

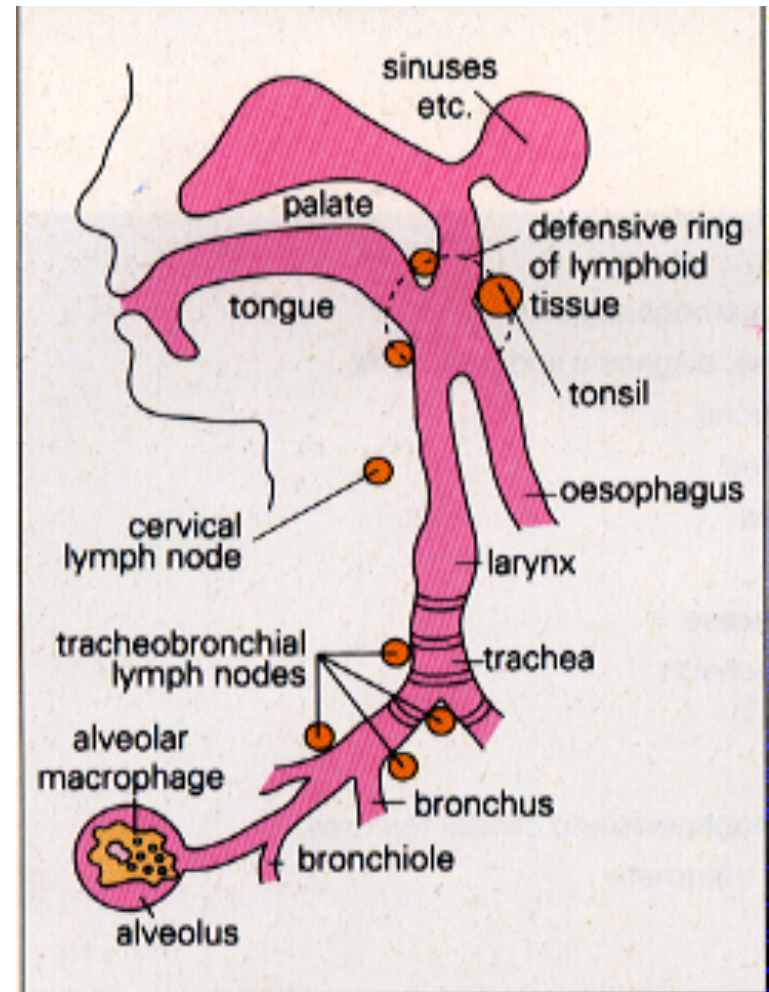
Outline: Upper Respiratory Infections

- Diphtheria
- Whooping Cough

Microbiological & clinical features, virulence factors, diagnosis, epidemiology and immunizations

Target sites for respiratory pathogens

- Upper respiratory tract
 - Sinuses
 - Middle ear
 - Oropharynx
 - Trachea
 - Bronchi
 - Bronchioles
- Lower respiratory tract
 - Alveoli and bronchoalveoli
 - alveolar macrophages



