveness to be 80% or better,[74,115,131,153,154] except when subpotent tetanus toxoid vaccine was inadvertently used.[128] Although no studies designed to measure the effect of tetanus toxoid on maternal tetanus are available, a hospital-based study in Vietnam, where the vaccination of women has been vigorously promoted, showed a 90% reduction in tetanus in women aged 20–40 years.[39]

Control: the Maternal and Neonatal Tetanus Elimination Initiative

Tetanus toxoid vaccination of pregnant women to prevent neonatal tetanus was included in WHO's Expanded Program on Immunization a few years after its inception in 1974. By contrast with the notable gains in child immunisation achieved in the 1980s, only 27% of pregnant women were receiving at least two doses of tetanus toxoid by 1989 (figure 1).[155] In recognition of the substantial burden of neonatal tetanus in developing countries, the 1989 World Health Assembly (WHA) adopted a resolution to eliminate neonatal tetanus by 1995, through the increased availability of tetanus toxoid and clean deliveries, and improved surveillance.[4,156] The elimination of neonatal tetanus was defined as fewer than 1 case per 1000 livebirths in every district.[3] This definition also has been adopted as a proxy for the elimination of maternal tetanus.[6]

When the WHA called for global elimination of neonatal tetanus, 90 countries had mortality rates above the elimination threshold. In areas with reasonably well-developed health services, improvements in tetanus toxoid vaccination coverage were fairly easy to achieve, leading to a 25% reduction in worldwide deaths from neonatal tetanus by 1992 .[155] However, elimination activities continued to miss communities with a high burden of neonatal tetanus and poor access to routine health services. The high-risk approach was introduced to address this shortcoming (panel 2, figures 5 and 6).[9,157] Women of childbearing age living in areas where the risk of neonatal tetanus is high are immunised against tetanus in campaigns, which are accompanied by community education programmes and followed by strengthening of routine services for pregnant women.[6]

The high-risk approach is an economical method for the reduction of neonatal tetanus, despite the higher costs typically associated with mass vaccination campaigns. The cost of provision of three doses of tetanus toxoid to each woman, including supplies, operational costs, and education about safe delivery, is about US$1·20.[14] A study in Pakistan showed the cost-effectiveness of these campaigns in an area with a high incidence of neonatal tetanus (23 cases per 1000 livebirths per year). The cost of three rounds of tetanus toxoid vaccination was $117 per averted death and $3·61 per disability-adjusted life year (DALY) averted.[160] By contrast, the cost of scaling up to provide complete tetanus toxoid vaccination to unimmunised women of childbearing age on a widespread basis in south Asia and sub-Saharan Africa is $3·28–4·06 per woman, with an overall incremental cost per death averted of $271–394 ($14 per DALY averted).[161,162]

As cost effective as tetanus toxoid campaigns are, in the absence of external funding to support the supplemental activities, the implementation of the high-risk approach was weak in the countries most in need. As a result, the 1995 target date for global elimination of neonatal tetanus was not met. In 2000, WHO, UNICEF, and UNFPA formed a partnership to relaunch efforts towards this goal, adding the elimination of maternal tetanus as a programme objective, and setting a new target date of 2005. Worldwide deaths caused by neonatal tetanus had decreased by 75% to 200 000 every year (figure 1), with 90% of these deaths occurring in 27 countries, mainly in south Asia and sub-Saharan Africa. The focus of the renewed programme for elimination of maternal and neonatal tetanus was to assist the 57 countries (now 58, since East Timor has been established as an independent country) where maternal and neonatal tetanus persisted as a public-health problem.[6,14]

By February 2007, 40 countries had implemented tetanus campaigns in high-risk areas, targeting more than 94 million women, and protecting more than 70 million with at least two doses of tetanus toxoid. Ten of the 58 priority countries showed elimination of maternal and neonatal tetanus, as did seven Indian states.[20] Many countries still striving to achieve elimination have improved tetanus toxoid coverage in most districts and are close to meeting elimination criteria (figure 2). With available and pledged funding, the elimination of maternal and neonatal tetanus is expected in all but 11 countries by 2009.

