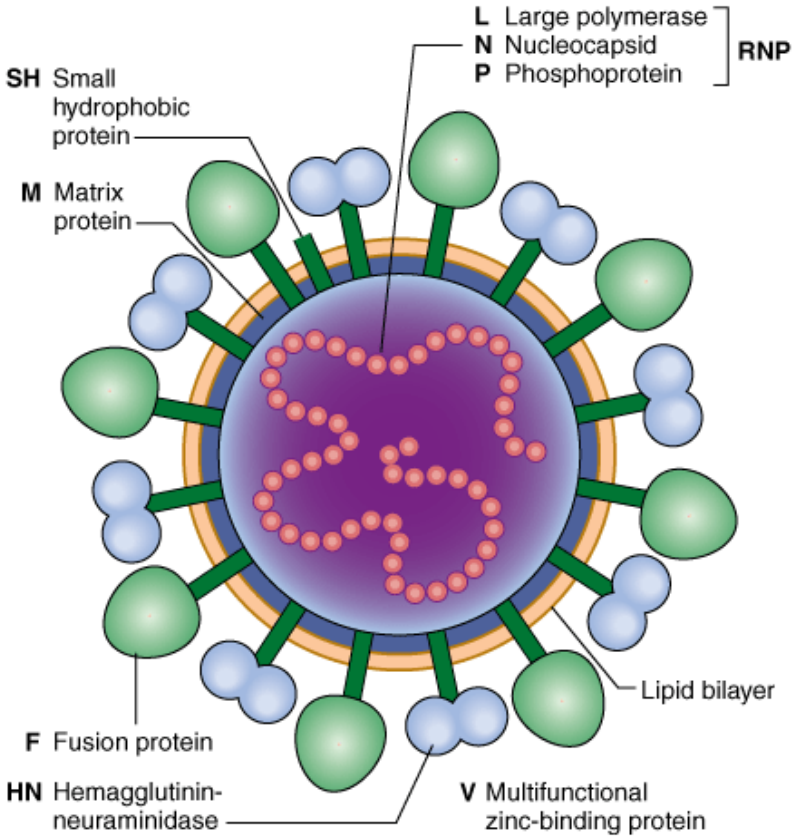
RNA ENVELOPED VIRUSES



Paramyxoviruses

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In This Lecture

- General Properties
- Structure & Composition
- Classification & Nomenclature
- Replication
- Parainfluenza Virus
- Respiratory syncytial virus
- Mump virus
- Measle and Rubeola viruses

Paramyxoviruses

- Include the most important agents of **respiratory** infections of infants and young children (**respiratory syncytial virus and the parainfluenza viruses**) as well as the causative agents of two of the most common contagious diseases of childhood (**mumps and measles**).

Properties of Paramyxoviruses

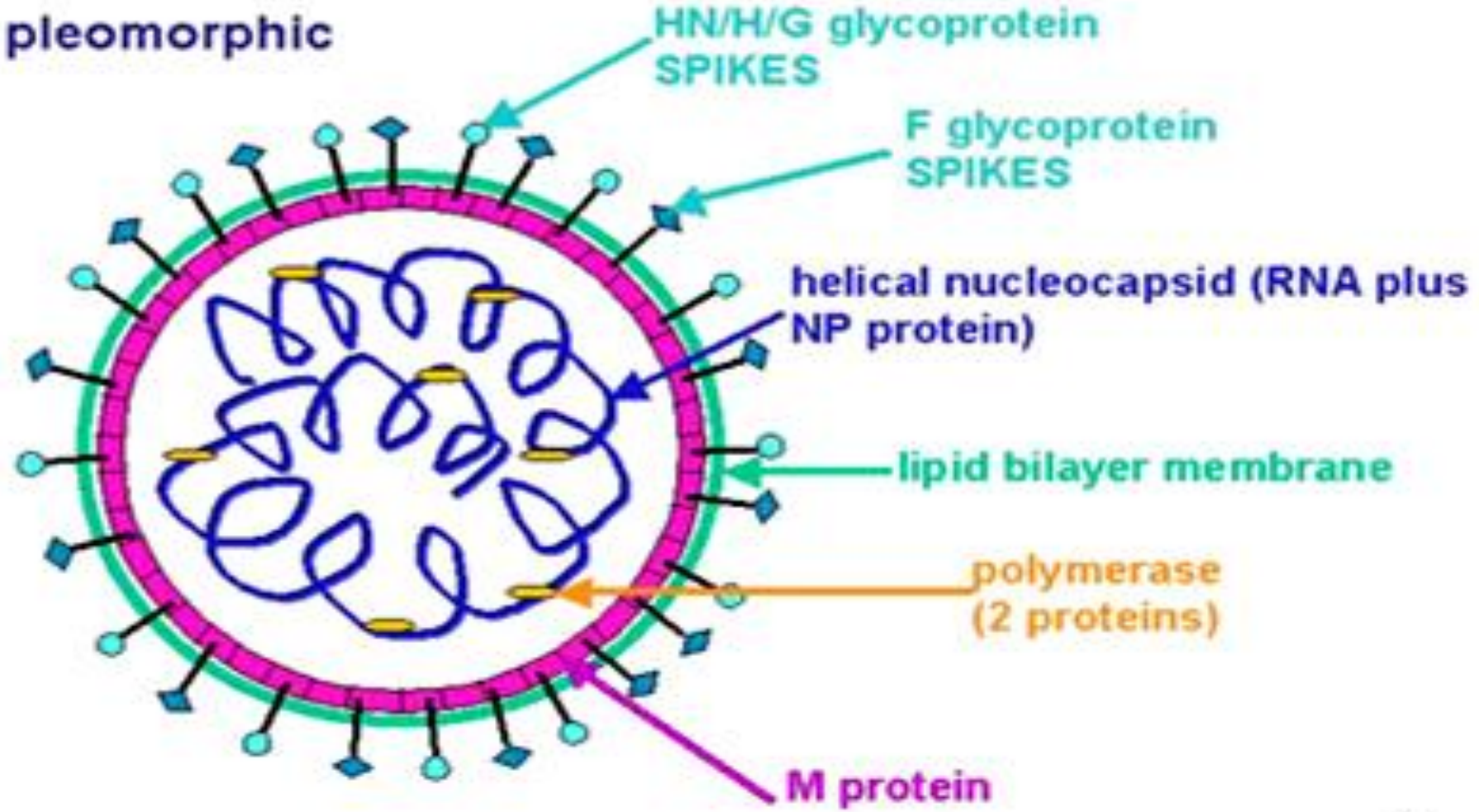
Virion: Spherical, pleomorphic, 150 nm or more in diameter (helical nucleocapsid
Composition: RNA (1%), protein (73%), lipid (20%), carbohydrate (6%)
Genome: Single-stranded RNA, linear, nonsegmented, negative-sense, noninfectious, about 15 kb
Proteins: Six to eight structural proteins
Envelope: Contains viral glycoprotein (G, H, or HN) (which sometimes carries hemagglutinin or neuraminidase activity) and fusion (F) glycoprotein; very fragile
Replication: Cytoplasm; particles bud from plasma membrane
Outstanding characteristics:
Antigenically stable
Particles are labile yet highly infectious

Orthomyxoviruses & Paramyxoviruses

Properties of orthomyxoviruses and paramyxoviruses.

