

وَقُلْ رَبِّ زِدْنِي عِلْمًا



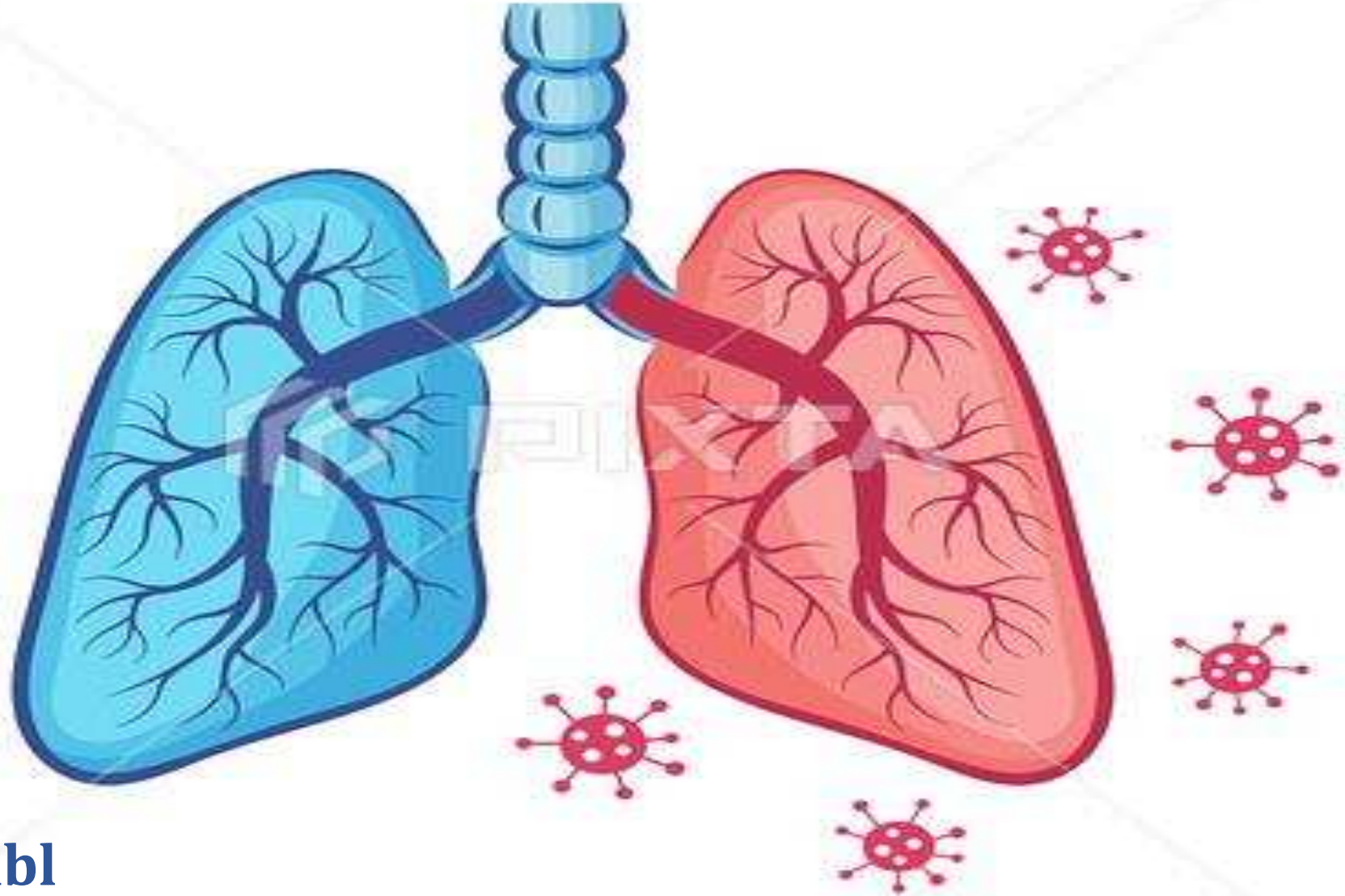
RESPIRATORY SYSTEM

HAYAT BATCH



SUBJECT : _____
LEC NO. : Most important (final)
DONE BY : Tabark Aldaboubi

RESPIRATORY TRACT INFECTIONS



By
Prof. Hala Tabl

INFLUENZA VIRUSES

Morphological characters:

➤ Medium sized, Spherical.

