

وَقُلْ رَبِّ زِدْنِي عِلْمًا



# RESPIRATORY SYSTEM

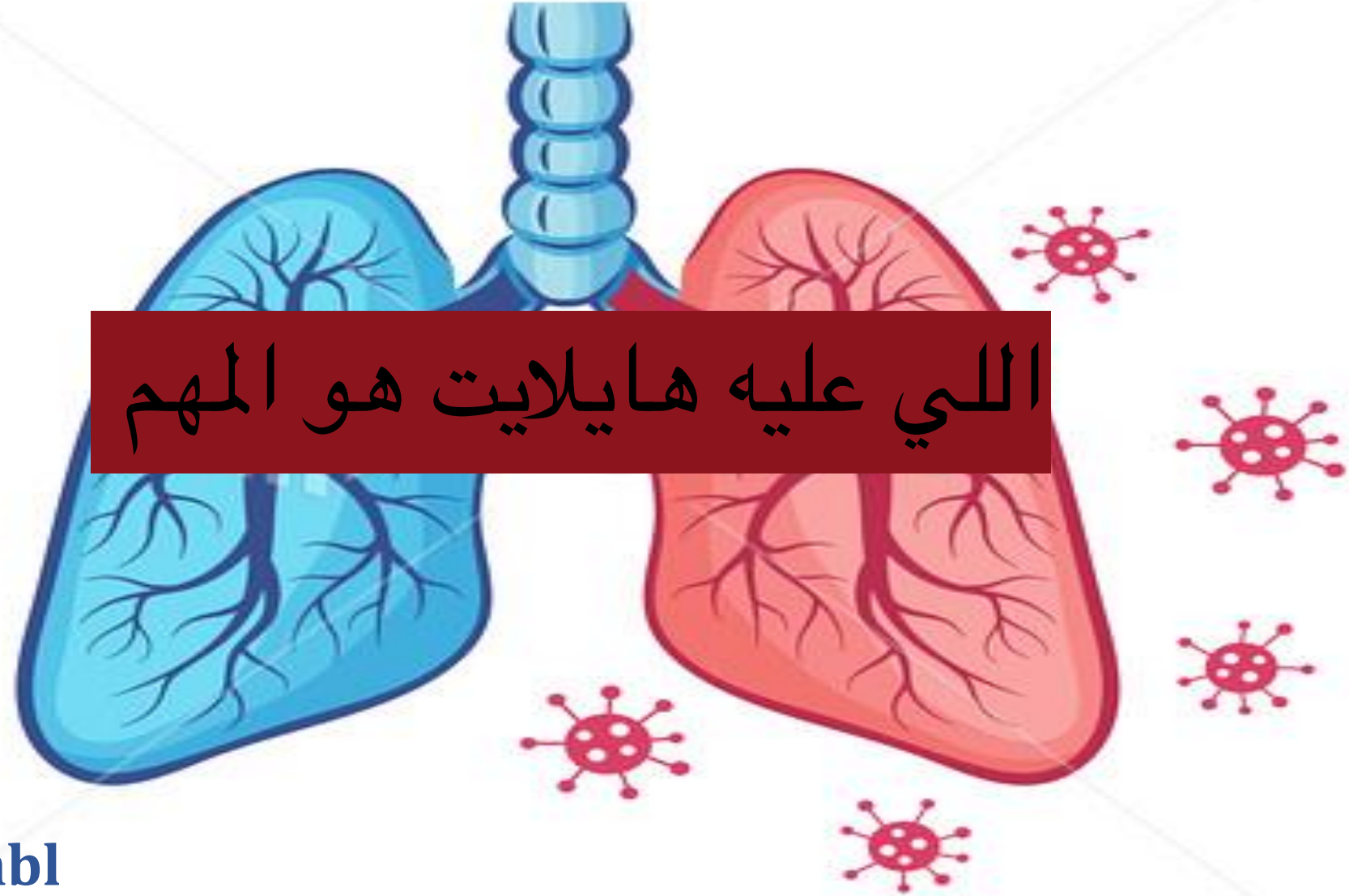
HAYAT BATCH

SUBJECT : Micro-most important

LEC NO. : Final

DONE BY : Abdullah Harahsheh

# RESPIRATORY TRACT INFECTIONS



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By  
Prof. Hala Tabl

# INFLUENZA VIRUSES

## Morphological characters:

### 1) Genome:

- Single-stranded RNA.
- **Segmented**, eight segments, each segments encode a certain viral protein.
- **Negative-polarity** (contains RNA-dependent RNA polymerase).

