Advances in Vaccines & Vaccination Research
AVVR, 5(1): 141-145
www.scitcentral.com

ISSN: 2688-6545

Review Article: Open Access

Global Tetanus Elimination How Far How Near

Martin Schlumberger*

*AGIRabcd, 40 rue Letort, 75018, Paris, France.

Received September 15, 2022; Revised September 23, 2022; Accepted September 26, 2022

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

Corresponding author: Martin Schlumberger, AGIRabcd, 40 rue Letort, 75018, Paris, France, Tel: +33625333591; E-mail: mschlumberger@wanadoo.fr

Citation: Schlumberger M. (2022) Global Tetanus Elimination How Far How Near. Adv Vaccines Vaccin Res, 5(1): 141-145.

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.

REFERENCES

1. Kerrin JC (1929) The distribution of Cl. Tetani in the intestines of animals. Br Med J 1929: 370-373.
2. Bauer JH, Meyer FK (1926) Human intestinal carriers of tetanus spores in California. J Inf Dis 38: 295-305.
3. Abrahamian S (2000) Fatal tetanus in a drug abuser with protective anti-tetanus antibodies. J Emerg Med 18: 189-193.
4. Cherubin CE (1968) Clinical severity of tetanus in narcotic addicts in New York City. Arch Inter Med 121:156-158.
5. Bleck TP, Brauner JS (2004) Tetanus, In: Scheld WM, Whitley RJ, Marra CM (eds). Infections of the Central Nervous System. 3rd ed. Philadelphia: Lippincott, William and Wilkins pp: 625-648.
6. Sanford JP (1995) Tetanus-forgotten but not gone [editorial]. N Engl J Med 332: 812-813.
7. Bleck TP (1987) Tetanus: Dealing with the continuing clinical challenge. J Crit Illness 2: 41-52.
8. Kascher JA, Mathisen G (2007) Acquiring tetanus after hemorrhoid banding and other gastrointestinal procedures. J Gastrointest Surg 4: 515-519.
9. Traverso HP, Kamil S, Rahim H, Samadi AR, Boring JR, et al. (1991) A reassessment of risk factors for neonatal tetanus. Bull World Health Organ 69: 573-579.
10. WHO (2021) Immunize all age-pregnant women. WHO/EPI/GEN/88.1, Geneva.
11. Carle A, Rattone G (1884) Studio esperimentale sull'etiologia del tetano. G Accad Med Torrino 32: 174.
12. Nicolaier A (1884) Über infectiösen Tetanus. Dtsch Med Wochenschr 10: 842-844.
13. von Behring E, Kitasato S (2007) Über das Zustandekommen der Diphterie-Immunität und der Tetanus-Immunität bei Thieren Dtsch Med Wochensch 16: 1113-1114.
14. Thuy DB, Campbell JI, Thanh TT, Thuy CT, Loan HT, et al. (2017) Tetanus in Southern Vietnam: Current situation. Am J Trop Med Hyg 96(1): 93-96.
15. Descombey P (1924) L'anatoxine tetanique. Can R Soc Biol 91: 239-241.
16. Ramon G, Zoeller C (1927) L'anatoxine tétanique et l'immunisation active de l'homme vis-à-vis du tétanos. Ann Inst Pasteur 41: 808-825.
17. Long AP, Sartwell PE (1947) Tetanus in the US army in WW2. Bull US Army Med Depart 7: 371-385.
18. Boyd JSK (1946) Tetanus in African and European theaters of war (1939-1945). Lancet 1: 113-119.
19. Spenney J, Lamb RN, Cobbs CG (1971) Recurrent tetanus. South Med J 64: 859.
20. Condrea I, Poenaru S (1933) L'immunité antitétanique chez les non-vaccinés. Igiena 14: 5.
21. Knerr H, Hottle GA (1936) Methoden zur titrierung kleiner mengen tetanusantitoxin Dtsh Med Wsch 12: S368-S380.
22. Istrati G, Kick L, Prigge R (1938) Experimentelle untersuchungen über active tetanus immunitat. Eine method zur Messung kleiner Antitoxin-mengen. Zbl Bakt 143: 106-109.
23. Ipsen J (1942) Experimentalle untd zuffällige fehlerquellen bey messung kleiner antitoxinmengen in tetanus-antitoxin. Zstchr Immunitatsforch 1943: 347-348.

24. Schlumberger M, Yvonnet B, Que HVT, Dy Bun C, Saliou P (2008) Serological study carried out in Cambodia during a tetanus vaccination in adults. Bull Soc Path Exo 1: 36-42.

25. Chatterjee SC (1946) A comparative study of Hemagglutination and bioassay procedures for the assay of guinea-pig anti-diphteria and anti-tetanus sera. Ind Med Res 52: 1241-1249.

26. Hardegree MC, Barile MF, Pittman M, Maloney CJ, Schoffield F, et al. (1970) Immunization against neonatal tetanus in New Guinea. IV: Comparison of tetanus antitoxin titers obtained by hemagglutination and toxin neutralization in mice. Bull World Health Organ 43: 461-468.

