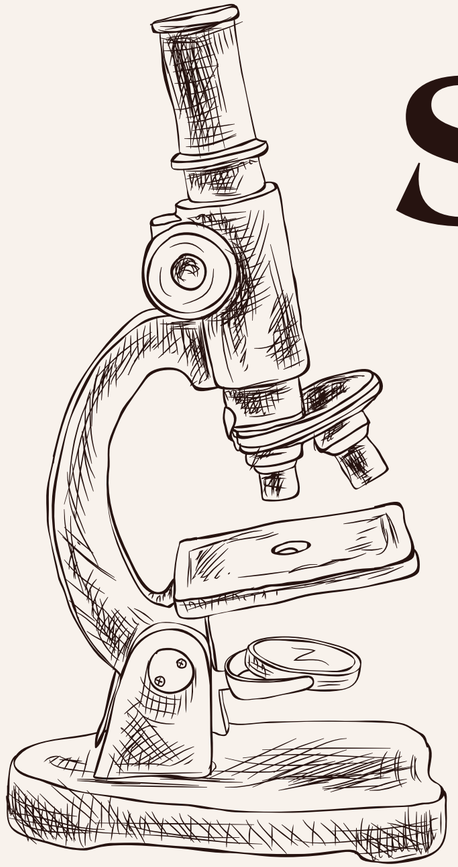
ICB5777 - Physiopathology of Infectious Diseases
Module IV

RESPIRATORY SYNDROMES:

COVID-19, PNEUMONIA, CRYPTOCOCCOSIS AND FILARIASIS



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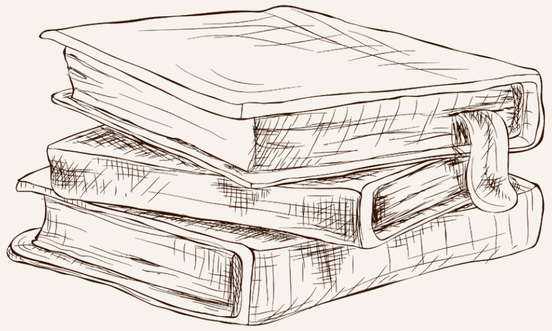
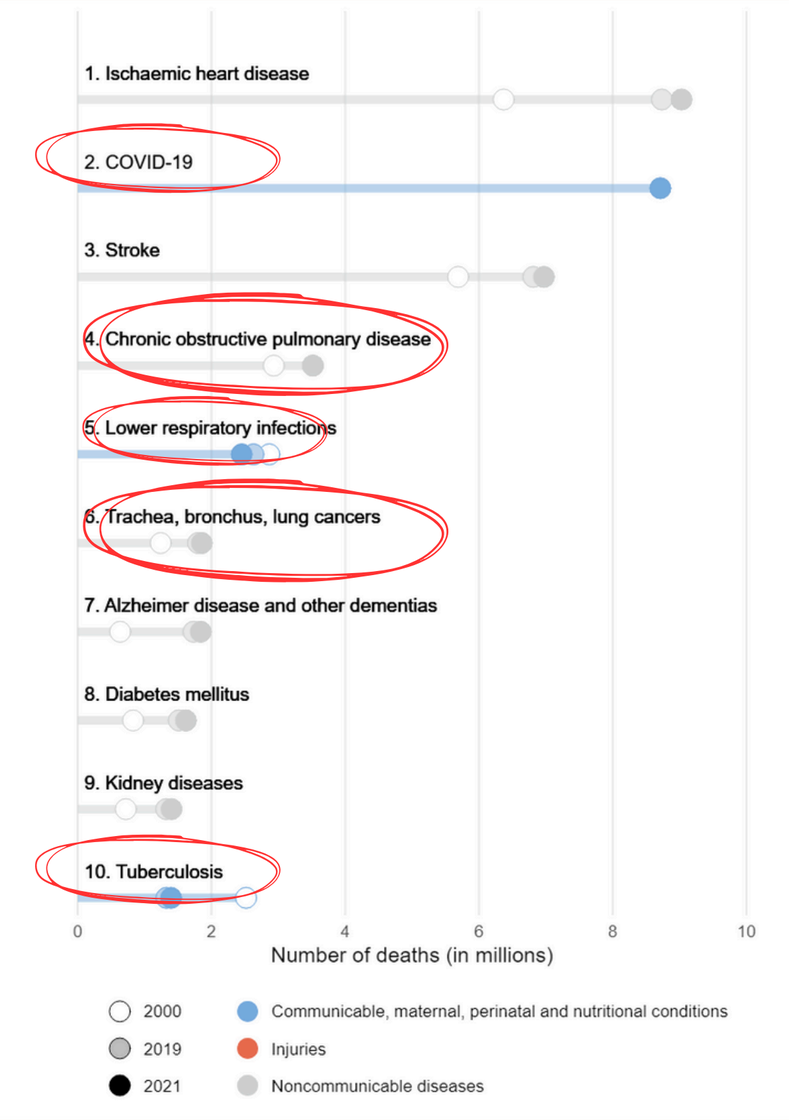


PROVOCATION: WHY WE TALK ABOUT RESPIRATORY SYNDROMES?

RECENT WORLDWIDE EPIDEMIOLOGY



According WHO data, globally 5 of top diseases are related to respiratory diseases;

Respiratory diseases are predominantly public health issues in low-middle and low income countries.

Source: WHO

MEANING OF RESPIRATORY SYNDROMES

Respiratory syndromes encompass various conditions affecting respiratory functions, most of all associated to decreased lungs function;

The lungs function could be pathologic altered by restrictive and obstructive conditions:

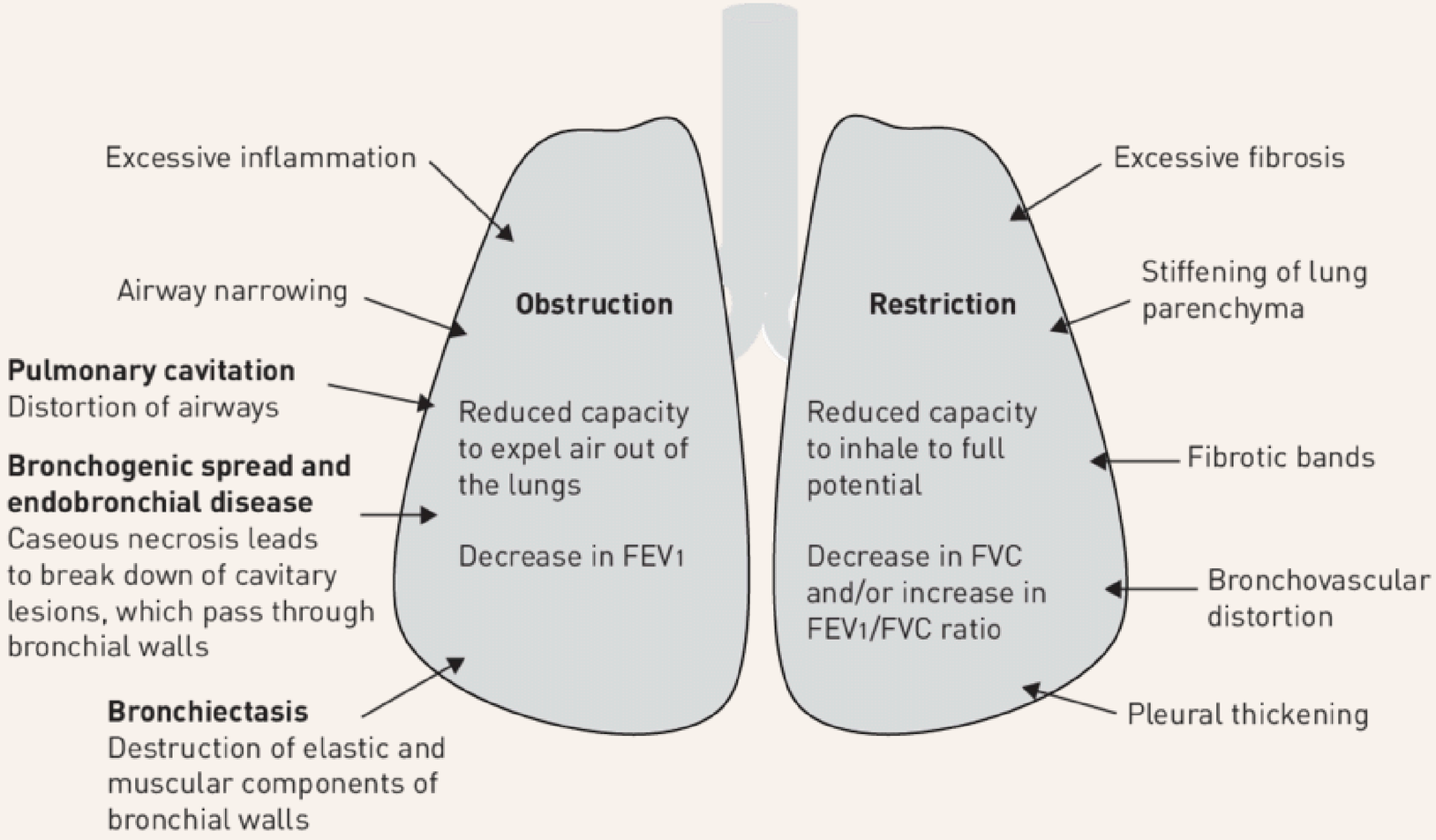
Restrictive

Reduction of airflow and compliance to the lungs

Obstructive

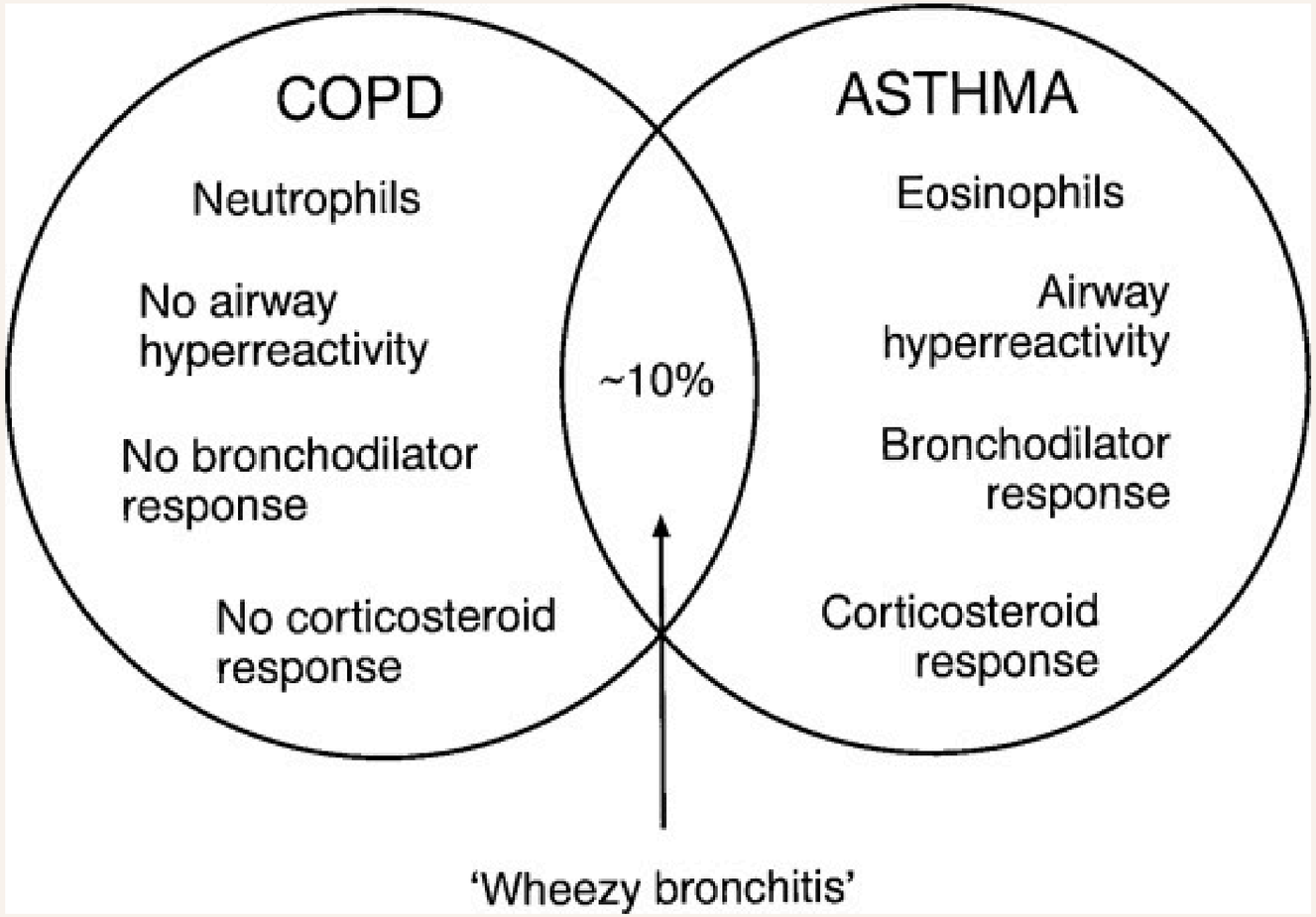
Reduction of lungs volume by any condition, generally by lesions

DIFFERENCES OF RESPIRATORY SYNDROMES



Source: Ravimohan, 2018

DIFFERENCES OF RESPIRATORY SYNDROMES



Source: Barnes, 2005

MAIN RESPIRATORY DISEASES

Obstructive	Restrictive
Asthma	Chronic bronchitis
Sarcoidosis	Emphysema
Idiopathic promonary fibrosis	Cystic fibrosis
Neuromuscular disease	Bronchiolitis
Pneumocystis pneumonia	Bronchioectasis
Tuberculosis	**COVID-19**
Tropical Pulmonary Eosinophilia	**Tuberculosis**
Loeffler Syndrome	**Bacterial pneumonia**
Aspergillosis	**Aspergillosis**

ACUTE RESPIRATORY DISTRESS SYNDROME

Syndrome with relationship of a initial non cardiogenic/pulmonary disease/condition that could recruit some immunological cells and mediators (chemokines, adhesion molecules, complementsystem molecules, cytokines, lipid mediators)

↓ EROS production

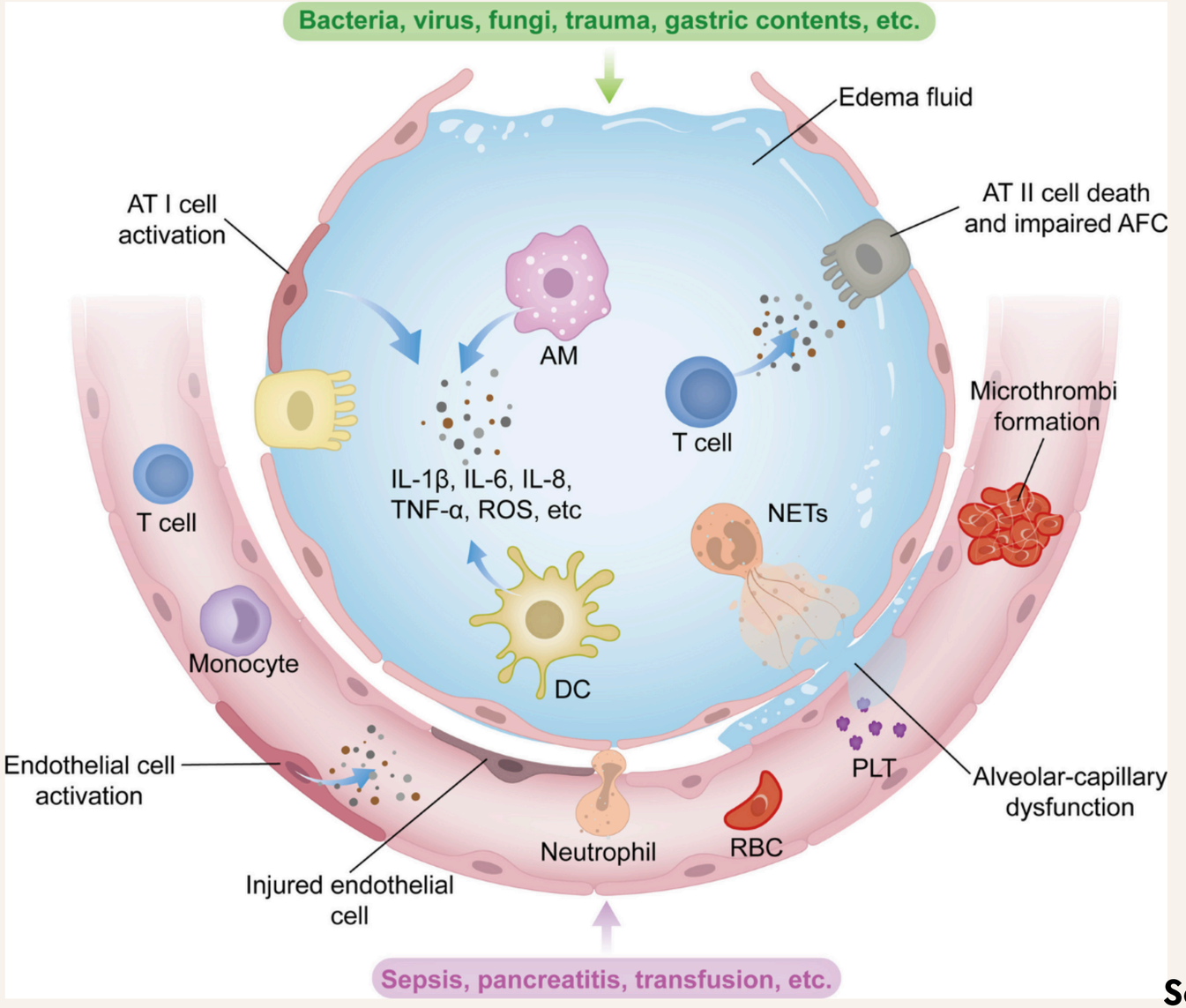
Activation of immunological cells, elevated leucocyte adhesion, capillar leaking, vasodilation and junctions instability and pulmonary edema = alveolar lesion

↓ Elevated alveolar lesions and edema

ARDS and possibility of reduction of blood flow and hypoxemia = higher chance to trigger multiple organ failure

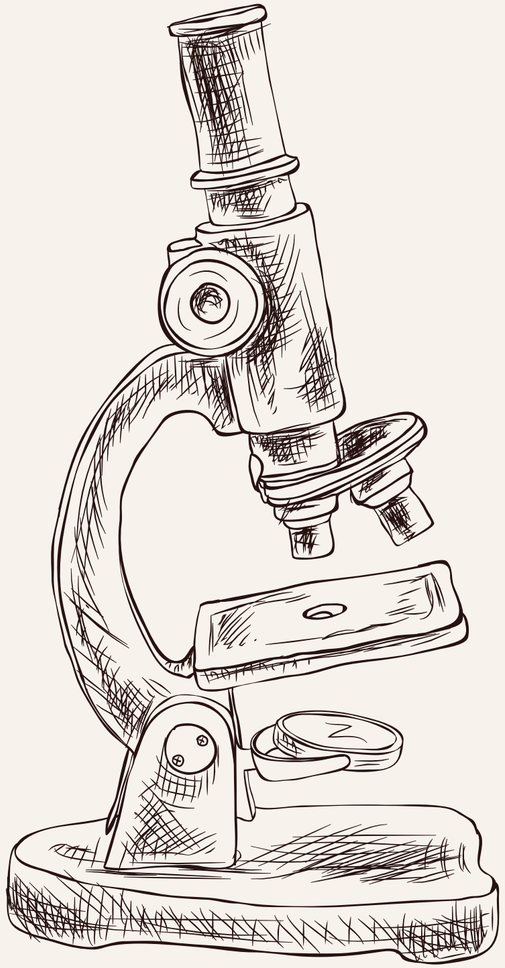
Source: Hussain et al, 2020; Huang et al, 2024

