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# Global Tetanus Elimination How Far How Near

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## ABSTRACT

Tetanus is a worldwide disease which cannot be eradicated, like smallpox and poliomyelitis, because of the persistence of the causative organism Clostridium tetani in the environment. Three clinical pictures are reminded: local tetanus, generalized tetanus and neonatal tetanus. Disinfection of the traumatic site, injection of specific antiserum and toxoid administration must be generalized if this disease is to be eliminated. Protection is best measured by mouse seroneutralization consisting of measuring the serum dilution protecting mouse against toxin lethal effect. This technique is in many countries forbidden because of the recent laws against death in tested animals. Spontaneous immunity has not been shown following soles cuts in peasants in Cambodia walking barefoot in contact of cow's dung around their dwelling. The decrease of tetanus cases is difficult to assess in general and newborn population but toxoid vaccine coverage is increasing following extended programme on vaccination in action since 1974. Improvement will follow better vaccines, better sensitization of population and the increased use of fast blood testing in at-risk patients.

**Keywords**: Tetanus, Tetanus elimination, Seroneutralization

## OBJECTIVES

To review the challenges of tetanus elimination programs.

## TETANUS CLINICAL DESCRIPTION

Tetanus is a unique infectious disease because it is not communicable. *Clostridium tetani*, the causative agent, is ubiquitous in the environment and is also present in digestive tract of many humans [1] and animals (especially herbivores like cows and horses) harboring and excreting its spores [2]. *C. Tetani* spores growing in anaerobic milieu give bacilli, which produce a Tetanus NeuroToxin (TeNT): Tetanospasmin. *C. Tetani* spores can contaminate necrotic wound injuries of any kind: burn, ulcer, abscess, tattoo, circumcision, sites of needle injection, notoriously in intravenous drug users [3,4]. Tetanus is known since Antiquity (Egypt, Greece: Hippocratus) [5], and must be diagnosed clinically in absence of a specific laboratory test [6,7].

Three clinical pictures are described [8]

1. **Localized tetanus**: Spasm of muscles in a confined area close to the site of infection
2. **Generalized tetanus**: With the diagnostic occurrence of spasm of mastication: trismus (lockjaw), after excluding teeth or jaw abscess. Spasm of facial muscles gives "risus sardonicus" with raised eyebrows, tight closure of eyelids, wrinkling of the forehead and extension of the corners of the mouth laterally. Neurologic and vegetative symptoms are dysphagia, labile blood pressure, paralysis of respiration, glottis spasm, dyspnea, urinary retention, constipation, occurring after even benign surgical interventions in unprotected seniors [9].

Severe cases see extension of spasm to neck, thorax, abdomen, back, and extremities, giving acute arching of the patient ("opisthotonos"). Fractures of vertebrae and long bones, along many neurologic sequelae, may follow in survivors, who, often admitted in a dedicated Intensive Care Unit (ICU), escape from a fatal incidence of 40-80% [8].

3. **NeoNatal Tetanus (NNT)**: Occurs in newborn infants of mothers not giving sufficient circulating tetanus antibodies to protect the infant passively. Delivery occurs with infection by *C. tetani* of newborn's umbilical stump, often after its unclean scission by contaminated instrument [10]. The NNT notification to Health Authorities is easy [11], with a newborn infant

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sucking normally at birth followed by appearance (after a 0-28 days delay) of inability to suck milk, generalized convulsions and suffocating apnea, until death occurs in 95% of cases, if not admitted urgently to a neonatal ICU [8].

## TETANUS SERO-PROTECTION

After bloody battles, during 19th century, tetanus was frequent in wounded soldiers. *C. Tetani* was isolated by Carle [12] in Italy and Nicolaier [13] in Germany. Von Behring and Kitasato, in Germany, produced, by repetitive TeNT injection in horses, a protective serum "Horse Tetanus Serum" (HTS), administered to wounded soldiers during World War 1 (WW1) [14].

Now Human Tetanus Immune Globulin (HTIG) is produced by repeated tetanus vaccination and bloodletting of human volunteers. It has a much better tolerance than less expensive HTS [15].

It's in Quebec [16] and France [17], that the formaldehyde action on TeTT gave the active vaccine: Tetanus Toxoid (TT) for at-risk rural population. Soldiers, in Allied Forces during WW2, showed an excellent protection after a 3 doses schedule [18,19].

TeNT is active on neurologic system at minute amount, not giving immunological protection after disease [20]. To measure sero-protection against tetanus, mice were used because of their extreme sensitivity to TeNT and their low body volume.