Property	Orthomyxoviruses	Paramyxoviruses
Viruses	Influenza A, B, and C viruses	Measles, mumps, respiratory syncytial, and parainfluenza viruses
Genome	Segmented (eight pieces) single-stranded RNA of negative polarity	Nonsegmented single-stranded RNA of negative polarity
Virion RNA polymerase	Yes	Yes
Capsid	Helical	Helical
Envelope	Yes	Yes
Size	Smaller (110 nm)	Larger (150 nm)
Surface spikes	Hemagglutinin and neuraminidase on different spikes	Hemagglutinin and neuraminidase on the same spike[1]
Giant cell formation	No	Yes

PARAMYXOVIRUSES



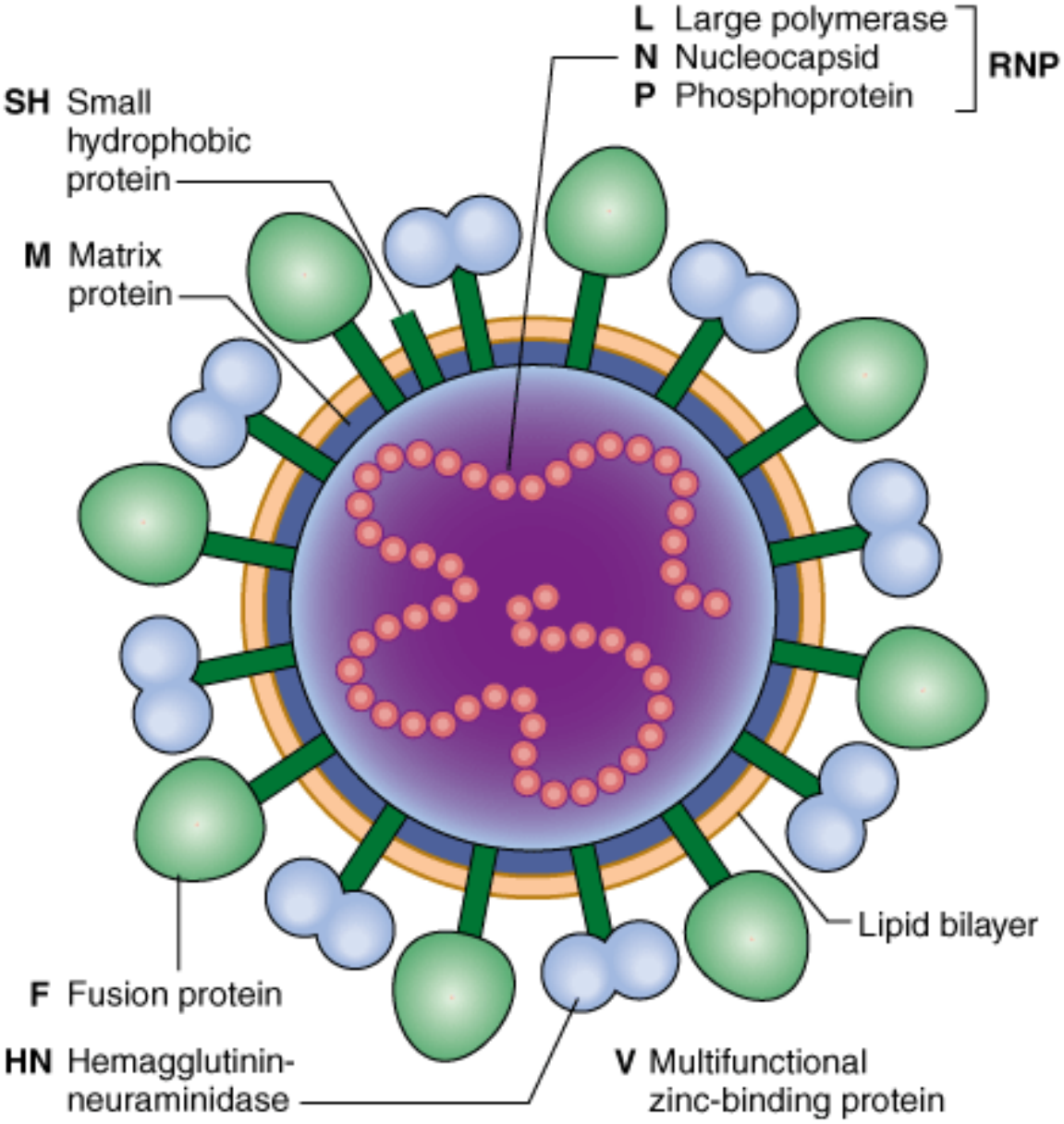
Paramyxoviruses

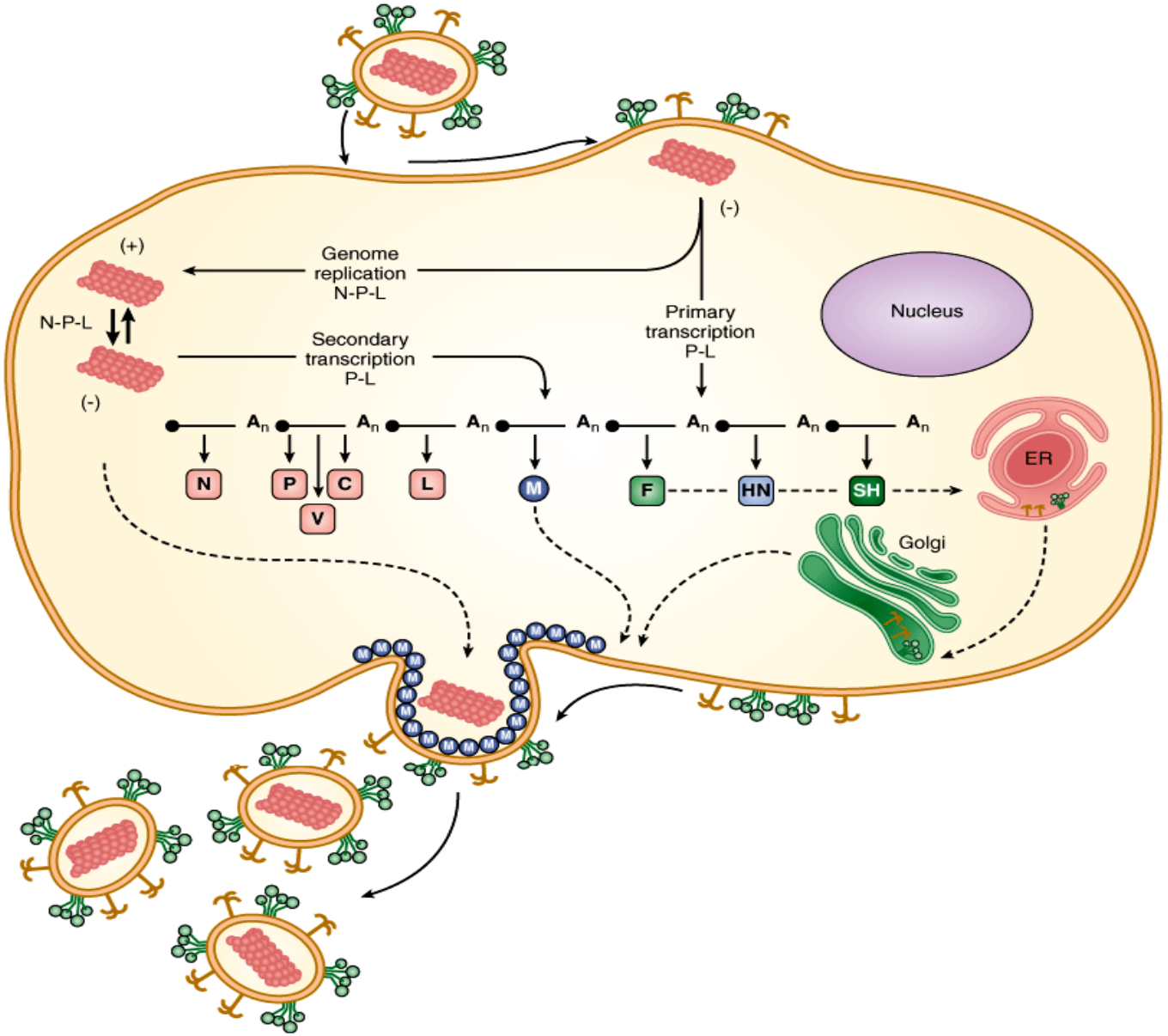
Most paramyxoviruses contain **six** structural proteins:

- **Three** proteins are complexed with
  - the viral RNA the **nucleoprotein (N)** that forms the helical nucleocapsid and represents the major internal protein.
  - **Two** large proteins **(P and L)**, which are involved in the viral polymerase activity that functions in transcription and RNA replication.

Paramyxoviruses

- Three proteins participate in the formation of the viral envelope.
  - A **matrix (M) protein** underlies the viral envelope; it has an affinity for both the N and the viral surface glycoproteins and is important in virion assembly.
  - The nucleocapsid is surrounded by a lipid envelope that is studded with spikes of **two different transmembrane glycoproteins**. The activities of these surface glycoproteins help differentiate the various genera of the Paramyxoviridae family.





Paramyxovirus life cycle. The infecting virus particle fuses with the plasma membrane and releases the viral nucleocapsid into the cytoplasm. Solid lines represent transcription and genome replication. Dotted lines indicate transport of newly synthesized viral proteins to plasma membrane. Progeny virions are released from the cell by a budding process. The entire paramyxovirus replication cycle takes place in the cell cytoplasm. (Copyright GD Parks and RA Lamb, 2006.)