DEFENSES

- Physical barriers

- Mucus
- Ciliated epithelium

- Mechanical

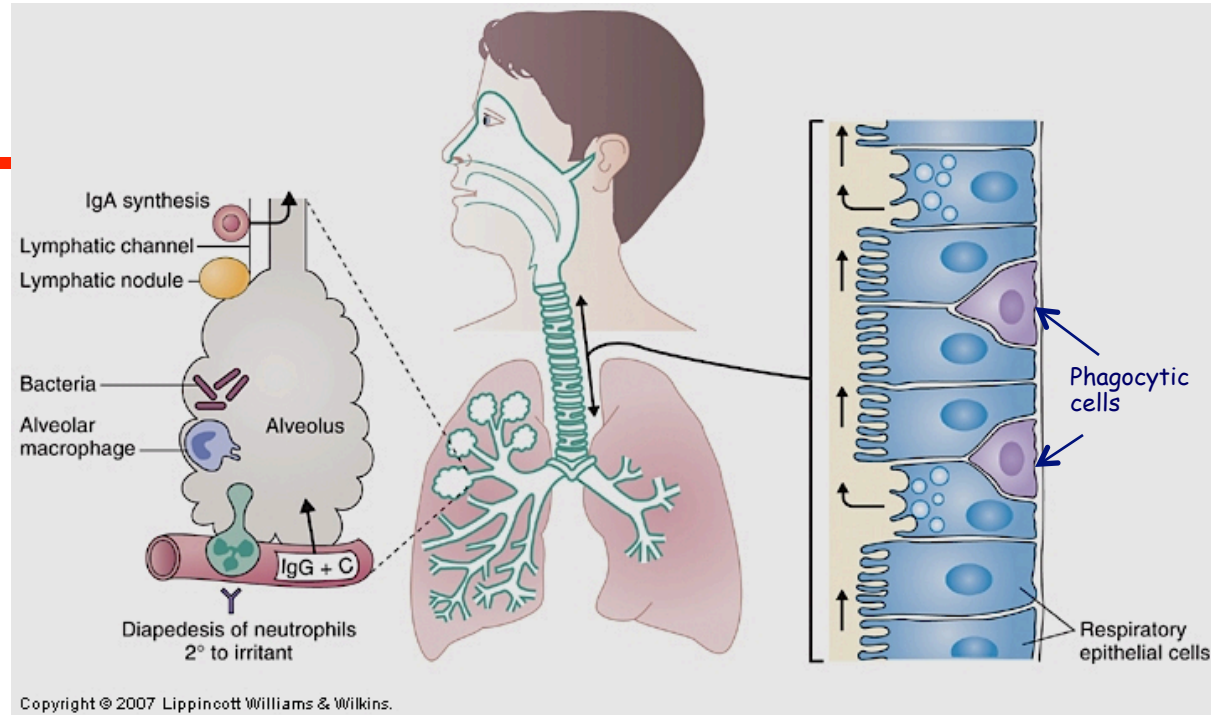
- Glottal reflex
- Coughing

- Cellular

- Alveolar macrophages
- Neutrophils - with inflammation

- Fluid

- IgA (upper)
- IgG and complement transudation from blood (lower)



Respiratory Infections

- Pharyngitis - sore throat (only 5-10% are bacterial)
 - *S. pyogenes*, *C. diphtheriae*, etc.
- Localized Upper Respiratory Tract (URT) infection with systemic consequences
 - Whooping cough - pertussis toxin
 - Diphtheria - diphtheria toxin
- Pneumonias - Low respiratory tract (LRT) and lung parenchyma
 - *S. pneumoniae*, *L. pneumophila*, *M. pneumoniae*, *M. tuberculosis*, *H. influenzae*, *S. aureus*, *K. pneumoniae*, *P. aeruginosa*, *C. pneumoniae*
- Otitis media - middle ear infection
 - *S. pneumoniae*, *H. influenzae*
- Epiglottitis
 - *H. influenzae* type b

ENCOUNTER

- Human
 - *Bordetella pertussis*
 - *Streptococcus pneumoniae*
 - *Mycoplasma pneumoniae*
 - *Mycobacterium tuberculosis*
- Environment
 - *Legionella pneumophila*
 - *Atypical mycobacteria*
 - *Pseudomonas aeruginosa*

ENTRY

- Colonization/infection of URT
 - *C. diphtheria*
 - *B. pertussis*
 - *M. pneumoniae*
- Colonization of URT followed by aspiration into LRT
 - *S. pneumoniae*
- Nasal inhalation into LRT from droplets
 - *M. tuberculosis*
 - *L. pneumophila*
- Hematogenous infection of the lung
 - *Streptococci viridans*

DAMAGE

- Host immune response (local)
 - Inflammation
 - *S. pneumoniae* (can be systemic)
 - *H. influenzae*
 - *Mycoplasma pneumoniae*
 - Cell-mediated immunity
 - *Mycobacteria tuberculosis*
 - *Legionella pneumophila*
- Toxins (systemic)
 - *C. diphtheriae* Diphtheria Toxin DT
 - *B. pertussis* Pertussis Toxin PT

Spreading - Multiplication

- Intracellular
 - Phagosome/phagolysosome
 - *Mycobacterium tuberculosis*
 - *Legionella pneumophila*
- Extracellular
 - Serous exudates
 - *S. pneumoniae*
 - *B. pertussis*
 - *C. diphtheriae*

