

Tetanus is an acute, often fatal, disease caused by an exotoxin produced by *Clostridium tetani*. It is characterized by generalized rigidity and convulsive spasms of skeletal muscles. The muscle stiffness usually involves the jaw (lockjaw) and neck and then becomes generalized.

Although records from antiquity (5th century B.C.) contain clinical descriptions of tetanus, it was Carle and Rattone who first produced tetanus in animals by injecting them with pus from a fatal human tetanus case in 1884. During the same year, Nicolaier produced tetanus in animals by injecting them with samples of soil. In 1889, Kitasato isolated the organism from a human victim, showed that it produced disease when injected into animals, and reported that the toxin could be neutralized by specific antibodies. In 1897, Nocard demonstrated the protective effect of passively transferred antitoxin, and passive immunization in humans was used during World War I. Tetanus toxoid was developed by Descombey in 1924, and the effectiveness of active immunization was demonstrated in World War II.

CLOSTRIDIUM TETANI

C. tetani is a slender, gram-positive, anaerobic rod that may develop a terminal spore, giving it a drumstick appearance. The organism is sensitive to heat and cannot survive in the presence of oxygen. The spores, in contrast, are very resistant to heat and the usual antiseptics. They can survive autoclaving at 121°C for 10-15 minutes. The spores are also relatively resistant to phenol and other chemical agents.

The spores are widely distributed in soil and in the intestine and feces of horses, sheep, cattle, dogs, cats, rats, guinea pigs, and chickens. Manure-treated soil may contain large numbers of spores. In agricultural areas, a significant number of human adults may harbor the organism. The spores can also be found on skin surfaces and in contaminated heroin.

Clostridium tetani produces two exotoxins, tetanolysin and tetanospasmin. The function of tetanolysin is not known with certainty. Tetanospasmin is a neurotoxin and causes the clinical manifestations of tetanus. Tetanospasmin is one of the most potent toxins known on a weight basis. The estimated minimum human lethal dose is 2.5 nanograms per kilogram of body weight (a nanogram is one billionth of a gram), or 175 nanograms for a 70 kg human.

PATHOGENESIS

C. tetani usually enters the body through a wound. In the presence of anaerobic (low oxygen) conditions, the spores germinate. Toxins are produced, and disseminated via blood and lymphatics. Toxins act at several sites within the central nervous system, including peripheral motor end plates, spinal cord, brain, and sympathetic nervous system. The typical clinical manifestations of tetanus are caused when tetanus toxin interferes with release of neurotransmitters, blocking inhibitor impulses. This leads to unopposed muscle

Tetanus

- First described by Hippocrates
- Etiology discovered in 1884 by Carle and Rattone
- Passive immunity used for treatment and prophylaxis during World War I
- Tetanus toxoid first widely used during World War II

Clostridium tetani

- Anaerobic gram-positive, spore-forming bacteria
- Spores found in soil, dust, animal feces; may persist for months to years
- Multiple toxins produced with growth of bacteria
- Tetanospasmin estimated human lethal dose = 2.5 ng/kg

Tetanus Pathogenesis

- Anaerobic conditions allow germination of spores and production of toxins.
- Toxin binds in central nervous system
- Interferes with neurotransmitter release to block inhibitor impulses.
- Leads to unopposed muscle contraction and spasm.

Tetanus Clinical Features

- Incubation period 8 days (range, 3-21 days)
- Three clinical forms: Local (uncommon), cephalic (rare), generalized (most common)
- Generalized tetanus: descending symptoms of trismus (lockjaw), difficulty swallowing, muscle rigidity, spasms
- Spasms continue for 3-4 weeks; complete recovery may take months

Neonatal Tetanus

- Generalized tetanus in newborn infant
- Infant born without protective passive immunity
- High fatality rate without therapy
- Estimated 215,000 deaths worldwide in 1998

Tetanus Complications

- Laryngospasm
- Fractures
- Hypertension
- Nosocomial infections
- Pulmonary embolism
- Aspiration
- Death

contraction and spasm. Seizures may occur, and the autonomic nervous system may also be affected.

