Diphtheria, Tetanus and Pertussis

Diseases and Associated Vaccines

Corynebacterium diphtheriae

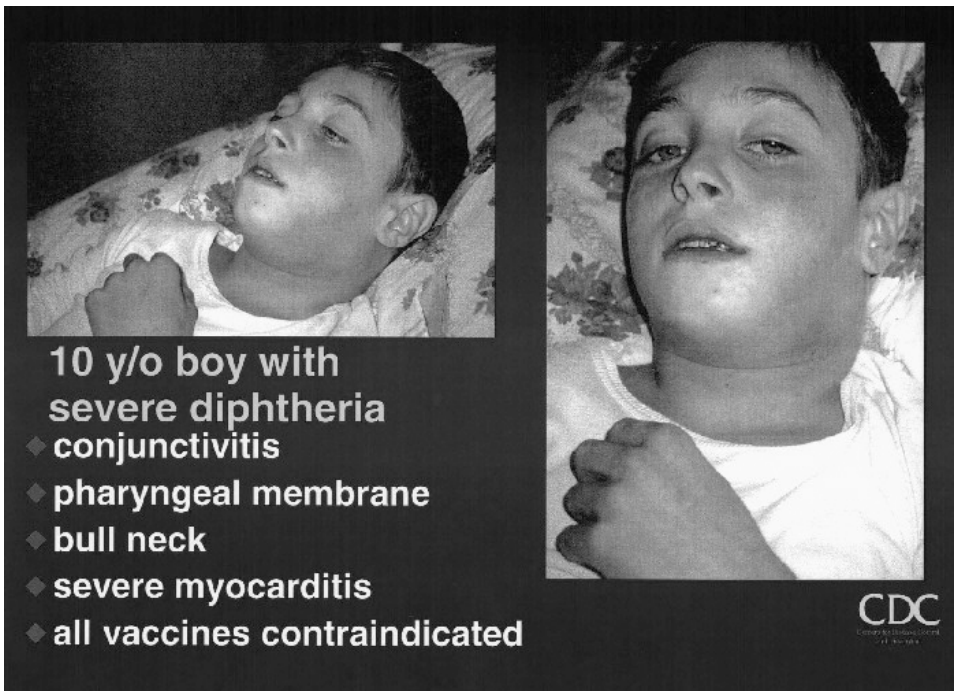
- Aerobic gram-positive bacillus
- Toxin production occurs only when *C. diphtheriae* infected by virus (phage) carrying tox gene
- If isolated, must be distinguished from normal diphtheroid
- Toxoid developed in 1920s

Diphtheria Clinical Features

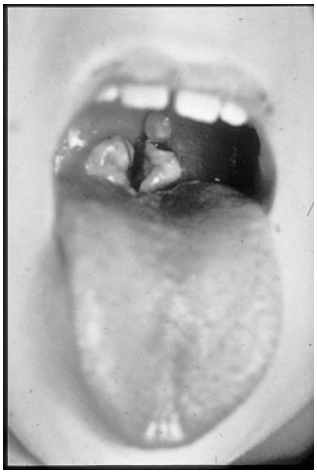
- Incubation period 2-5 days (range, 1-10 days)
- May involve any mucous membrane
- Classified based on site of infection
  - anterior nasal
  - pharyngeal and tonsillar
  - laryngeal
  - cutaneous
  - ocular
  - genital

