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# Tetanus toxoid vaccine

## Elimination of neonatal tetanus in selected states of India

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**Tetanus is caused by a neurotoxin produced by *Clostridium tetani (C. tetani),* a spore-forming bacterium. Infection begins when tetanus spores are introduced into damaged tissue. Tetanus is characterized 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 (MNT) are caused by unhygienic methods of delivery, abortion, or umbilical-cord care. Maternal and neonatal tetanus are both forms of generalized tetanus and have similar clinical courses. 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 during the first two days of life. Overall case fatality rates for patients admitted to the hospital with neonatal tetanus in developing countries are 8–50%, while the fatality rate can be as high as 100% without hospital care. Tetanus toxoid (TT) vaccination of pregnant women to prevent neonatal tetanus was included in WHO's Expanded Program on Immunization (EPI) a few years after its inception in 1974. In 2000, WHO, UNICEF, and UNFPA formed a partnership to relaunch efforts toward this goal, adding the elimination of maternal tetanus as a program objective, and setting a new target date of 2005. By February 2007, 40 countries had implemented tetanus vaccination campaigns in high-risk areas, targeting more than 94 million women, and protecting more than 70 million subjects with at least two doses of TT. In 2011, 653 NT cases were reported in India compared with 9313 in 1990. As of February 2012, 25 countries and 15 States and Union Territories of India, all of Ethiopia except Somaliland, and almost 29 of 34 provinces in Indonesia have been validated to have eliminated MNT.**

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Tetanus is caused by a neurotoxin produced by *C. tetani,* a gram-positive, obligate anaerobic rod-shaped bacterium that forms spores. *C. tetani* spores are distributed 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.[1,2] 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 in tissue, the bacillus needs low 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.[1,3] Tetanus toxin, the endotoxin responsible for tetanus, is one of the most potent toxins ever identified, with a minimum human lethal dose of < 2.5 ng/kg.[1,4]

Tetanus is characterized by muscle rigidity and painful muscle spasms caused by the toxin's blockade of inhibitory neurons that normally oppose and modulate

the action of excitatory motor neurons. MNT are forms of generalized 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[5,6] (median 8 days[7,8]), although exceptional cases have been reported with incubation periods as short as one day or longer than a month.[9,10] 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.[6,11,12]

Tetanus muscle rigidity usually begins in the masseter muscles, resulting in trismus (lockjaw). Dysphagia, 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.[13,14] In neonatal tetanus, trismus and lip muscle rigidity interfere with normal sucking and feeding, which is the hallmark of disease onset.[15] 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 long-lasting excruciating spasms of many muscle groups. In severe tetanus, sudden generalized 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.[16]

Overall case fatality rates for patients admitted to hospital with neonatal tetanus in developing countries are 8–50%, while the fatality rate can be as high as 100% without hospital care.[17] The true extent of the tetanus death toll is not known, since many newborns and mothers die at home and neither the birth nor the death is reported. MNT cases are clustered in poor, remote, and disenfranchised communities where unhygienic obstetric and postnatal practices prevail, and access to maternal tetanus toxoid immunization 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.[18] In industrialized countries, neonatal tetanus ceased to be a substantial problem by the mid-20th century: once TT vaccination became widespread, neonatal tetanus disappeared.[19,20] By contrast, mortality rates as high as 67–110 per 1,000 live births were identified in rural populations in developing countries in the 1960s and 1970s,[21,22] with neonatal tetanus accounting for 50% or more of all neonatal deaths and 25% of infant mortality in some countries. However, this situation has improved in the past 20 years.[23]

MNT is easily preventable through:[24]

- Immunization of women with TT vaccine for protection against Tetanus _ a child born to a woman protected against tetanus is also protected from the disease in the first few months of life
- Hygienic birth practices to assure that infection is not contracted by mother or newborn during the birth process
- Proper cord care to ensure that contamination of cord does not put the newborn at risk

MNT prevention relies on avoidance of unsafe delivery, abortion, and umbilical cord care practices, and promotion of maternal tetanus immunization. The powerful effect of puerperal and umbilical stump hygiene in the prevention of neonatal tetanus is evident from the history of developed countries before the availability of TT vaccine.