CLINICAL FEATURES

The **incubation period** varies from 3 to 21 days, usually about 8 days. In general the further the injury site is from the central nervous system, the longer the incubation period. The shorter the incubation period, the higher the chance of death. In neonatal tetanus, symptoms usually appear from 4 to 14 days after birth, averaging about 7 days.

On the basis of clinical findings, three different forms of tetanus have been described.

Local tetanus is an uncommon form of the disease, in which patients have persistent contraction of muscles in the same anatomic area as the injury. These contractions may persist for many weeks before gradually subsiding. Local tetanus may precede the onset of generalized tetanus, but is generally milder. Only about 1% of cases are fatal.

Cephalic tetanus is a rare form of the disease, occasionally occurring with otitis media (ear infections) in which *C. tetani* is present in the flora of the middle ear, or following injuries to the head. There is involvement of the cranial nerves, especially in the facial area.

The most common type (about 80%) of reported tetanus is **generalized tetanus**. The disease usually presents with a descending pattern. The first sign is trismus or lockjaw, followed by stiffness of the neck, difficulty in swallowing, and rigidity of abdominal muscles. Other symptoms include a temperature rise of 2°-4°C above normal, sweating, elevated blood pressure, and episodic rapid heart rate. Spasms may occur frequently and last for several minutes. Spasms continue for 3-4 weeks. Complete recovery may take months.

Neonatal tetanus is a form of generalized tetanus that occurs in newborn infants. Neonatal tetanus occurs in infants born without protective passive immunity, because the mother is not immune. It usually occurs through infection of the unhealed umbilical stump, particularly when the stump is cut with an unsterile instrument. Neonatal tetanus is common in some developing countries (estimated >215,000 deaths worldwide in 1998), but very rare in the United States.

COMPLICATIONS

Laryngospasm (spasm of the vocal cords) and/or spasm of the muscles of respiration leads to interference with breathing.

Fractures of the spine or long bones may result from sustained contractions and convulsions. **Hyperactivity of the autonomic nervous system** may lead to hypertension and/or an abnormal heart rhythm.

Nosocomial infections are common because of prolonged hospitalization. Secondary infections, which may include sepsis from indwelling catheters, hospital-acquired pneumonias, and decubitus ulcers. **Pulmonary embolism** is particularly a problem in drug users and elderly patients. **Aspiration pneumonia** is a common late complication of tetanus, found in 50%-70% of autopsied cases. In recent years, tetanus has been fatal in approximately 11% of reported cases. Cases most likely to be fatal are those occurring in persons age ≥ 60 years (18%), and unvaccinated persons (22%). In about 20% of tetanus deaths, no obvious pathology is identified and death is attributed to the direct effects of tetanus toxin.

LABORATORY DIAGNOSIS

There are no laboratory findings characteristic of tetanus. The diagnosis is entirely clinical and does not depend upon bacteriologic confirmation. *C. tetani* is recovered from the wound in only 30% of cases, and can be isolated from patients who do not have tetanus. Laboratory identification of the organism depends most importantly on the demonstration of toxin production in mice.

MEDICAL MANAGEMENT

All wounds should be cleaned. Necrotic tissue and foreign material should be removed. If tetanic spasms are occurring, supportive therapy and maintenance of an adequate airway are critical.

Tetanus immune globulin (TIG) is recommended for persons with tetanus. TIG can only help remove unbound tetanus toxin. It cannot effect toxin bound to nerve endings. A single intramuscular dose of 3000 to 5000 units is generally recommended for children and adults, with part of the dose infiltrated around the wound if it can be identified. Intravenous immune globulin (IVIG) contains tetanus antitoxin and may be used if TIG is not available.

Due to the extreme potency of the toxin, tetanus disease does not result in tetanus immunity. Active immunization with tetanus toxoid should begin or continue as soon as the person's condition has stabilized.