EVASION OF DEFENSES

- URT

- Mechanisms to avoid IgA & ciliated cells

- LRT

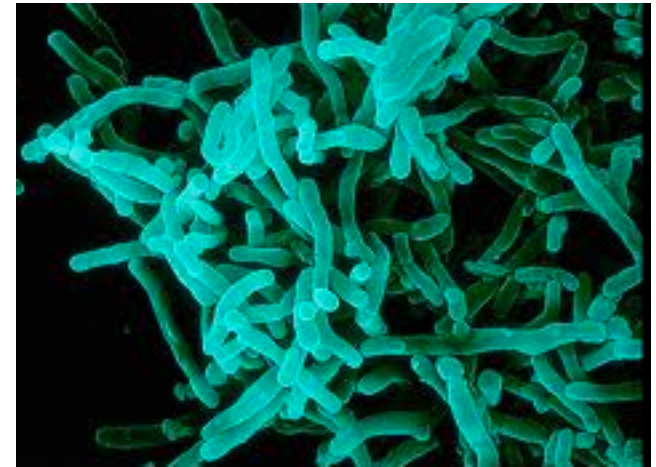
- Mechanisms to avoid complement & Igs, anti-phagocytic capsules

Diphtheria: *Corynebacterium diphtheriae*

- Gram-positive, aerobic rod

Fastidious- use serum tellurite for growth in vitro

- Encounter -
 - Humans only known reservoir
 - Asymptomatic carriers
 - Inhabits human mucous membranes (nose and throat) and skin
- Entry - Restricted to URT
- Spread - local
- Damage - Diphtheria toxin = Major virulence factor!