PARAINFLUENZA VIRUSES

- They are major pathogens of **severe respiratory** tract disease in **infants** and **young children**.
- Only **respiratory syncytial virus**, and perhaps human **metapneumovirus**, causes more cases of **serious** respiratory disease in children.
- **Reinfections** with parainfluenza viruses are common.

PARAINFLUENZA VIRUSES

- Virus replication limited to **respiratory epithelia**.
- **Viremia**, if it occurs at all, is uncommon.
- The infection may involve only the **nose** and **throat**, resulting in a harmless "**common cold**" syndrome.

PARAINFLUENZA VIRUSES

- However, infection may be more extensive and, especially with types 1 and 2, may involve the **larynx** and **upper trachea**, resulting in **croup** (**laryngotracheobronchitis**). Croup is characterized by respiratory obstruction due to swelling of the larynx and related structures.

- The infection may spread deeper to the **lower trachea** and **bronchi**, culminating in **pneumonia** or **bronchiolitis**, especially with type 3.

PARAINFLUENZA VIRUSES

Clinical Findings:

- CROUP, in children younger than 5 years of age. It is characterized by harsh cough and hoarseness.
- Other respiratory diseases: common cold, pharyngitis, otitis media, bronchitis.

PARAINFLUENZA VIRUSES

Laboratory Diagnosis:

- Antigen Detection (Immuno fluorescent [IF])
- Nucleic Acid Detection (RT-PCR)
- Virus isolation by cell culture
- Serology: Rise in Ab titer

Treatment and prevention

- The antiviral drug **ribavirin** has been used with some benefit in treatment of **immunocompromised** patients with lower respiratory tract disease
- **No** vaccine available.

PARAINFLUENZA VIRUSES

Transmission & Epidemiology:

- Viruses are transmitted via respiratory droplets.
- Large proportion of infections are subclinical.