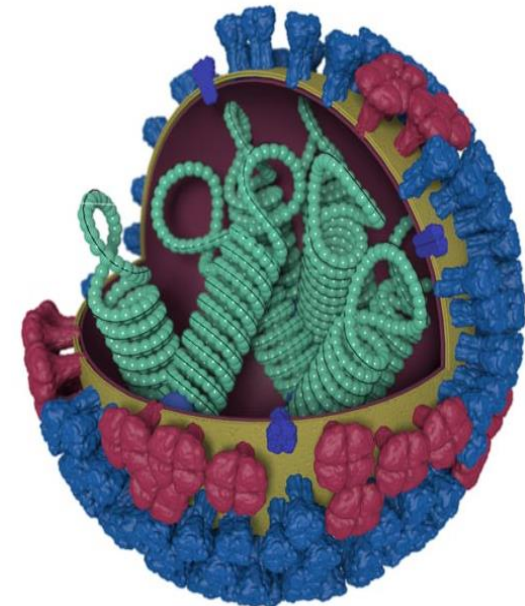
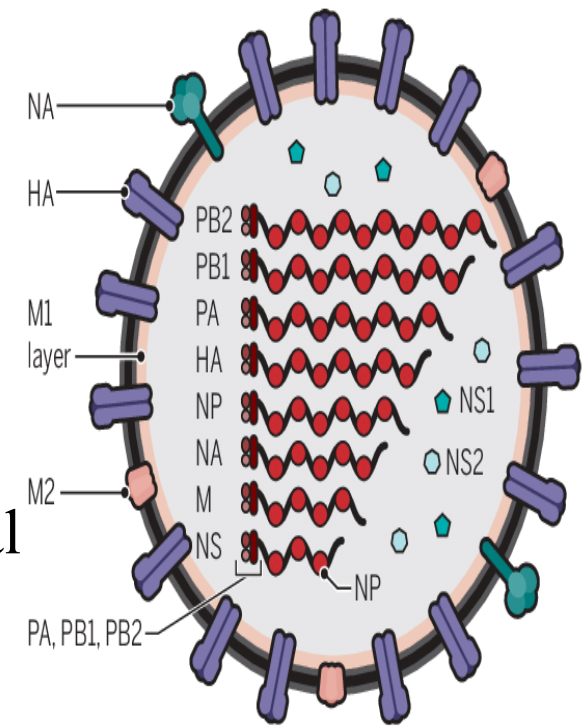
### 2) Helical capsid symmetry.

### 3) Enveloped:

The envelope carries 2 types of projections:

**Hemagglutinin spikes (HA) & Neuraminidase spikes (NA).**

- Replication takes place in the **nucleus**.







## Haemagglutinin spikes (HA)

- Bind to the cell surface receptor (**neuraminic acid, sialic acid**) to initiate (**entry**) of the cell.
- Cleaved by cellular proteases to mediate **fusion** with endosomal membrane.
- HA functions **at the beginning** of the life cycle.
- It is the target of **neutralizing antibody** (i.e., antibody against the hemagglutinin **inhibits infection** of the cell).
- **Agglutinates** red blood cells.
- Encoded by segment 4.



## Neuraminidase spikes (NA)

- Degrades the protective layer of mucus in the respiratory tract.
- Cleaves neuraminic acid (sialic acid) to **release** progeny virus from the cell.
- Inactivate the **free receptor**.
- NA function **at the end** of the life cycle.
- Antibody against the neuraminidase **NOT prevent infection**, it reduce amount of virus released, reducing spread of virus.
- Encoded by segment 6.

# Genetic variations of Influenza viruses:

Influenza viruses have two types of antigens:

(1) **The internal ribonucleoprotein:** *Suptivae*

distinguishes influenza into three types; A, B, and C.