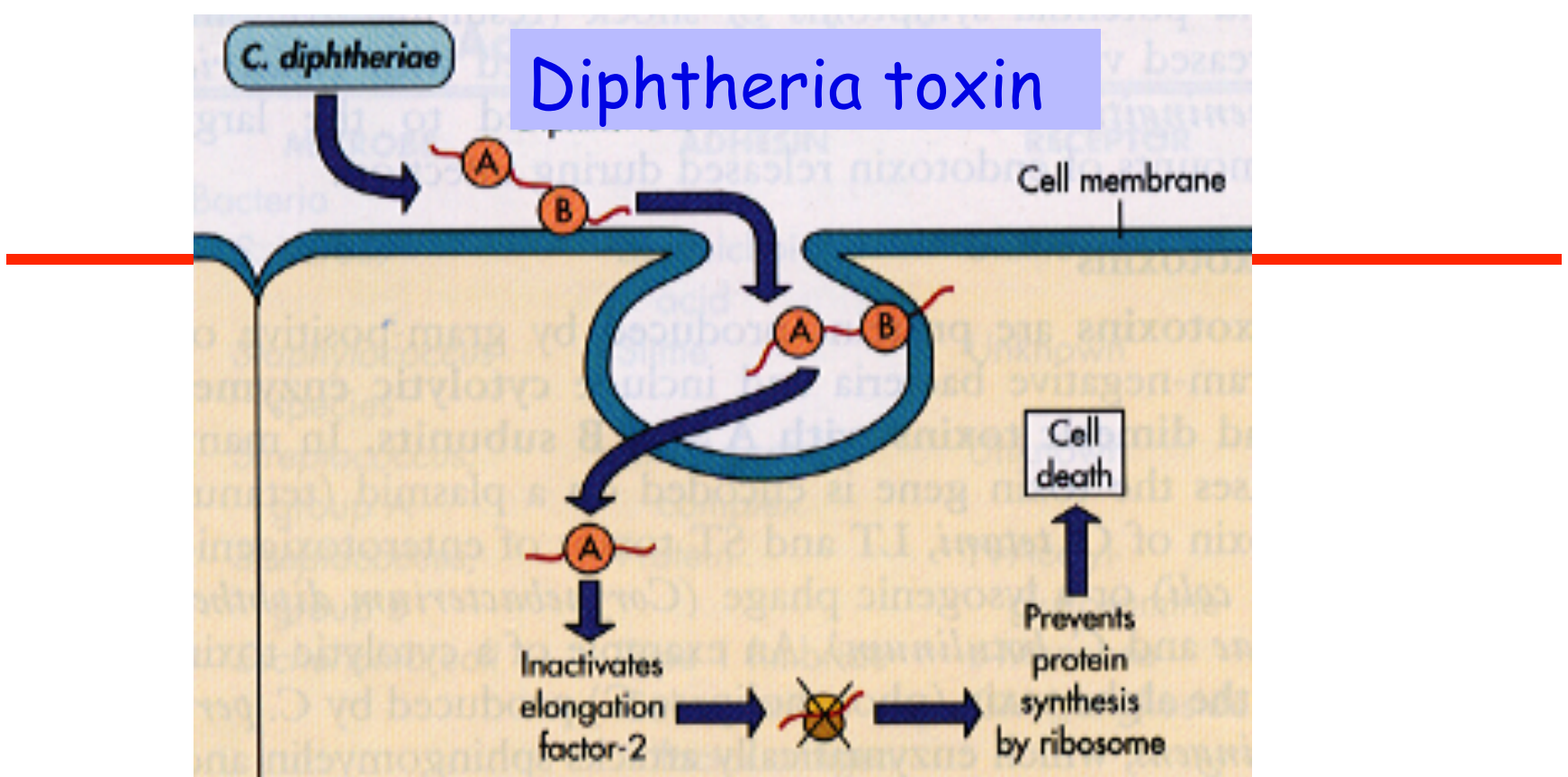


Diphtheria Toxin

- **Toxin** can disseminate to other sites in the body affecting several organs causing:
 - ◆ myocarditis
 - ◆ polyneuritis
 - ◆ renal tubular necrosis
 - ◆ and other systemic toxic effects
 - ◆ A milder form can be restricted to the skin.

Diphtheria Toxin

- Large protein (60,000 kDa) composed of two components (A and B) held together by a disulphide bond.
- **Fragment B** recognizes a plasma membrane receptor on host epithelial cell which is **heparin-binding ECGF-like growth factor**
- This binding signals the cell allowing entry of the toxin via endocytosis within an endosome and then the toxin is split into A and B fragments
- The low pH of the endosome activates B to form pores in the endosome membrane promoting release of A into cytosol which in turn inhibits protein synthesis



- Encoded on bacteriophage (lysogenic conversion)
- A-B type toxin
 - B portion binds Heparin-binding EGF precursor
 - A portion ADP ribosylates EF-2 (elongation factor)
 - Damages heart, nerve and kidneys, *etc.*
 - Death from heart/nervous system damage

Diphtheria - Clinical features

- Symptoms:
 - sore throat (pharyngitis)
 - low grade fever
 - running nose
 - chills
 - difficulty breathing
 - blueish coloration of the skin
 - cough
 - pain when swallowing
 - "pseudomembrane"

Diphtheria “Strangling Angel of Children”

- Diphtheria is from the Greek root for “leather”, describing the tough pharyngeal membrane of the disease



Diphtheria - Pharyngeal Membrane

- Gray-brown adherent pseudomembrane
- Removal leads to bleeding edematous submucosa
- Caused by DT - local tissue necrosis: dense necrotic coagulum of fibrin, RBCs, inflammatory cells

Diphtheria - “Strangling Angel of Children”

- Membrane + edema can cause airway obstruction
- Most common cause of death is suffocation due to aspiration of the membrane
- 2/3 of patients develop carditis
- Neurotoxicity is high in severe disease

Diphtheria - “Bull Neck”

- Fatality 5-10%, but in <5 or >40 year olds, could be 20%.
- 50-60% mortality due to suffocation or cardiac failure
- Lymphadenitis & edema
- Paralysis of the palatal muscles
- Larynx affected



Diphtheria

- **Transmission**

- Spread by direct contact or breathing airborne particles (highly contagious) from infected person or asymptomatic carrier

- **Vaccine**

- Toxoid (non-toxigenic form of DT) in a triple vaccine:
DTaP - Diphtheria, Tetanus, & acellular Pertussis

- **Treatment**

- Antibiotics (Penicillin & Erythromycin) & Anti-toxin

Epidemiology

- Still endemic in multiple areas of the world
- Ex-Soviet Union 1991-98, >200,000 cases with >5000 deaths
- Outbreaks are rare, but still occur even in developed nations

Microbiology

- Early recognition of disease and diagnosis is crucial
- Nasopharyngeal and pharyngeal swab for culture
- Selective media - Loeffler with tellurite

Diphtheria - in the U.S.