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 1,000 live births was achieved with the introduction of a program 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 < 1.0 per 1,000 per year in the intervention villages throughout a decade of observation, while remaining unchanged in control villages.[25]

The efficacy of TT vaccine 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 1,000 live births. In the first trial, three doses of TT vaccine (without adjuvant; immunologically equivalent to two doses of aluminum-adsorbed tetanus toxoid) had an efficacy of 94% for the prevention of deaths from neonatal tetanus. Anti-tetanus-toxin antibodies are actively transported by the placenta from an immunized mother to her fetus, providing passive protection against tetanus during the neonatal period and the following month or two of life. Maternal and neonatal anti-tetanus antibody concentrations at the time of delivery are usually similar.[26]

TT vaccination of pregnant women to prevent neonatal tetanus was included in the EPI) a few years after its inception in 1974. By contrast with the notable gains in child immunization achieved in the 1980s, only 27% of pregnant women were receiving at least two doses of TT vaccine by 1989.[27] 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 TT vaccine, clean deliveries, and improved surveillance.[28]

In 2000, WHO, UNICEF, and UNFPA formed a partnership to relaunch efforts toward this goal, adding the elimination of maternal tetanus as a program objective, and setting a new target date of 2005. Worldwide deaths caused by neonatal tetanus had decreased by 75% to 200,000 per year, with 90% of these deaths occurring in 27 countries, mainly in south Asia and sub-Saharan Africa. The focus of the renewed program for elimination of MNT was to assist the 58 countries where maternal and neonatal tetanus persisted as a public-health problem.[29]

By February 2007, 40 countries had implemented TT vaccine campaigns in high-risk areas, targeting more than 94 million women, and protecting more than 70 million with at least two doses of vaccine. Ten of the 58 priority countries showed elimination of maternal and

neonatal tetanus, as did seven Indian states.[30] Yet according to the Child Health Epidemiology Reference Group (CHERG) estimates from 2008, an estimated 59,000 newborns die of the disease each year;[31] this translates into ~164 deaths in children under one month of age every day or one death every 9 min. Several thousand mothers are also estimated to die of maternal tetanus. Many countries still striving to achieve elimination have improved vaccine coverage in most districts and are close to meeting elimination criteria. The goal of the initiative is to eliminate MNT through focus on the TT-Supplementary Immunization Activities (SIA). MNT elimination in a country is defined as neonatal tetanus rate of less than one case of neonatal tetanus per 1,000 live births in every district of the country.

UNICEF and WHO's role in this global effort is:

- To advocate with partners including the national governments to commit to the goal of MNT elimination and support it through allocation of needed resources
- To raise fund for the initiative to meet the gaps in funding needs for the target countries
- To support national ministries of health in preparing technically and financially sound plan
- To procure and deliver the TT vaccines and injections supplies for the campaigns and ensure cold chain maintenance
- To provide technical assistance for implementation of high quality campaigns
- To monitor progress toward MNT elimination
- To validate (usually through community-based mortality surveys) whether the elimination level has been reached in a country following the country's claim of elimination.
- To work with countries on strategies for maintaining MNT elimination including strengthening of routine immunization.

## Progress Between 1999 and February 2012[31]

Through the joint efforts of partners much progress has been made between 1999 and February 2012. More than 90 million women have been immunized with two or more doses of TT vaccine:

- 25 countries (Bangladesh, Benin, Burundi, Burkina Faso, Comoros, Egypt, Eritrea, Ghana, Liberia, Malawi, Mozambique, Myanmar, Namibia, Nepal, Rwanda, Senegal, South Africa, Republic of Congo, Rwanda, Togo, Turkey, Uganda, Vietnam, Zambia, and Zimbabwe), and 15 States and Union Territories of India, all of Ethiopia except Somaliland, and almost 29 of 34 provinces in Indonesia have been validated to have eliminated MNT.
- As of 2008, approximately 90% reduction of Neonatal Tetanus mortality had been achieved in the past 20 y.

Since 1983 in India, the nationwide EPI policy has been implemented to provide two doses of TT vaccine to all pregnant women (preferably the first dose as soon as pregnancy is detected and the second dose one month after the first dose) during each pregnancy (one dose is provided if < 3 y have passed since the previous pregnancy, and this is designated as TT-Booster).[32] The policy aims at preventing MNT. This policy, along with the establishment of hospitals and primary health centers where clean deliveries can be performed and the deployment of trained auxiliary nurse-midwives and other trained birth attendants, has contributed to reducing the burden of NT in India. In 2011, 653 NT cases were reported in India compared with 9313 in 1990.[33]

However, the true neonatal tetanus burden in India is substantially higher than the numbers reported. Additionally, under the National Rural Health Mission (NRHM), launched in 2005, the Government of India is in the process of providing training to medical officers at primary health centers and to auxiliary nurse-midwives to enable them to become skilled birth attendants; the mission also encourages institutional deliveries through interventions such as the "Janani Suraksha Yojana" ("Mothers' protection scheme").[34]

By February 2012, nearly 50% of Indian States have been validated to have eliminated MNT. This progress is due to the increase in use of TTs vaccines in the routine immunization program, the implementation of tetanus immunization campaigns to increase protection levels among women of reproductive age living in high-risk areas, and better use of skilled birth attendants. Sustaining elimination will require improvements in health service infrastructures and universal access to health services. One of the milestones, i.e., elimination of neonatal tetanus, is being achieved by some states of India through the MNT elimination program. The rest of the Indian states should follow such strategies and strengthen tetanus immunization coverage so that lives of mothers and children can be saved.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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