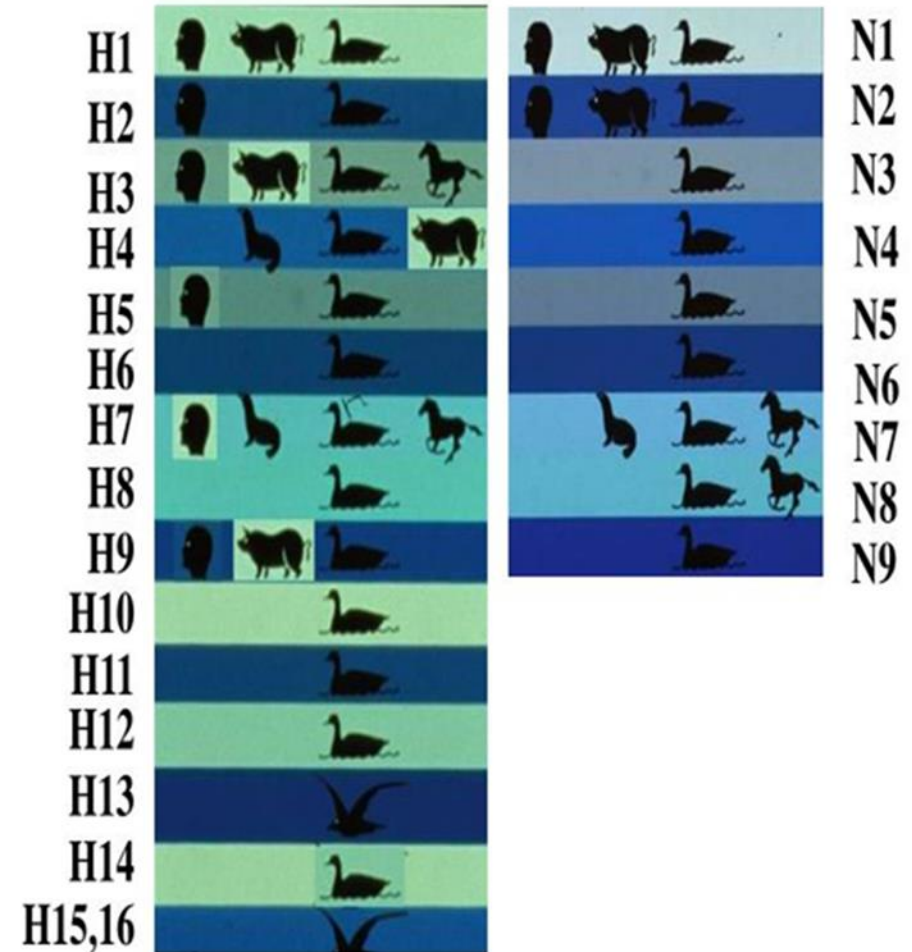
(2) **The surface HA & NA:**

➤ **Influenza A** virus has **16** antigenically distinct types of HA and **9** antigenically distinct types of NA.

Some of these types cause diseases in humans, but most of them typically cause diseases in other **animal** species such as birds, horses, and pigs.

➤ **Influenza B** virus **almost exclusively infects humans**.

## Species Infected by Influenza A, HA and NA Subtypes



➤ **Influenza A & B**, are unique among viruses, that have the ability to change their surface antigens (HA and NA) from time to time. These genetic variations result in emergence of new strains and thus resulting in outbreaks, epidemics or pandemics. جائون تفشي الوباء

➤ **Type C is almost antigenically stable**, does not cause major outbreaks.

It can infect human and pigs.

➤ Two types of antigenic variations can occur **in type A & B**:

- **Antigenic shift.**
- **Antigenic drift.**

# Antigenic shift:



- A **major change** in one or both of surface antigens of the virus.
- Results from **genetic reassortment** between two different virus strains (e.g. one of human and the other of animal origin; <sup>طائر</sup>avian or <sup>خنزیر</sup>swine), when a host cell is infected at “the same time” with both strains.
- In reassortment, **entire segments of RNA are exchanged**, each one of which codes for a single protein (e.g., hemagglutinin).
- Yielding a new strain showing **NO** serologic relationship with the parent strains, so that the preexisting immunity of population is **NO longer effective**.
- **Pigs** serve as important “**mixing vessel**” within which the human, avian, and swine viruses reassort.
- **Occurs only in type A** (Not in type B.....Why???)
- Responsible for influenza **pandemics (worldwide epidemics)**.
- Although occurs infrequently (10-40 years), it occurs suddenly, unpredictable and drastic devastating.

## Antigenic drift:

- A **minor change** in the surface antigenic structure.
- Result from **single spontaneous mutations** in the genome RNA.
- Yielding a strain retaining a **degree of serologic relationship** with the circulating parent strain.
- Occurs in **both types, A and B.**
- Responsible for **yearly influenza outbreaks & epidemics.**



# Pathogenesis:

- Influenza occurs in the **winter months**, transmitted by **airborne respiratory droplets**.
- It causes inflammation in both upper and lower respiratory tract and **viremia rarely occurs**.
- Immunity depends mainly on **secretory IgA** in the respiratory tract and the disease is **NOT** followed by **long-lasting immunity** due to frequent antigenic variations.  
بعض الافعال قد تستجيب للمناعة بينه - تخرج منها
- ✂ Incubation period 24 to 48 hours & the symptoms resolve spontaneously in 4 to 7 days.
- “Severe myalgia coupled with respiratory symptoms are typical of influenza”.
- Complications: Influenzal pneumonia, Secondary bacterial pneumonia, Reye’s syndrome.
- Very young, elderly, immunocompromised, those with heart or lung diseases are more prone to complications

## Laboratory Diagnosis:

1. Detection of viral antigen: by rapid test as ELIZA or IF.
2. Serology: Detection of specific antibodies.
3. Virus isolation: The virus is detected by hemagglutination or hemadsorption tests and typed by hemagglutination or hemadsorption inhibition with specific antisera.

## Treatment:

**1) Amantadine and rimantadine:** Effective only against influenza A.

- Act by inhibiting uncoating of the virus.

**2) Neuraminidase inhibitors:** Effective against both influenza A and B viruses.

- Must be given within 48 hours of the onset of symptoms.

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# **Prophylaxis: Influenza Vaccines**

- Contains **both influenza A and B viruses**.
- These vaccines especially **recommended for those at high risk**.
- **Types** of influenza vaccines:

## **1- Inactivated whole virus vaccine**

**2- Subunit (subvirion) vaccine:** contain purified HA and NA glycoproteins.

**3- Live attenuated vaccine:** given intranasally, induce IgA.

- **Immunity is NOT absolute & NOT long lasting.**
- Because vaccine is prepared in eggs, the **egg proteins may lead to hypersensitivity**.
- Newer vaccines prepared in kidney cell culture or by genetic engineering, can be given to those with egg allergy.