➤ Structure:

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.** eight segments → eight Helical

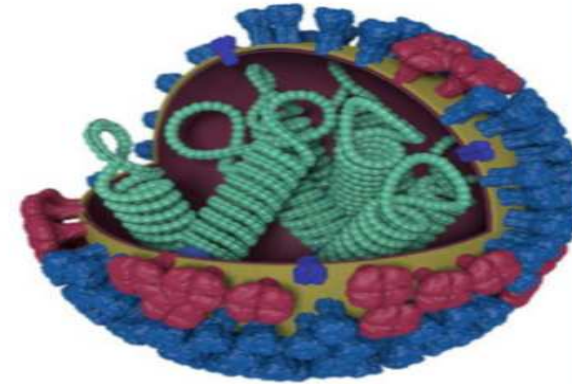
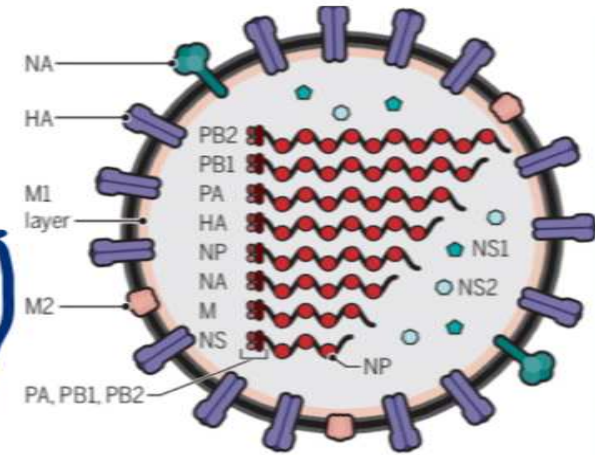
3) **Enveloped:**

The envelope carries 2 types of projections:

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

➤ Influenza virus (and retroviruses) are the only RNA viruses that have an important stage of their replication takes place in the **nucleus.** influenza virus + Retroviridae, like HIV → replication in the nucleus

يعني ال RNA تاعه ما بنفع يترجم و يقوم بدور ال mRNA فلازم يكون عندي RNA polymerase طيب من وين بجيبه ؟ قاعدة كل ال Negative sense يكون معها ال RNA polymerase داخل ال virion



Negative-polarity (contains RNA-dependent RNA polymerase).

بس تذكر من ال general microbiology بس للفهم

Negative-sense RNA refers to RNA molecules that are complementary to the mRNA (messenger RNA) and cannot be translated directly into proteins. In the case of influenza viruses, their genome consists of single-stranded RNA that is negative-sense. This means that before the virus can replicate and produce proteins, it needs to first synthesize a complementary positive-sense RNA strand using an RNA polymerase enzyme carried by the virus. This complementary strand then serves as a template for protein synthesis. The negative-sense RNA genome of influenza viruses makes them reliant on RNA-dependent RNA polymerase to carry out replication and transcription processes within the host cell.



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. مهم في ال diagnosis
- 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:**

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

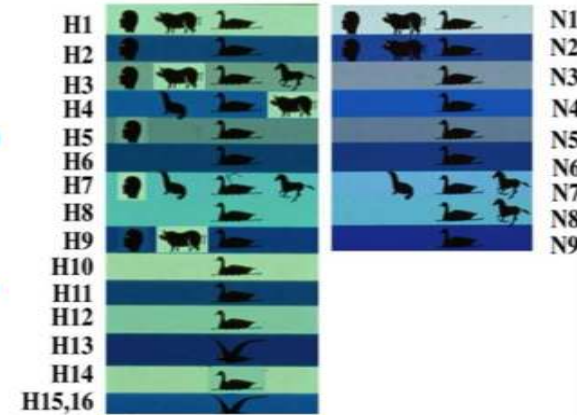
(2) **The surface HA & NA:**

➤ **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



تذكروا أيام الرياضيات وحدة الاحتمالات ونرد $\frac{1}{6}$
نفس الفكرة ممكن يكون عندك H1 مع N1 او H1 مع N2 وهكذا
احتمالات كثيرة
+ ركزوا كل الأنواع بتعمل infection عند الطيور

➤ **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.**

➤ **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; avian or 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.** لهيك هي خطيرة
- **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.**

وَقُلْ رَبِّ زِدْنِي عِلْمًا

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.
- 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

بوخذ عينات ونجلاها detection to final عن طريق (ELISA و IF)

Laboratory Diagnosis:

Specimens: nasal or throat washings, nasal or throat swabs, or sputum.