Pharyngeal and Tonsillar Diphtheria

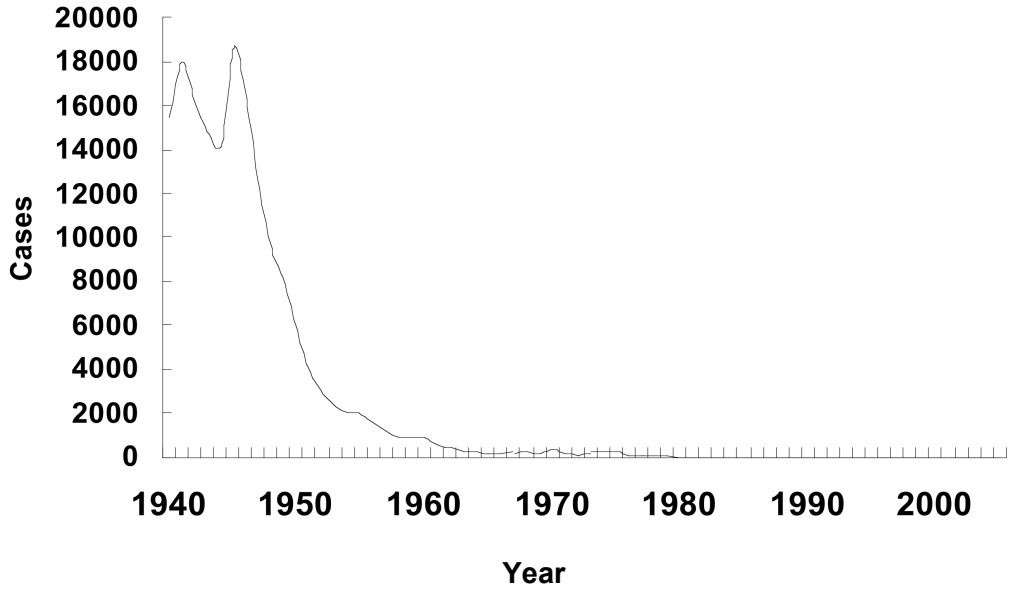
- Insidious onset
- Exudate spreads within 2-3 days and may form adherent membrane
- Membrane may cause respiratory obstruction
- Pseudomembrane: fibrin, bacteria, and inflammatory cells, no lipid
- Fever usually not high but patient appears toxic



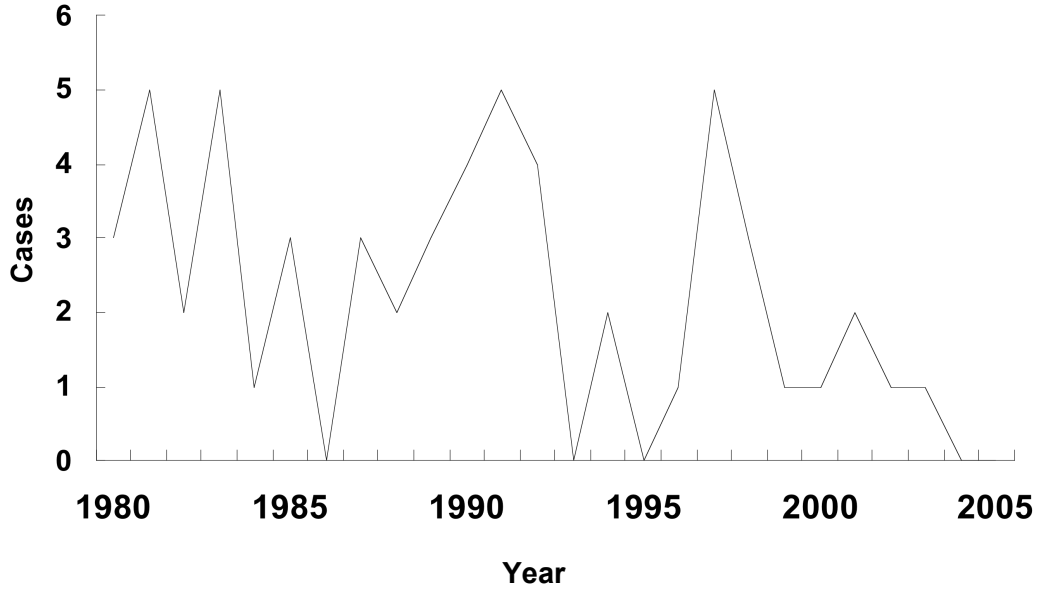
Tonsillar Diphtheria



Diphtheria - United States, 1940-2005



Diphtheria - United States, 1980-2005



Diphtheria Complications

- Most attributable to toxin
- Severity generally related to extent of local disease
- Most common complications are myocarditis and neuritis
- Death occurs in 5%-10% for respiratory disease

Diphtheria Epidemiology

• Reservoir	Human carriers Usually asymptomatic
• Transmission	Respiratory, aerosols Skin lesions
• Temporal pattern	Winter and spring
• Communicability	Up to several weeks without antibiotics

Diphtheria vaccine

- Detoxified bacterial, protein toxin
- Injectable, IM administration
- Toxigenic *Corynebacterium diphtheriae* (infected with β phage)
- Produced in horses (old)
- First used in the U.S. in 1891
- Used only for treatment of diphtheria
- Neutralizes only unbound toxin
- Lifetime of Ab: 15 days – 3 weeks, wait 3-4 weeks before giving toxoid. Only given once.