WOUND MANAGEMENT

Antibiotic prophylaxis against tetanus is neither practical nor useful in managing wounds; proper immunization plays the more important role. The need for active immunization, with or without passive immunization, depends on the condition of the wound and the patient's immunization history (see table). Rarely have cases of tetanus occurred in persons with a documented primary series of tetanus toxoid.

Persons with wounds that are neither clean nor minor, and who have had 0-2 prior doses or have an uncertain history of prior doses, need tetanus immune globulin (TIG) as well as Td toxoids. This is because early doses of toxoid do not induce immunity, but

Tetanus Wound Management

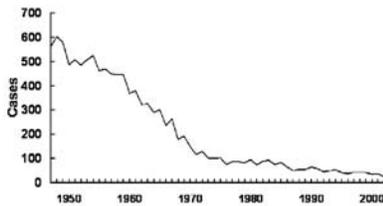
Vaccination History	Clean, minor wounds		All other wounds	
	Td	TIG	Td	TIG
Unknown or <3 doses	Yes	No	Yes	Yes
3+ doses	No*	No	No**	No

* Yes, if >10 years since last dose
 ** Yes, if >5 years since last dose

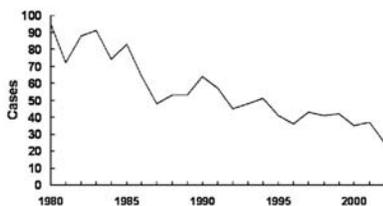
Tetanus Epidemiology

- **Reservoir** Soil and intestine of animals and humans
- **Transmission** Contaminated wounds
Tissue injury
- **Temporal pattern** Peak in summer or wet season
- **Communicability** Not contagious

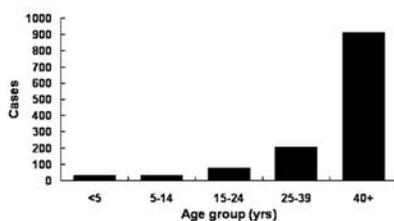
Tetanus - United States, 1947-2002



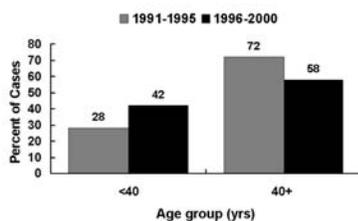
Tetanus - United States, 1980-2002



Tetanus - United States, 1980-2002 Age Distribution



Age Distribution of Reported Tetanus Cases, 1991-1995 and 1996-2000



only prime the immune system. The TIG provides temporary immunity by directly providing antitoxin. This ensures that protective levels of antitoxin are achieved even if an immune response has not yet occurred.

EPIDEMIOLOGY

OCCURRENCE

Occurrence is worldwide, but is most frequently encountered in densely populated regions in hot, damp climates with soil rich in organic matter.

RESERVOIR

Organisms are found primarily in the soil and intestinal tracts of animals and humans.

MODE OF TRANSMISSION

Transmission is primarily by contaminated wounds (apparent and inapparent). The wound may be major or minor. In recent years, however, a higher proportion of cases had minor wounds, probably because severe wounds are more likely to be properly managed.

Tetanus may follow elective surgery, burns, deep puncture wounds, crush wounds, otitis media (ear infections), dental infection, animal bites, abortion, and pregnancy.

COMMUNICABILITY

Tetanus is not contagious from person to person. It is the only vaccine-preventable disease that is infectious, but not contagious.

SECULAR TRENDS IN THE UNITED STATES

A marked decrease in mortality occurred from the early 1900s to the late 1940s. In the late 1940s, tetanus toxoid was introduced into routine childhood immunization and tetanus became nationally notifiable. At that time, there were 500-600 cases reported per year (approximately 0.4 cases per 100,000 population).

After the 1940s, reported tetanus incidence rates fell steadily. Since the mid-1970s, 50-100 cases have been reported annually (~0.05 cases per 100,000). The death-to-case ratio has declined from 30% to approximately 10% in recent years. An all-time low of 25 cases (0.01 cases per 100,000) were reported in 2002.