Respiratory syncytial virus

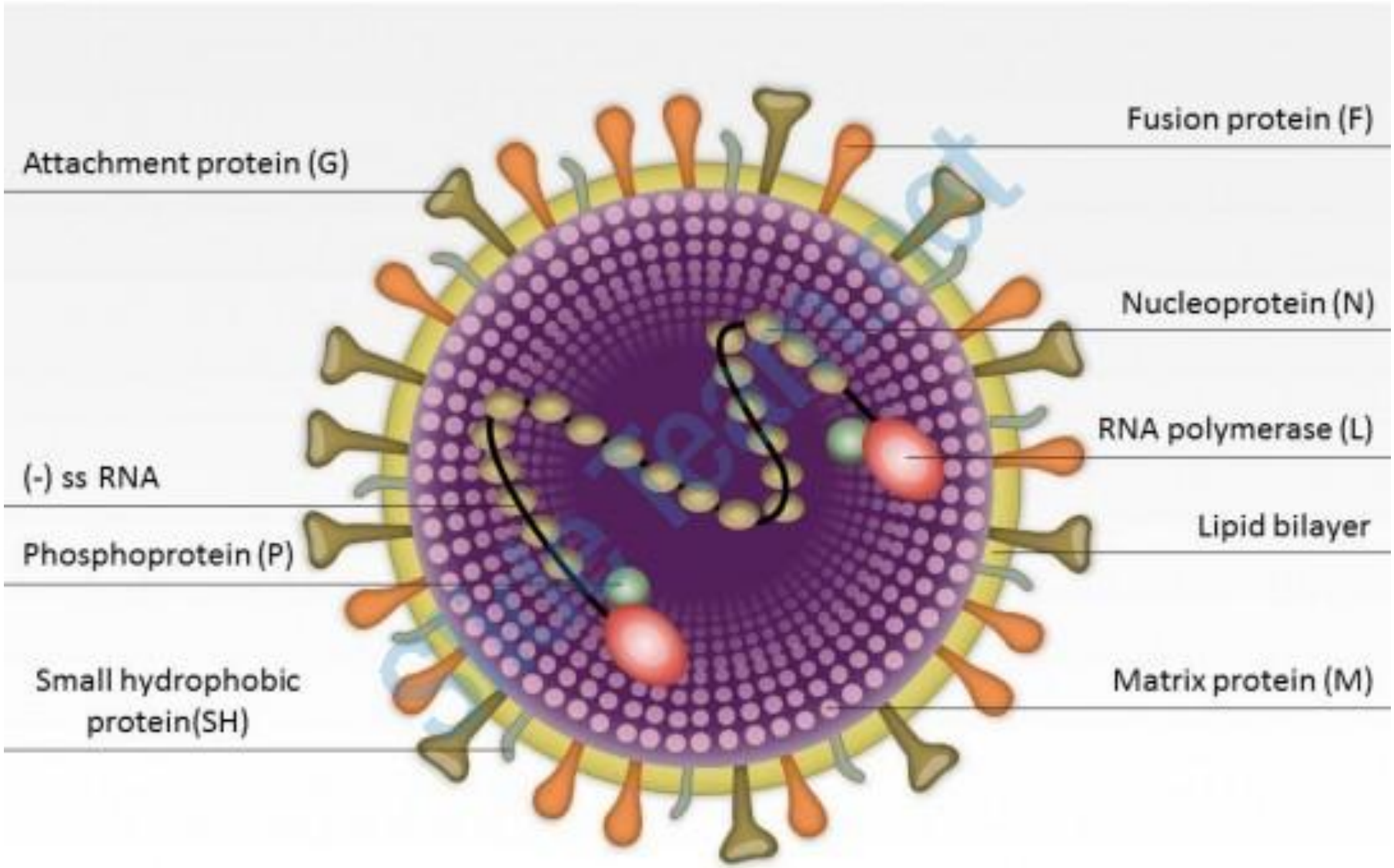
Disease:

It is the **most** important cause of pneumonia and bronchiolitis in **infants**

Important properties:

Its surface spikes are fusion proteins, not hemagglutinins or neuraminidases. **Fusion** protein causes cells to fuse, forming multinucleated giant cell (**syncytia**), which give rise to the name of this virus.

RSV VIRUS


Attachment protein (G)
Fusion protein (F)
Nucleoprotein (N)
RNA polymerase (L)
(-) ss RNA
Lipid bilayer
Phosphoprotein (P)
Small hydrophobic protein(SH)
Matrix protein (M)

Respiratory syncytial virus

Transmission and Epidemiology:

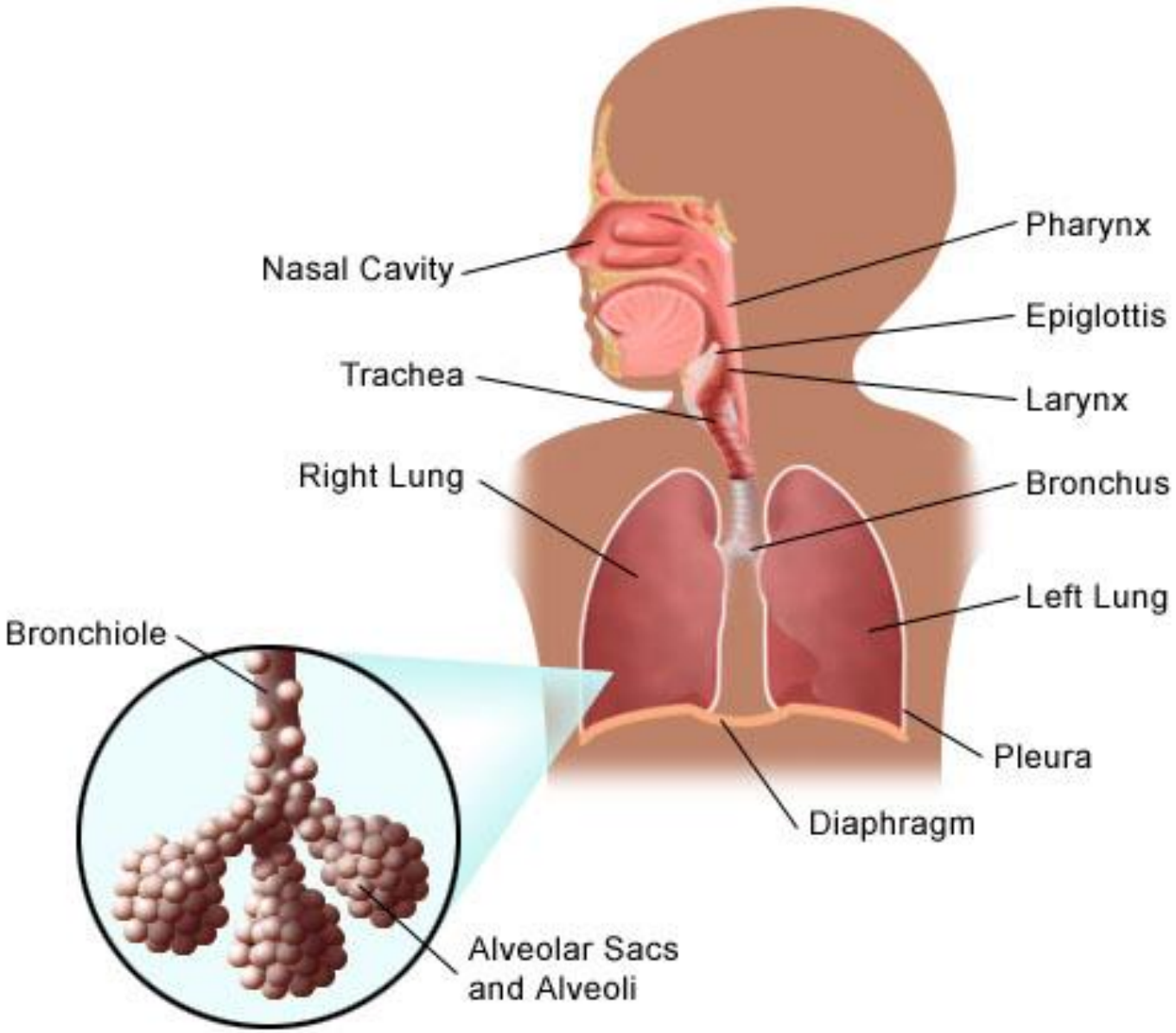
- Transmission occurs via respiratory droplets and by direct contact of contaminated hands with the nose or mouth.
- RSV causes outbreaks of respiratory infection in infants every winter.
- It causes outbreaks of respiratory infections in hospitalized **infants**.