Manufacturing Process

- Toxigenic strain of *C. diphtheriae* grown in Fenton medium with a bovine extract
- After suitable growth, toxin purified from cells by centrifugation
- Toxoided by incubation with formaldehyde for several weeks
- Concentrated with ultrafiltration
- Purified by precipitation, dialysis and sterile filtered
- Adsorbed onto aluminum hydroxide, $Al(OH)_3$

Routine DTaP Primary Vaccination Schedule

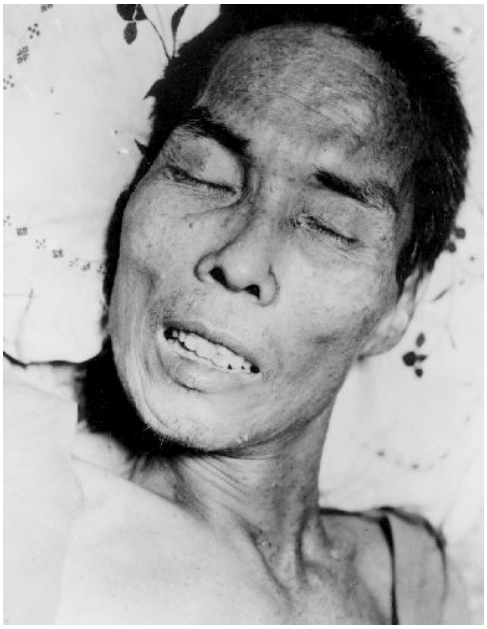
Dose	Age
Primary 1	2 months
Primary 2	4 months
Primary 3	6 months
Primary 4	15-18 months
	4-6 yrs
	11-12 yrs
	Every 10 yrs

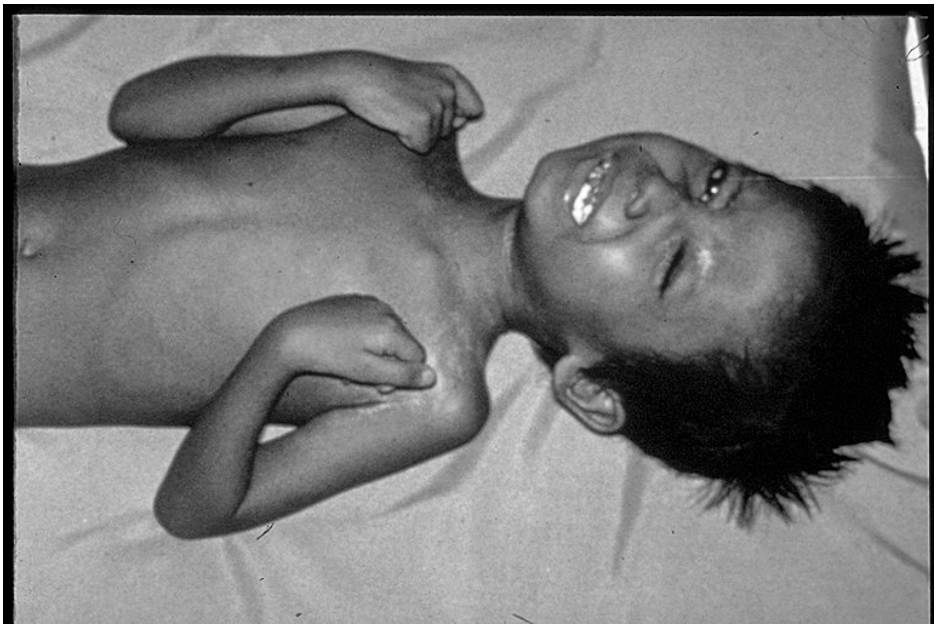
Diphtheria Toxoids Adverse Reactions

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

Tetanus

- First described by Hippocrates
- Etiology discovered in 1884 by Carle and Rattone
- Passive immunization 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, 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