Efforts are underway to estimate the present burden of neonatal tetanus, taking into account the progress in tetanus toxoid immunisation of women of childbearing age made through the many campaigns of the past few years. Despite increased awareness of neonatal tetanus, surveillance has not improved much, and reporting is still below 10% in countries in which this disease continues to be a substantial public-health problem.[6,163] Systematic community-based surveys of neonatal tetanus, like those undertaken in the 1970s and 1980s, have not been repeated since the initiation of the neonatal tetanus elimination programme. Thus, estimates of the burden of neonatal tetanus, and progress in its elimination, derive from mathematical models that compute the yearly incidence and mortality for each country using the baseline rate of neonatal tetanus before introduction of tetanus toxoid and promotion of clean deliveries, with adjustment for the estimated proportion of women immunised with tetanus toxoid and deliveries assisted by trained personnel.[2,3] Modelled estimates of neonatal tetanus burden probably provide reasonable approximations of continuing worldwide burden and the effect of activities to eliminate maternal and neonatal tetanus. However, variations in assumptions and data sources used in the modelling process have led to large differences in estimates, with broad uncertainty intervals that highlight the limitations of the available data.[2,164] Improved surveillance of maternal and neonatal tetanus, and systematic community-based surveys, are clearly needed to validate assumptions used in the models, and to improve the accuracy of present estimates of burden.

Sustaining elimination

Sustaining elimination of maternal and neonatal tetanus will be a challenge, especially in places where the high-risk approach is needed. Worldwide, 62% of deliveries are attended by trained personnel, with skilled attendant coverage of only 32% in the least developed countries. Antenatal care attendance (at least one visit) is far below 50% in many countries in which neonatal tetanus has yet to be eliminated.[165] Routine immunisation with tetanus toxoid has been stagnant over the past decade, with only 50–54% of pregnant women worldwide receiving adequate immunisation, a situation largely unchanged since the late 1980s (figure 1).[166] Although data for vaccine coverage underestimate the true proportion of protected women because of unregistered doses of tetanus toxoid, and the increasing number of women who received a primary series of tetanus toxoid-containing vaccine in infancy,[167] the continued need to increase the routine vaccination of women of childbearing age is indisputable.

The rejuvenated worldwide commitment to improvement of maternal and child health, and special attention to the importance of neonatal survival, catalysed by the child and maternal mortality Millennium Development Goals (MDG4 and MDG5), is heartening.[168] Many initiatives and partnerships have been developed to ensure that effective and affordable interventions are successfully applied, in an integrated continuum-of-care framework that recognises the important inter-relationships between maternal, neonatal, and child health.[169–171] The proposed packages of interventions include improved antenatal care, tetanus toxoid immunisation of mothers, and promotion of hygienic delivery and postpartum cord-care, all of which will directly contribute to prevention of maternal and neonatal tetanus.[149,172] Similarly, the Global Immunization Vision and Strategy, launched by WHO and UNICEF in 2005, includes strategies to increase routine tetanus toxoid coverage in hard-to-reach, previously underserved populations that will contribute to the expansion and maintenance of maternal and neonatal tetanus elimination strategies.[173] If the WHO recommendations for booster doses of tetanus toxoid in childhood and adolescence can be widely implemented, the need for repeated doses during pregnancy will be reduced, increasing the likelihood that elimination can be sustained.[13] Since *C tetani* cannot be removed from the environment, continued worldwide elimination of maternal and neonatal tetanus will depend on universal access to immunisation and health services.

Conflict of interest statement

MR worked as a consultant for WHO on this subject and other work related to tetanus and neonatal tetanus. JV is a staff member of UNICEF seconded to WHO. FG is a staff member of UNICEF. WHO and UNICEF are major partners in the Maternal and Neonatal Tetanus Initiative. No external funding was used to support this work. The authors alone are responsible for the views expressed in this publication; they do not necessarily represent the decisions, policy or views of WHO or UNICEF.

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Search strategy and selection criteria

We searched PubMed without date or language restrictions for the terms: “tetanus”, “Clostridium tetani”, “tetanus toxin”, and “tetanus toxoid”, alone and in combination with relevant secondary terms (“physiopathology”, “therapy”, “diagnosis”, “complications”, “mortality”, “immunology”, “neonatal” “maternal”, “epidemiology”, and “prevention and control”). Additional references were identified from citations in articles retrieved in the initial search. We searched the Cochrane database for “tetan us”. We also searched WHO’s website and electronic library for the terms “tetanus” and ‘neonatal tetanus”. Articles were selected for their importance and relevance to the understanding of maternal and neonatal tetanus. Preference was given to articles published in the past 10 years.