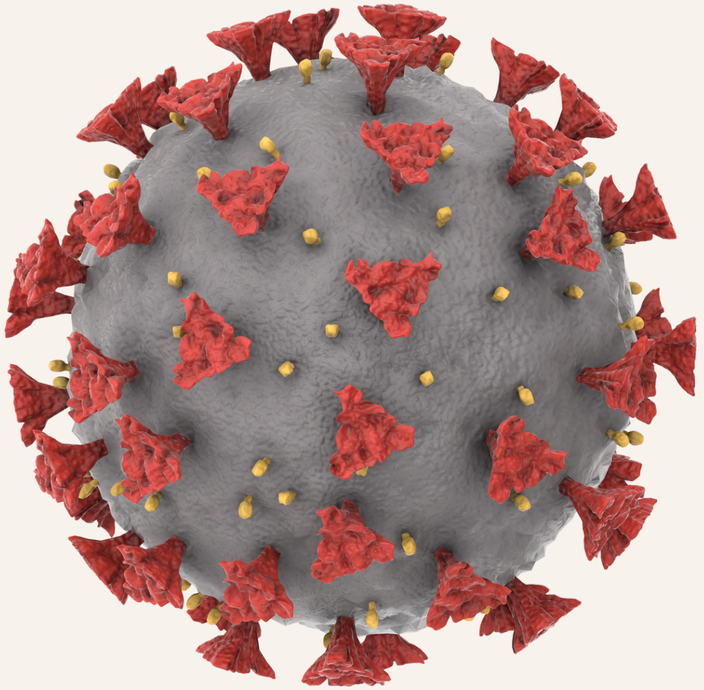
ARDS IMMUNOLOGICAL MECHANISM

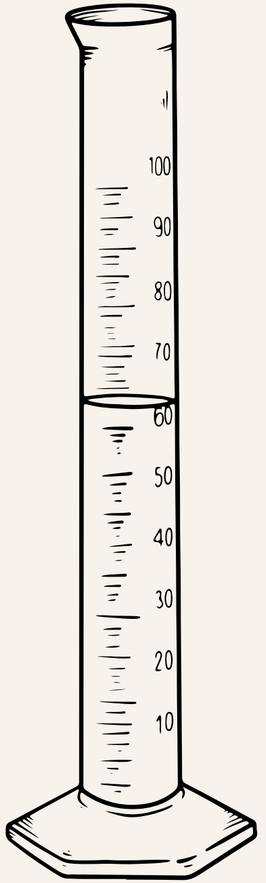


Source: Huang et al, 2024

COVID-19

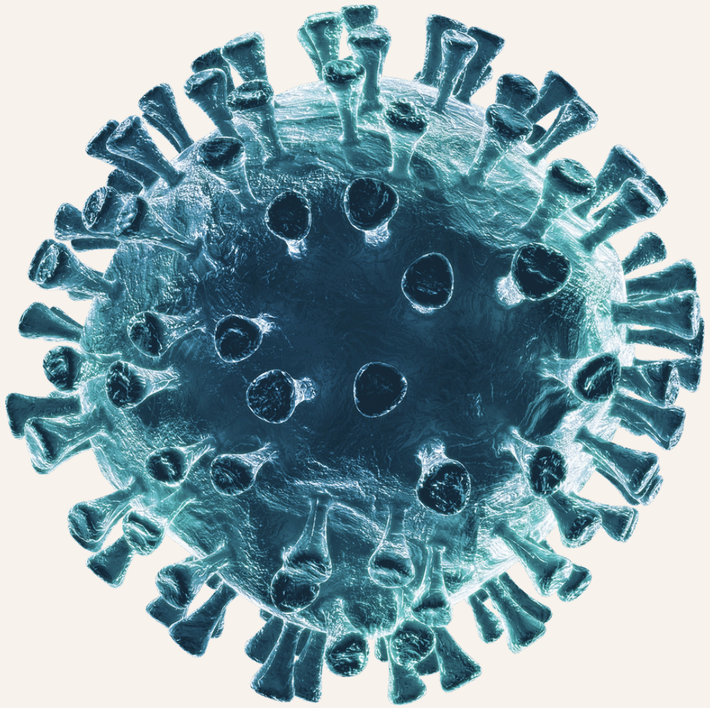






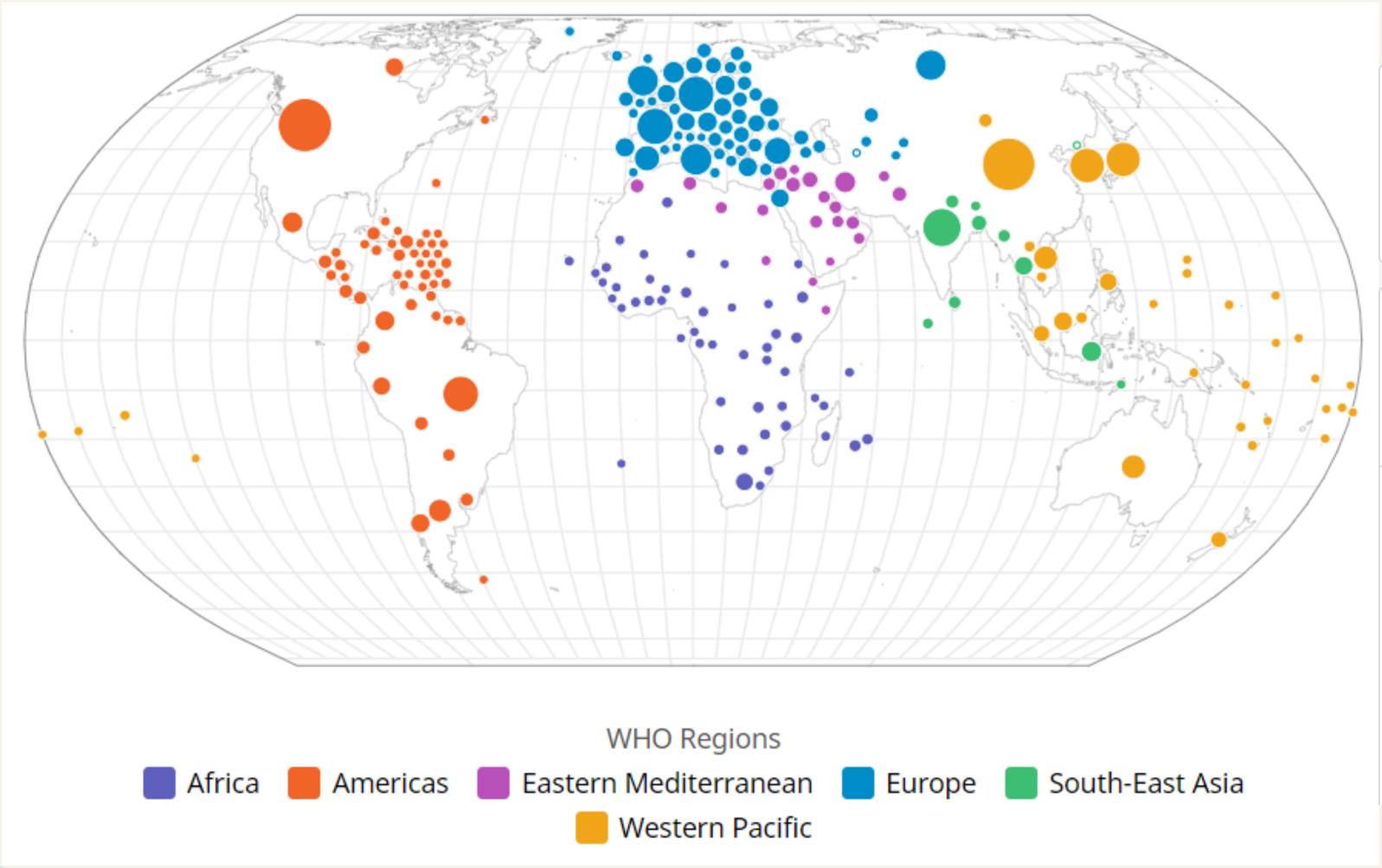
COVID-19

- Viral diseases transmitted by SARS-CoV-2
- Responsible for the latest global pandemic
- First emerged from Wuhan, in China



EPIDEMIOLOGY

Number of COVID-19 cases reported to WHO (cumulative total)



776,281,230 +74,418 increase on previous 7 days

Reported COVID-19 cases

World, 7 days to 15 September 2024

Number of COVID-19 cases reported to WHO (cumulative total)

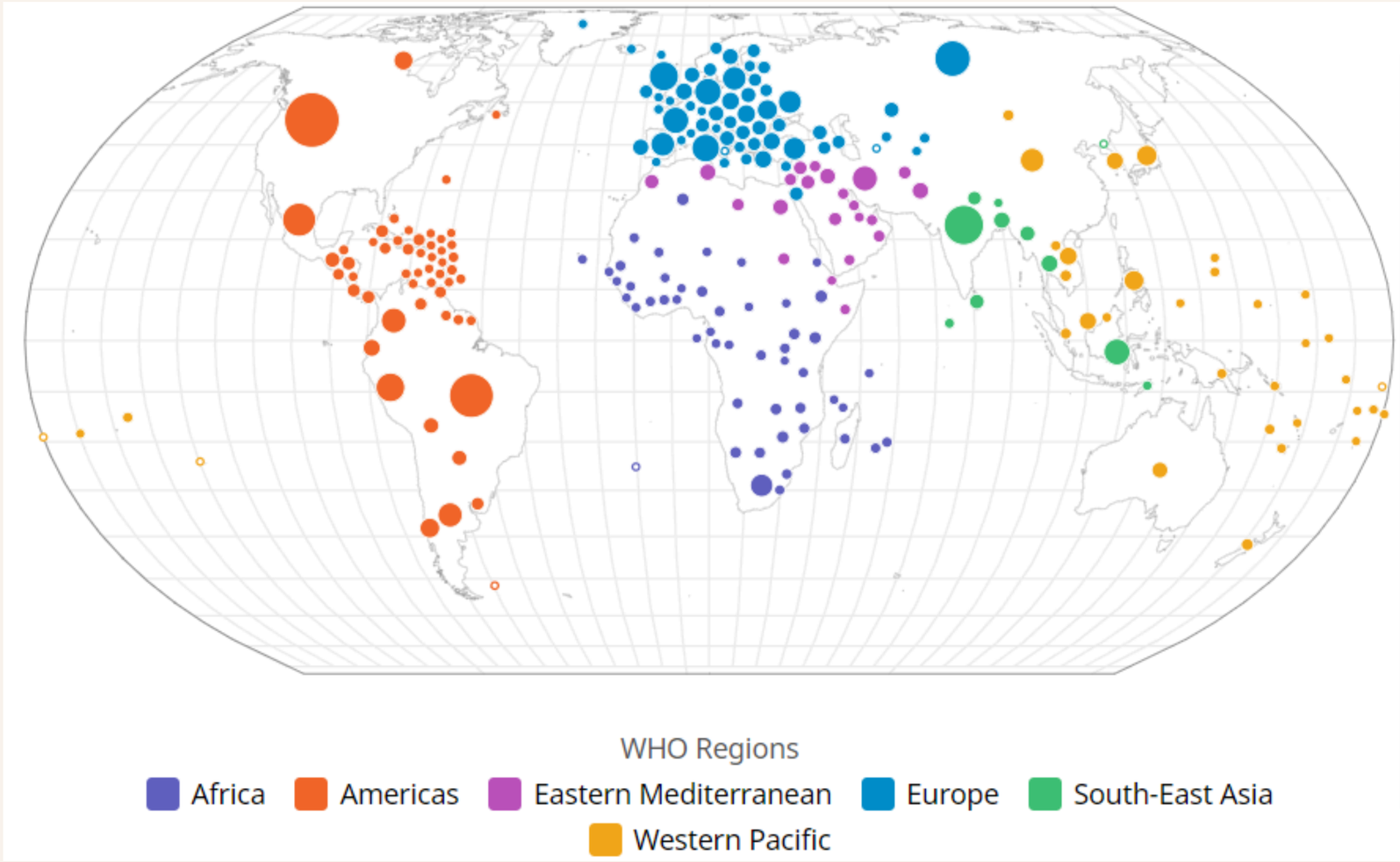
World

Country	Cases
World	776m
United States of America	103m
China	99.4m

https://data.who.int/dashboards/covid19/cases?n=c

EPIDEMIOLOGY

Number of COVID-19 deaths reported to WHO (cumulative total)



7,067,260 +931
increase on previous 7 days

Reported COVID-19 deaths

World, 7 days to 22 September 2024

Number of COVID-19 deaths reported to WHO (cumulative total)

World

Country	Deaths
World	**7.1m**
United States of America	1.2m
Brazil	702k

https://data.who.int/dashboards/covid19/deaths?n=c

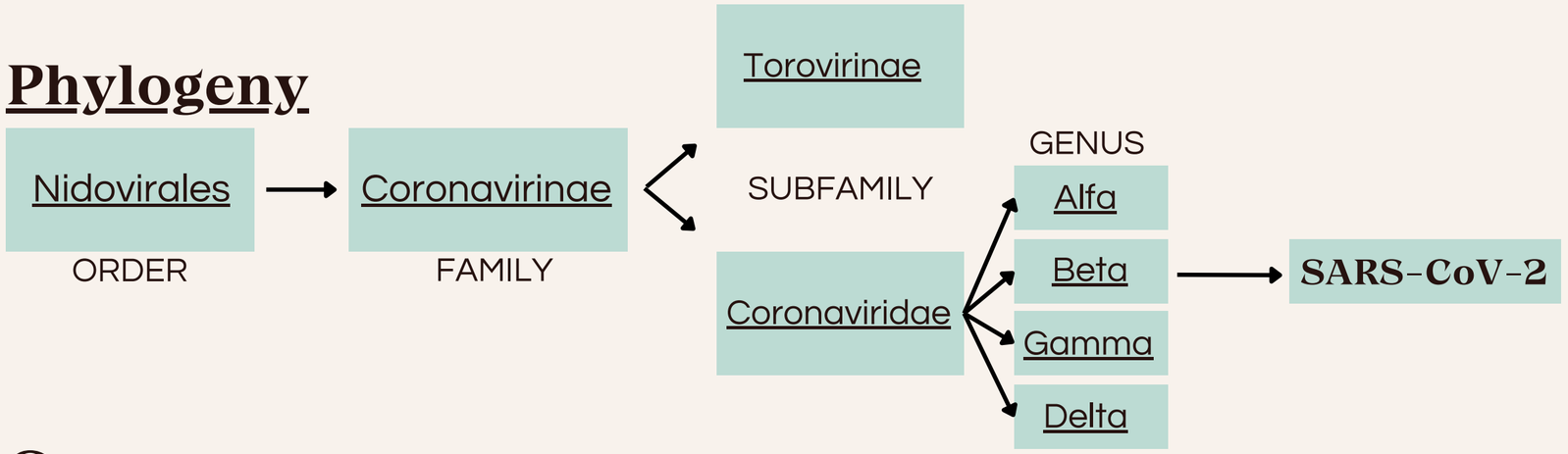
EPIDEMIOLOGY

COUNTRY	POP.*	CASES	DEATHS	INCIDENCE	MORTALITY	LETALITY
CHINA	1,441,800,000	99,380,194	122,352	7%	0,008%	0,12%
USA	334,201,000	103,436,829	1,200,360	31%	0,36%	1,1%
BRASIL	203,062,512	37,511,921	702,116	18,5%	0,35%	1,8%

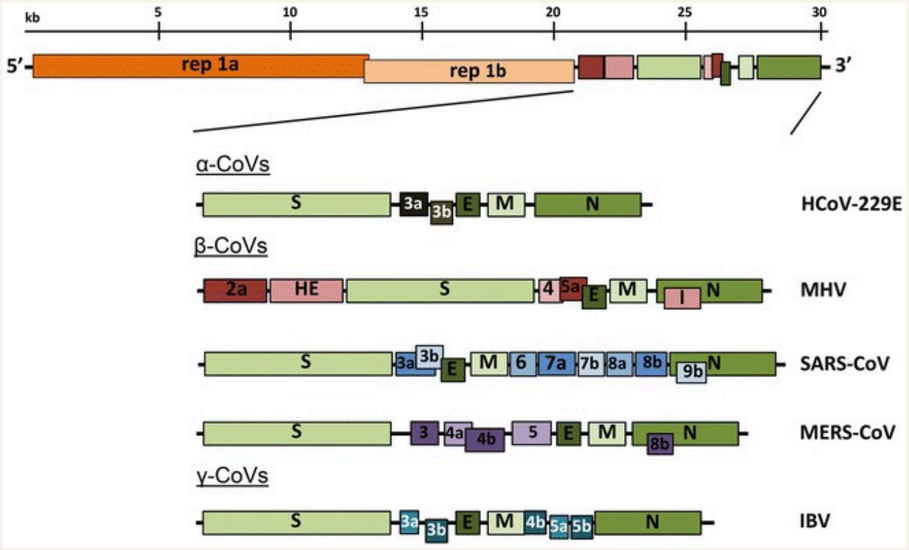
* The population size was considered at the midpoint of the period from the beginning of the pandemic until today - 2022.

SARS-CoV-2

- **Phylogeny**

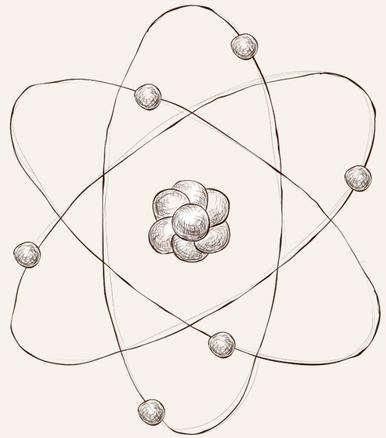


- **Genome**



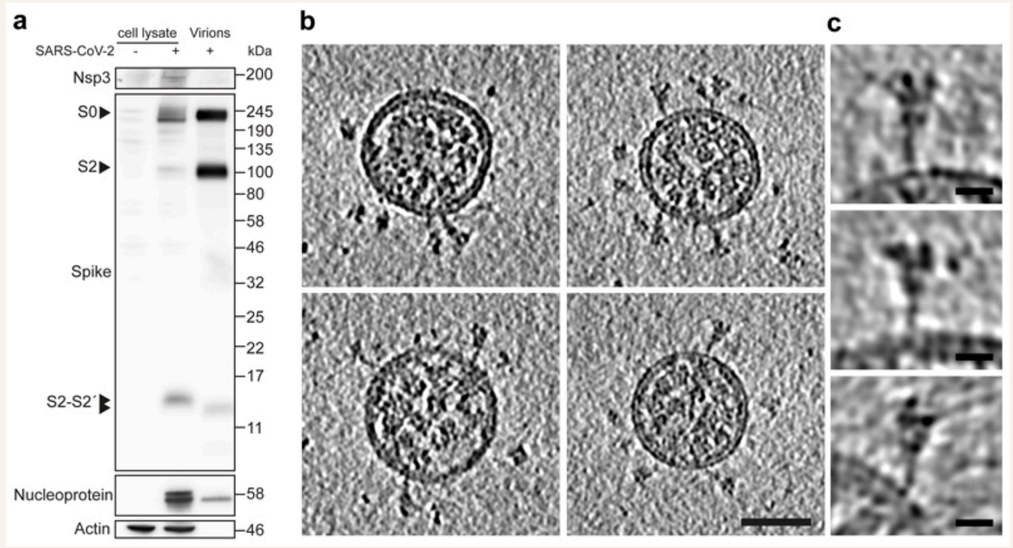
FEHR and PERLMAN (2015)

- RNA genome of ~30kb
- 4 structural proteins:
  - Spike (S)
  - Envelop (E)
  - Membrane (M)
  - Nucleocapsid (E)
- 5' cap and 3' poli A tail



SARS-CoV-2

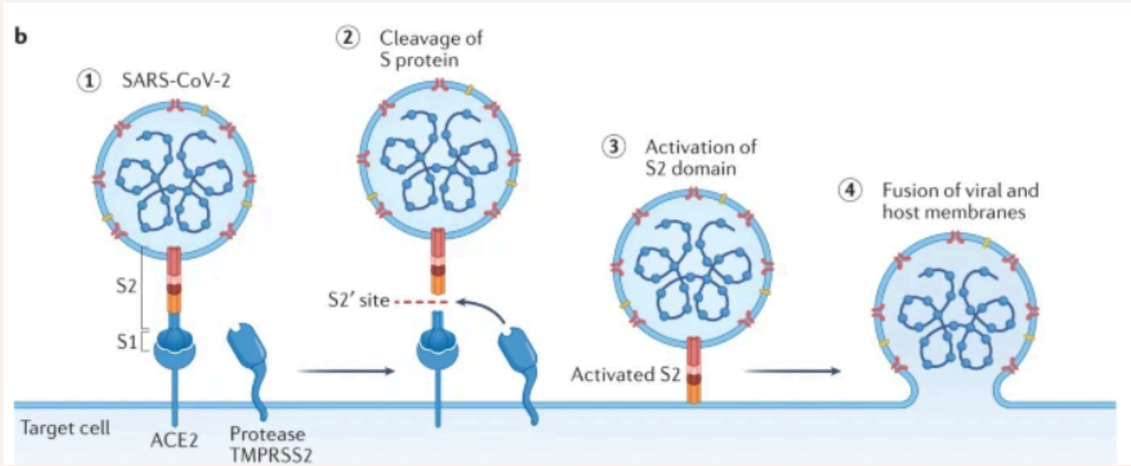
- **Virion**



KE Z. et al. (2021)