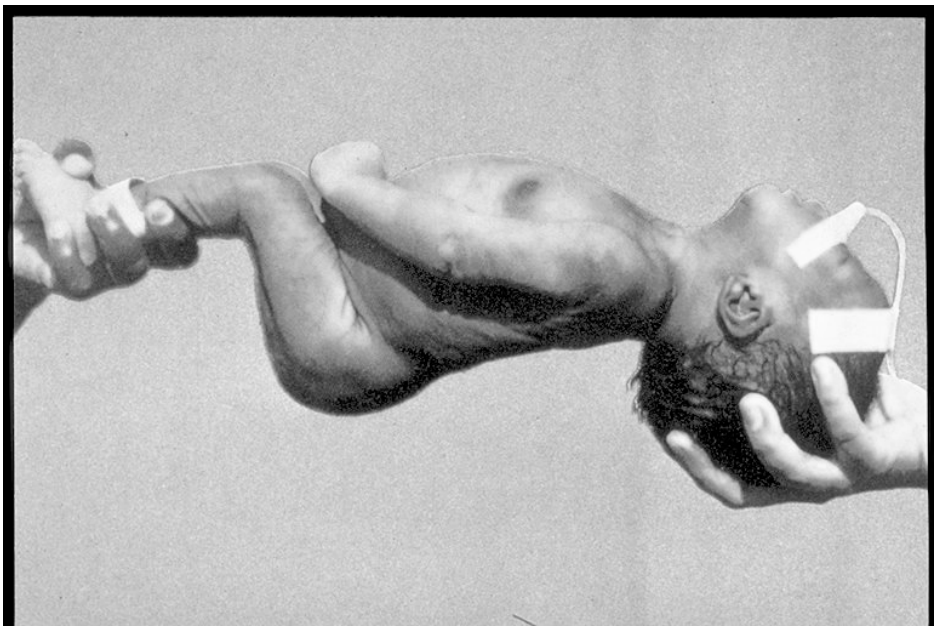
- Incubation period; 8 days
  (range, 3-21 days)
- Generalized tetanus: descending symptoms of trismus (lockjaw), difficulty swallowing, muscle rigidity, spasms
- Spasms continue for 3-4 weeks; complete recovery may take months
- Fatality rate ~90% w/o treatment
  ~30% w/ treatment

Neonatal Tetanus

- Generalized tetanus in newborn infant
- Infant born without protective passive immunity
- Estimated >215,000 deaths worldwide in 1998

Complications

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



>270,000 cases worldwide per year

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 toxins

- Tetanolysin - possible role in establishing infection at inoculation site
- Tetanospasm
  - accumulates intracellularly during log-phase growth
  - released into medium upon autolysis
  - Minimum human lethal dose ~ 2.5 ng/kg

Tetanus disease

- Tetanospasms
  - localized - spasm of muscles close to site of injection; weeks to months duration; rare but may precede generalized symptoms
  - generalized - 80% of cases
- Complications of the spasms:
  - fractures of the long bones and vertebrae
  - asphyxia from glottic obstruction