# PARAINFLUENZA VIRUS

## Morphological characters:

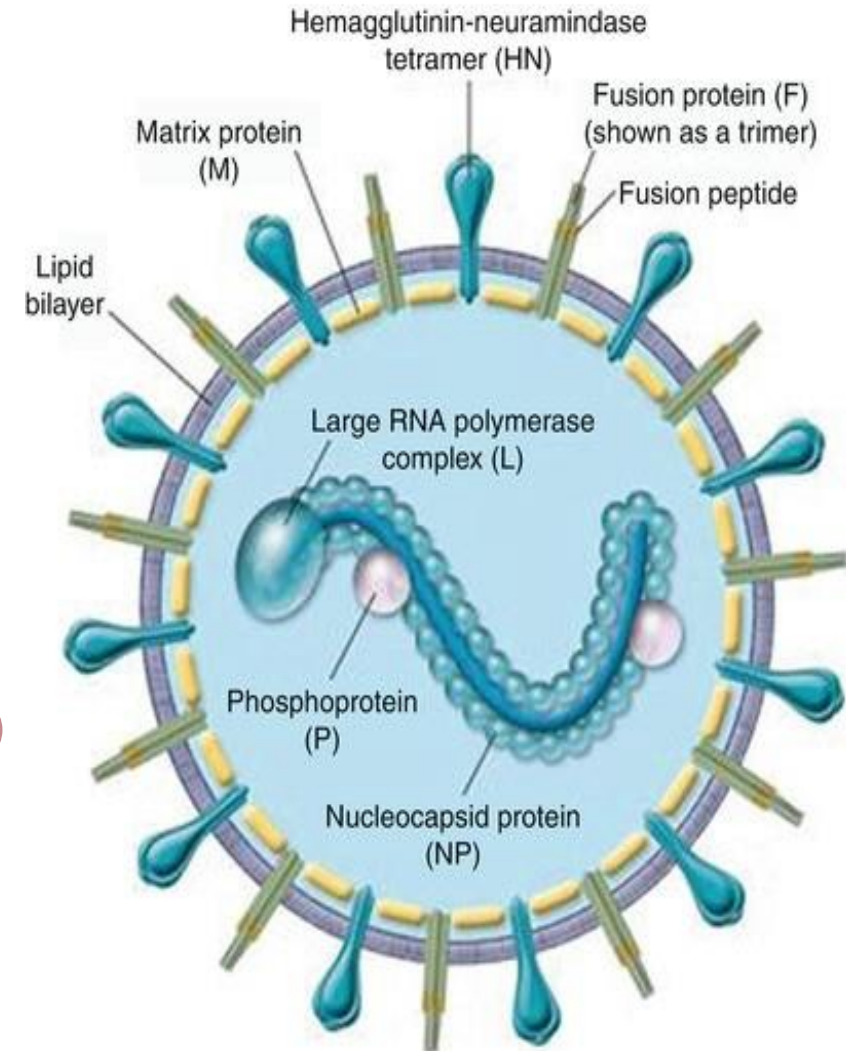
### ➤ Genome:

- **Non-segmented** single-stranded RNA genome.
- **Negative-polarity** (RNA-dependent RNA polymerase).

### ➤ Helical capsid symmetry.

### ➤ Enveloped:

- The envelope carries 2 types of spikes:  
**Hemagglutinin-Neuraminidase (HN)** on the same spike and **Fusion (F)** on a separate spike.
- F protein mediates the formation of multinucleated giant cells (syncytia).
- Replication takes place in the **cytoplasm**.



## Clinical Findings:

- There are four types, 1, 2, 3, 4 and two subtypes 4a and 4b.
- Parainfluenza viruses (type 1 and 2): the most common causes of croup (acute laryngo-tracheobronchitis) in children younger than 5 years of age. Clinically it presents with fever, barking cough, hoarseness of voice and inspiratory stridor due to mucosal edema.

## Laboratory Diagnosis:

1. Detection of viral antigen:
2. Virus isolation: The virus is detected by hemadsorption RBCs. Typing of the virus is done by hemadsorption inhibition test.
3. Serology: Detection of specific antibodies.