  - Spike protein
  - Virion are approximately spherical
  - Contain granular density ⟶ N-packeged genome
  - Diameter: 91 ± 11 nm

- **Invasion of the Cell**



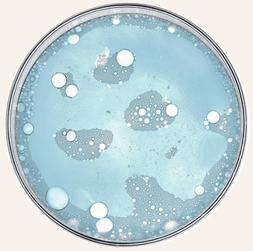
LAMERS and HAAGMANS (2022)

  - The first cells targeted are likely multiciliated cells in the nasopharynx or trachea, or sustentacular cells in the nasal olfactory mucosa
  - S protein attaches to the receptor
  - Protein S cleavage
  - Membranes fusion

THE SYMPTOMS

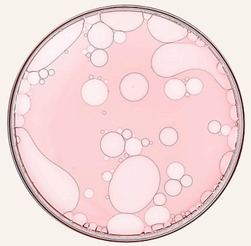
- **Mild Disease**

  81% with fever, fatigue and dry cough. Less common symptons: headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting



- **Severe Disease**

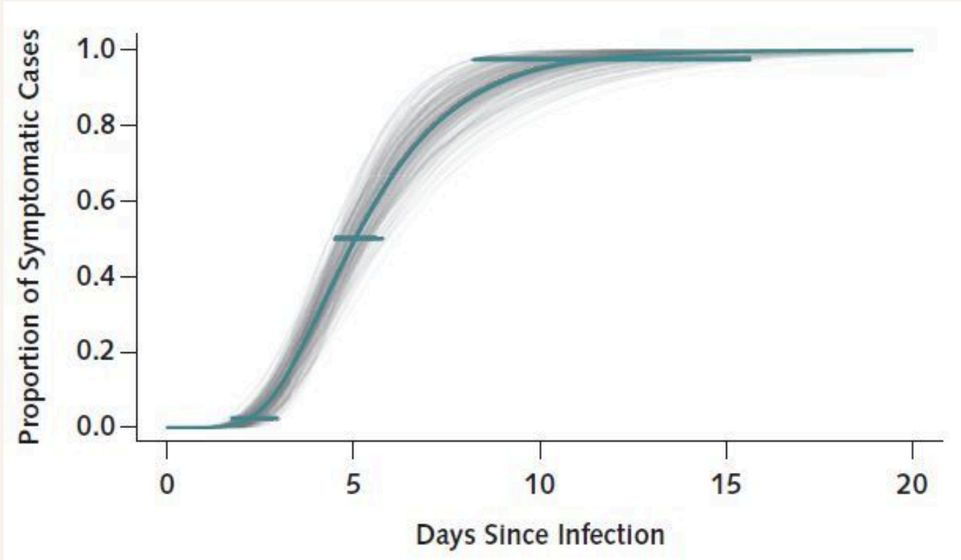
  14% with dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24 to 48 hours



- **Critical Disease**

  5% with respiratory failure, septic shock, and/or multiple organ dysfunction or failure

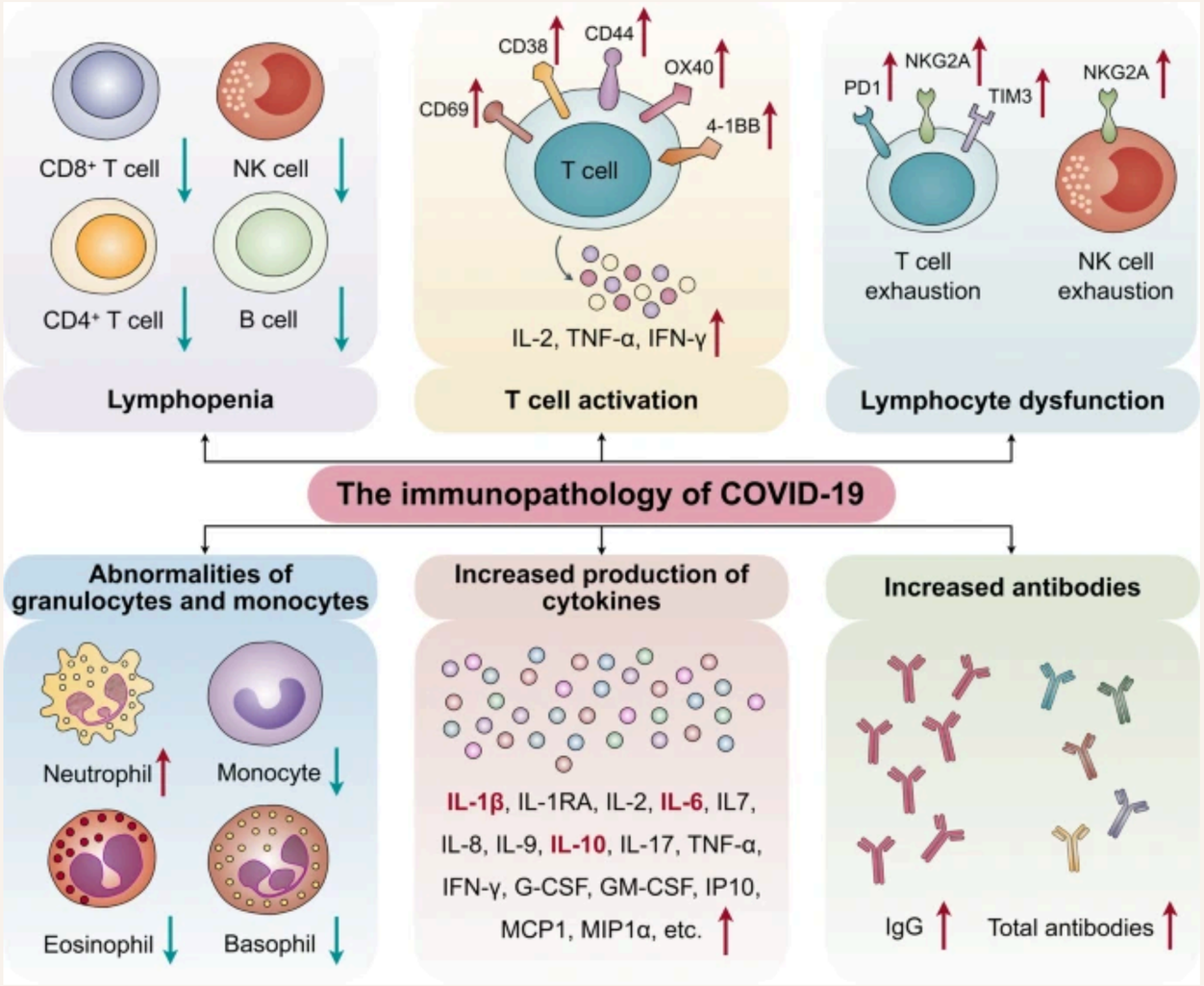
- **Incubation period estimation**



LAUER et al. (2020)

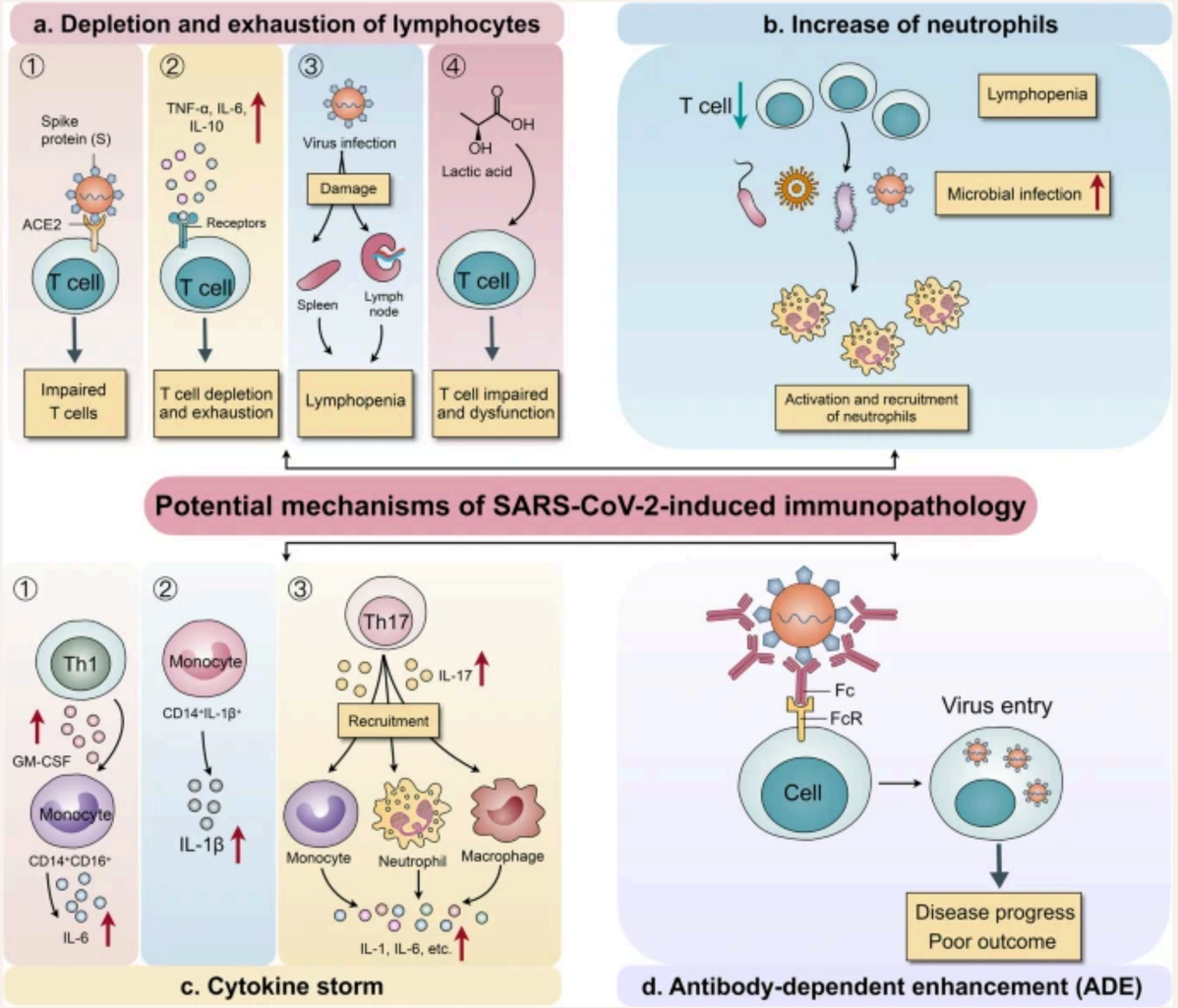
- Incubation period: 5.1 days
- Symptom onset will occur within 11.5 days (CI, 8.2 to 15.6 days) for 97.5% of infected persons

IMMUNOPATHOLOGY



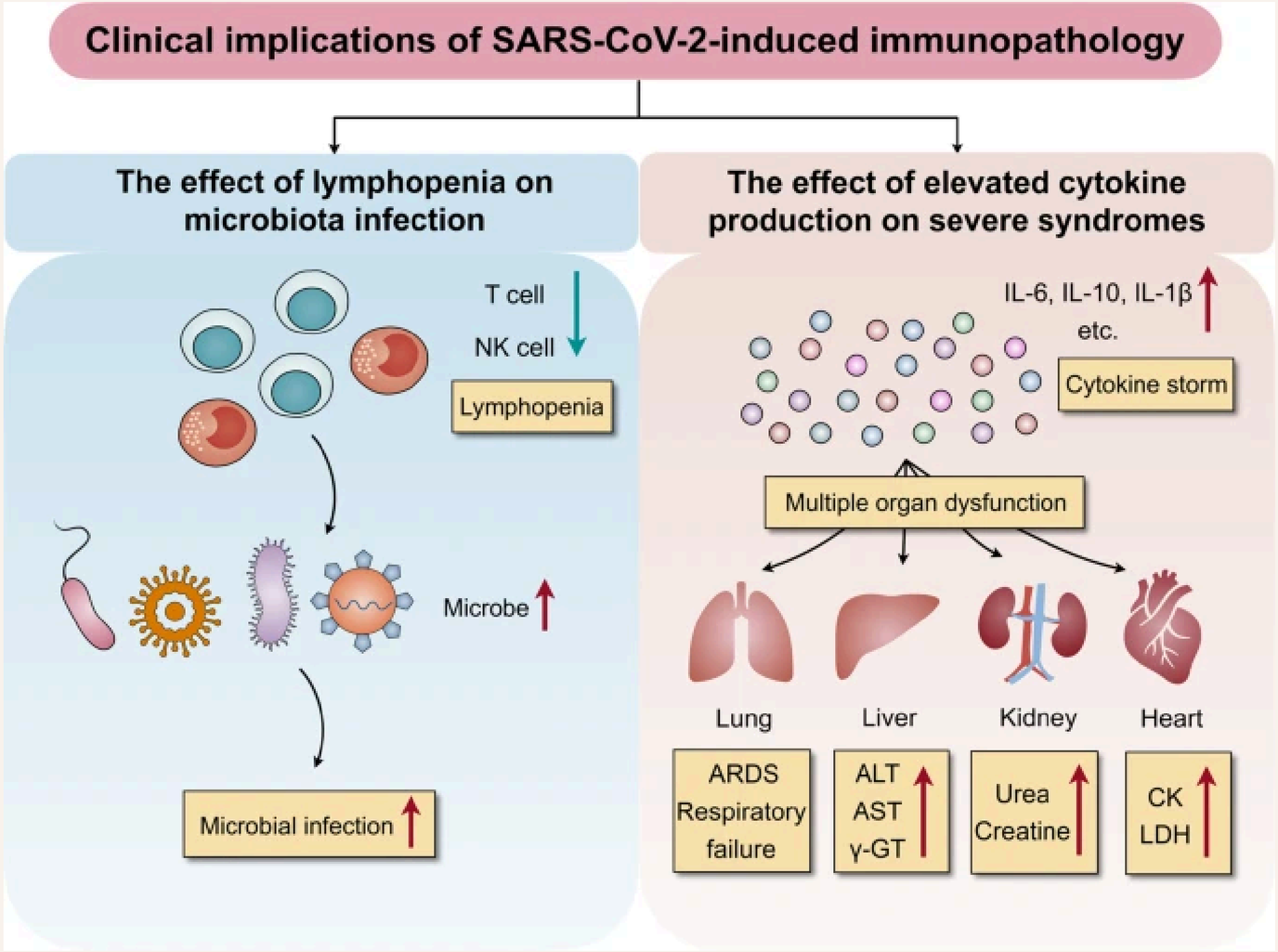
YANG et al (2020)

IMMUNOPATHOLOGY



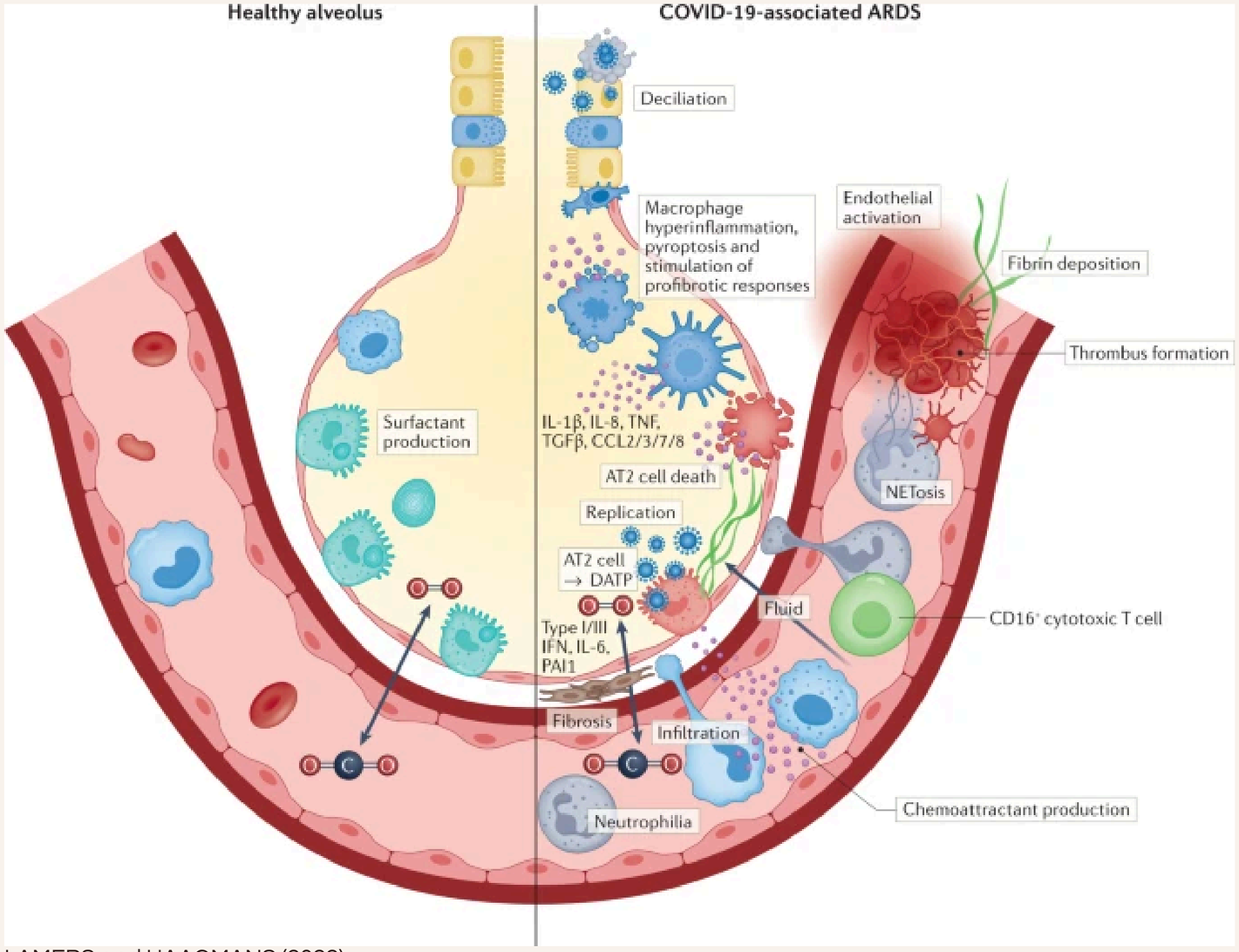
YANG et al (2020)

IMMUNOPATHOLOGY



YANG et al (2020)