From 1980 through 2000, 70% of reported cases of tetanus were among persons 40 years of age or older. From 1980 through 1990, a median of 21% of reported cases were age <40 years. The age distribution of reported cases shifted to a younger age group in the last half of the 1990s. Persons <40 years increased from 28% of cases during 1991-1995 to 42% of cases during 1996-2000. This change in age distribution is a result of both an increase in cases in

persons <40 years and a decrease in cases in older people. The increase in cases among younger persons is related in part to an increased number of cases among young injection drug users in California in the late 1990s.

Almost all reported cases of tetanus are in persons who have either never been vaccinated, or who completed a primary series, but have not had a booster in the preceding 10 years.

Heroin users, particularly persons who inject themselves subcutaneously, appear to be at high risk for tetanus. Quinine is used to dilute heroin and may support the growth of *C. tetani*.

Neonatal tetanus is rare in the United States, with only 2 cases reported since 1989. Neither of the infants' mothers had ever received tetanus toxoid.

During 1998-2000 (the most recent years data are available) acute injuries or wounds preceded tetanus in 94 (73%) of the 129 cases for which information was available. Among the most frequent wound types were puncture wounds (50%), lacerations (33%), and abrasions (9%). The most common puncture wound was from stepping on a nail (15 cases). Other puncture wounds involved barbed wire, splinters, animal or insect bites, self-piercing, and self-performed tattoos. The environment in which acute injuries occurred was indoors or at home in 45%, in the yard, garden, or farm in 31%, and other outdoor locations in 23%.

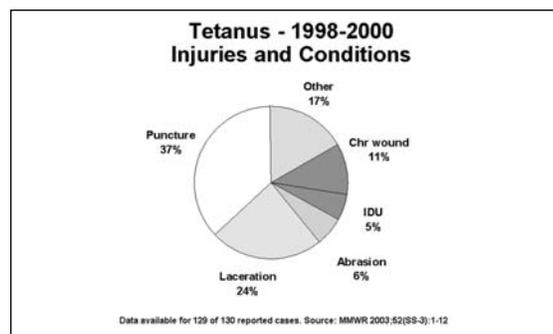
Five percent of reported cases were intravenous drug users without other known injury, and 11% had chronic wounds. Twenty patients were reported to have received at least a primary series of tetanus toxoid; 18 had an outcome reported. Of these 18 patients, one (6%) death occurred; the death was in an injection-drug user (IDU) whose last dose of tetanus toxoid was 11 years before the onset of tetanus. A total of 110 patients reported <3 doses of tetanus toxoid or had an unknown vaccination history; 95 of these patients had an outcome reported. Nineteen deaths (20%) occurred among these 95 patients.

TETANUS TOXOID

CHARACTERISTICS

Tetanus toxoid was first produced in 1924. Tetanus toxoid immunizations were used extensively in the armed services during World War II. Tetanus cases among this population dropped from 70 in World War I (13.4/100,000 wounds and injuries) to 12 in World War II (0.44/100,000). Of the 12 cases, half had received no prior toxoid.

Tetanus toxoid consists of a formaldehyde-treated toxin. The toxoid is standardized for potency in animal tests according to Food and Drug Administration (FDA) regulations. Occasionally, potency is mistakenly equated with Lf units, which are a measure of the



DTaP, DT, and Td

	Diphtheria	Tetanus
DTaP, DT	7-8 Lf units	5-12.5 Lf units
Td (adult)	2 Lf units	5 Lf units

Pertussis vaccine and pediatric DT used through age 6 years. Adult Td used for persons 7 years and older.

Tetanus Toxoid

- Formalin-inactivated tetanus toxin
- Schedule Three or four doses + booster
Booster every 10 years
- Efficacy Approximately 100%
- Duration Approximately 10 years
- Should be administered with diphtheria toxoid as DTaP, DT, or Td

Routine DTaP Primary Vaccination Schedule

Dose	Age	Interval
Primary 1	2 months	---
Primary 2	4 months	4 wks
Primary 3	6 months	4 wks
Primary 4	15-18 months	6 mos

quantity of toxoid, not its potency in inducing protection.