اهم اشياء

1. Detection of viral antigen: by rapid test as ELISA or IF.

2. Serology: Detection of specific antibodies.

3. Virus isolation: Sample is inoculated in: *tissue culture* ازرع العينات على

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.

Prophylaxis: Influenza Vaccines

- Contains **both influenza A and B viruses**. كل انواع ال influenza Vaccine تحتوي به.
- The vaccine is usually **reformulated each year** to contain the current antigenic strains. كل سنة قذال influenza Virus بالتالي ال Vaccine بتغير كل سنة.
- These vaccines especially **recommended for those at high risk**. مو اسياري

➤ **Types** of influenza vaccines:

1- **Inactivated whole virus vaccine:**

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

3- **Live attenuated vaccine:** given intranasally.

induce IgA.

- The live vaccine should **not** be given to pregnant women or to immunocompromised individuals. لصيلت اذله فومين استخواني common اكثر

live virus فلما بيرخل بجمل replication في ال nasal mucosa لصيلت بجمل induce immunity بصورة IgA بجمل better immunity عند بقاء اللقاح

— Immunity is **NOT absolute & NOT long lasting**

— Because vaccine is **prepared in eggs**, the egg proteins may lead to **hypersensitivity**.

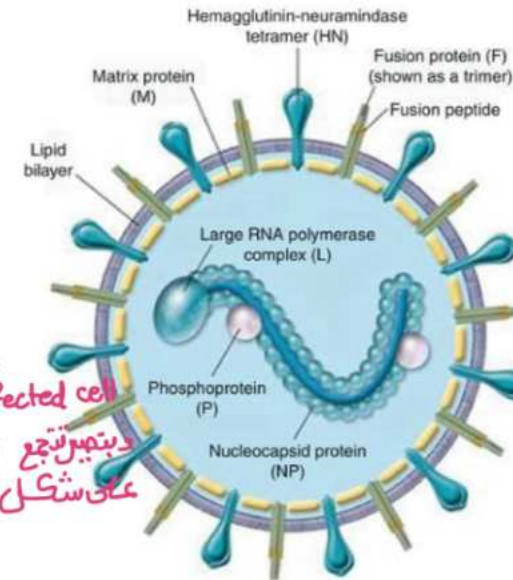
— Newer vaccines prepared in kidney cell culture or by genetic engineering can be given to those with egg allergy

PARAINFLUENZA VIRUS

Morphological characters:

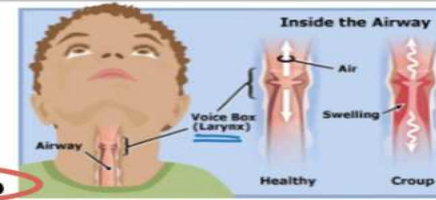
- Medium sized, Pleomorphic.
- **Genome:**
 - **Non-segmented** single-stranded RNA genome.
 - **Negative-polarity** (RNA-dependent RNA polymerase).
- **Helical capsid symmetry.**
- **Enveloped:**
 - The envelope carries 2 types of spikes:
 - ! **Hemagglutinin-Neuraminidase (HN)** on the same spike and **Fusion (F)** on a separate spike. *lose the septa between infected cell*
 - F protein mediates the formation of multinucleated giant cells (syncytia). *دیتھیر نتیجہ عکس شکل*
- Replication takes place in the cytoplasm.

RNA
Virus



Pathogenesis & Clinical Findings: ^{inflammation and edema of upper respiratory tract}

1. 2. 3. 4. The most common cause of croup
- There are four types, 1, 2, 3, 4 and two subtypes 4a and 4b.
 - Parainfluenza viruses (type 1 and 2): are **major causes of croup** ^{disease affected} (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.



قراءته الدكتور قراة (هو نفس) ال diagnosis تاع النوع ال (influnza virus)

Laboratory Diagnosis:

1. Detection of viral antigen:

2. Virus isolation:

virus is detected by hemadsorption of human group O RBCs

the virus is done by hemadsorption inhibition test

3. Serology: Detection of specific antibodies

The

Typing of

Treatment & Prevention:

NO vaccine.