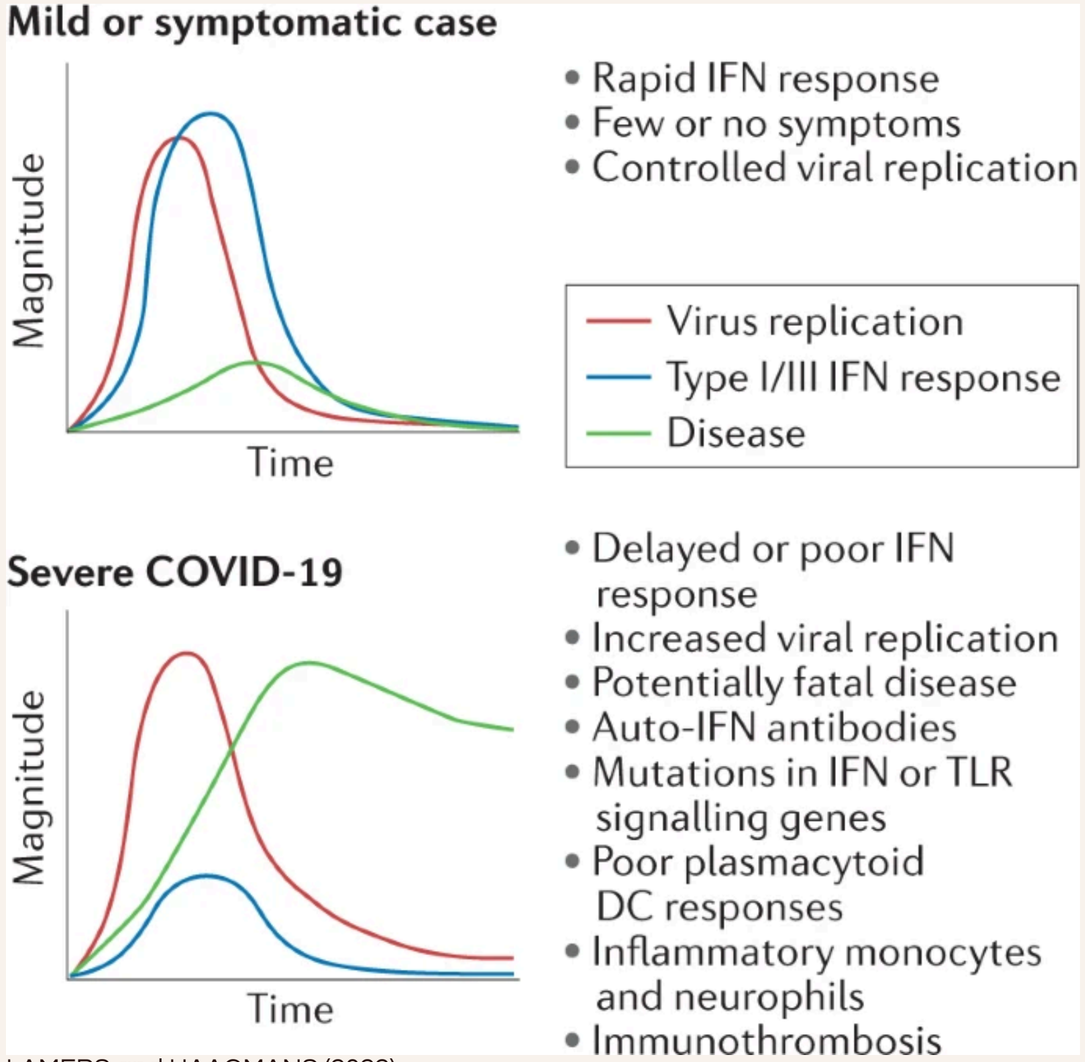
ARDS



LAMERS and HAAGMANS (2022)

- Infections starts with the infection of ciliated cells in the upper conducting airways
- The virus can spread donw to the bronchiotracheal tree to the alvoli

ARDS

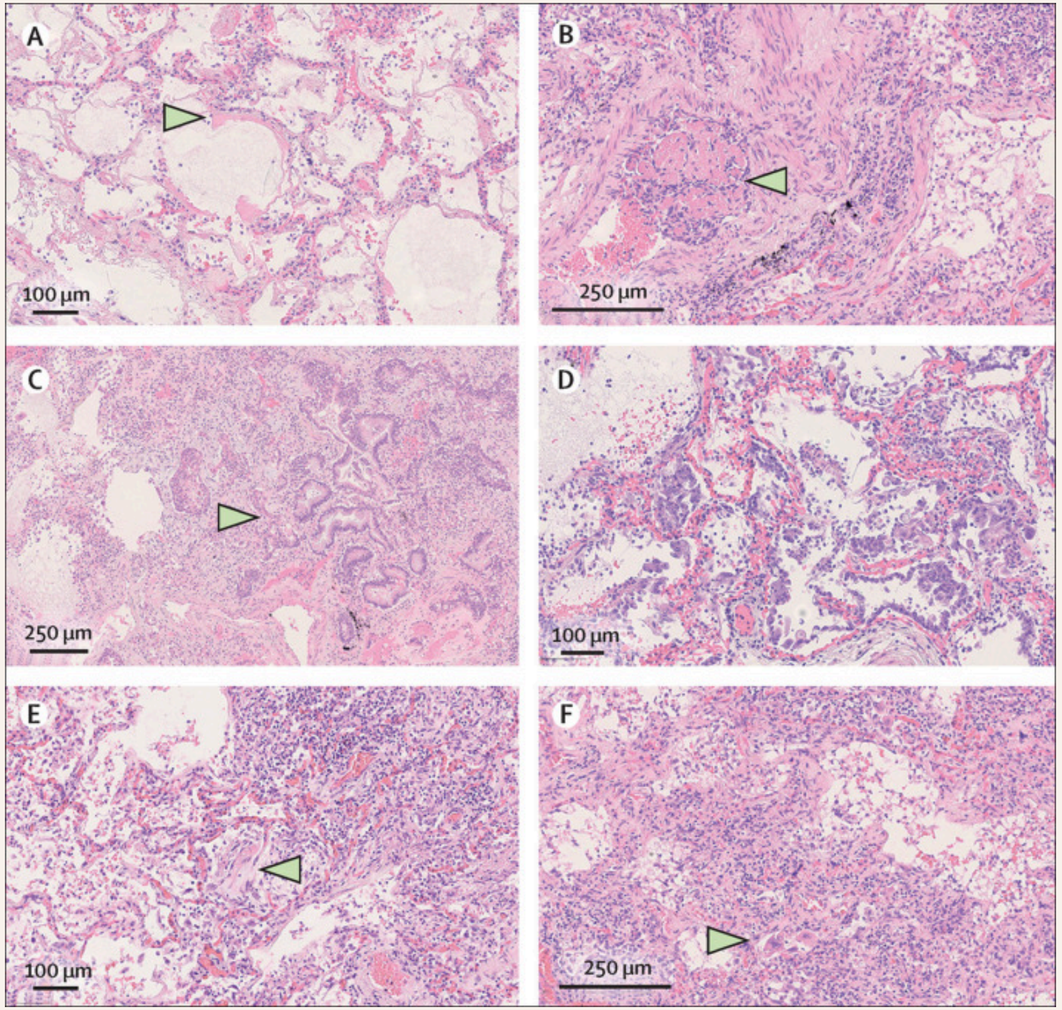


LAMERS and HAAGMANS (2022)

- The virus spread likely is a result of poor or mistimed immune responses
- Especialy IFN I and III

ARDS

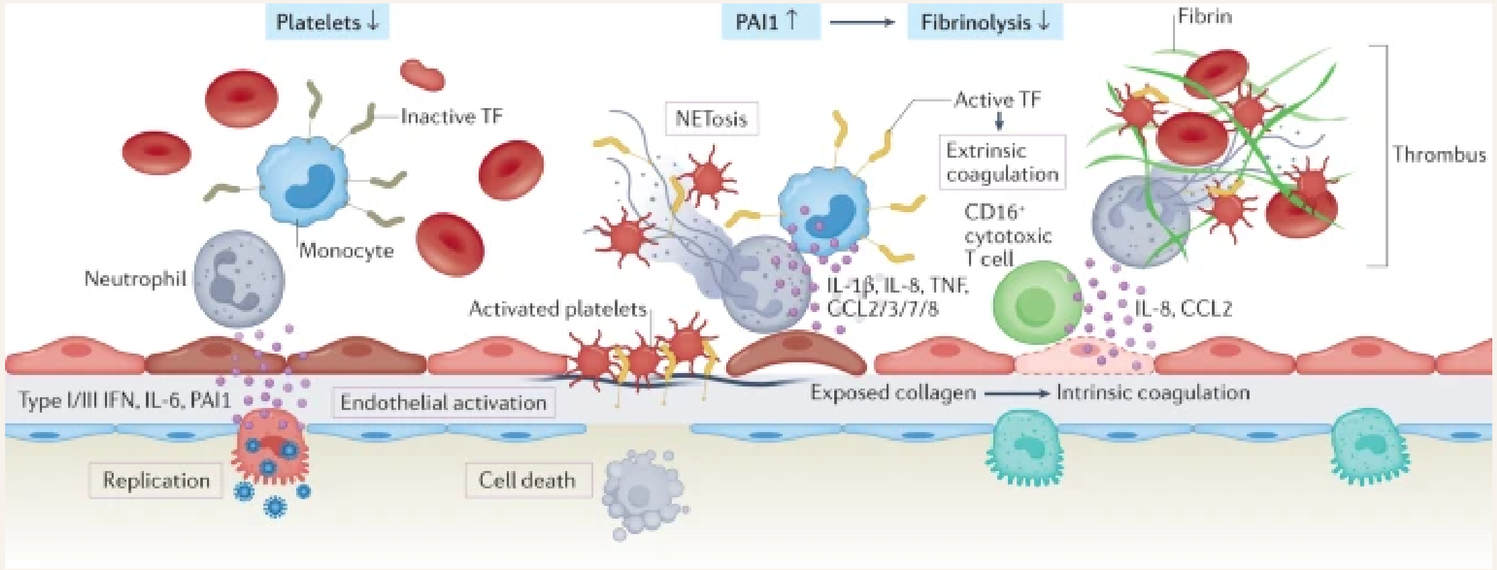
- **Alveolar Damage**
  - May be direct effect of the infection of alveolar type 2 (AT2) cells or an indirected effect caused by local inflamation
  - AT2 cells are responsible for secreting surfactants
  - DAPT:
    - damage-associated transient progenitor phenotype
    - lung injury and failure to fully diferentiate into AT2 cells
  - The disrupted epithelium and endothelium allow fluid to leak into the alveoli



DIS (2020)

ARDS

- **Immunothrombosis:**

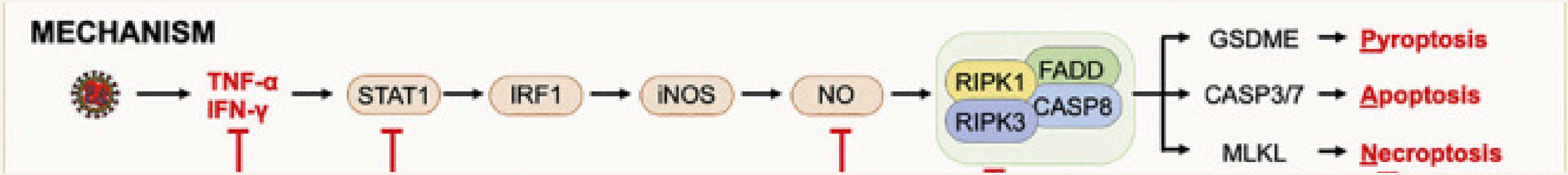


LAMERS and HAAGMANS (2022)

- Exposion of subendothelial extracellular matrix attracts and activates platelets, iniciating coagulation and leading to fibrin deposition
- Immune cells, like monocytos and neutrophils are attracted, but these have dysfunctional phenotypes and promote inflammation and coagulation
- Neutrophils release NETs, promoting microthrombi
- Finally, leads to the formation of fibrin thrombi and depletion of platelets
- Fibrinolysis may be reduced owing to thigh plasminogen activator inhibitor 1 (PAI1)

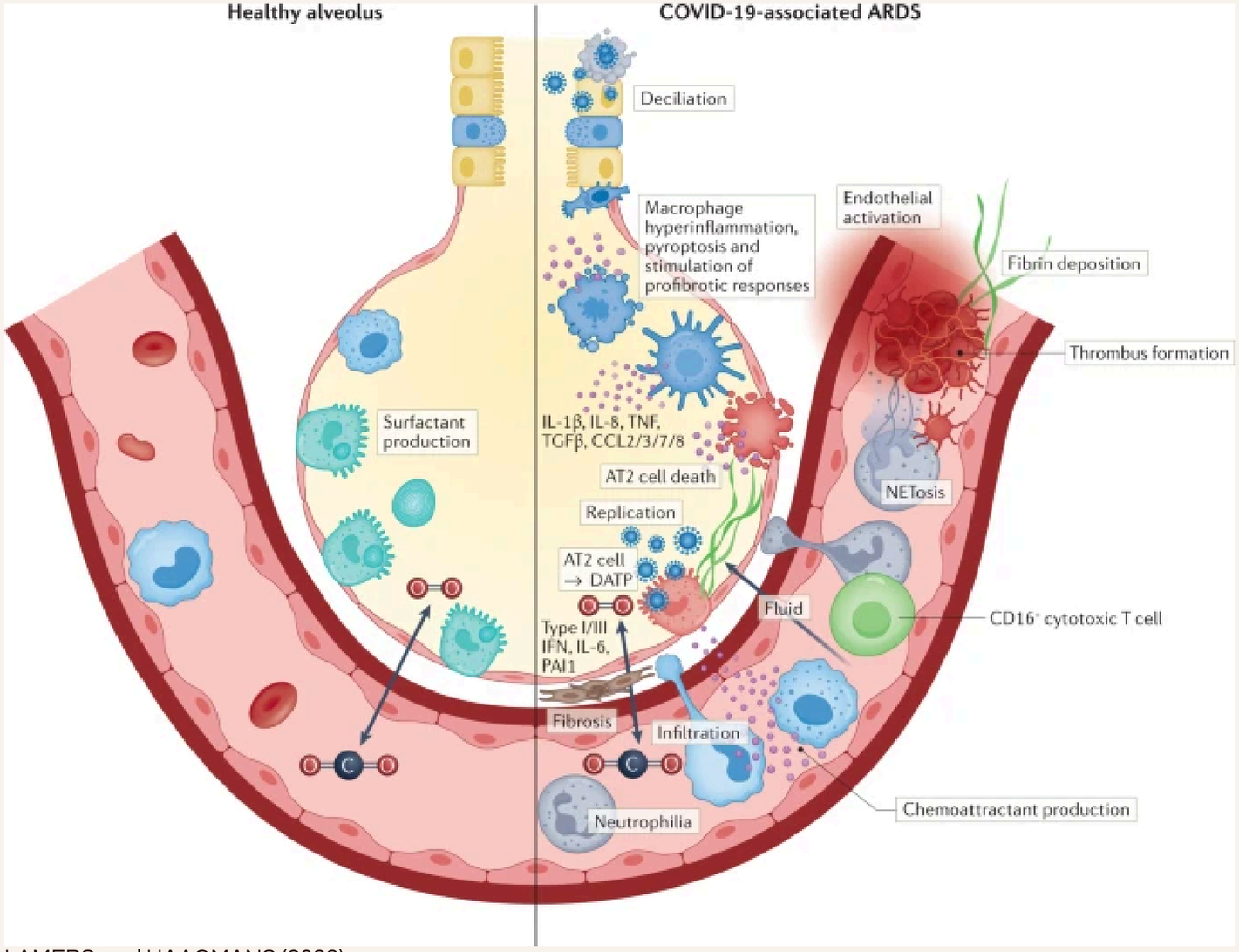
ARDS

- **Apoptosis:**
  - Macrophages in the alveoli may adopt a pro-inflammatory profibrotic phenotype and when infect may go into pyroptosis
  - Pyroptosis: programmed cell death primarily associated with the immune response to infections
  - Hiperinflammation may promote PANoptosis of T cells
  - PANoptosis: programmed cell death that integrates features of apoptosis, pyroptosis, and necroptosis



KARKI et al (2020)

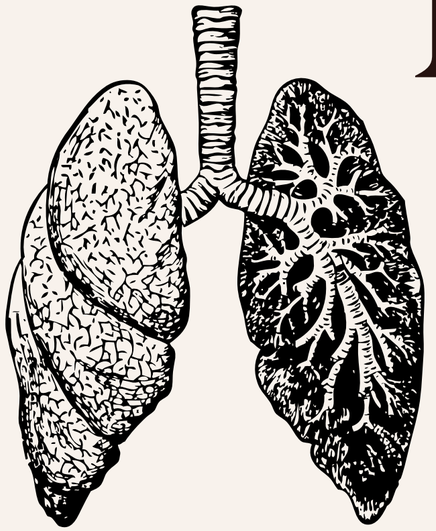
ARDS

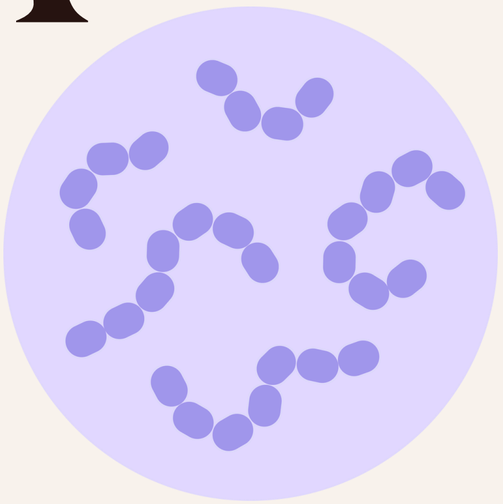


LAMERS and HAAGMANS (2022)

The end result is a focal pattern of highly inflamed and flooded lung tissue, impairing oxygen exchange and leading to hypoxaemia.

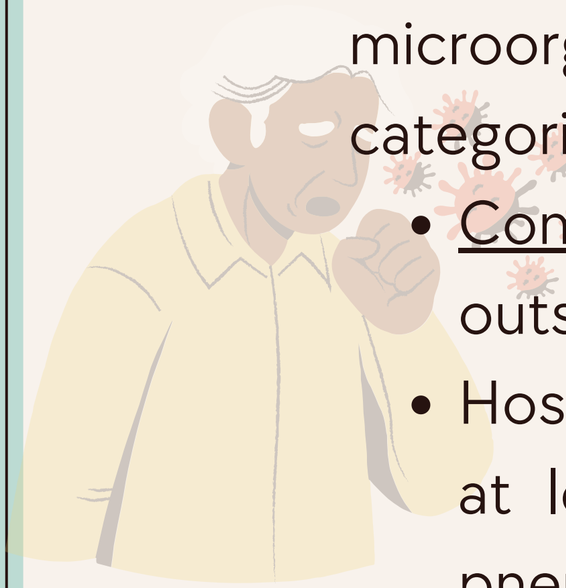
BACTERIAL PNEUMONIA



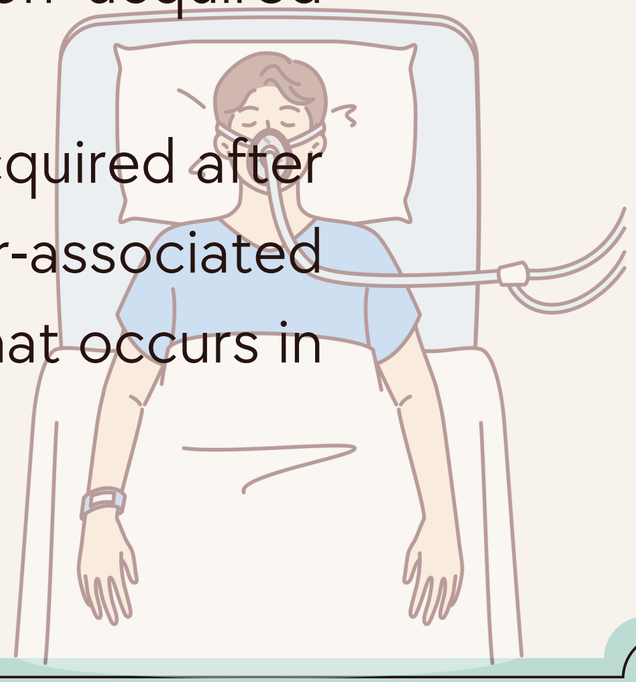


PNEUMONIA

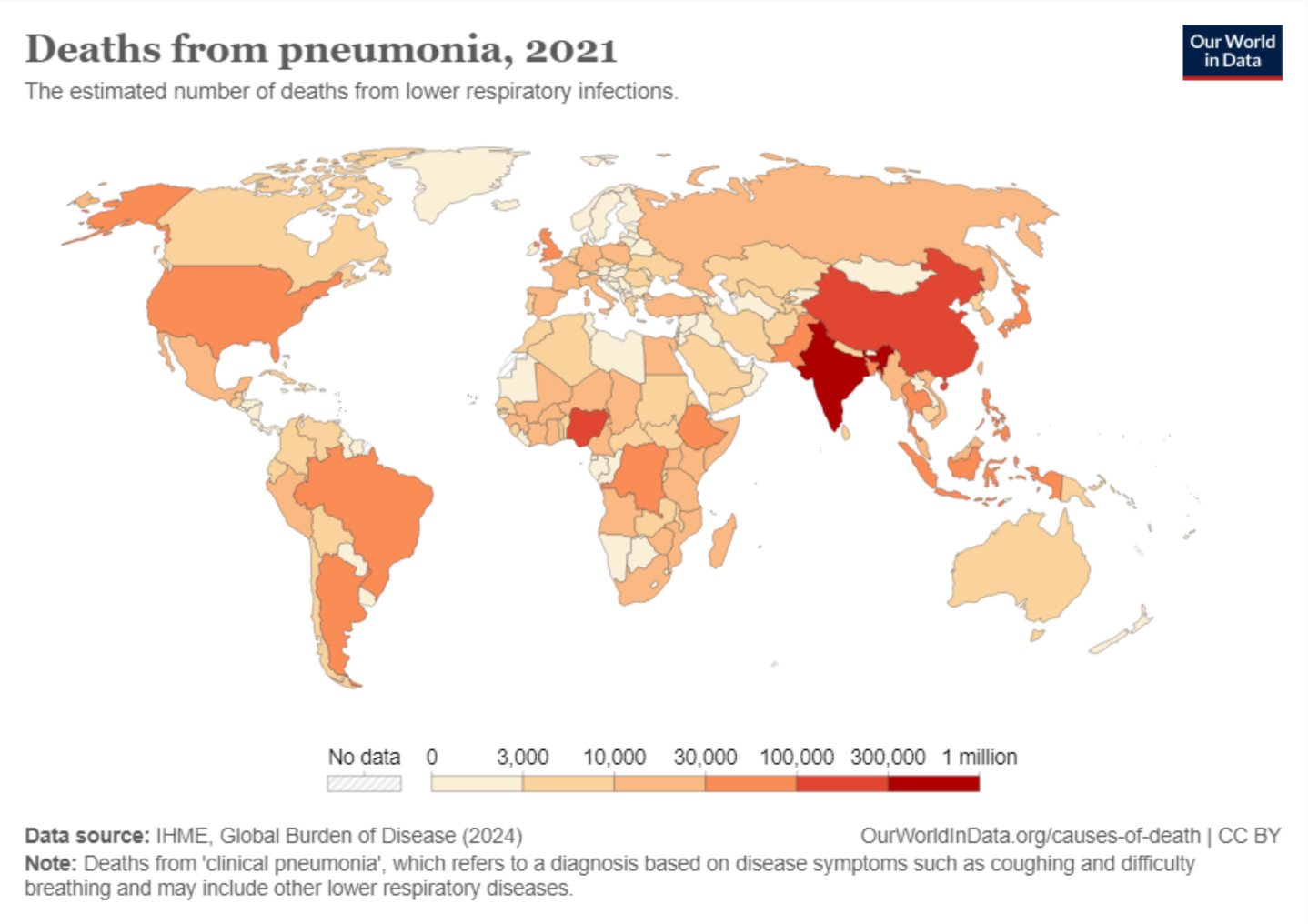
Pneumonia is the **acute inflammation of the lower respiratory tract and lung parenchyma**. It can be caused by a wide variety of microorganisms, including bacteria, viruses, and fungi. Common categories of pneumonia include:



- Community-acquired pneumonia (CAP): infection acquired outside of the hospital setting.
- Hospital-acquired pneumonia (HAP): infection acquired after at least 48 hours of hospitalization. Ventilator-associated pneumonia (VAP) is also a subcategory of HAP that occurs in patients receiving mechanical ventilation.