Respiratory syncytial virus

Pathogenesis & Immunity:

- Infection in infants is more severe and more often involves the lower respiratory tract than in older children and adults in whom it causes mild upper respiratory infections.
- The infection is localized to the respiratory tract, viremia does not occur.
- Most individuals have multiple infections caused by RSV indicating that immunity is incomplete. The reason for that is unknown, but it is not due to antigenic variation of the virus, IgA respiratory antibody reduces the frequency of RSV infection as a person ages.

Bronchiolitis “Respiratory syncytial virus”



Respiratory syncytial virus

Clinical Findings:

- In newborns & infants, RSV is an important cause of lower respiratory tract diseases such as bronchiolitis and pneumonia.
- Otitis media in young children
- Upper respiratory tract infection as common cold in older children and adults.

Respiratory syncytial virus

Lab Diagnosis:

- Virus can be detected rapidly by **immunofluorescence** on smears of respiratory epithelium.
- Nucleic Acid Detection by **RT-PCR**
- Isolation in cell culture, **CPE** is formation of **multinucleated** giant cells
- Serology: rise in Ab titer of at least 4-folds.

Respiratory syncytial virus

Treatment:

- **Aerosolized ribavirin** (Virazole) is recommended for severely ill hospitalized infants.
- A combination of ribavirin and hyperimmune globulins against RSV may be effective.

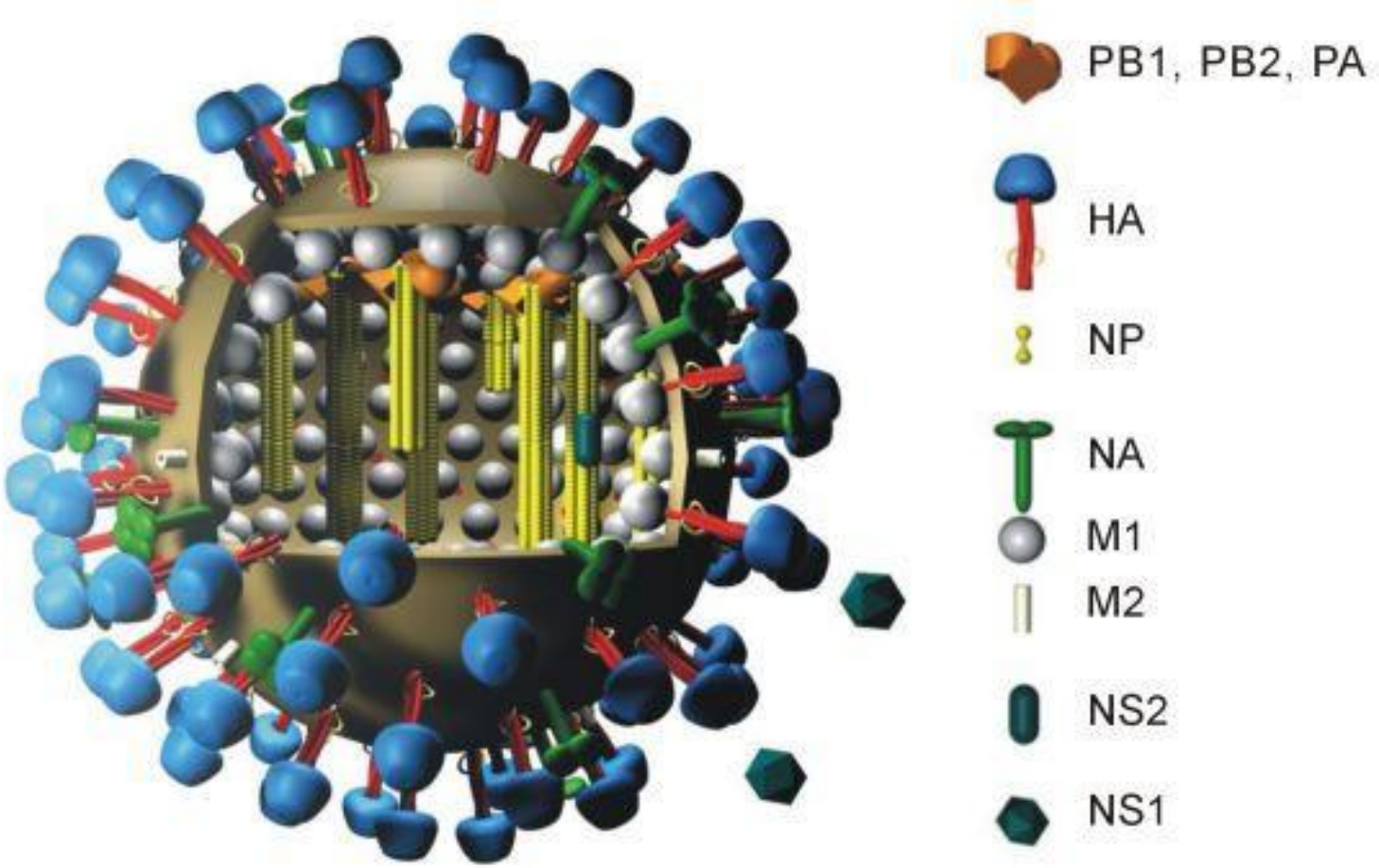
Prevention:

- There is no vaccine.
- Passive immunization with a monoclonal Ab directed against the fusion protein of RSV can be used for prophylaxis in **premature** and **immunocompromized** infants.

Mumps Virus Infections

- **Mumps** is an acute **contagious** disease characterized by nonsuppurative **enlargement** of one or both **salivary** glands.
- Mumps virus mostly causes a **mild** childhood disease, but in adults complications including **meningitis** and **orchitis** are fairly common.
- More than **one-third** of all mumps infections are **asymptomatic**.

Mumps Virus



Pathogenesis & Pathology

- **Humans** are the **only** natural **hosts** for mumps virus.
- Primary replication occurs in **nasal or upper respiratory tract epithelial cells**. **Viremia** then disseminates the virus to the **salivary** glands and other major **organ** systems.
- Involvement of the **parotid** gland is **not** an **obligatory** step in the infectious process.