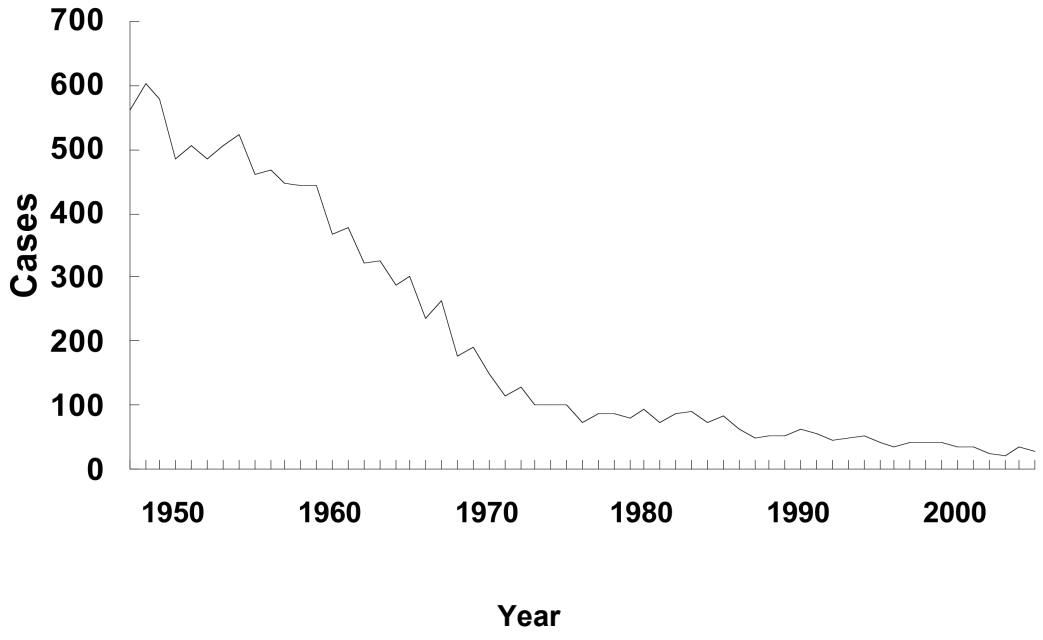
Nervous system effects

- Toxin travels up nerve endings by intra-axonal transport
- Gains entry to neuromuscular junctions by binding to gangliosides
- Interferes with release of neurotransmitters from presynaptic inhibitory fibers
- Excitatory reflexes multiply unchecked, causing spasms

Tetanus Transmission

- Not a communicable disease
- The only vaccine-preventable infection that is not communicable
- Disease acquired through exposure to bacterial spores in the environment
  - inoculation of bacterial spores into body by puncture or deep cut

Tetanus—United States, 1947-2005



Manufacturing Process

- Growth of *C. tetani* in modified Latham broth in fermenters
- Harvest extracellular toxin by filtration
- Purify
- Detoxify with formaldehyde for ~3 weeks
- Adsorb with Alum adjuvant
- Diafiltration

Tetanus Toxoid

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

Pertussis (Whooping Couth)

- Highly contagious respiratory infection caused by *Bordetella pertussis*
- Outbreaks first described in 16th century
- *Bordetella pertussis* isolated in 1906
- Estimated 294,000 deaths worldwide in 2002
- Primarily a toxin-mediated disease

Bordetella pertussis

- Fastidious gram-negative bacteria
- Antigenic and biologically active components:
  - pertussis toxin (PT)
  - filamentous hemagglutinin (FHA)
  - agglutinogens
  - adenylate cyclase
  - pertactin
  - tracheal cytotoxin

Pertussis Pathogenesis

- B. pertussis binds to and multiplies on ciliated cells (respiratory mucosa). The infection is not systemic.
- Inflammation occurs which interferes with clearance of pulmonary secretions
- B. pertussis binds via at least 2 adhesion proteins to the ciliated cells
    - Filamentous hemagglutinin
    - Pertussis toxin (Ptx, A5B exotoxin)
- Ptx is also released into the extracellular fluid and can affect host cells

Pertussis Clinical Features

- Incubation period 5-10 days (range 4-21 days)
- Insidious onset, similar to minor upper respiratory infection with nonspecific cough
- Fever usually minimal throughout course of illness
- Catarrhal stage 1-2 weeks
- Paroxysmal cough stage 1-6 weeks
- Convalescence Weeks to months

Pertussis Epidemiology

- Reservoir — Human
  Adolescents and adults
- Transmission — Respiratory droplets
- Communicability — Maximum in catarrhal stage
  Secondary attack rate
  up to 80%

Pertussis Among Adolescents and Adults

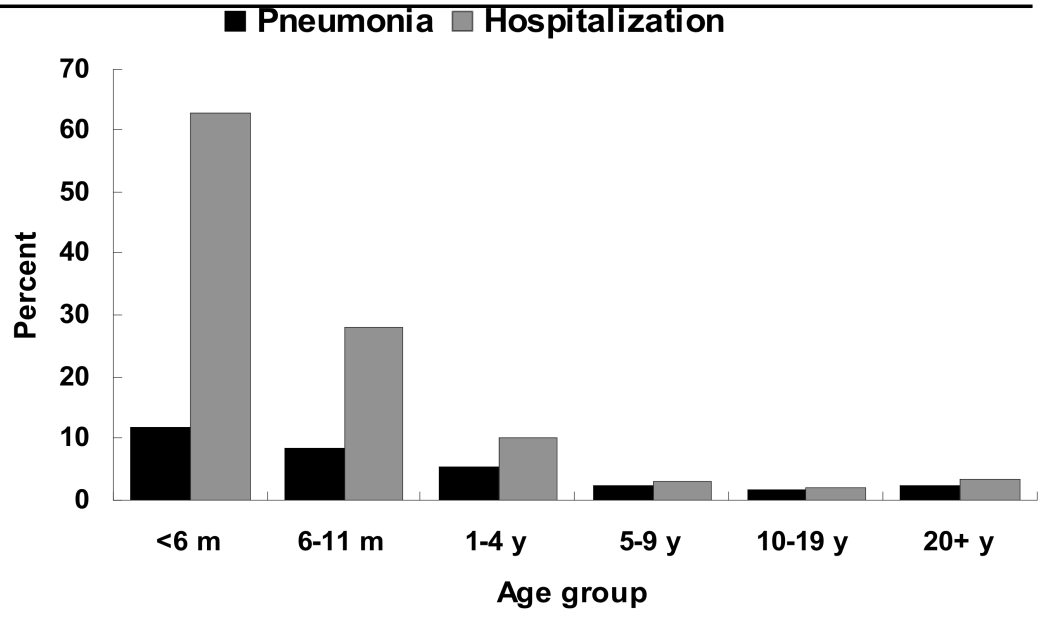
- Disease often milder than in infants and children
- Infection may be asymptomatic, or may present as classic pertussis
- Persons with mild disease may transmit the infection
- Older persons often source of infection for children