EPIDEMIOLOGY



GROUPS OF RISK

Pneumonia occurs when an organism's ability to penetrate and infect the lung parenchyma overcomes the host's defense mechanisms, being most common at the extremes of life:

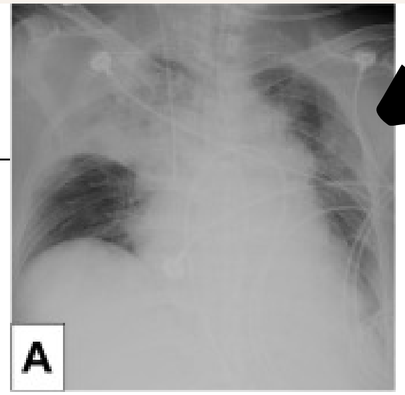
- Children under 5 years old: lack specific splenic functions required for immunoglobulin responses to polysaccharide antigens
- Elderly people: breaches in their defense systems, associated with risk factors (tobaco smoking and comorbidy conditions)

MOST COMMON PATHOGENS

- Among patients who seek medical attention, *S pneumoniae* is by far the most commonly isolated bacterial pathogen, accounting for more than 25% of cases of CAP worldwide.
- Milder presentations are more likely to be caused by *M pneumonia*, *C pneumoniae*, and viruses, although *S pneumoniae* still predominates
- More severe presentations commonly involve *Staphylococcus aureus*, *Legionella*, and *H influenzae*
- Most found in ICU include bacilli gram-negative as *Acinetobacter spp and P. aeruginosa*.

SYMPTOMS

Pneumococcal pneumonia in humans.



Clinical presentation	• fever • chills • cough • productive sputum • dyspnea • pleuritic chest pain
Complications	• mental status changes • shock • respiratory failure

PATTERNS:

- CAP: Lobar pneumonia
- HAP: bronchopneumonia
- Atypical pneumonias: interstitial pattern

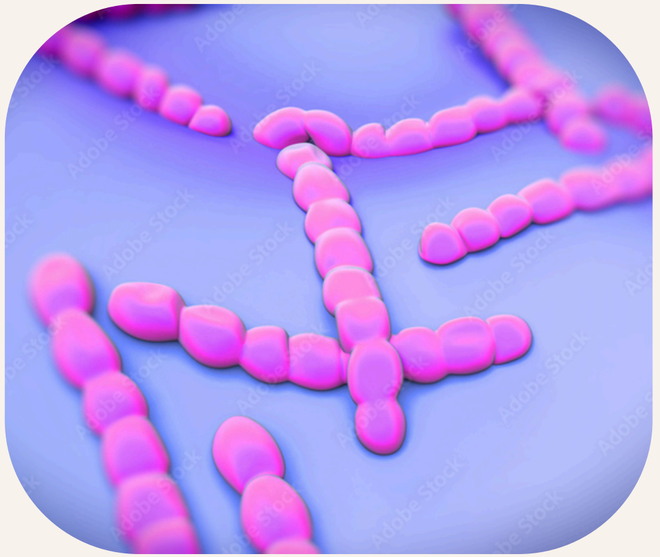
EXAMS:

- Imaging: chest radiograph, chest ultrasound, or chest tomography
- Laboratory changes: leukocytosis or leukopenia

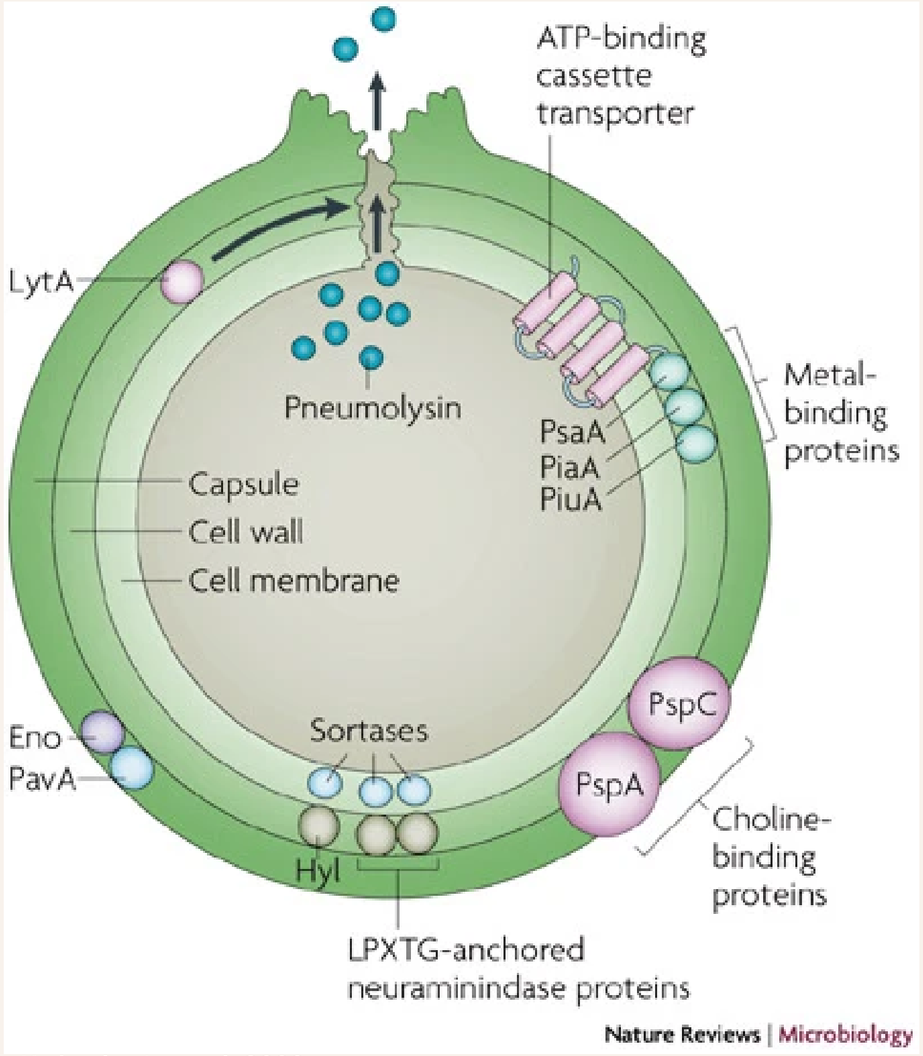
Source: Borsa N,et al. 2019

STREPTOCOCCUS PNEUMONIAE

- Gram-positive bacteria
- Natural competent (risk of acquired resistance)
- Colonizes the mucosal surfaces of the host nasopharynx and upper airway, but can spread to the sterile regions of the lower respiratory tract, leading to pneumonia



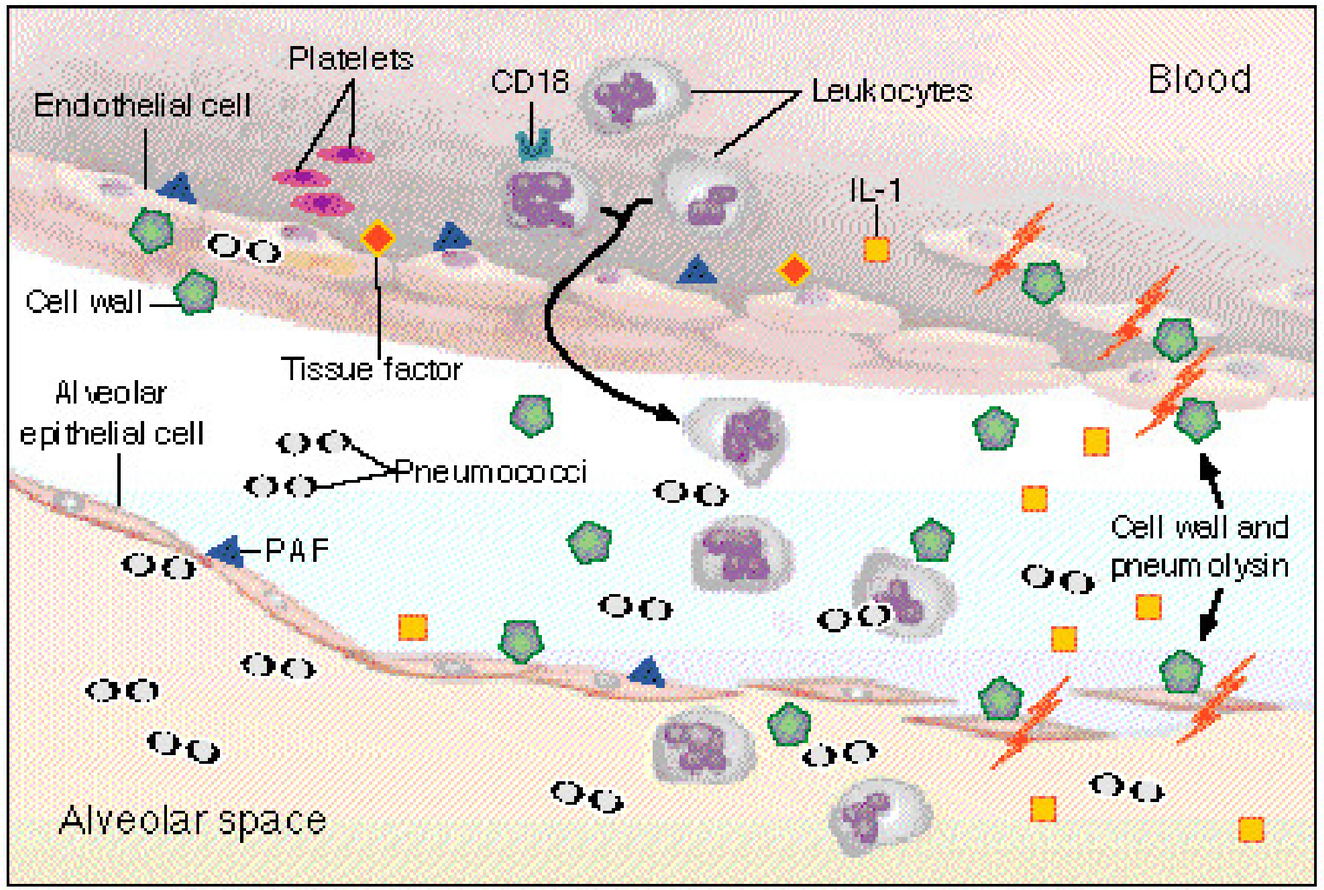
VIRULENCE



Kadioglu, A., et al. 2008

- Capsular polyssacharide: prevents entrapment in the nasal mucus and protects from phagocytosis.
- Cell Wall: teichoic acid with phosphorylcholine (ChoP), which mediates bacterial adherence to the receptor for platelet-activating factor (rPAF)
- Surface proteins: PspA inhibits complement-mediated opsonization and prevents bactericidal activity of apolactoferrin; PspC induces the process of endocytosis, binds to IgA and factor H, preventing formation of C3b
- Other proteins: pneumolysin, neuraminidases, etc.
- Serotypes

PATHOPHYSIOLOGY



Tuomanen EI, Austrian R, Masure HR. Pathogenesis of pneumococcal infection. N Engl J Med.

1. Invasion and Colonization

2. Inflammatory Response

3. Exudate and Consolidation:

-pulmonary consolidation = alveoli fill with fluid

-red hepatization

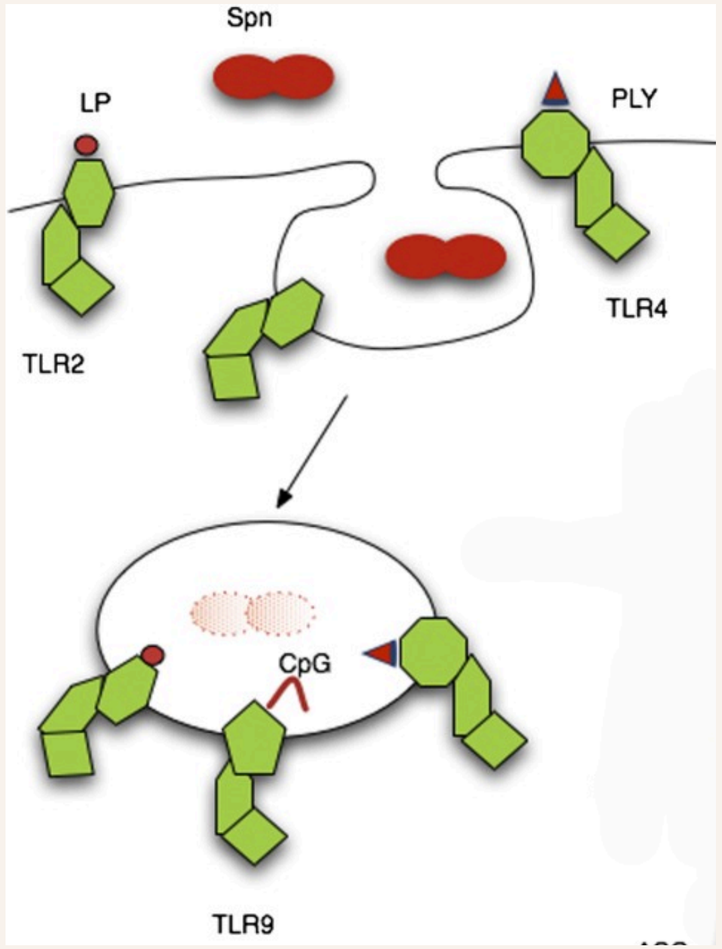
-gray hepatization

4. Alterations in Gas Exchange

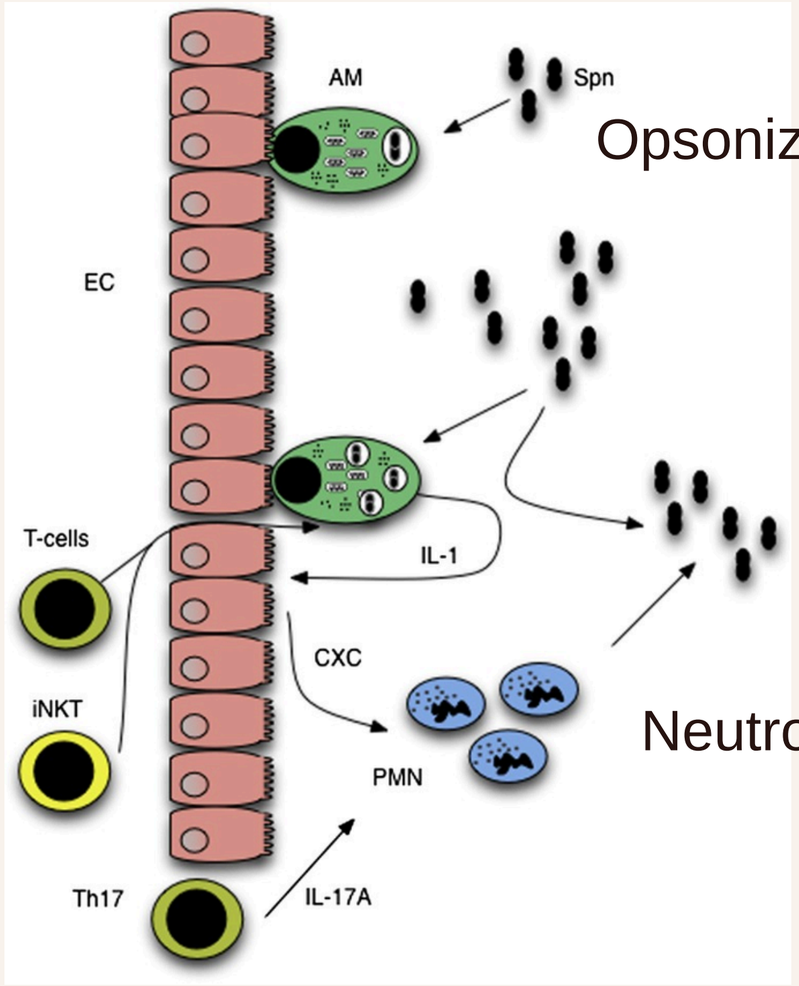
5. Complications (cell wall liberation with lysis): pulmonary abscesses, empyema , sepsis