RESPIRATORY SYNCYTIAL VIRUS

سبيكة الـ Parainfluenza
زبي الـ
virus

Morphological characters:

➤ Genome:

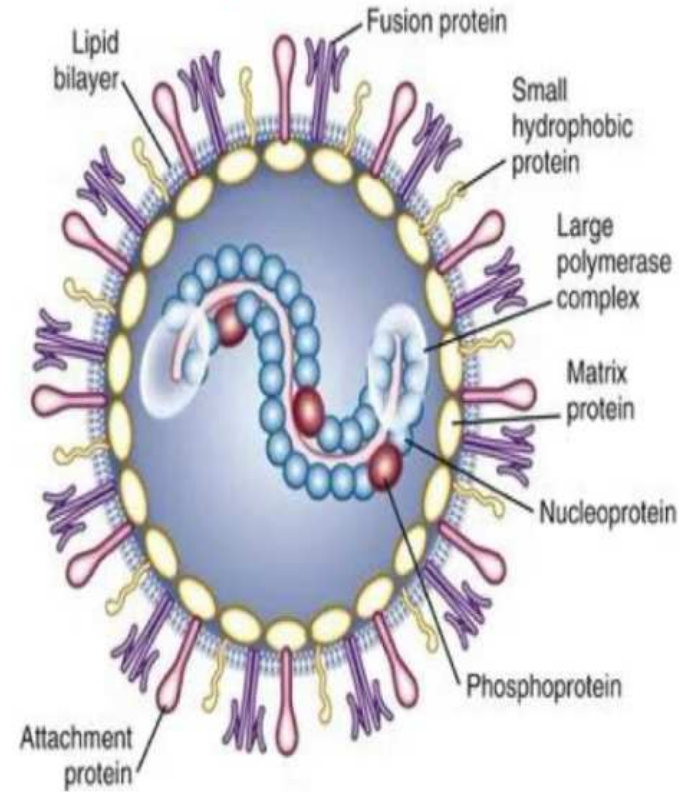
- **Non-segmented** single-stranded RNA genome.
- **Negative-polarity** (RNA-dependent RNA polymerase).

➤ Helical capsid symmetry.

➤ Enveloped:

- Its surface spikes are ¹ **fusion (F)**, ² **attachment (G)** **NOT** 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**.

اسم الفيروس تسعين عاى
اساسها



Clinical Findings:

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

* نفس المري بيافتي انواع الفيروسس المري خوف

Laboratory Diagnosis:

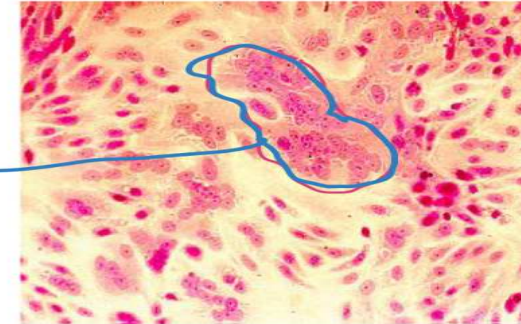
1. Detection of viral antigen:

2. Virus Isolation:

ما هتج حيا بتكون

The characteristic CPE of syncytia of multinucleated giant cells can be seen.

3. Serology: Detection of specific antibodies



Prevention:

➤ There is NO vaccine.

RHINOVIRUSES

- Rhinoviruses are **the most common cause of common cold (30-50%)** followed by **coronaviruses (10-30%)**.
- **Non-Enveloped** (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.

CORONAVIRUS (CoV)

Morphological characters:

➤ Genome:

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

the RNA can be directly translated by the host cell's machinery to produce viral proteins.

➤ Helical symmetry.

➤ Enveloped:

- **Obtained from the endoplasmic reticulum,**

عكس ال influenza virus

- The envelope has large, widely spaced **club or petal 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)**.
↳ Rhinoviruses الالتهاب
 - 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**.