**Prevention: NO vaccine.**



# RESPIRATORY SYNCYTIAL VIRUS

## Morphological characters:

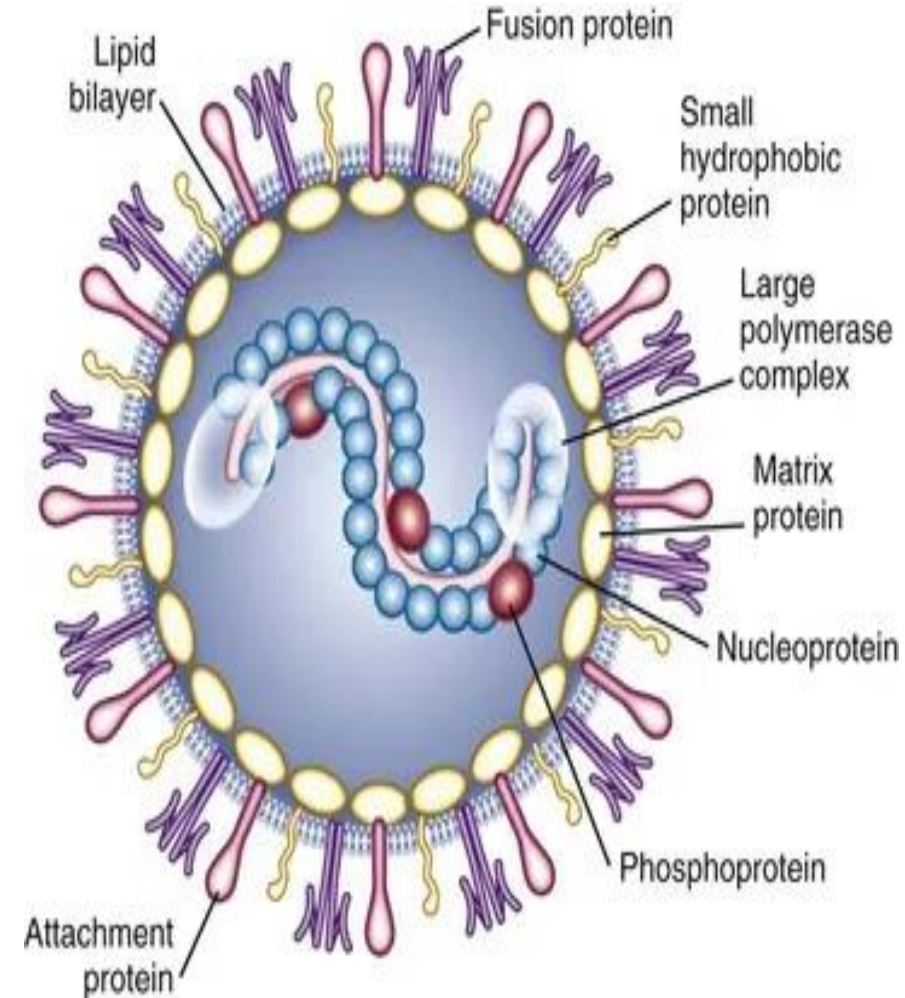
### ➤ Genome:

- **Non-segmented** single-stranded RNA genome.
- **Negative-polarity** (RNA-dependent RNA polymerase).

### ➤ Helical capsid symmetry.

### ➤ Enveloped:

- Its surface spikes are **fusion (F), attachment (G)**
  - **NO** hemagglutinins or neuraminidases
  - The F protein causes cells to fuse, forming **multinucleated giant cells (syncytia)**, which give rise to the name of the virus.
- Replication takes place in the **cytoplasm**.



## **Clinical Findings:**

RSV is the most important cause of lower respiratory tract diseases such as bronchiolitis and pneumonia in infants < 1 year.

## **Laboratory Diagnosis:**

1. Detection of viral antigen
2. Virus Isolation: The characteristic CPE of syncytia of multinucleated giant cells can be seen.
3. Serology: Detection of specific antibodies.

**Prevention: NO vaccine.**

# RHINOVIRUSES

- Rhinoviruses are **the most common cause of common cold** (30-50%) followed by <sup>ssRNA</sup> **coronaviruses** (10-30%).
- **Non-Enveloped** (<sup>lipid</sup> Ether resistant).
- Icosahedral capsid symmetry.
- Genome: **ssRNA virus, +ve sense**.
- Replication occurs in the **cytoplasm**.
- There are **more than 100** antigenic types.
- They are There is **NO long lasting immunity** because of **antigenic multiplicity** of the viruses.

الاصح

# CORONAVIRUS (CoV)

## Morphological characters:

### ➤ Genome:

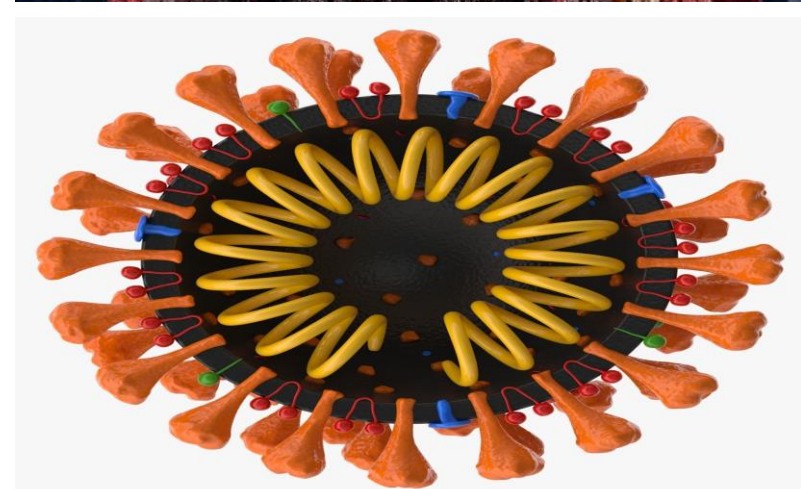
- **Non-segmented** single-stranded RNA.
- **Positive-polarity** (NO RNA polymerase in the virion).

### ➤ Helical symmetry.

### ➤ Enveloped:

سے بنا آل اے پلاسما

- Obtained from the endoplasmic reticulum.
- The envelope has large, widely spaced **club** or **petal**<sup>بتک</sup> shaped spikes in the form of a **corona**.
- Replication occurs in the **cytoplasm**.