Pertussis Complications*

Condition	Percent reported
Pneumonia	4.9
Seizures	0.7
Encephalopathy	0.1
Hospitalization	16
Death	0.2

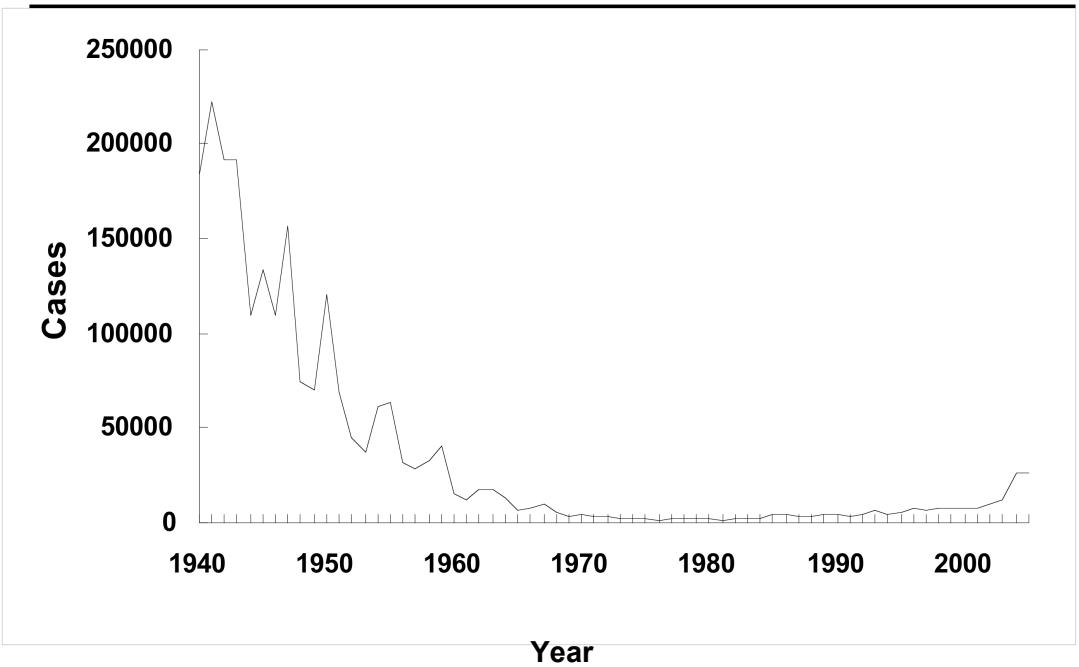
*Cases reported to CDC 2001-2003 (N=28,998)