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)

اول Step لما رح يمسك ال receptor مع ال spike حتى ال virus يدخل receptor لهيبك اصابتهم اقل
دهسا عند الاطفال في عدد قليل من ال

Methods of Transmission:

- Inhalation of respiratory droplets ($> 5\mu\text{m}$) (distributed up to 1 meter).
- Respiratory aerosols ($< 5\mu\text{m}$) (suspended longer in air & distributed > 6 feet ≈ 2 meters).
- 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.**

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.
- 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) المريض بحس الطعم غريب يتشم أشياء غريبة فقدان حاسة الشم
 - **GIT:** Nausea, vomiting, and diarrhea.
 - **Cardiac & Thrombo-embolic.** سبب extrapulmonary صهي ال
- **“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

معالجة امراض العرض

A) Non specific supportive & symptomatic treatment:

- Analgesic antipyretic e.g. paracetamol
المحشان الحرارة

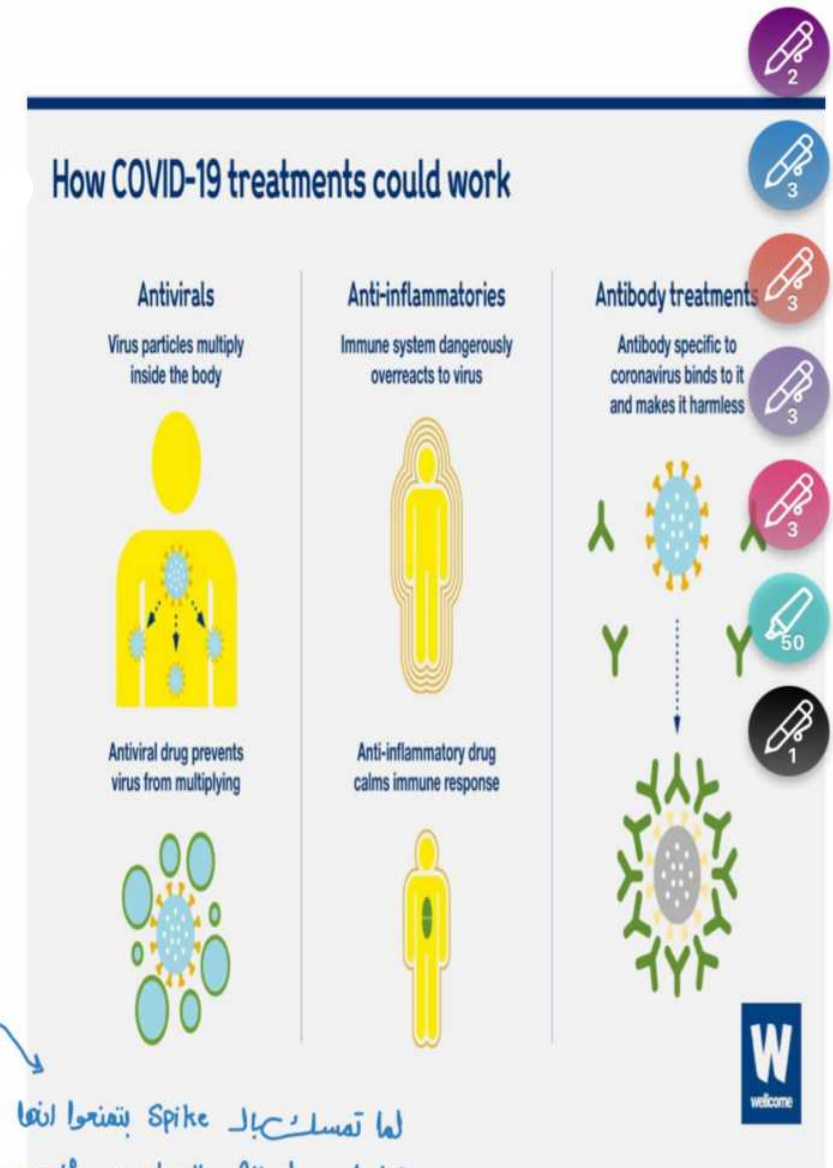
- Supplemental oxygen and respiratory support “mechanical ventilators” may be needed in severe cases.

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.



لما تمسك بال Spike بتعزلوا انبعا
تقل Attachement ل specific receptor
بتقل (inhibit infection)

How do different Covid-19 vaccines work?