IMMUNE RESPONSE

TOLL-LIKE RECEPTORS



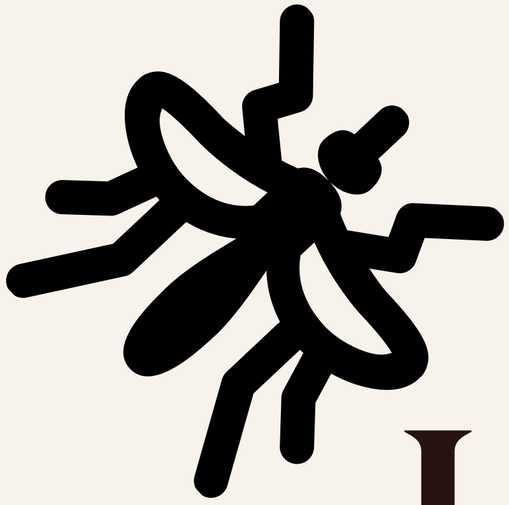
IMMUNE CELLS DYNAMIC



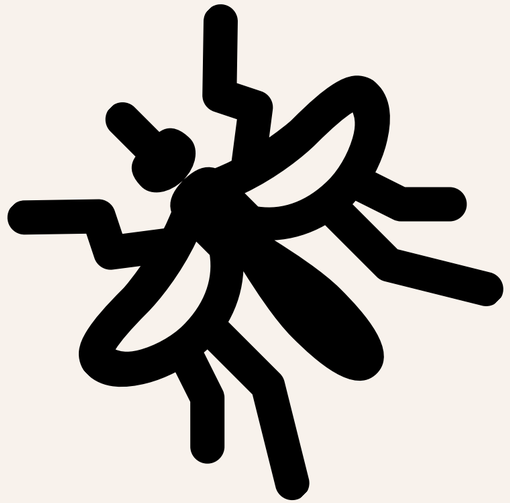
Opsonization + Phagocytosis

Neutrophills

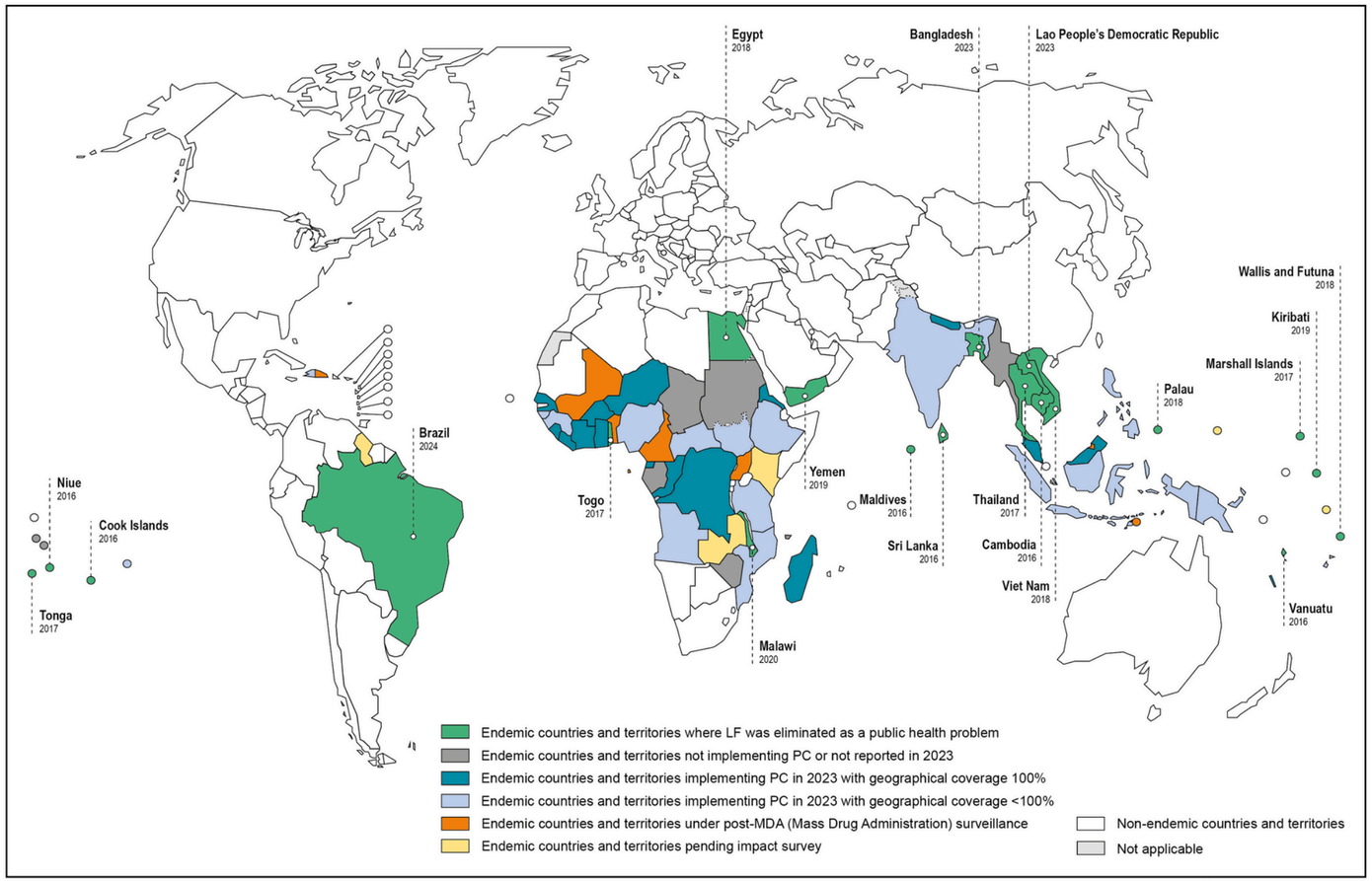
Dockrell DH, Whyte MKB, Mitchell TJ. Pneumococcal pneumonia: mechanisms of infection and resolution



LYMPHATIC FILARIASIS (LF)



LF EPIDEMIOLOGICAL STATUS



Since 2000, the WHO goal to eliminate LF as public health issue;

Distributed mainly at Tropical and Subtropical countries worldwide;

Affects about 120 million people in 72 endemic countries.

Source: WHO

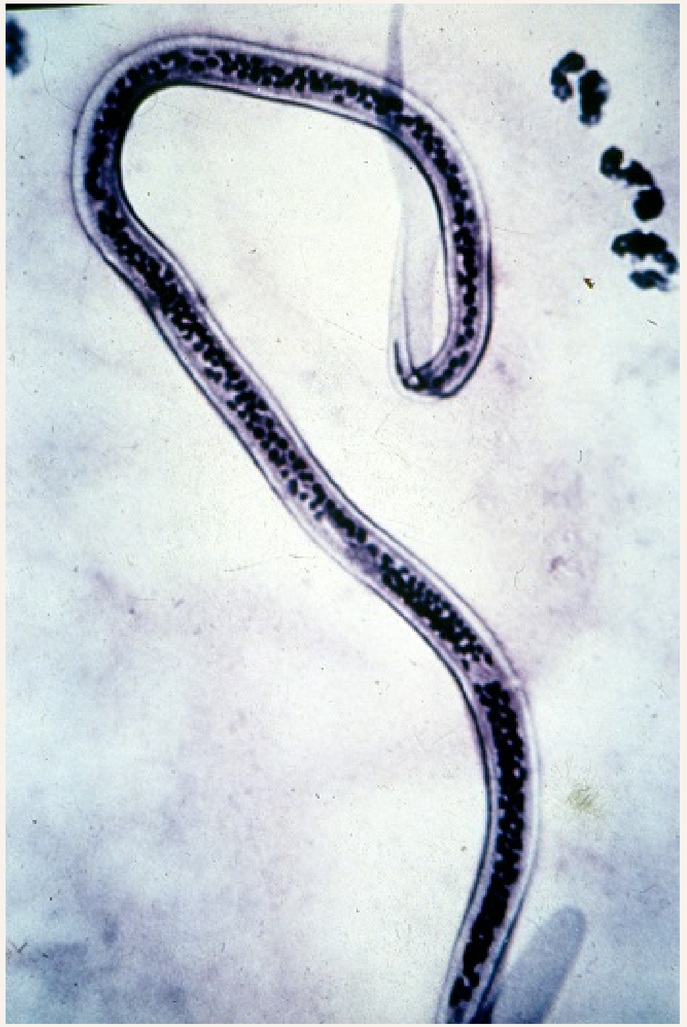
LF ETIOLOGY

Popularly known as elephantiasis

Mosquito-borne infection by repeated bites of infected female Aedes spp./Anopheles spp./Culex spp./Mansonia spp. genus with L3 larvae state of nematods (also known worms) of Filarioidea family:

- Wuchereria bancrofti (90% of total registered cases)
- Brugia malayi
- Brugia timori;

Described as one of Neglected Tropical Diseases (NTDs);



Source: FIOCRUZ and USP

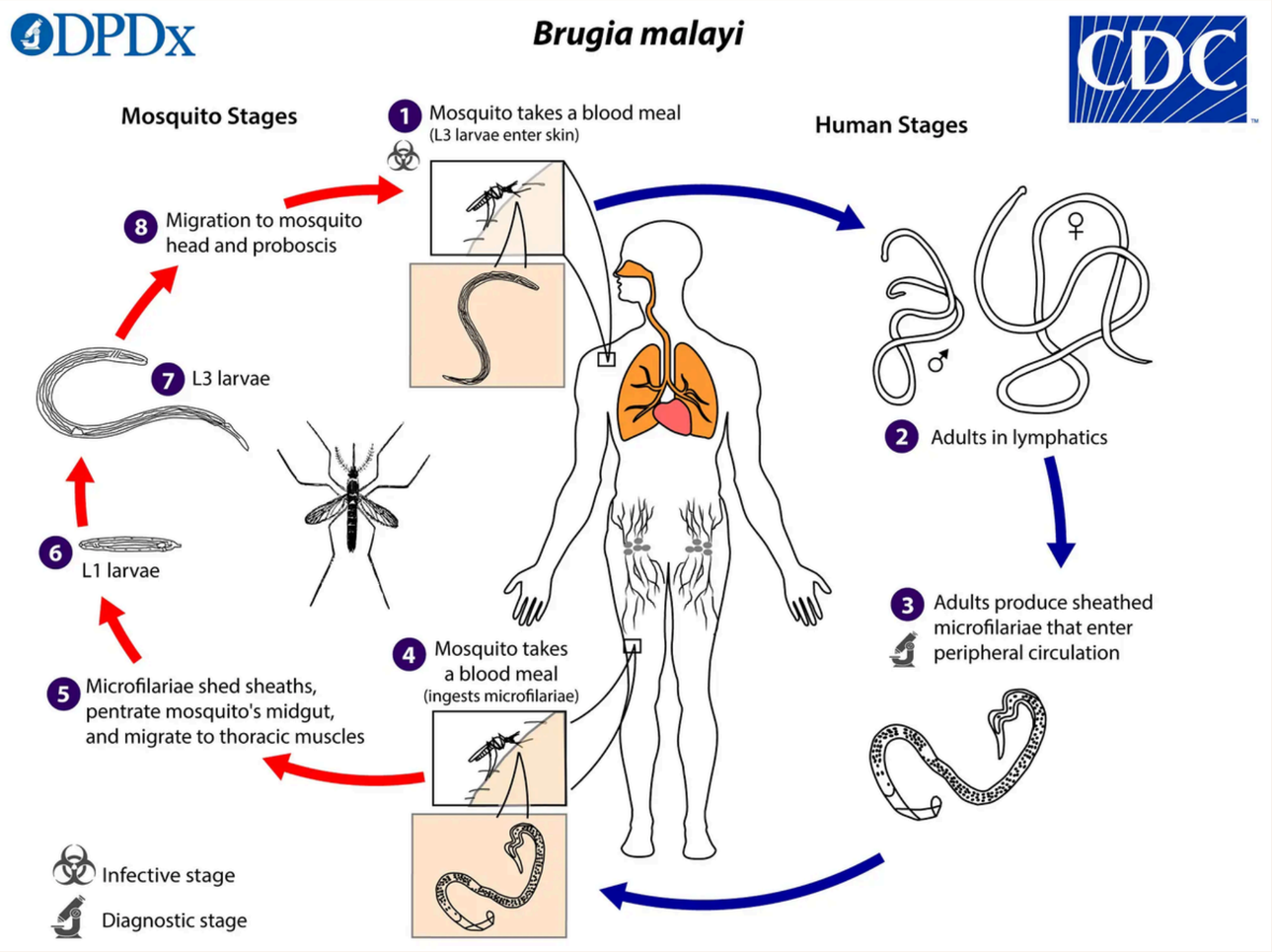
LF LIFE CYCLE

Metaxenic cycle;

L3 larvae state is the infective form;

Adults will be fixed on lymphatic vessels;

Female worms release microfilariae state to enter blood peripheral circulation.



Source: DPDx/CDC

LF CLINICAL FEATURES

Asymptomatic

Hidden damage on lymphatic vessels and circulatory organs as kidney

Acute symptoms

Most commom symptoms like pain, fever, edema, nausea, fatigue and vomiting by filarial attack;

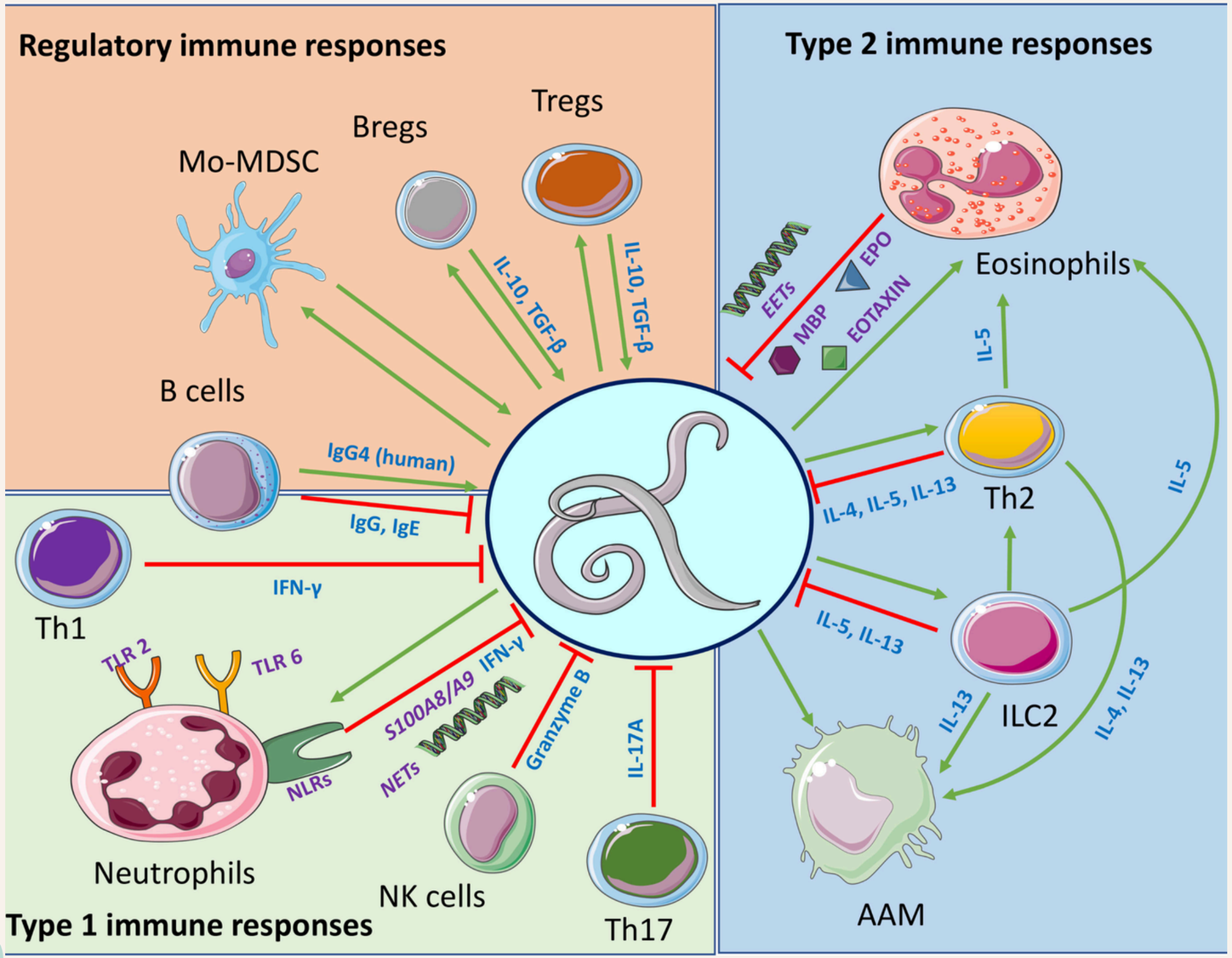
Could increase severity to chronical state.

Chronical symptoms

Lymphangiectasis, lymphedema, hydrocoele, chylocoele, elephantiasisis

Source: Andrea Peterson (www.neglecteddiseases.gov)

LF IMMUNOPATHOLOGY



After recognition by antigen presentation, adults and microfilariae guides to majoritary Th2 immunological response;

Cytokines and macrophage activation profile are mainly to antinflammatory profile;

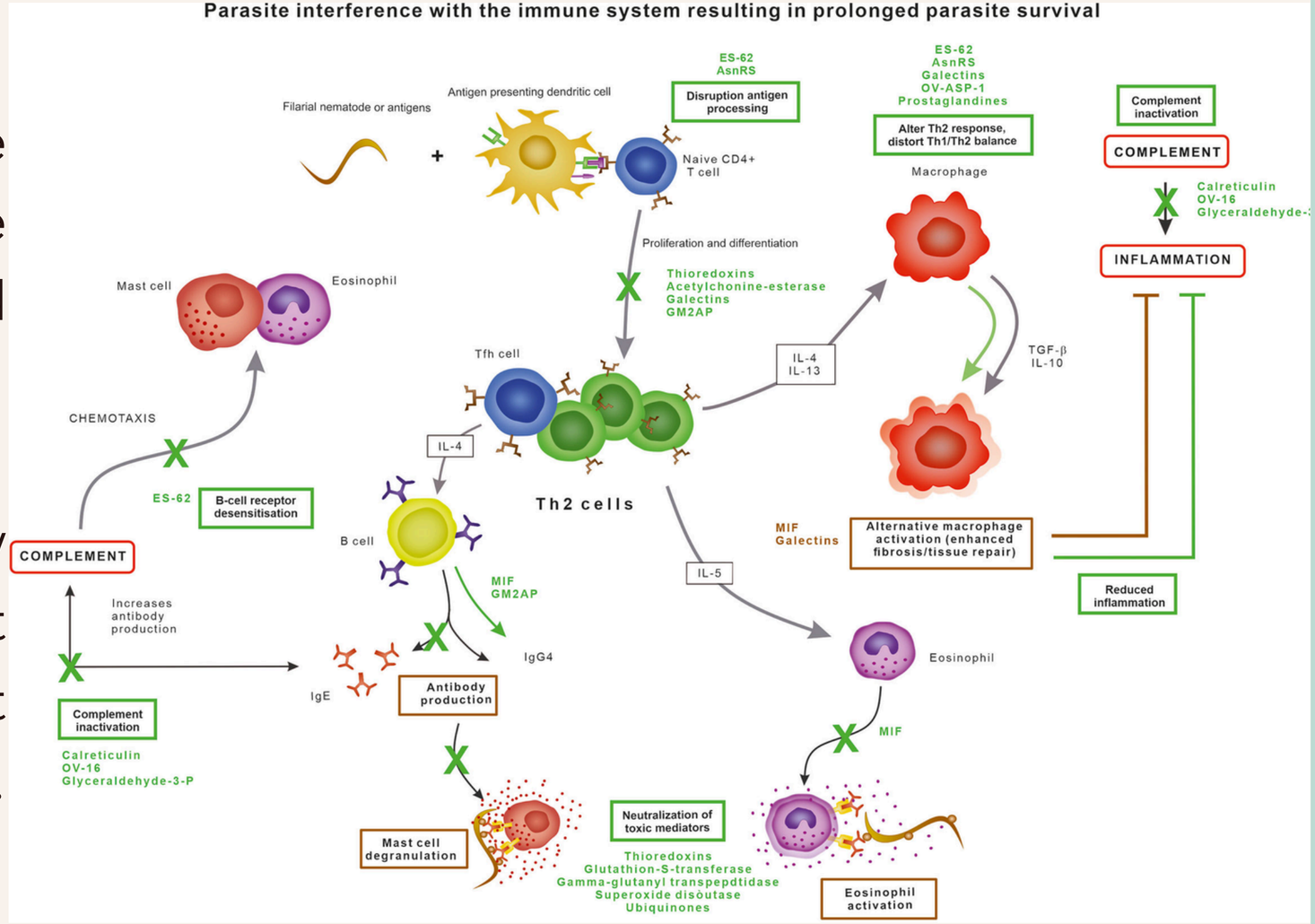
Eosinophils proliferation are upregulated by Th2 profile.

Source: Ehrens et al., 2022

LF IMMUNOPATHOLOGY

Again, adults and microfilariae drives the innate and adaptive response to antinflammatory and allergenic profile;

Inhibition of inflammatory mediators like complement system is an important mechanism to roundworm survival.