## Epidemiology:

- There are **many animal CoV** and they suspected of being a **source for human infections**.
- There are **seven** serotypes of **human** coronaviruses:
  - Four causing **upper** respiratory tract infections, such as the **common cold (the second common cause after Rhinoviruses)**.
  - The other three cause **lower** respiratory tract infections, they are;
  - **SARSCoV, (Severe Acute Respiratory Syndrome Coronavirus)**.
  - **MERSCoV, (Middle East respiratory syndrome Coronavirus)**
  - **SARSCoV2, the causative agent of (COVID19)**, with spike protein antigens on its surface to which **NO one had antibodies**, causes a **global pandemic** emerged in December 2019, in Wuhan, China. **Bats and pangolin are important reservoirs.**

حقائق

حیوان



## Cell Receptors for SARSCoV2:

A) The main receptor is the ACE2 (angiotensin-converting enzyme 2).

The relatively low number of cases of COVID19 in children is attributed to the low number of the ACE2 receptor displayed on their cells.

B) Another recently discovered receptor is neuropilin1 (NRP1)

### Methods of Transmission:

- Inhalation of respiratory droplets ( $> 5\mu\text{m}$ ) (distributed up to 1 meter). الاتساع يكون قليل ← أقل من متر
- Respiratory aerosols ( $< 5\mu\text{m}$ ) (suspended longer in air & distributed  $> 6$  ~~feet~~  $\approx 2$  meters). contact
- Direct contact or indirect contact with surfaces containing virus.
- Fecal-oral route does not seem to be an important route.
- Virus survives on hands 15-30 minutes, 3 hours airborne and 2-3 days on plastic and stainless-steel surfaces. تقل

### Shedding of virus by an infected patient (Infectiousness):

- Typically begins 2 to 3 days before symptom onset A rough approximation is, therefore, about 10 days after the time of infection. incubation period
- Asymptomatic persons can also shed the virus.

## Pathogenesis & Clinical Findings:

- **The incubation period:** ranges from 2 to 14 days with a mean of 5 days.
- **General manifestations & Respiratory manifestations:** dry cough and **shortness of breath.**
- **Extra-pulmonary manifestations:**
  - **Neurological:** anosmia, parosmia, dysgeusia) طعم زيب شم جنات غيبه فقدان حاسة الشم
  - **GIT:** Nausea, vomiting, and diarrhea.
  - **Cardiac & Thrombo-embolic.**

“Cytokine Storm” overproduction of cytokine release, resulting in severe damage to the alveolar membrane and ARDS (**Acute Respiratory Distress Syndrome**) & Extra-pulmonary manifestations.

## Diagnosis:

Nasopharyngeal swabs

**RT-PCR** to detect viral RNA, **the most sensitive and specific** method for diagnosis.

Immunoassay to detect viral antigen e.g. ELIZA, Immunochromatography.

# Treatment

## A) Non specific supportive & symptomatic treatment:

Analgesic <sup>مسكن</sup> antipyretic e.g. paracetamol, supplemental oxygen and respiratory support “mechanical ventilators” may be needed in severe cases.

## B) Specific therapeutic modalities: 3 main lines

a) Antiviral drugs: Inhibit viral replication

b) Monoclonal antibodies directed against spike protein.

c) Drugs inhibit (Cytokine Storm) e.g. Corticosteroids.

## Prevention:

### A) Follow prevention guidelines.

e.g. physical distance, wearing masks, hand wash, disinfectants,...

<sup>حجر</sup> Quarantine period of 10 to 14 days is recommended for significantly exposed persons.

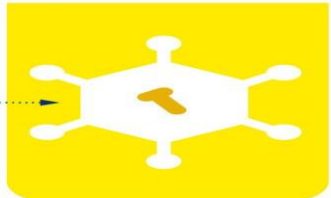
## B) Vaccination

### How do different Covid-19 vaccines work?



#### Viral vector

Uses a harmless virus which is altered to contain part of Covid-19's genetic code



The code tells our cells to make the Covid-19 'spike' protein, which triggers an immune response



Oxford-AstraZeneca  
Johnson & Johnson

#### RNA (nucleic acid)

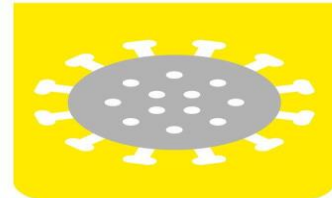
Contains a synthetic version of part of Covid-19's genetic code (messenger RNA)