The reference test is mice Seroneutralization (SN). After injection of fixed volume of WHO-calibrated TeNT, thoroughly mixed with fixed titers of diluted human sera, the titer of mice seroprotection against death gives a direct biological titration of protection against TeNT. This technique has been used, after Condrea [21], Knerr [22] and Istrati [23], by Ipsen in Germany during WW2, [24]. This technique, widely used, was recently used in Vietnam by Schlumberger because of the restriction of testing mice to death in many countries on ethical grounds [25]. The level of 0.01 WHO International Unit (IU) is still the reference antibody titer for protection.

Indirect methods: Radio Immuno Assay, Hemagglutination [26-28], Indirect ELISA [25,29-31], often with double-antigen, were shown to be less specific and sensitive than SN. Toxi-Binding test [32], Rapid Quantitative micro-enzyme linked Immunosorbent assay [33], and colorimetric Quick diagnostic test, were used to assess protection of at-risk surgical attendants [34,35]. These fast-tests were shown to be equally sensitive but however less specific than SN [36], giving the risk with false-positive reactions of not administering TIG to tetanus unprotected patients.

Treatment includes, besides Tetanus wound cleansing, debridment of the traumatic area, administration of TT and HTIGT/EGT, antibiotics to kill vegetative *C. Tetani* bacteria (Bactrim at high doses, Cephalosporins) and drugs to control spasms (Valium at high doses, morphine, Phenothiazide, Curare) with intubation and anesthesia, in ICU providing solutes, nutrients and oxygen support [8].

Indirect testing methods: Radio Immuno Assay, Hemagglutination [26-28], Indirect ELISA [29-31], were shown to be less specific and sensitive than SN. Toxi-Binding test [32], Rapid Quantitative micro-enzyme linked Immunosorbent assay [33] as Quick Diagnostic test, are easier to perform and, were used to assess in ICU seroprotection of tetanus at-risk attendants [34, 35]. They were shown, against SN to be equally sensitive but less specific [36], with the risk of not administering TIG to false positive tetanus patients.

## TETANUS ELIMINATION

### Neonatal tetanus

Starting in 1990 the WHO objective was to get less than 5 NNT/10,000 population/year in newborns. The objective was delayed to 1995, 2000 and 2010 and modified to include Maternal Tetanus elimination: Maternal Neonatal Tetanus (MNT). The number and causes of NNT cases, by country still notifying NNT cases, is approximated in a recent study to 5/10,000/year [37].

### Elimination of tetanus in other age-groups

Knowing the low report of cases and death in the underdeveloped part of the world, especially in conflict areas [38], deaths from tetanus has been approximated to 50,000/year [39]. Instead, it has been suggested to better estimate Extended Programme on Immunization (EPI) coverage [40], better reported by Ministers of Health (MOH) to WHO which initiated it in 1974 [41]. EPI concerned now, in 2022, a large proportion of the general population in all countries. Tetanus is however still reported in developed countries in unimmunized children, due to parent's reluctance to vaccinate offspring [42].

## DISCUSSION

### Methods

SN is the more sensitive and specific method to determine even very low amount of tetanus antibodies. This has been recognized in many studies. However, due to ethical laws on experimentation on animals, this type of study will be very difficult to perform [43].

In most countries the NNT incidence samples use the technique of "Low Quality Assurance System" (LQAS), with a much reduced sample size, analyzing reports at Health Center level, in a district, instead of questioning all the families of the district [44] or with a random bi-variate sample at the national population level [45], as suggested by Henderson [46].

**Results**

NNT incidence is under-reported by WHO, as shown in NNT studies conducted at district level in Cambodia [44] and at national level in Niger [45], showing that 95% of cases were unreported to MOH. Contrary to many experts, the spontaneous tetanus seroconversion, from Cambodian peasants with barefoot soles contaminated by *C. Tetani* spores coming from cattle dung scattered under their house [47] was not demonstrated in a retrospective study [48], as suggested by Veronesi [49]. Of course a prospective study with a control group not vaccinated is unethical.

Tetanus, as a disease we cannot eradicate, shows a graduate, but difficult to measure, decline of cases, contrary to infectious diseases which can be eradicated, like smallpox and poliomyelitis, but we see resurging.

## RECOMMENDATIONS

1. Use better epidemiological techniques to certify NNT and tetanus elimination.
2. Improve quality of tests and vaccines. The better analysis of modes of action of TeNT should increase of value of diagnostics tests and vaccines, with the aim of using a "one shot" tetanus vaccine, as formerly suggested [50]. The better use of ELISA "double antigen" method should be generalized in epidemiological studies. With better understanding of antibodies against TeNT, the quality of vaccines will be improved meaning better seroprotection.
3. Improve quality of rapid-tests to better check-up protection of at-risk patients. Notoriously elderly population is notorious to, often, refrain to receive tetanus booster.

## CONFLICT OF INTEREST

The author declares that there is no conflict of interest regarding the preparation of this manuscript.

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