- Early 1890s: diphtheria was one of the leading causes of death in infants
- 1920s: 200,000 cases/yr, 13,000 deaths
- 1945: 19,000 cases after immunization became available
- 1970s: 196 cases/yr
- 1980 - 2004: 57 cases reported
- 1990 & 1996: isolated cases in Florida and focal outbreaks in South Dakota
- Since 2000: 0-2 cases per year reported

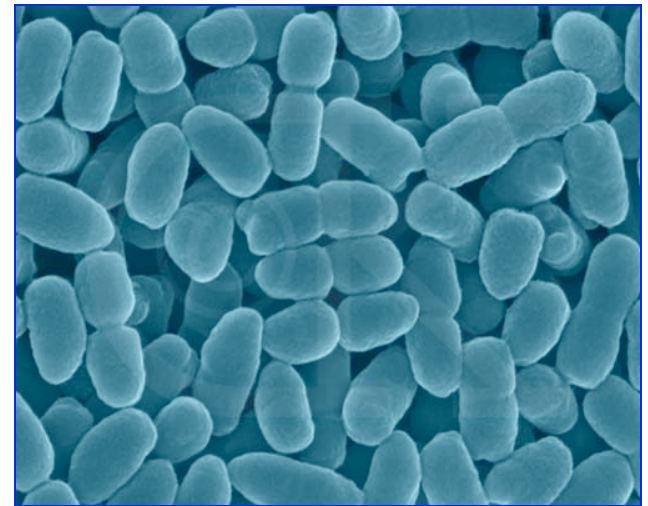
Immunization Schedule

Diphtheria Toxoid-containing Vaccine

- Primary series - 2, 4, 6 months of age
DTaP - Diphtheria, Tetanus, and acellular Pertussis
- Boost @ 15-18 months and 4-6 years w/ DTaP
- Boost @ 11 years of age and every 10 years -
with reduced doses of diphtheria toxoid
and acellular pertussis

Bordetella pertussis

- Gram-negative, pleomorphic bacillus
- Humans are only host
- Fastidious - requires Bordet-Gengou plates
- Adhesins:
 - ◆ Filamentous hemagglutinin FHA
 - ◆ Pili
- **Multiple toxins:**
 - Adenyl cyclase
 - Pertussis toxin (PT)
 - Tracheal cytotoxin
 - Dermonecrotic toxin



Whooping cough

- Primarily in infants and children
- “Violent cough”, “the cough of 100 days”
- Globally, 50 million cases & 300,000 deaths/year; Up to 3% mortality in infants
- **Encounter** - only from humans by inhalation
- **Entry** - airway colonized by *B. pertussis*, adherence to ciliated epithelium via FHA & pili
- **Spread** - restricted to URT, extracellular

DAMAGE

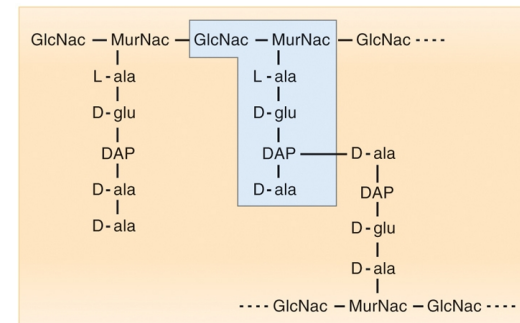
- Pertussis toxin

- A₁-B₅ type toxin
 - ADP-ribosylates G protein, increases cAMP
- Localized tissue damage
- Systemic toxicity
 - hypoglycemia, leukocytosis, neurological damage

- Tracheal cytotoxin (TCT)

- Peptidoglycan building block derivative
 - Disaccharide-tetrapeptide
- Destroys ciliated cells - cough
- Stops mucus flow