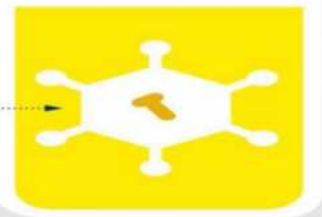
بصفا كل واحد ال principle والنوع تاعتق



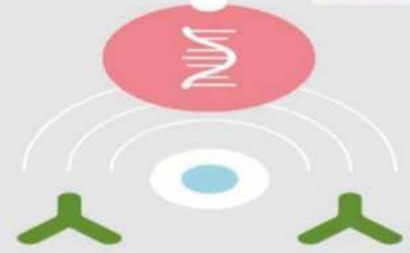
بستخد الفيروس ويخليه inactive يحمل عليه
جزء ال genetic تاعه
لما يدخل للجسم بأثر ال الخلايا
جزء ال genetic تاع ال Covid 19 يترجم
بالسينتوبلازما وينتج spike

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

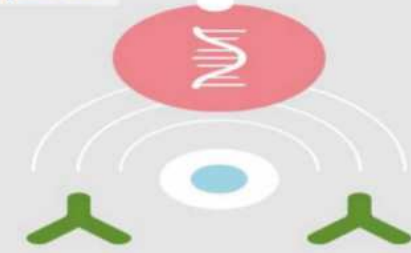


Oxford-AstraZeneca
Johnson & Johnson

عبارة عن جزء ال messenger RNA تاع الكوفيد
لما يدخل عال الجسم يترجم بالسينتوبلازما وينتج spike

RNA (nucleic acid)

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

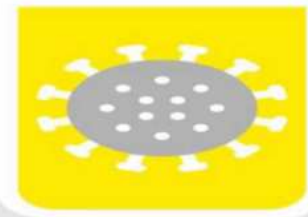


Pfizer-BioNTech
Moderna

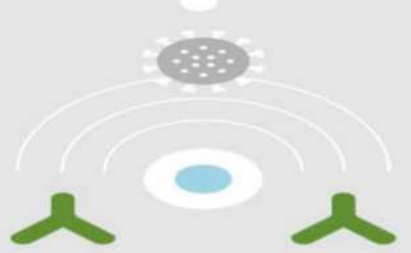
نفس ال inactivation to covid 19
بالعزارة مبالعواد الكيمياء

'Whole' virus

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



This triggers an immune response



Sinopharm
Sinovac

Protein subunit

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



Novavax,

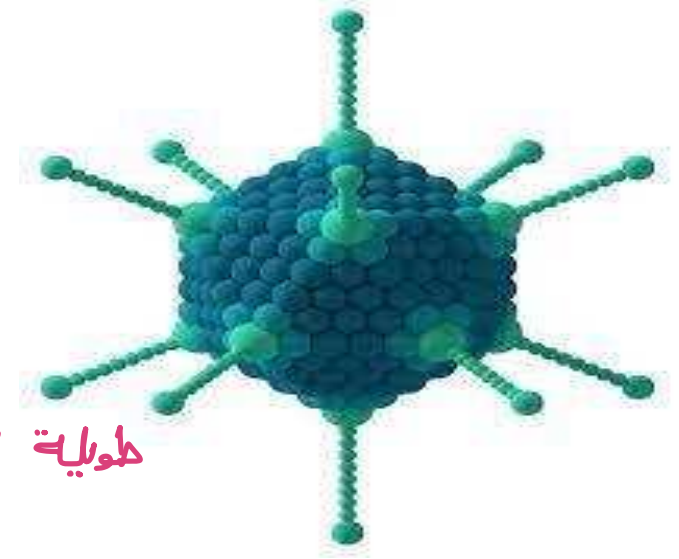
بجيب ال spike
نفس ال تحضيره برا
ويظروا جاصل ال
Vaccine



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 causes a variety of diseases:

1- Respiratory infections:

(especially types 3,4,7&21):

- Pharyngitis. ← Adenovirus + EBV
- 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":

Tumor ← شئ ← X-ray ← يبين بال ←

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

Cavity ← يتوجها ال ←



2- Invasive Aspergillosis:

- Mainly occurs in **immunocompromised**
- Fungus invades lung tissues giving rise to pneumonia and hemoptysis. (blood in sputum)
- Dissemination to other organs occur leading 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: *فيلم مصبوغ بالـ lactophenol cotton blue* يظهر *septa hyphae* ويتخلف الأنواع عد بعضها بشكل ال head

➤ **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, *in room temperature* بعد حوالي ٣ اسابيع

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

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

invasive و disseminated

HISTOPLASMA CAPSULATUM

mold بدرجة حرارة الفريجة يتنمو

Yeast بدرجة حرارة ٣٧ يتنمو

- 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

Specimen: Sputum, Bone marrow aspirate or blood.