Figure 1: Estimated deaths from neonatal tetanus and vaccine coverage with two doses of tetanus toxoid, 1980–2005[3,7–12]

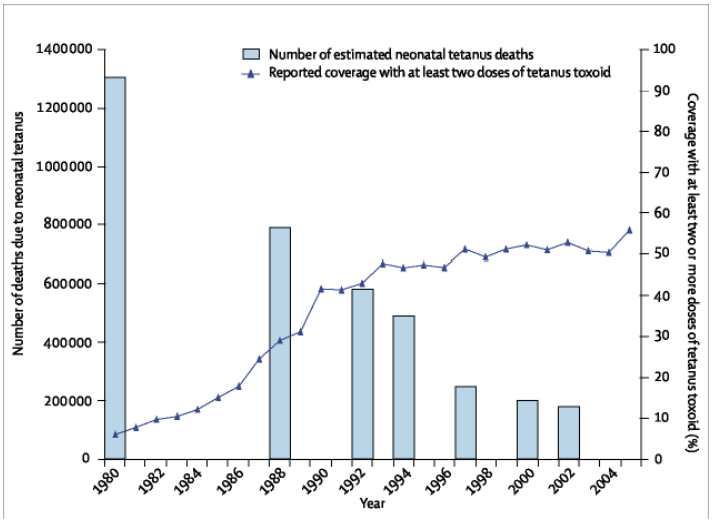


Figure 2: Maternal and neonatal tetanus elimination status by country

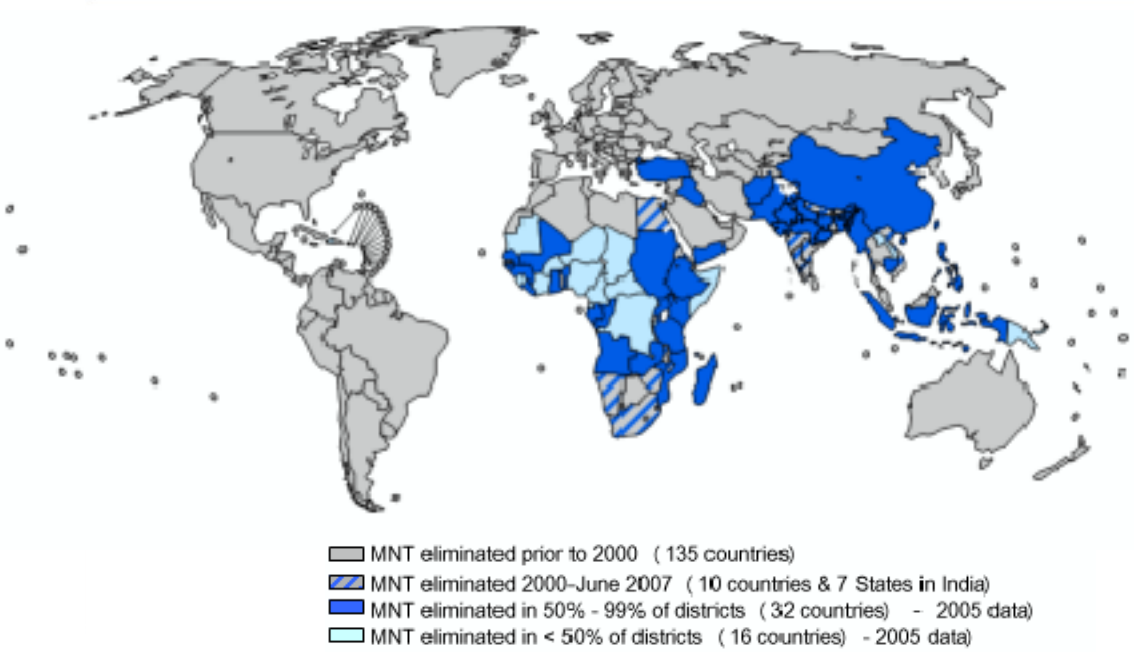


Figure 3: Photograph of newborn child with neonatal tetanus

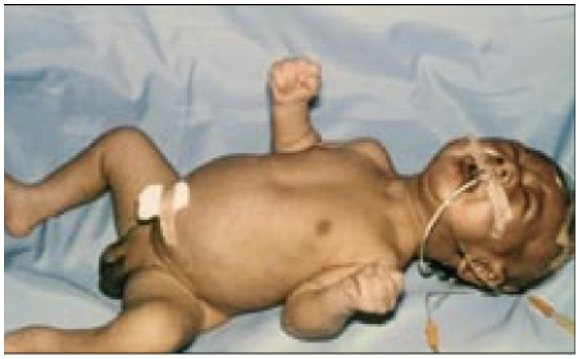


Figure 4: Antibody response to tetanus toxoid (74)