- LPS = endotoxin



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Whooping cough

- Transmission - highly contagious
 - Inhalation of aerosoles or direct contact with secretions of infected child
- Symptoms
 - Severe coughing
 - spasms
 - inspiratory whoop
 - vomiting
 - Lymphocytosis

Whooping cough

- Stages of disease
 - 7-10 days incubation -> **Catarrhal** - mild coughing, sneezing, running nose
 - 1-2- wks later **Paroxysmal** -> forceful coughs, high-pitched whoop, struggle to breath in
 - 2-8 wks later, **Convalescent**
- Usually self-limiting
 - Neurological sequelae
 - Secondary respiratory infections
 - Secondary aspiration pneumonia
 - leading cause of death

Pertussis - Clinical Features

- Begins as mild symptoms: cough, sore throat, congestion, runny nose
- Fever absent or minimum
- Can progress to paroxysms of cough with vomiting
- Apnea in very young, pneumonia and secondary infections, Toxin effects
- **Treatment:** Azitromycin, Erythromycin

Clinical presentation of *B. pertussis* disease

	Incubation	Catarrhal	Paroxysmal	Convalescent
Duration	7-10 days	1-2 weeks	2-4 weeks	3-4 weeks (or longer)
Symptoms	None	Rhinorrhea, malaise, fever, sneezing, anorexia	Repetitive cough with whoops, vomiting, leukocytosis	Diminished paroxysmal cough, development of secondary complications (pneumonia, seizures, encephalopathy)
Bacterial culture				

PREDICTIVE FACTORS FOR PERTUSSIS

Positive Factors

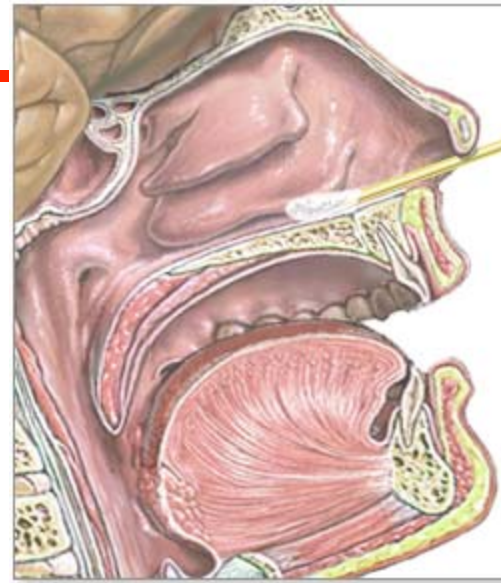
- Coughing contact
- Incomplete immunization
- Years since immunization
- Pure or predominant cough
- Paroxysmal cough
- Well between paroxysms
- Whoop
- Post-tussive vomiting
- Apnea, bradycardia (infant)
- Choking, gasping spells
- Petechiae above the clavicles
- Lymphocytosis (normal cells)

Negative Factors

- Fever
- Diarrhea
- Exanthem
- Enanthem
- Tachypnea
- Wheezes
- Rales
- Lymphadenopathy
- Neutrophilia
- Neutropenia
- Lymphocytosis (atypical cells)

Microbiology Lab: Nasopharyngeal Swab for Culture

- Clinical diagnosis
 - ◆ Symptoms, Chest X-ray
- In the catarrhal or early paroxysmal phase
- NP swab to produce a cough
- Selective media - Bordet-Gengou agar
- Incubate for 7-14 days
- Direct fluorescent assay (DFA)
- PCR - increased sensitivity