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, produce filamentous growth.

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

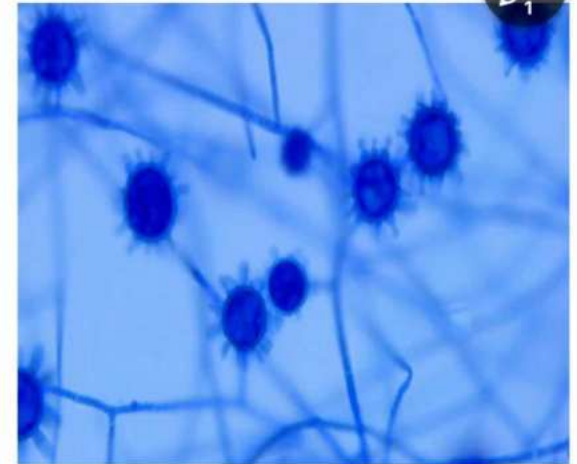
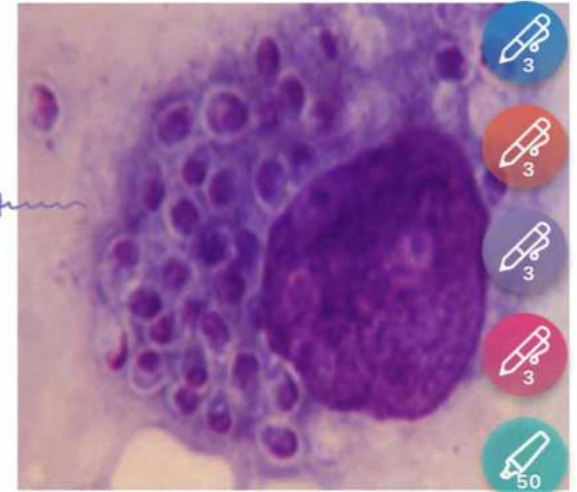
- At 37°C produce the yeast form (budding cells)

Antigen detection: in serum and urine by ELISA

PCR

اذا ما عرفت
افضل ال organism
بجمل Antigen detection

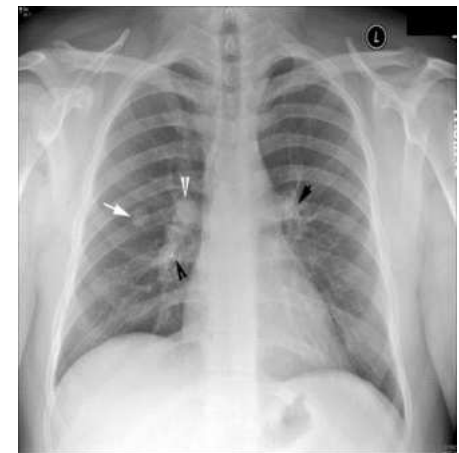
intracellular
macrophage داخل ال
budding cell يظهر كـ



mold → out side the body
spherul → in the tissue

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: microscope
lung biopsy →

spherules ليشوق ال

➤ In tissue specimens, **spherules (filled with endospores)** are seen microscopically.