27. Gupta RK, Maheshwari SC, Singh H (1984) The titration of tetanus antitoxin *in vivo* 3. A comparison of evaluation of indirect hemagglutination and toxin neutralization test of human sera. J Biol Stand 2: 143-149.

28. Melville-Smith ME, Seagroatt VA, Watkins JT (1983) A comparison of enzyme-linked immunosorbent assay (ELISA) with the toxin neutralization test in mice as a method for the estimation of tetanus antitoxin in human sera. J Biol Stand 11: 137-144.

29. Gupta RK, Siber GR (1994) Comparative analysis of tetanus antitoxin titers of sera from immunized mice and guinea-pigs determined by neutralization tests and ELISA. Biological 3: 215-219.

30. Kristiansen M, Aggerbeck H, Heron I (1997) Improved ELISA for determination of anti-diphteria and/or anti-tetanus antitoxin antibodies in sera. APMIS: Act Path Microb Imm Scand 105: 843-853.

31. Hendricksen CF, van der Gun JW, Nagel J, Kreeftenberg JG (1988) The ToBi test as a reliable in vitro alternative to the toxin neutralization test in mice for the estimation of tetanus antitoxin in human sera. J Biol Dtand 16: 287-297.

32. Sedgwick AK, Ballow M, Sparks K (1983) Rapid quantitative micro-enzyme linked immunosorbent assay for tetanus antibodies. J Clin Microb 18: 104-109.

33. N'Diaye DS, Scwarzinger M, Obarch D, Poissy J, Matheron S, Casalino E, et al. (2014) Effectiveness and cost of quick diagnostic test to determine tetanus immunity in patients with a wound in French emergency department. BMC Infect Dis 14: 603.

34. Afzali H, Sharif MR, Mousavi S (2015) Determination of tetanus antibody levels in trauma patients' referred to Shahid Beheeshti Hospital in Kashan, Iran, 2014. Arch Trauma Res 4(3): e30687.

35. Schlumberger M, Yvonnet B, Lesage G, Tep B (2015) Low specificity of two tetanus rapid test in Cambodia. Med Mal Infect 2015: 25-33.

36. Yusuf N, Reza AA, Chang-Blanc D, Ahmed B, Hailegebriel T, et al. (2022) Progress and barriers towards maternal and neonatal tetanus elimination in the remaining 12 countries: A systematic study review. Lancet Glob Health 10(2): e185.

37. Finkelstein P, Teisch L, Allen VJ, Ruiz G (2017) Tetanus: A potential public health threat in times of disaster. Prehosp Disaster Med 32: 339-342.

38. Kyu HH, Hirmford JE, Stanaway JD, Barber RM, Hancock JR, et al. (2017) Mortality from tetanus between 1990-2015, finding from the global burden of disease study 2015. BMC Public Health 17: 179.

39. Peck M, Garcia-Dobo M, Diallo MS, Nedelec Y, Sodha SV, et al. (2019) Global Routine Vaccination Coverage 2018. MMWR Morb Mort Wkly Rep 68: 937-942.

40. WHO (2021) Extended Programme on Immunization. EPI/GEN/74. Geneva.

41. Dolman KM, Plötz FB, Wolfs TF, Beunders JH, van Vught AT (2002) Tetanus in a young unvaccinated girl after a fall in the street. Ned Tijdschr Genereskd 146(14): 668-671.

42. Ong H, Hendricks J (1999) The use of alternatives to animal tests in developing countries. Dev Biol Stand 101: 209-214.

43. Ly S, Schlumberger M (2004) Impact on Neo-Natal Tetanus and poliomyelitis after a collective vaccination in a rural district of Cambodia. Report, Medical Conference "Cambodge-Santé", Phnom Penh 2004: 92-97.

44. Henderson RH (1995) Vaccination: Success and challenges. In "Vaccination and world health" eds: Cutts FT, Smith PG, John Wiley and sons, Chichester, England pp: 3-16.

45. Schlumberger M (2021) No mechanism found for spontaneous immunity in rural Cambodia. SL Vaccin Vaccin J 1: 121.

46. Schlumberger M (2007) Spontaneous tetanus research by seroneutralization during a tetanus adult immunization in Cambodia. Sciences Thesis Tours (France) pp: 1-92.

47. Veronesi R, Bizzini B, Focaccia R, Coscina AL, Mazza CC, et al. (1983) Naturally acquired antibodies to tetanus toxin in humans and animals from Galapagos islands. J Infect Dis 147: 308-311.

48. Rosskopf U, Noeske K, Wermer E (2005) Efficacy demonstration of tetanus vaccines by double antigen ELISA. Pharmenropa Bio 1: 31-52.

49. Breman JG, Wright GG, Levine L, Latham WC, Compaore KD (1981) The primary serological response to a single dose of adsorbed tetanus toxoid, high concentration type. Bull World Health Organ 58: 745-752.

50. Pirazzini M, Montecucco C, Rossetto O (2022) Toxicology and pharmacology of botulinium and tetanus neurotoxin: an update. Arch Toxicol 96(2): 1521-1539.