A sterile swab is passed gently through the nostril and into the nasopharynx

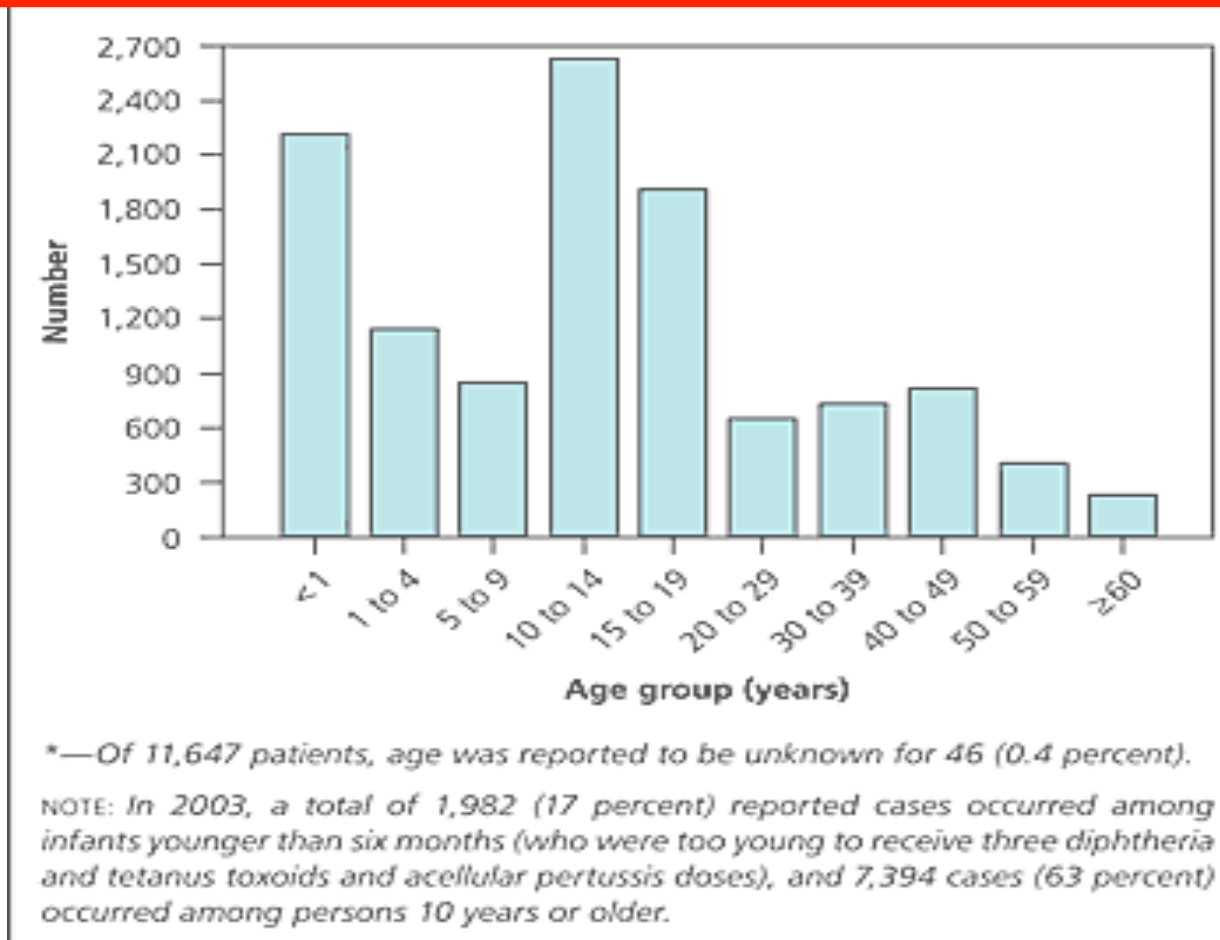
Vaccine

- Killed whole cell
 - May cause neurological problems
- Acellular vaccine
 - Pertussis toxoid + FHA

Pertussis Epidemiology - USA

- Transmission by close contact with respiratory secretions from infected; 90% of unimmunized home contacts infected
- More severe in children less than 1 yr old
- Adolescents/Adults can now be 50% of reported cases, but can occur at any age

Reported pertussis complications by age group in the United States from 1997 to 2000 (n = 28,187).



Adapted from Centers for Disease Control and Prevention. National Immunization Program. Pertussis and pertussis vaccine. Epidemiology and prevention of vaccine-preventable diseases. <http://www.cdc.gov/nip/ed/slides/pertussis8p.ppt>.

Reasons for Pertussis Increase

- Decreasing immunization of the young
- Waning immunity in adolescents/adults
- Atypical presentation in older patients
- Possible carrier state even with immunization