Pertussis Complications by Age

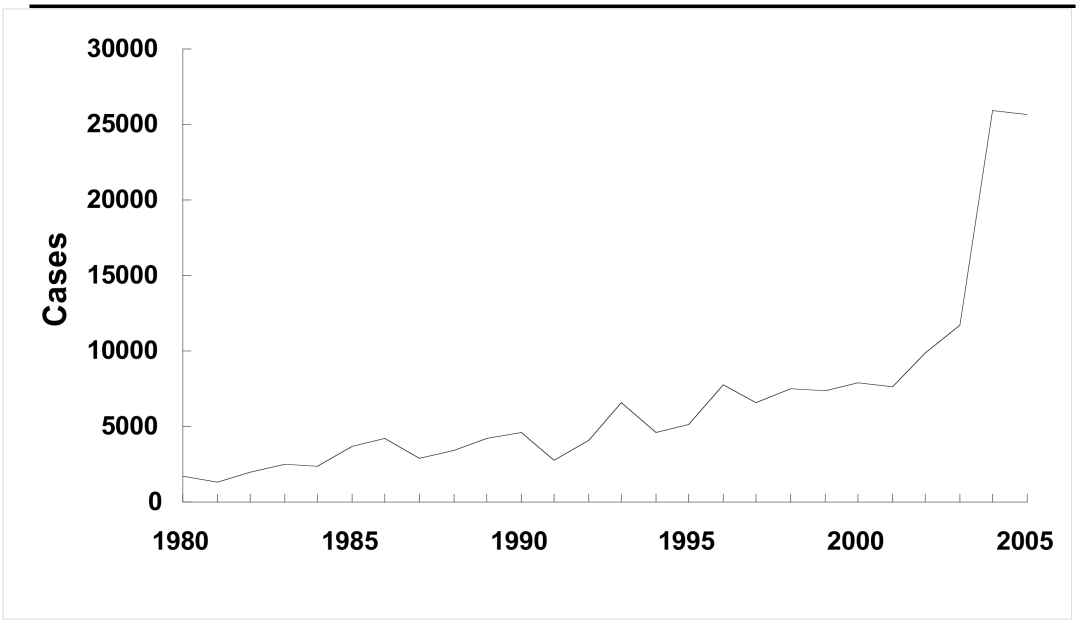


*Cases reported to CDC 1997-2000 (N=28,187)

Pertussis—United States, 1940-2005



Pertussis—United States, 1980-2005



Pertussis (vaccines)

- Killed Whole cell -
  - old, not licensed in U.S. or Europe
  - still used in developing countries
  - relatively cheap
- Acellular (aP) -
  - currently licensed in U.S., Japan and Europe
  - some are recombinant
  - expensive

Pertussis-containing Vaccines

- DTaP (pediatric)
  - approved for children 6 weeks through 6 years (to age 7 years)
  - contains same amount of diphtheria and tetanus toxoid as pediatric DT
- Tdap (adolescent and adult)
  - approved for persons 10-18 years (Boostrix) and 11-64 years (Adacel)
  - contains lesser amount of diphtheria toxoid and acellular pertussis antigen than DTaP

Interchangeability of Different Brands of DTaP Vaccine

- Whenever feasible, the same DTaP vaccine should be used for all doses of the series
- Limited data suggest that “mix and match” DTaP schedules do not adversely affect safety and immunogenicity
- If vaccine used for earlier doses is not known or not available, any brand may be used to complete the series

DTaP Adverse Reactions

- Local reactions 20%-40%
  (pain, redness, swelling)
- Temp of 101^{o}F 3%-5%
  or higher
- More severe adverse reactions
  not common
- Local reactions more common following 4th and 5th doses

DTaP Contraindications

- Severe allergic reaction to vaccine component or following a prior dose
- Encephalopathy not due to another identifiable cause occurring within 7 days after vaccination

DTaP Precautions*

- Moderate or severe acute illness
- Temperature ≥105°F (40.5°C) or higher within 48 hours with no other identifiable cause
- Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours
- Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours
- Convulsions with or without fever occurring within 3 days

***may consider use in outbreaks**

DTaP Vaccine Formulations

Component, per 0.5 ml dose	GSK Infanrix, Pediarix	AP Inc (sanofi pasteur) Tripedia	AP LTd (sanofi pasteur) Daptacel
Diphtheria Toxoid	25 Lf	6.7 Lf	15 Lf
Tetanus Toxoid	10 Lf	5 Lf	5 Lf
PT, inactivated	25 µg	23.4 µg	10 µg
FHA, inactivated	25 µg	23.4 µg	5 µg
PRN (69kD OMP)	8 µg		3 µg
Fimbriae 2	0	0	5 µg
Fimbriae 3			
2-phenoxyethanol (PE), preservative	2.5 mg	0	0.6%
NaCl	4.5 mg		
Aluminum adjuvant	<0.625 mg	<0.17 mg	0.33 mg
Formaldehyde, residual	100 µg	<100 µg	< 0.02%
Glutaraldehyde, residual			< 0.1%
Polysorbate 80 (Tween 80)	100 µg		
Thimerosal, preservative	0	Trace (single -dose) 25 µg/dose (multi - vial)	