Pfizer-BioNTech  
Moderna

#### 'Whole' virus

Contains a weakened or inactivated version of the Covid-19 virus



Sinopharm  
Sinovac

#### Protein subunit

Uses pieces of the Covid-19 virus - sometimes fragments of the 'spike' protein

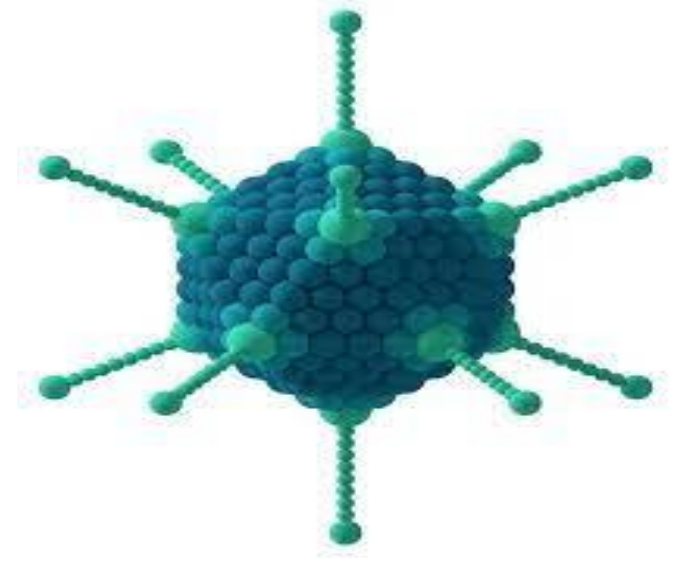


Novavax,

# ADENOVIRUS

## Classification & Morphological characters:

- **Non-Enveloped.**
- Icosahedral capsid symmetry.
- **Genome: Double stranded DNA**
- Virion has unique “Spike” or “Fiber” projecting from each of 12 vertices of the capsid. The fiber is the organ of attachment and is a hemagglutinin.
- **Replication occurs in the nucleus.**
- There are 57 accepted human adenovirus serotypes classified into seven groups (A to G).
- Adenoviruses have a pronounced affinity for the mucous membranes of the respiratory tract, alimentary tracts, conjunctiva and for lymphoid tissue (adenoidal and tonsillar tissues of the throat) where the virus may be **latent** for long periods.





## Clinical findings:

- Adenovirus **outbreaks** occur among recruits e.g. **military recruits** or **summer camps**.
- Adenovirus causes a variety of diseases:
  - 1- **Respiratory infections:** (especially types **3,4,7&21**):
    - **Pharyngitis.**
    - **Pharyngo-conjunctival fever** may occur in outbreaks in summer camps (swimming pool conjunctivitis).
    - **Common cold.**
    - **Pneumonia.**
  - 2- **Eye infections:** conjunctivitis and keratoconjunctivitis “**pink eye**”.
  - 3- **Gastroenteritis in infants.**

## Prevention:

- Three live, monovalent vaccines against serotypes 4, 7, and 21.
  - Used only by the military (not for civilian use).

# Aspergillus species

**Aspergillus Fumigatus:-** Causes **pulmonary Aspergillosis**, (in patients with a pre-existing lung disease).

## 1- Aspergilloma or " Fungus ball":

- Fungus grow in a **pre- existing cavity e.g. T.B. cavity.**
- X- ray shows **fungus ball (radiopaque structure).**

## 2- Invasive Aspergillosis: in immunocompromised.

- Fungus invades lung tissues giving rise to pneumonia and hemoptysis and may progress to **disseminated Aspergillosis.**

## 3- Allergic bronchopulmonary aspergillosis (ABPA).

- Leads to asthmatic attacks **in hypersensitive persons.**

**Aspergillus Niger:** Causes **otomycosis**, chronic infection of the external auditory meatus.



## Laboratory Diagnosis:

- **Direct Microscopy**:- in lactophenol cotton blue preparations.

Shows **filamentous septate hyphae** with characteristic **aspergillus head**:

**Flask shaped in A. Fumigatus & Rounded in A. Niger.**

- **Culture**:- On Sabouraud's agar,

**Smoky green growth in A. Fumigatus & black growth in A. Niger**

- **Antigen detection in serum**: is of value in invasive aspergillosis,

# HISTOPLASMA CAPSULATUM

- It is a **dimorphic** fungus (exists as a **mold** in soil and as a **yeast** in tissue).
- It grows in soil, particularly contaminated with **bird excreta, especially bats.**
- It is an **intracellular organism** which particularly infect **reticuloendothelial cells (macrophages)** in which found as **budding cells.**
- Infection may be either:
  - **Asymptomatic.**
  - **Acute pulmonary disease**
  - **Chronic progressive pulmonary disease:** progress to **cavitary lung lesions** (on chest radiographs) which resemble tuberculosis.
  - **Severe disseminated histoplasmosis:**
    - Especially in infants and **immunocompromised.**
    - **Ulcerated lesions on the tongue** are typical of disseminated histoplasmosis.
    - Pancytopenia, lymphadenopathy, hepatosplenomegally.