There are two types of toxoid available — adsorbed (aluminum salt precipitated) toxoid and fluid toxoid. Although the rates of seroconversion are about equal, the adsorbed toxoid is preferred because the antitoxin response reaches higher titers and is longer lasting than following the fluid toxoid.

Tetanus toxoid is available as a single antigen preparation, combined with diphtheria as pediatric DT or adult Td, and with both diphtheria toxoid and acellular pertussis vaccine as DTaP. Pediatric formulations (DT and DTaP) contain a similar amount of tetanus toxoid as adult Td, but contain 3-4 times as much diphtheria toxoid. Children younger than 7 years of age should receive either DTaP or pediatric DT. Persons 7 years of age or older should receive the adult formulation (adult Td), even if they have not completed a series of DTaP or pediatric DT. There is virtually no reason to use single antigen tetanus toxoid. Tetanus toxoid should be given in combination with diphtheria toxoid, since periodic boosting is needed for both antigens.

IMMUNOGENICITY AND VACCINE EFFICACY

After a primary series of three properly spaced doses of tetanus toxoid in persons ≥ 7 years of age and four doses in children < 7 years of age, essentially all recipients achieve antitoxin levels considerably greater than the minimal protective level of 0.01 IU/ml.

Efficacy of the toxoid has never been studied in a vaccine trial. It can be inferred from protective antitoxin levels that a complete tetanus toxoid series has a clinical efficacy of virtually 100%; cases of tetanus occurring in fully immunized persons whose last dose was within the last 10 years are extremely rare.

Following a properly administered primary series, almost all persons develop a protective level of antitoxin. Antitoxin levels decrease with time. While some persons may be protected for life, most persons have antitoxin levels that approach the minimal protective level by 10 years after the last dose. As a result, routine boosters are recommended every 10 years.

In a small percentage of individuals, antitoxin levels fall below the minimal protective level before 10 years have elapsed. To ensure adequate protective antitoxin levels in individuals who sustain a wound that is other than clean and minor, a booster is recommended for these persons if more than 5 years have elapsed since their last dose. (See **Wound Management** for details on persons who previously received fewer than three doses.)

VACCINATION SCHEDULE AND USE

DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine) is the vaccine of choice for children 6 weeks through 6 years of age. The usual schedule is a primary series of 4 doses at 2, 4, 6, and 15-18 months of age. The first, second, and third doses of

DTaP should be separated by a minimum of 4 weeks. The fourth dose should follow the third dose by no less than 6 months, and should not be administered before 12 months of age.

If a child has a valid contraindication to pertussis vaccine, pediatric DT should be used to complete the vaccination series. If the child was less than 12 months old when the first dose of DT was administered (as DTaP or DT), the child should receive a total of four primary DT doses. If the child was 12 months of age or older at the time that the first dose of DT was administered, three doses (third dose 6-12 months after the second) completes the primary DT series.

If the fourth dose of DTaP, DTP, or DT is administered before the fourth birthday, a booster dose is recommended at 4-6 years of age. The fifth dose is not required if the fourth dose was given on or after the fourth birthday.

Because of waning antitoxin titers, most individuals have antitoxin levels below the optimal level 10 years after the last dose of DTaP, DTP, DT, or Td. As a result, additional booster doses of tetanus and diphtheria toxoids (as Td) are required every 10 years to maintain protective antitoxin titers. The first booster dose of Td may be given at 11-12 years of age, if at least 5 years have elapsed since the last dose of DTaP, DTP, or DT. If a dose is given sooner as part of wound management, the next booster is not needed for 10 years thereafter. More frequent boosters are not indicated and have been reported to result in an increased incidence and severity of local adverse reactions.