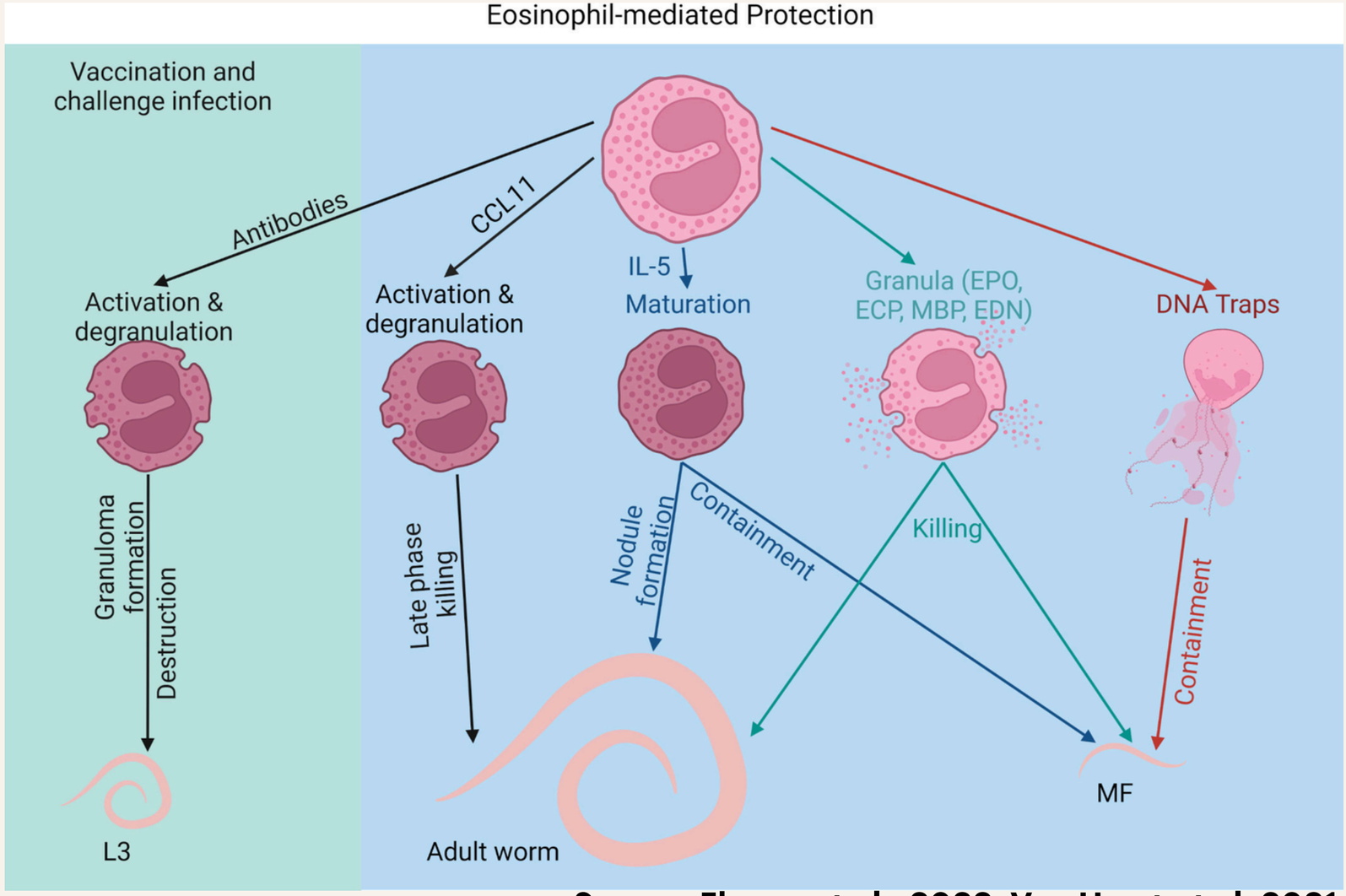


Source: Karakunan et al., 2023

WHY EOSINOPHIL RESPONSE IS IMPORTANT?

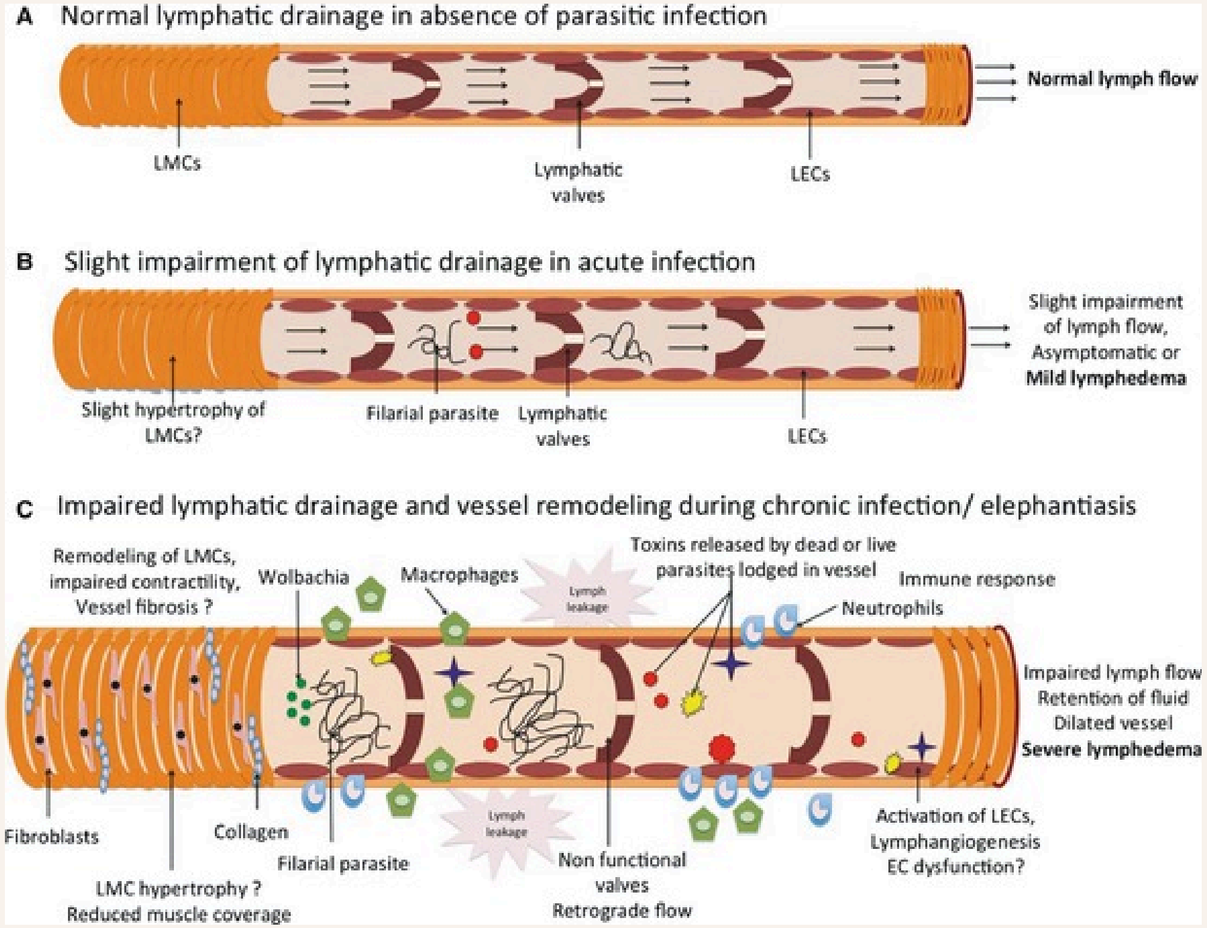
Main innate cell associated to LF response;

The eosinophilic response is related to progression of disease by “protection”



Source: Ehrens et al., 2022; Van Hurst et al, 2021

LF PATHOPHYSIOLOGY



Source: Chakraborty et al., 2013

Chronical status relates by live and dead adult forms still on lympathic vessels, causing lymphangiectasia;

Depends many cofactors to disease's evolution like bacterial infections to guides lymphedema

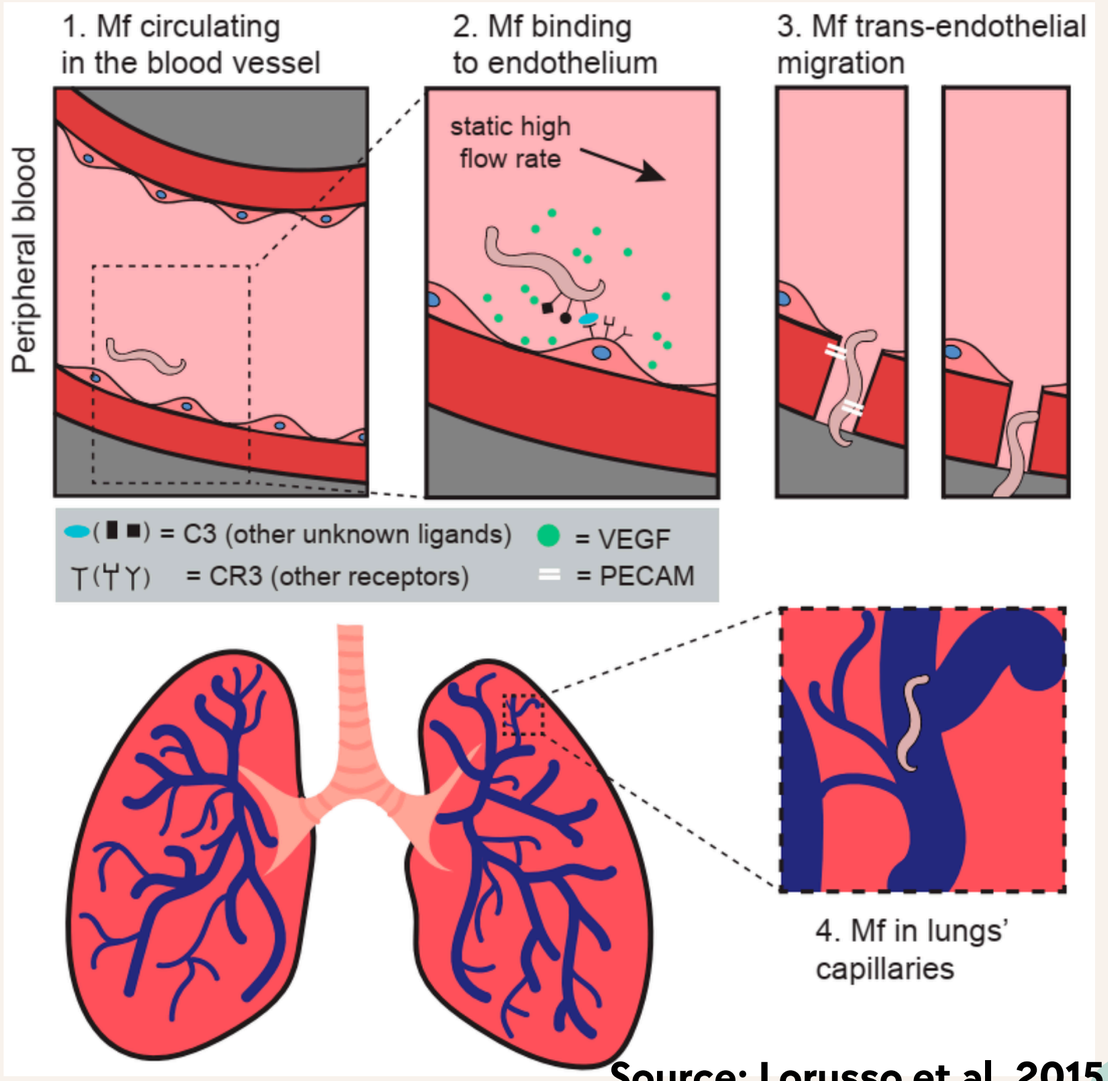
This lymphedema could evolute to elephantiasis

LF PATHOPHYSIOLOGY

Although of adults concentration in lymphatic vessels, microfilariae (MF) migrate between blood vessels;

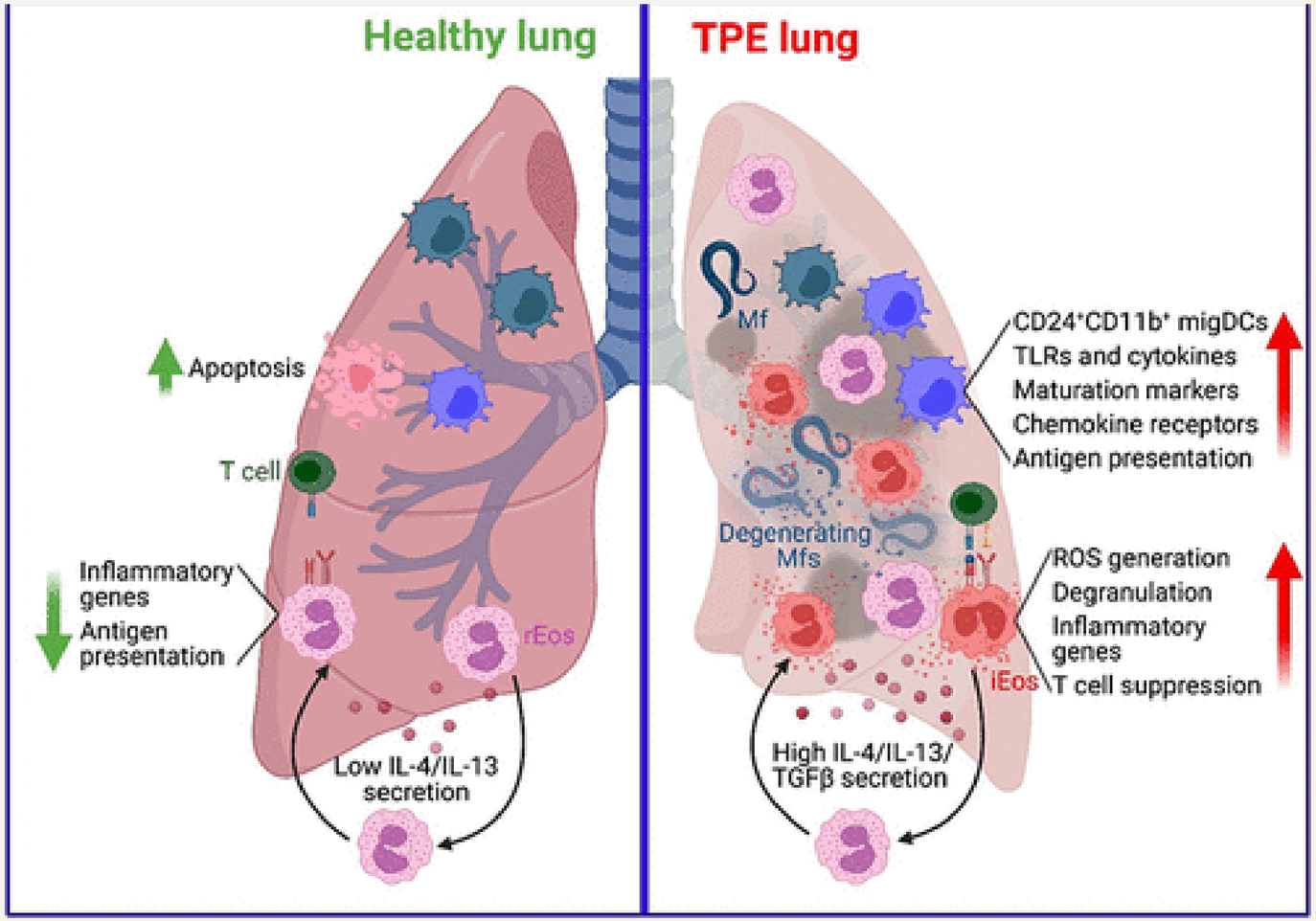
Could migrate by trans-endothelial junctions by binding and endothelium activation;

One of majoritary organs affected by this MF activity are lungs.



Source: Lorusso et al, 2015

TROPICAL PULMONARY EOSINOPHILIA



Source: Ganga et al, 2023

Excess of MF on pulmonary capillars -> granuloma

Induction of excessive antinflammatory and regulatory T and B profile cells and cytokines;

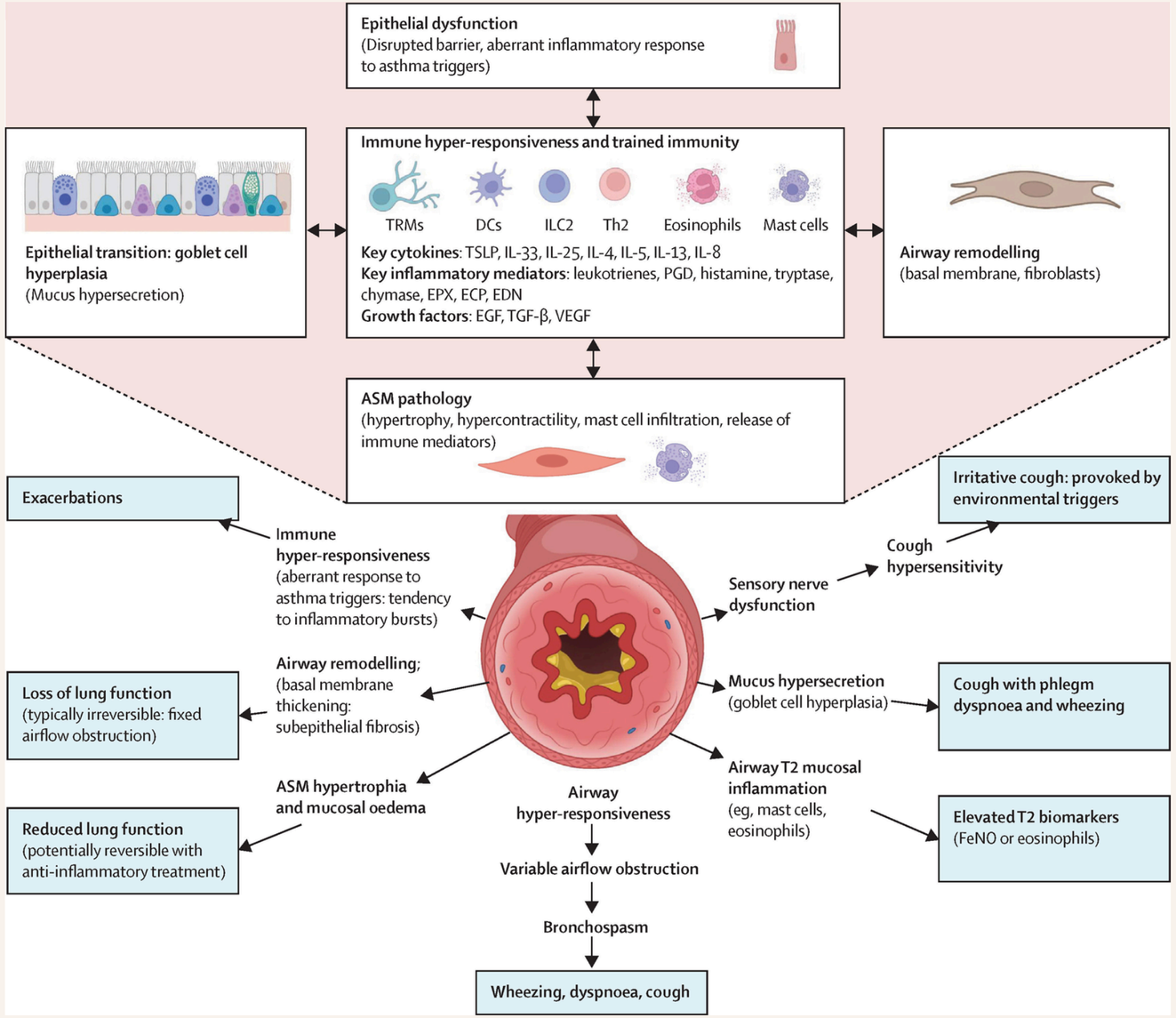
Excessive eosinophilic cells and use of containment mechanisms.

Source: Khemasukan et al, 2016;

TPE–LF PATHOPHYSIOLOGY

Peripheral eosinophilic allergenic response (5000–80,000/mm3)-> asthma-like are related to TPE

Malaise, anorexia, weight loss, dry cough and dyspneia.