# Laboratory diagnosis

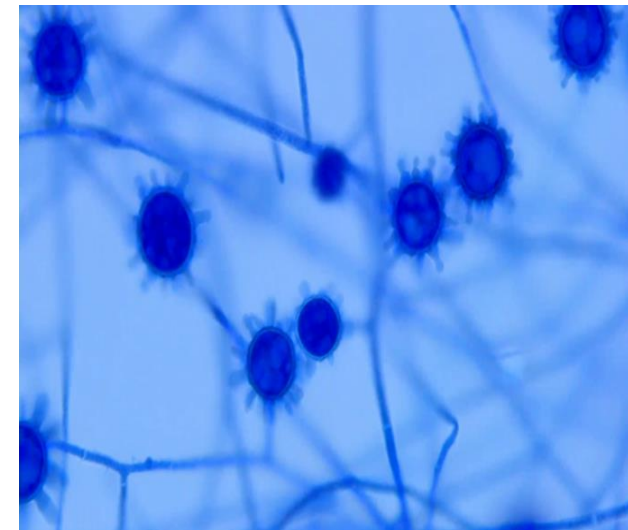
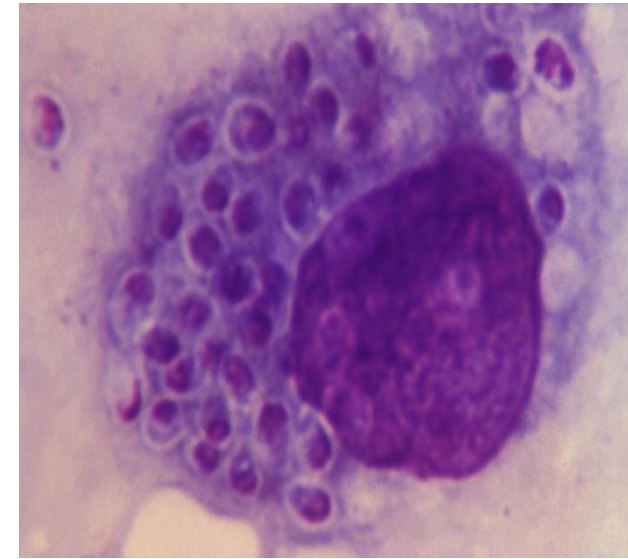
## Direct Microscopy

In **Giemsa** stained preparations, **yeast form** can be seen **intracellular** as round or oval **budding cells**.

**Culture:** On sabouraud's agar at room temperature:

A lactophenol cotton blue stained film from this culture shows **septate hyphae** and **rounded thick walled spores** with **finger like projections**.

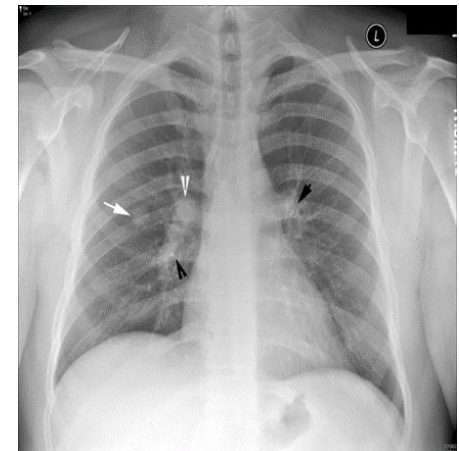
## Antigen detection





# COCCIDIOIDES IMMITIS

- It is a **dimorphic** fungus (In soil, as a mold, **arthrospores** (Barrel shaped). In tissues, as a **spherule** (**Thick walled and filled with endospores**)).
- The infection acquired by **inhalation of arthrospores**.
- Infection may be:
  - **Asymptomatic**: in endemic areas (e.g. **Arizona, New Mexico, California**).
  - **Acute Coccidioidomycosis “Valley fever” “Desert rheumatism”**: Triad, Respiratory manifestations (fever and cough), erythema nodosum (EN) and arthralgias.
  - **Chronic Coccidioidomycosis**: prolonged cough & **Pulmonary nodule commonly seen on chest X-ray**.
  - **Disseminated Coccidioidomycosis**: In immunocompromised



## Diagnosis:

- In tissue specimens, **spherules (Thick walled sac, filled with spores)** are seen microscopically.
- Cultures on Sabouraud's agar at room temp.: A lactophenol cotton blue stained film from this culture shows **septate hyphae with arthrospores**.
- Serologic testing to detect specific antibodies.



# Pneumocystis jiroveci

- It is a **fungus**, present in lung tissue as spores or sporocysts. Its cell wall contain  **$\beta$ -glucan**,  
however,
  - It **lacks ergosterol** so, antifungal drugs targeting ergosterol are ineffective
  - It does not grow on fungal media.
- Is an important cause of pneumonia **in immuno-compromised individuals**  
**(Pneumocystis pneumonia) = (Plasma cell pneumonia)**
- **Diagnosis:**
  - **Microscopic examination:** The **sporocysts** can be visualized with silver or Giemsa in lung biopsy.
  - **Detection of  $\beta$ -glucan.**

# Paragonimus Westermani (Trematode of the lung)

## Life cycle

**Habitat:** Lung.

**Definitive host:** Man.

**1<sup>st</sup> Intermediate host:** Snail. <sup>حلیزرت</sup>

**2<sup>nd</sup> Intermediate host:** crabs and crayfish. <sup>جواد</sup>

**Infective stage:** Metacercariae. <sup>کبوریہ</sup>

**Mode of infection:** eating raw crabs and crayfish.

**Diagnostic stage:** Operculated eggs in sputum or stool.

The main symptom is a chronic cough with bloody sputum, dyspnea and chest pain.





بالتوفيق