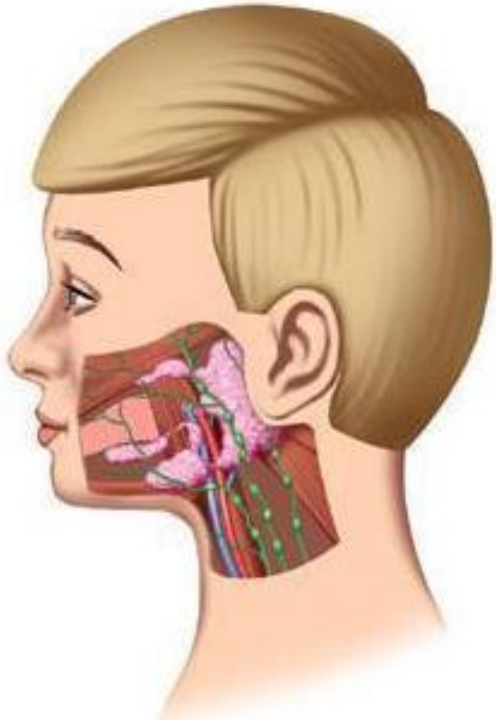
Pathogenesis & Pathology

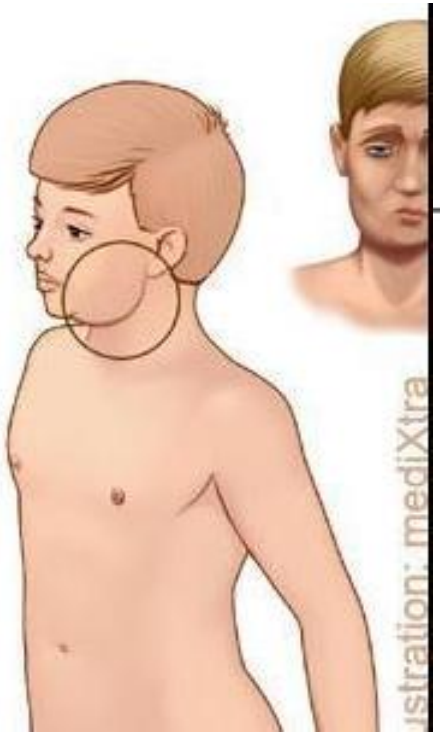
- The **incubation period** may range from **2** to **4** weeks but is typically about **14-18 days**.
- Virus is shed in the **saliva** from about **3** days **before** to **9** days **after** the onset of salivary gland swelling.
- About **one-third** of infected individuals do not exhibit obvious symptoms (**inapparent infections**) but are equally capable of transmitting infection.
- It is **difficult to control transmission** of mumps because of the variable incubation periods, the presence of virus in saliva before clinical symptoms develop, and the large number of asymptomatic but infectious cases.

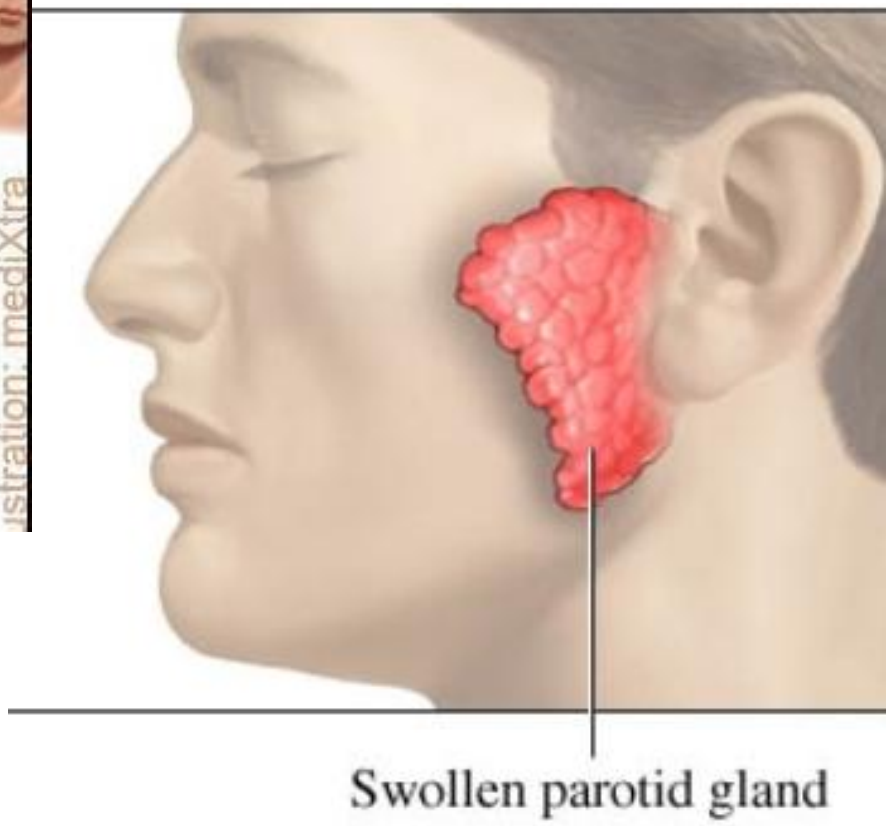
Clinical Findings

- At least **one-third** of all mumps infections are **subclinical**, including the majority of infections in children under **2 years** of age.
- Characteristic feature of symptomatic cases is **swelling** of the **salivary** glands, which occurs in about **50%** of patients.
- **Malaise** and **anorexia** is followed by rapid **enlargement** of parotid glands, the enlargement is associated with **pain**.
- **CNS** involvement is common **(10-30%)** of cases. Mumps causes **aseptic meningitis.**

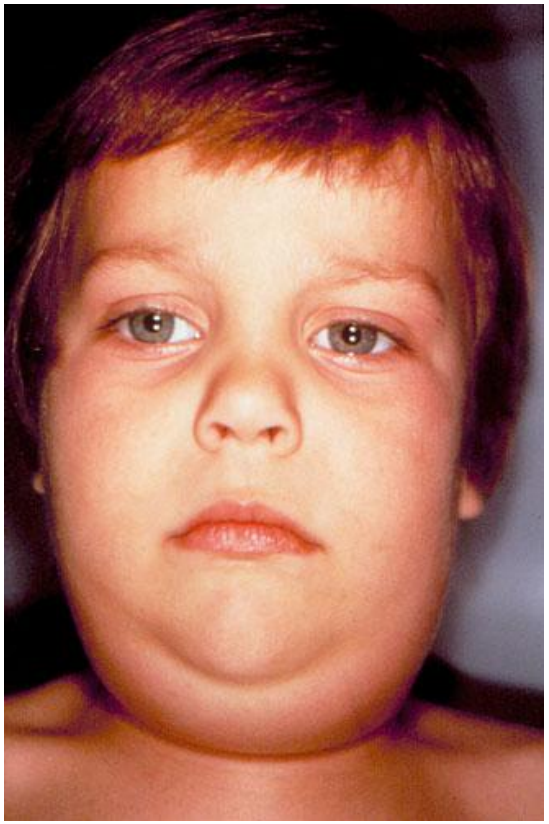
Mumps Virus







Mumps Virus



Clinical Findings

- The **testes and ovaries** may be affected, especially after puberty. **20-50%** of men who are infected with mumps virus develop **orchitis** (often unilateral).
- Because of the lack of elasticity of the tunica albuginea, which does not allow the inflamed testis to swell, the **complication** is extremely painful.
- **Atrophy** of the testis may occur as a result of pressure necrosis, but only rarely does **sterility** result.
- Mumps **oophoritis** occurs in about 5% of women.
- **Pancreatitis** is reported in about 4% of cases.

Immunity

- Immunity is **permanent** after a single infection. There is only one antigenic type of mumps virus, and it does not exhibit significant antigenic variation.
- **Passive immunity** is transferred from mother to offspring; thus, it is rare to see mumps in infants under 6 months of age.