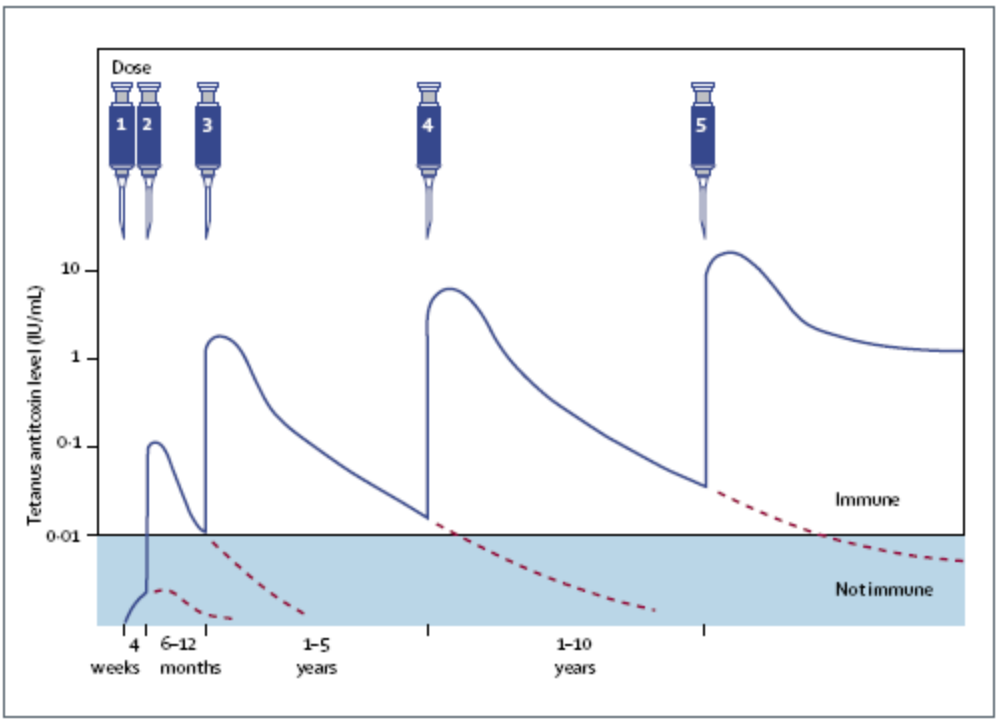


Figure 5: Algorithm fro identification of districts at high risk of maternal or neonatal tetanus (6)

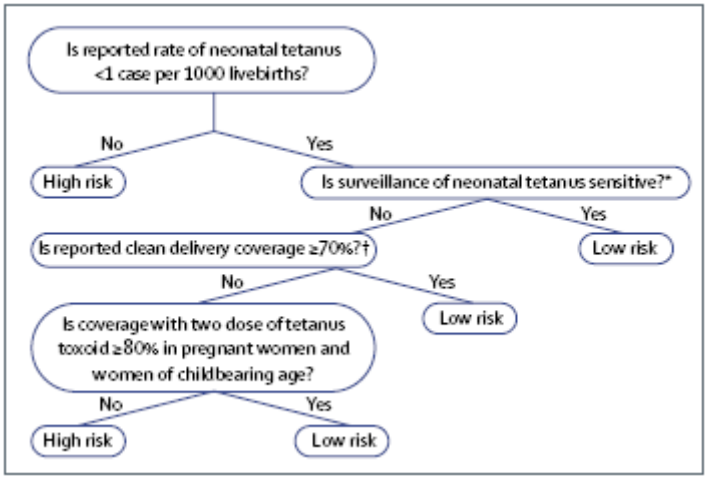
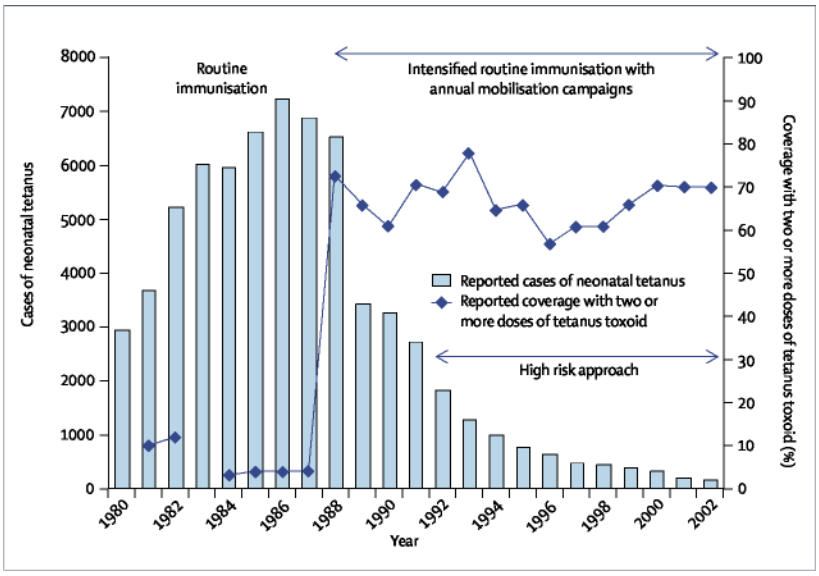