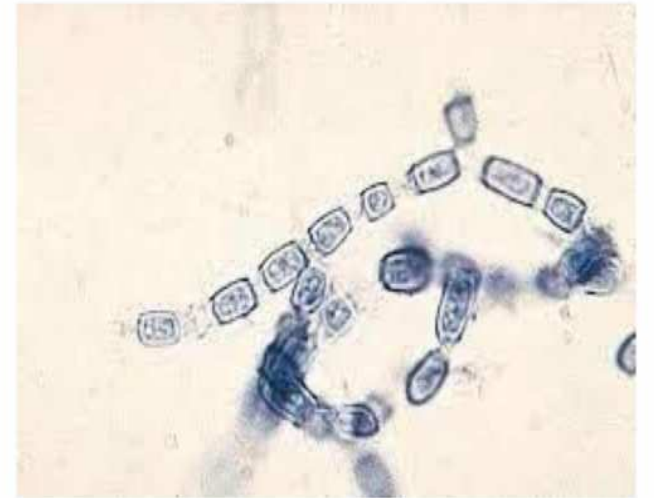
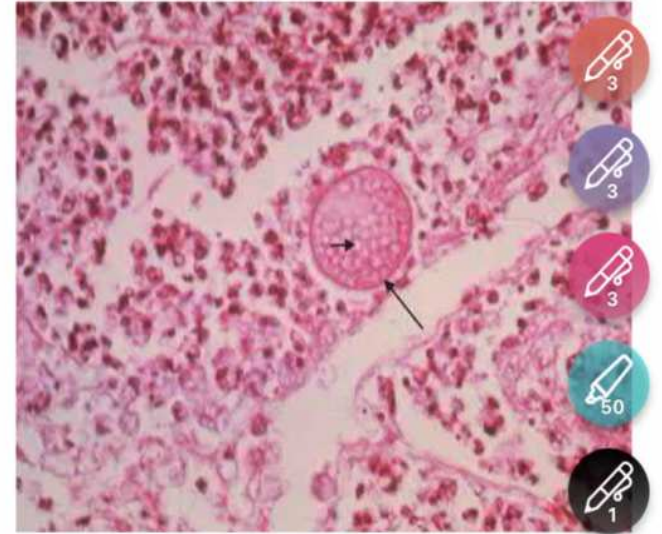
➤ Cultures on Sabouraud's agar at **room temp.:**
mold.

show **septate hyphae with arthrospores** with

بنظير هيك

lactophenol cotton blue stain. بن استخدم هاي الصبغة

➤ Serologic testing to detect specific antibodies.
disseminated disease



Pneumocystis jiroveci

Parasite كانوا مفكرين انها
Tissue لانها موجودة جوا ال
Cyst بصورة

➤ It is a **fungus**, present in lung tissue as spores or sporocysts. Its cell wall contain **β-glucan**,

however,

تختلف عن ال Fungi ب : فيها glucan بس
① فيها chitin

② 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 β-glucan.**

Paragonimus Westermani (Trematode of the lung)

Life cycle

Habitat: Lung.

Definitive host: Man.

1st Intermediate host: Snail.

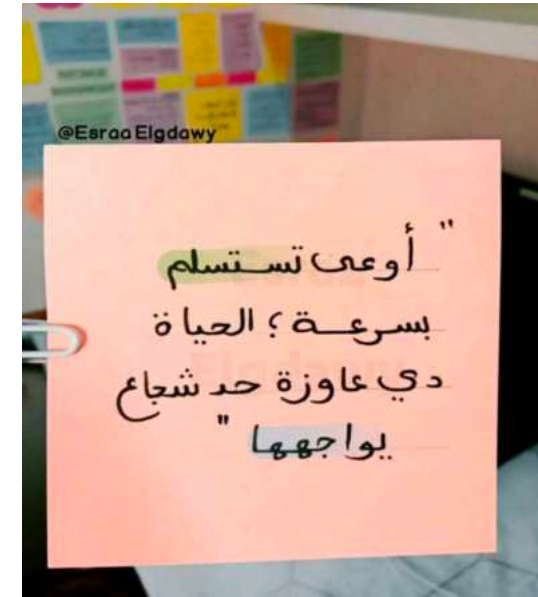
2nd Intermediate host: crabs and crayfish.

Infective stage: Metacercariae.

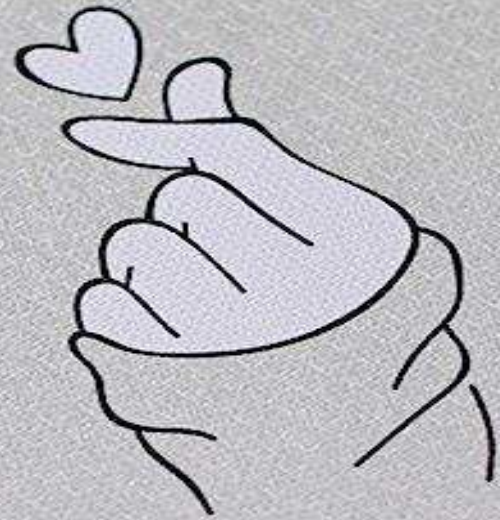
Mode of infection: eating raw crabs and crayfish.

Diagnostic stage: Operculated eggs in sputum or stool.

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



لا تنسوني من دعواتكم 🙏❤️



بالتوفيق