Laboratory Diagnosis

- Isolation & Identification of Virus:
  - Clinical samples for viral isolation are saliva, cerebrospinal fluid, and urine.
  - Culture systems, cytopathic effects typical of mumps virus consist of cell rounding and giant cell formation.
- Nucleic Acid Detection:
- Serology:
  - The ELISA or HAI test is commonly used.
  - ELISA can be designed to detect either mumps-specific IgM antibody or mumps-specific IgG antibody.

Epidemiology

- Mumps occurs endemically **worldwide**.
- Cases appear throughout the year in **hot climates** and **peak** in **winter and spring** in temperate climates.
- **Outbreaks** occur where **crowding** favors dissemination of the virus.
- Mumps is primarily an infection of **children**. The disease reaches its highest incidence in **children aged 5-9 years**.

Epidemiology

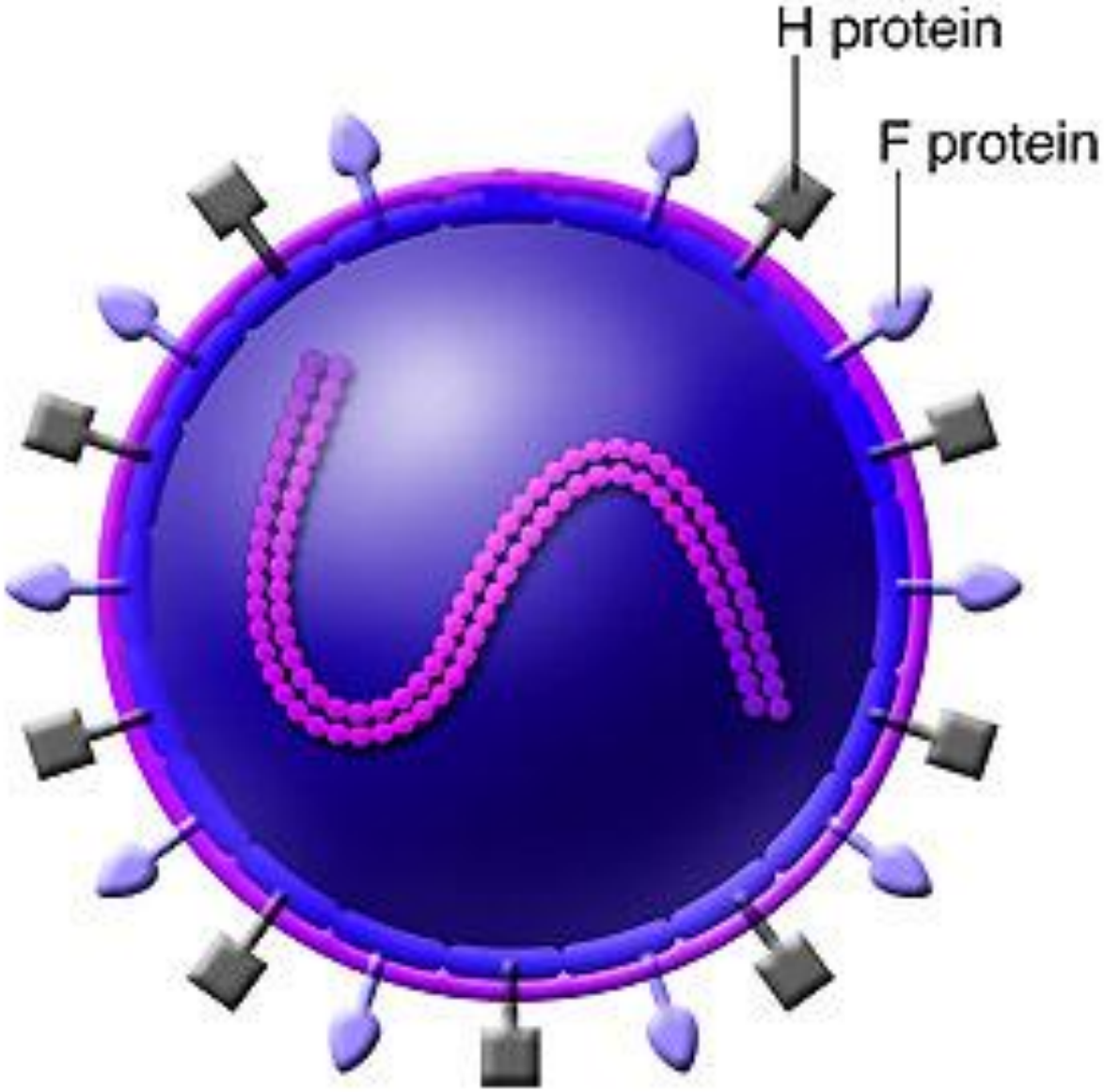
- In **children** under 5 years of age, mumps may commonly cause upper respiratory tract infection without parotitis.
- The virus is **transmitted** by **direct contact**, **airborne droplets**, or **fomites** contaminated with saliva or urine.
- **Closer contact** is necessary for transmission of mumps than for transmission of measles or varicella .