Td is the vaccine of choice for children 7 years and older, and for adults. A primary series is three or four doses, depending on whether the person has received prior doses of diphtheria-containing vaccine, and the age these doses were administered. The number of doses recommended for children who received one or more doses of DTP, DTaP, or DT before age 7 years is discussed above. For unvaccinated persons 7 years and older (including persons who cannot document prior vaccination), the primary series is three doses. The first two doses should be separated by at least 4 weeks, and the third dose given 6 to 12 months after the second. A booster dose of Td should be given every 10 years.

Interruption of the recommended schedule or delay of subsequent doses does not reduce the response to the vaccine when the series is finally completed. There is no need to restart a series regardless of the time elapsed between doses.

Tetanus disease does not confer immunity because of the very small amount of toxin required to produce illness. Persons recovering from tetanus should begin or complete active immunization with tetanus toxoid (Td) during convalescence.

Children Who Receive DT

- The number of doses of DT needed to complete the series depends on the child's age at the first dose:
 - if first dose given at <12 months of age, 4 doses are recommended
 - if first dose given at ≥12 months, 3 doses complete the primary series

**Routine DTaP Schedule
Children <7 years of age**

Booster Doses

- 4-6 years, before entering school
- 11-12 years of age if 5 years since last dose (Td)
- Every 10 years thereafter (Td)

**Routine Td Schedule
Unvaccinated Persons ≥7 Years of Age**

<u>Dose</u>	<u>Interval</u>
Primary 1	---
Primary 2	4 wks
Primary 3	6-12 mos

Booster dose every 10 years

Diphtheria and Tetanus Toxoids Adverse Reactions

- Local reactions (erythema, induration)
- Exaggerated local reactions (Arthus-type)
- Fever and systemic symptoms not common
- Severe systemic reactions rare

Diphtheria and Tetanus Toxoids Contraindications and Precautions

- Severe allergic reaction to vaccine component or following prior dose
- Moderate or severe acute illness

ADVERSE REACTIONS FOLLOWING VACCINATION

Local adverse reactions (*e.g.*, erythema, induration, pain at the injection site) are common, but are usually self-limited and require no therapy. A nodule may be palpable at the injection site of adsorbed products for several weeks. Abscess at the site of injection has been reported. Fever and other systemic symptoms are not common.

Exaggerated local (Arthus-like) reactions are occasionally reported following receipt of a diphtheria-or tetanus-containing vaccine. These reactions present as extensive painful swelling, often from shoulder to elbow. They generally begin from 2 to 8 hours after injections, and are reported most often in adults, particularly those who have received frequent doses of diphtheria or tetanus toxoid. Persons experiencing these severe reactions usually have very high serum antitoxin levels; they should not be given further routine or emergency booster doses of Td more frequently than every 10 years. Less severe local reactions may occur in persons who have multiple prior boosters.

Severe systemic reactions such as generalized urticaria (hives), anaphylaxis, or neurologic complications have been reported after receipt of tetanus toxoid. A few cases of peripheral neuropathy and Guillain-Barré Syndrome (GBS) have been reported following tetanus toxoid administration. Following a recent review, the Institute of Medicine (IOM) concluded that the available evidence favors a causal relationship between tetanus toxoid and both brachial neuritis and GBS, although these reactions are very rare.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

A **severe allergic reaction** (acute respiratory distress or collapse) following a prior dose of tetanus toxoid is a contraindication to receipt of tetanus toxoid. If a generalized reaction is suspected to represent allergy, it may be useful to refer an individual for appropriate skin testing before discontinuing tetanus toxoid immunization. A **moderate or severe acute illness** is reason to defer routine vaccination, but a minor illness is not.

If a contraindication to using tetanus toxoid-containing preparations exists, passive immunization with tetanus immune globulin (TIG) should be considered whenever an injury other than a clean minor wound is sustained.

VACCINE STORAGE AND HANDLING

DTaP, DT (pediatric), Td, DTP/Hib, and tetanus toxoid should be stored continuously at 2° - 8°C (35° - 46°F). The vaccine may be out of refrigeration for up to 4 days, but should be refrigerated immediately when received. Freezing reduces the potency of the tetanus component.

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