Figure 6: Effect of the high-risk approach in Egypt (Adapted from reference 9)



Panel 1: Risk factors associated with neonatal and maternal tetanus

Factors associated with unsafe procedures

- Deliveries or medical procedures done outside health-care facilities*[5,120–122†,123,124]
- Birth attendants without medical training*[5,120†,122†,123,125†,126†,127]
- Unclean hands* and instruments*[120†,123,127–131†]
- Dirt,* straw,* or other unclean materials as delivery surface[117†,120†,129†]
- Animals kept inside or adjacent to home (for home deliveries)[117†,123]
- Animal dung used for fuel[126†,129]
- Traditional substances used during labour, delivery, or abortion (ie, cow ghee* and other animal or vegetable oils,* juices or herbs)[121†,124,127,128†,129†,132†]
- Traditional substances used for umbilical cord care (ie, cow dung,* rat faeces, cow ghee, other oils or juices, herbs, ash,* surma,* soil, sand)[121†,122†,124,126†,130†,133†,134]
- Neonates swaddled in animal dung* or soil[129†,135]
- Traditional neonatal surgeries (ie, circumcision, ritual scarification, ear piercing, uvulectomy)[124,136†]

Immunisation-related factors

- Absent or incomplete immunisation with tetanus toxoid[120†,123,130†,131†]

Factors associated with unsafe procedures or incomplete immunisation, or both

- Poverty*[117†,123,137†]
- Absent or poor maternal* or paternal education,* or both[117†,121†,123,131†,137†]
- Poor antenatal-care attendance*[123,124,131†,137†]
- Young maternal age or first pregnancy,* or both[120†,123,137†]
- Cultural constraints to women's movements and contacts[124,138]

Other factors

- Death of a previous child in a family from neonatal tetanus (predictive of subsequent cases)*[122†,125†,126†,128†]
- Male sex (increased risk of neonatal tetanus)‡[2]

Specific factors can be related to unsafe delivery, abortion, or cord-care practices, or to inadequate immunisation with tetanus toxoid, or both. *Identified as independent risk factors for neonatal tetanus by multivariate analysis. †References for studies using multivariate analysis to identify independent risk factors. ‡Inconsistent findings in community-based and hospital-based studies; unclear if related to differential cord care, maternal recall, or medical-care seeking for males,[1,22,136] or because of a

biological difference between boys and girls

Panel 2: The high-risk approach

Since its inception in 1990 the neonatal tetanus elimination initiative has stressed focus on communities traditionally missed by routine immunisation and maternal and child health services, because of geographical and sociocultural barriers to health-service access. These high-risk communities typically have a disproportionately high neonatal tetanus burden, and high infant and maternal mortality in general. As the programme matured, guidelines were developed for systematically identifying high-risk districts or areas with the algorithm in figure[5,6,158]

Core indicators for identification of high-risk areas include data from tetanus surveillance, clean delivery coverage, and the proportion of women who received at least two doses of tetanus toxoid in their last pregnancy, or the proportion of women whose last child was protected at birth on the basis of their mother's vaccination history. Since the reliability of core indicator data varies, surrogate indicators such as the proportion of deliveries that take place in health-care facilities, availability of trained delivery attendants, antenatal care attendance, and infant coverage with three doses of diphtheria-tetanus-pertussis vaccine are also used to help classify and prioritise districts needing intensive efforts.[6,158]

After high-risk areas have been selected, supplemental immunisation activities are organised, targeting all women of childbearing age (usually 15–45 years) with three doses of tetanus toxoid. Additionally, educational programmes and materials stressing the importance of immunisation against tetanus, and hygienic delivery and cord-care practices, are developed specifically for the targeted communities. After these campaigns, efforts are made to systematically strengthen routine immunisation and perinatal services.[6,158]

When done successfully, such campaigns result in a rapid reduction in neonatal tetanus cases and deaths. Because efforts are focused on a relatively small number of communities with high burden of neonatal tetanus, the reductions in the disease are often more striking than improvements in national tetanus toxoid coverage rates.[6,158] Figure 6 shows the effect of the high-risk approach in Egypt.[6,159]

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