Treatment, Prevention, & Control

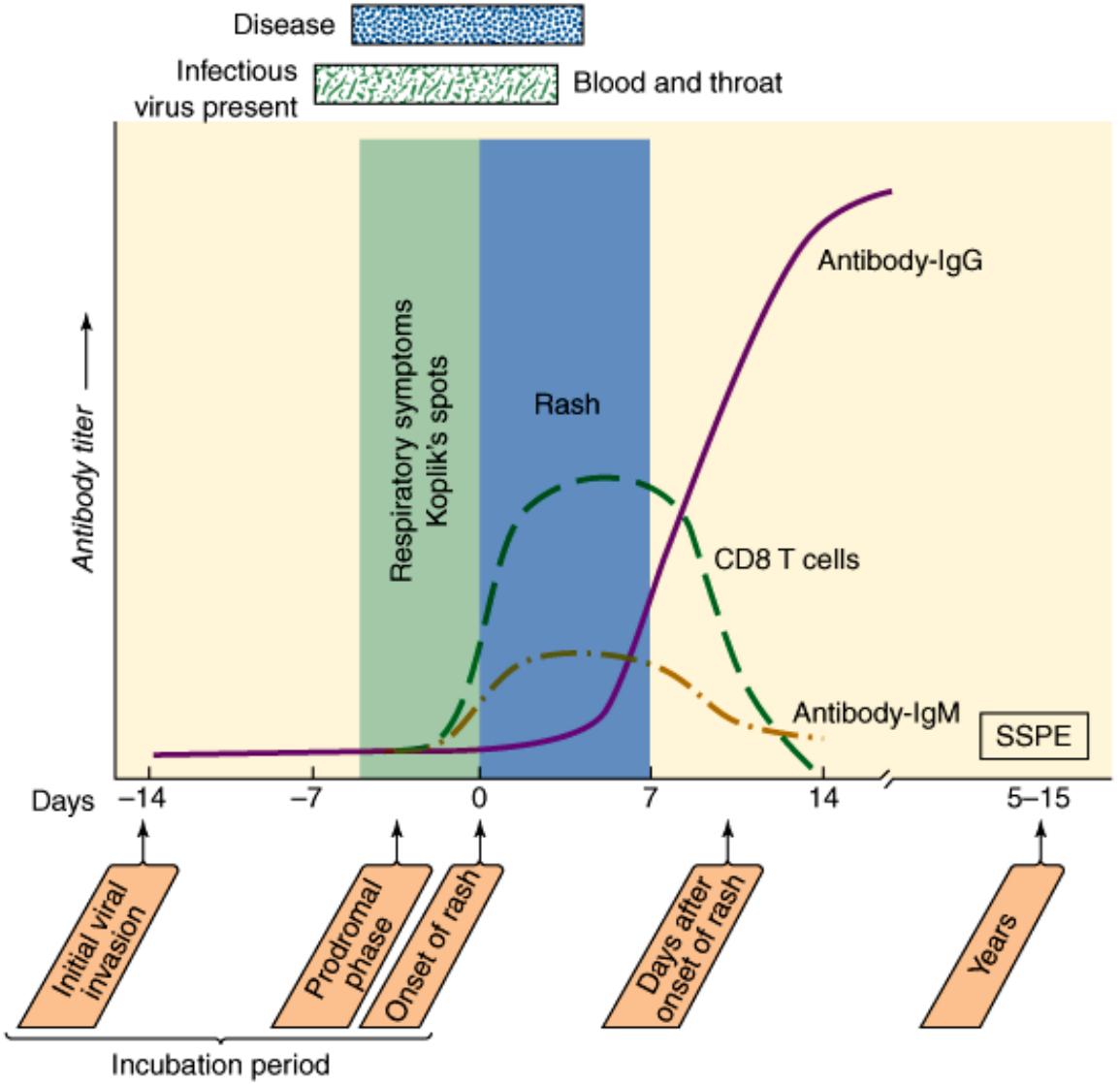
- There is **no specific therapy**.
- Immunization with **attenuated live mumps** virus vaccine is the best approach to reducing mumps.
- Mumps vaccine is available in combination with **measles and rubella (MMR)** live-virus vaccines. Combination live-virus vaccines produce antibodies to each of the viruses in about **78-95% of vaccinees**.
- **Two doses of MMR** vaccine are recommended for school entry.

Measles (Rubeola) Virus Infections

- Measles is an acute, **highly infectious** disease characterized by **fever**, **respiratory** symptoms, and a **maculopapular rash**.
- **Complications** are common and may be quite **serious**.
- The introduction of an **effective live-virus vaccine** has dramatically **reduced** the incidence of this disease, but measles is still a leading cause of **death of young children** in many developing countries.



Measles virus



Natural history of measles infection. Viral replication begins in the respiratory epithelium and spreads to monocyte-macrophages, endothelial cells, and epithelial cells in the blood, spleen, lymph nodes, lung, thymus, liver, and skin and to the mucosal surfaces of the gastrointestinal, respiratory, and genitourinary tracts. The virus-specific immune response is detectable when the rash appears. Clearance of virus is approximately coincident with fading of the rash. (SSPE, subacute sclerosing panencephalitis.)

Pathogenesis & Pathology

- The virus gains access to the human body via the **respiratory tract**, where it multiplies locally;
- Then spreads to the **regional lymphoid** tissue, where further multiplication occurs.
- **Primary viremia** disseminates the virus, which then replicates in the **reticuloendothelial** system.
- Finally, a **secondary viremia** seeds the epithelial surfaces of the body, including the skin, respiratory tract, and conjunctiva, where focal replication occurs.
- **Multinucleated** giant cells with **intranuclear inclusions** are seen in lymphoid tissues throughout the body.

Pathogenesis & Pathology

- During the **prodromal phase** (2-4 days) and the first 2-5 days of rash, virus is present in tears, nasal and throat secretions, urine, and blood.
- The characteristic **maculopapular** rash appears about day 14 just as circulating antibodies become detectable, the viremia disappears, and the fever falls.
- The rash develops as a result of interaction of **immune T cells** with virus-infected cells in the small blood vessels and lasts about 1 week.

Clinical Findings

- After an **incubation period** of 8-12 days, measles is typically a 7- to 11-day illness (with a prodromal phase of 2-4 days followed by an eruptive phase of 5-8 days).
- prodromal phase is characterized by **fever**, **sneezing, coughing, running nose, redness of the eyes, Koplik spots, and lymphopenia**.
- The cough and coryza reflect an **intense inflammatory reaction** involving the mucosa of the respiratory tract.
- The **conjunctivitis** is commonly associated with **photophobia**.


© CDC

Complications

- The most common complication of measles is **otitis media** (5-9% of cases).
- **Pneumonia** is the most common life-threatening complication of measles, caused by **secondary bacterial** infections. This occurs in less than **10%** of cases in developed countries but is much more frequent (**20-80%**) in developing countries.
- **Pulmonary** complications account for more than **90%** of measles-related **deaths**. Pneumonia develops in 3-15% of adults with measles.

Complications

- Involvement of **CNS** are the most serious. About 50% of children with regular measles register electroencephalographic changes.
- **Acute encephalitis** occurs in about 1:1000 cases. There is no apparent correlation between the severity of the measles and the appearance of neurologic complications.
- **Postinfectious encephalomyelitis (acute disseminated encephalomyelitis)** is an autoimmune disease associated with an **immune** response to myelin basic protein.
- The **mortality** rate in encephalitis associated with measles is about **10-20%.** The majority of survivors have neurologic sequelae.

Laboratory Diagnosis

- Antigen & Nucleic Acid Detection
- Isolation & Identification of Virus
  - Measles virus grows slowly; typical cytopathic effects (multinucleated giant cells containing both intranuclear and intracytoplasmic inclusion bodies) take 7-10 days
- Serology

Epidemiology

- Transmission occurs predominantly via the **respiratory** route (by inhalation of large droplets of infected secretions).
- Measles is **endemic** throughout the world. In general, **epidemics** recur regularly every 2-3 years.
- the disease will flare up when there is an accumulation of susceptible **children.**
- Measles cases occur throughout the year in **temperate** climates. Epidemics tend to occur in late **winter** and early **spring**.

Treatment, Prevention, & Control

- **Vitamin A** treatment in developing countries has decreased mortality and morbidity.
- **Attenuated live** measles virus **vaccine** has been available since 1963. Measles vaccine is available in monovalent form and in combination with live attenuated rubella vaccine (MR), live attenuated rubella and mumps vaccines (**MMR**).
- **Contraindications** to vaccination include **pregnancy**, allergy to eggs or neomycin, immune compromise (except that due to infection with human immunodeficiency virus), and recent administration of immunoglobulin.