Source: Porsjberg et al., 2023

TPE AND LF DIAGNOSIS AND TREATMENT

Diagnosis

Clinical and epidemiological features/evidences;

Laboratory diagnosis:
Direct detection by MF in fluids and adults worms by biopsy; chest ultrasonography;

Indirect by allergic tests for eosinophilia and hypersensibility and serological tests

Treatment

Diethylcarbamazine (DEC) is the main drug option to treatment to adults and MF;

Association DEC with albendazole or ivermectin

Source: Ottesen, 2006; Newman et al, 2023

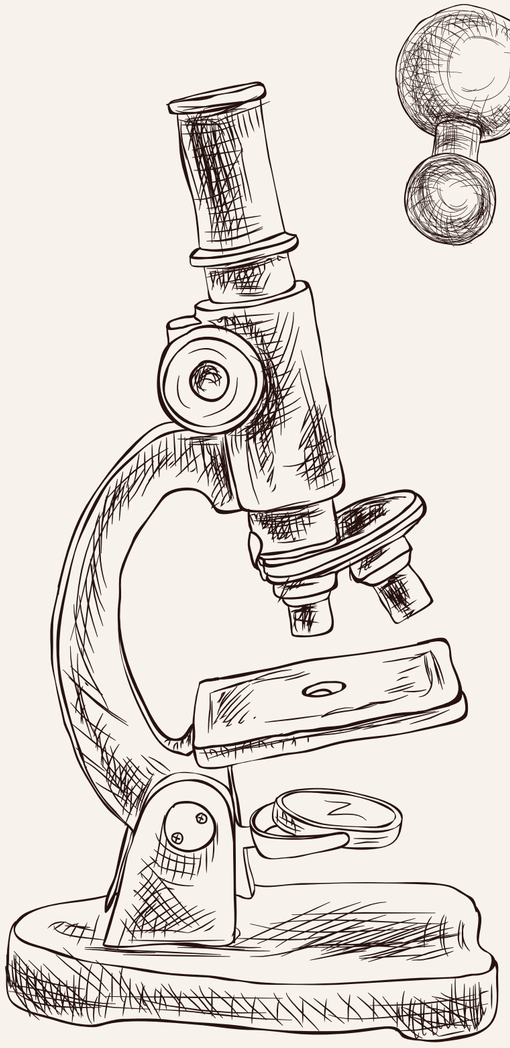
LF CONTROL

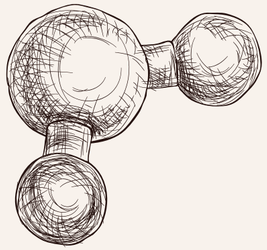
Vector surveillance and control;

Health politics associated to One Health approach;

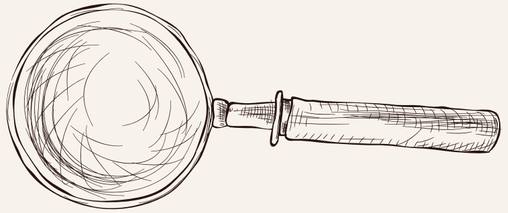
Sanitary education to population

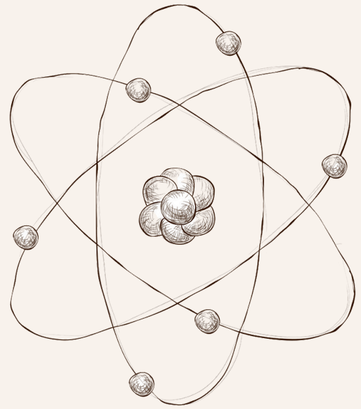
Source: OPAS/WHO; Newman et al, 2023

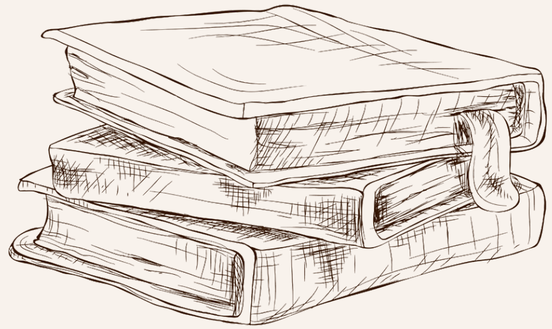




CRYPTOCOCCAL INFECTIONS

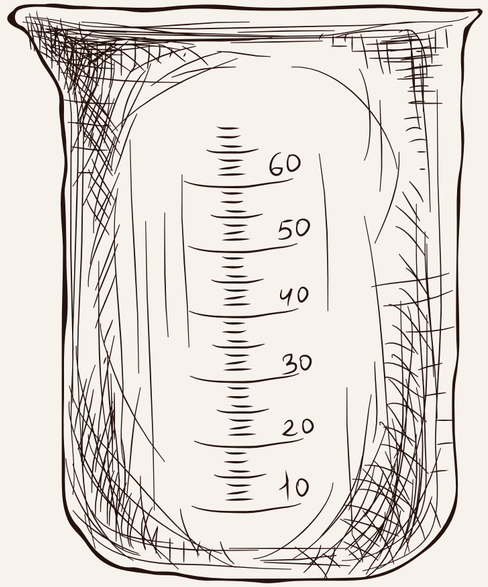


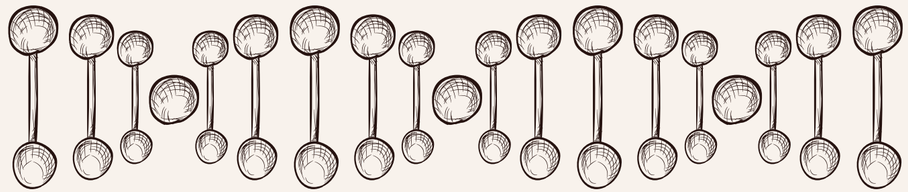




Topics

- Characteristics
- Epidemiology
- Infection Mechanisms
- Immunological mechanisms
- ARDS





Characteristics

- Encapsulated Fungi (C. gattii and C. neoformans)
- Infects Principally the Lungs, skin and Brain (can infect other parts)
- C. neoformans is more common in immunocompromised patients
- C. gattii is more common in immunocompetent patients.

Epidemiology

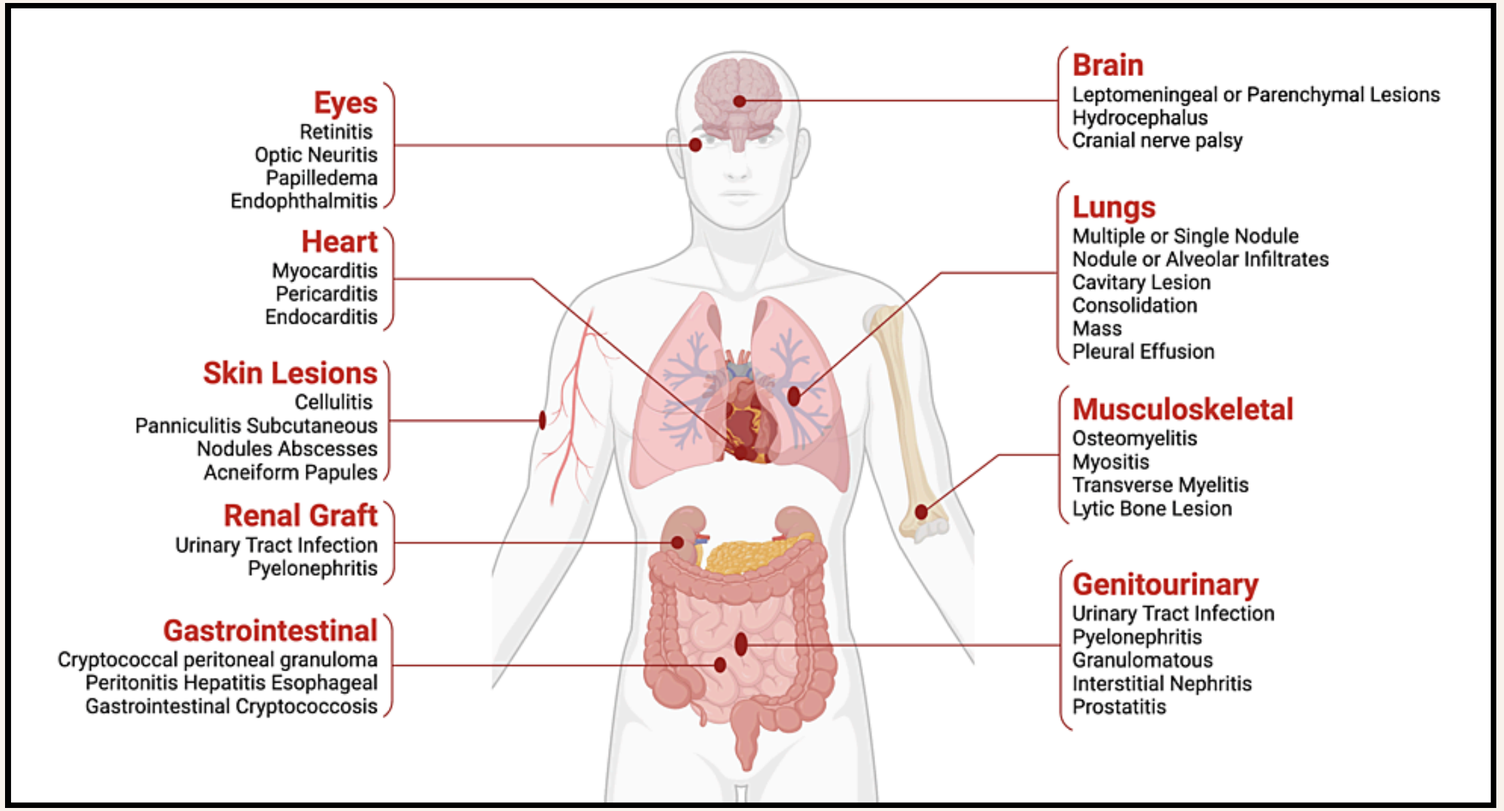
C. neoformans is found worldwide, mainly in pigeon droppings and other bird droppings. It is a common cause of fungal meningitis, especially in patients with HIV. C. gattii, on the other hand, is more prevalent in tropical and subtropical regions, such as Australia and the northwestern United States, where it also affects individuals without overt immunosuppression.

More recent studies report an annual global cryptococcal burden of 223,100 cases, with Sub-Saharan Africa showing the largest burden of the disease, with a reported annual mortality of 181,100

Source: Rajasingham R, Smith RM, Park BJ, et al.

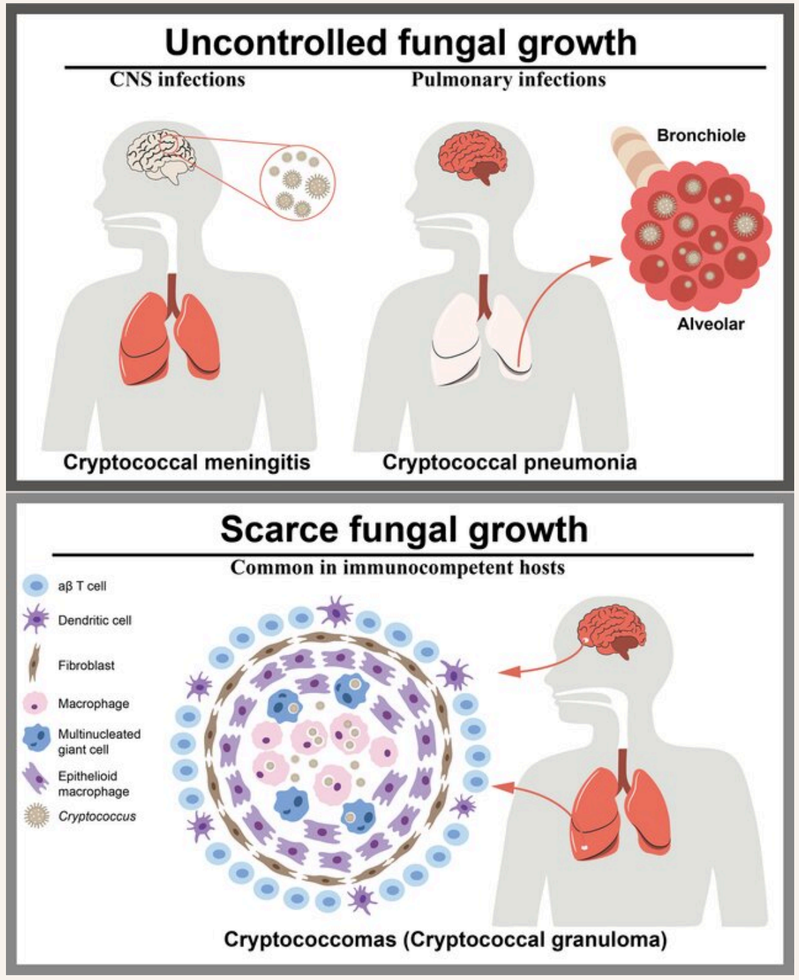
Symptoms

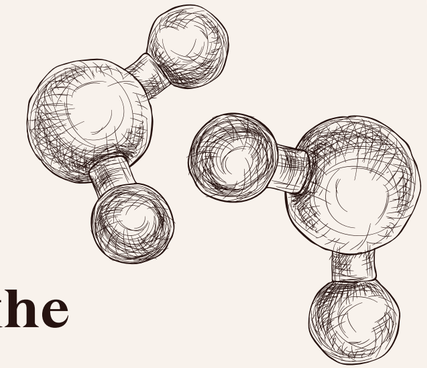
Cryptococcosis symptoms depend on which part of the body is affected. Symptoms of lung infections can include cough, shortness of breath, chest pain, and fever. Symptoms of cryptococcal meningitis can include headache, neck pain, sensitivity to light and confusion, or altered behavior



Conditions caused by Cryptococcal infection in the host

Source: Qureshi Z A, Ghazanfar H, Altaf F, et al.



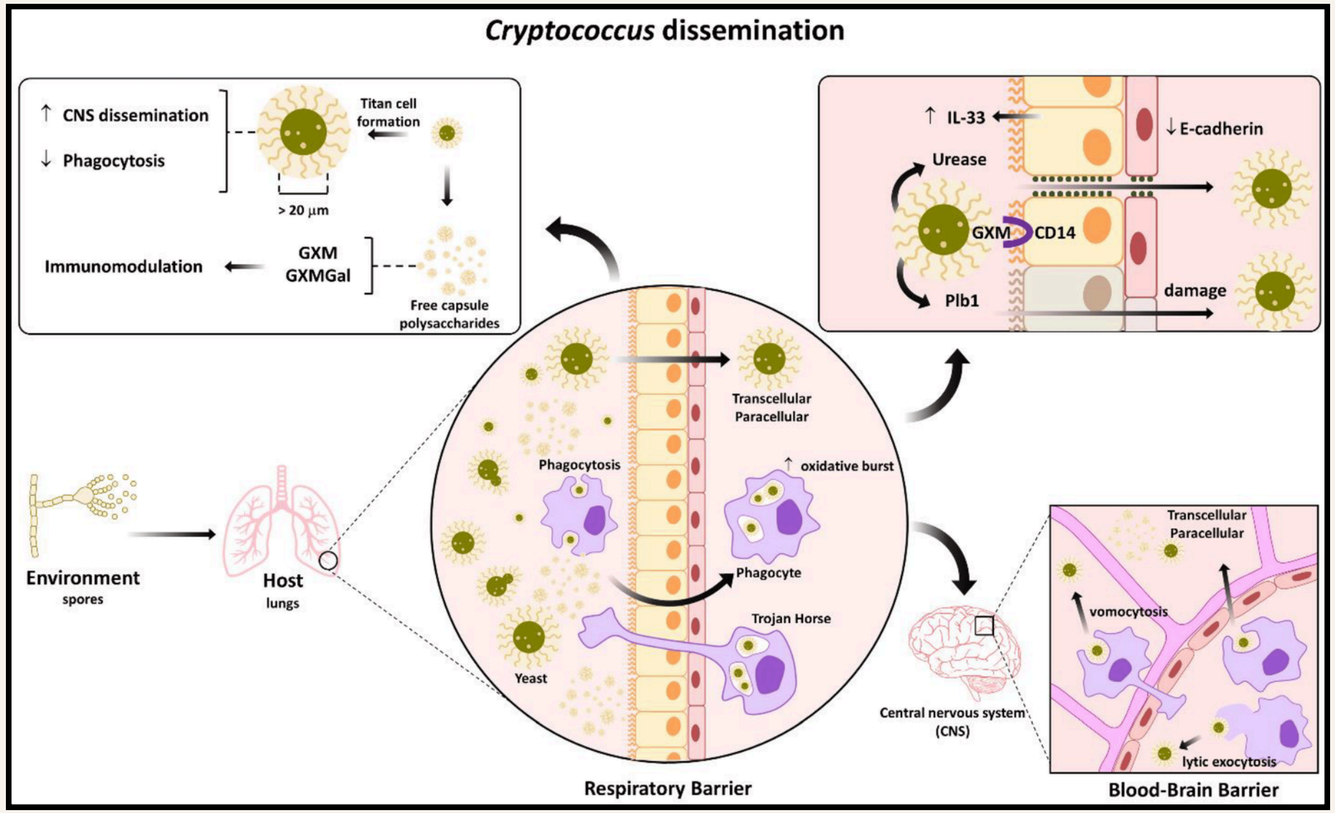


Conditions caused by Cryptococcal infection in the host

"Clinical manifestation of cryptococcal infection. The most common clinical manifestation of cryptococcal infection are CNS infections, which cause cryptococcal meningitis (Left in the upper panel). Pulmonary infections are the result of initial infection through inhalation of infectious propagules (Right in the upper panel). Another manifestation is cryptococcomas (Lower panel), which is formed by an inflammatory response in brain, lungs, skin, and other organs, thus it is more common in immunocompetent hosts. It may subsequently appear in a complex granuloma, including various macrophages. CNS Central nervous system"

Source: Zhao, Y., Ye, L., Zhao, F. et al.

Infection Mechanisms

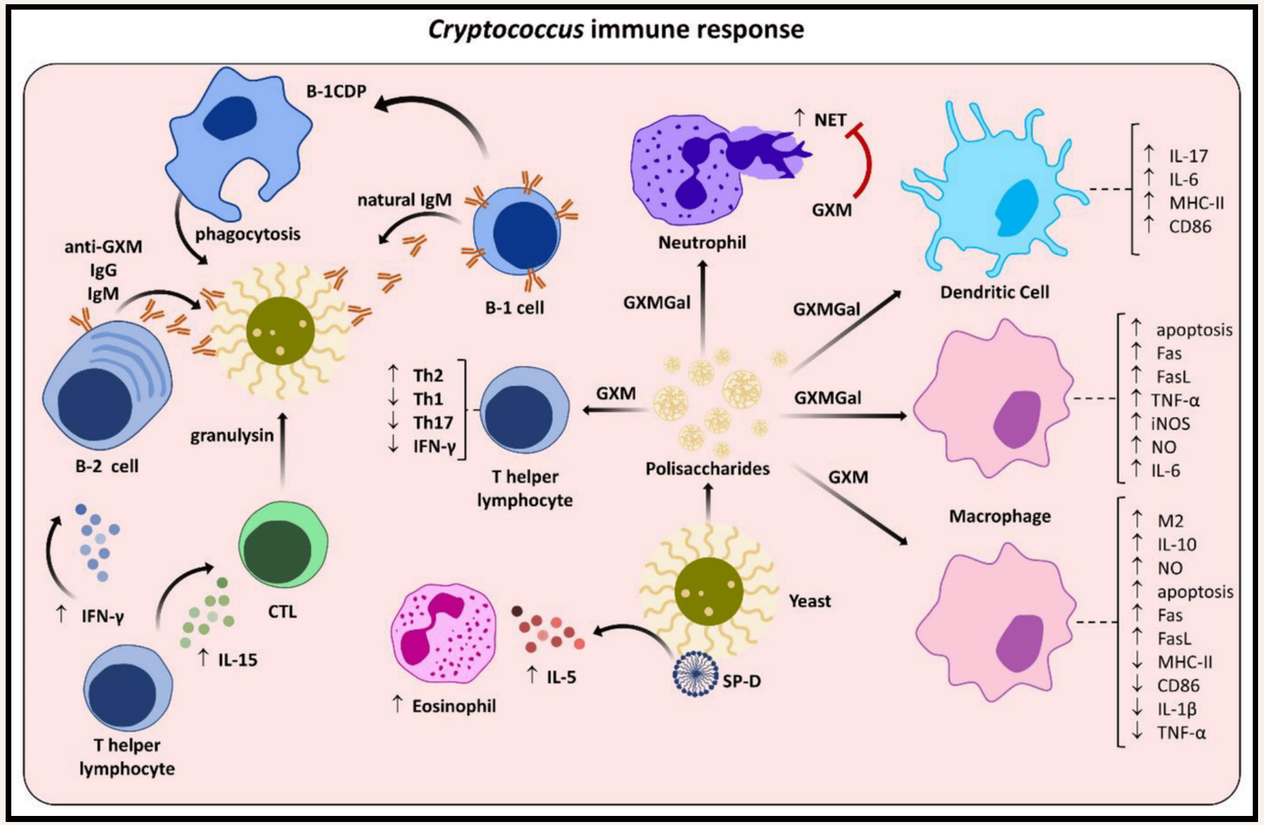


Source: Diniz-Lima I, Fonseca LMd, Silva-Junior EBd, Guimarães-de-Oliveira JC, Freire-de-Lima L, Nascimento DO, Morrot A, Previato JO, Mendonça-Previato L, Decote-Ricardo D, et al.

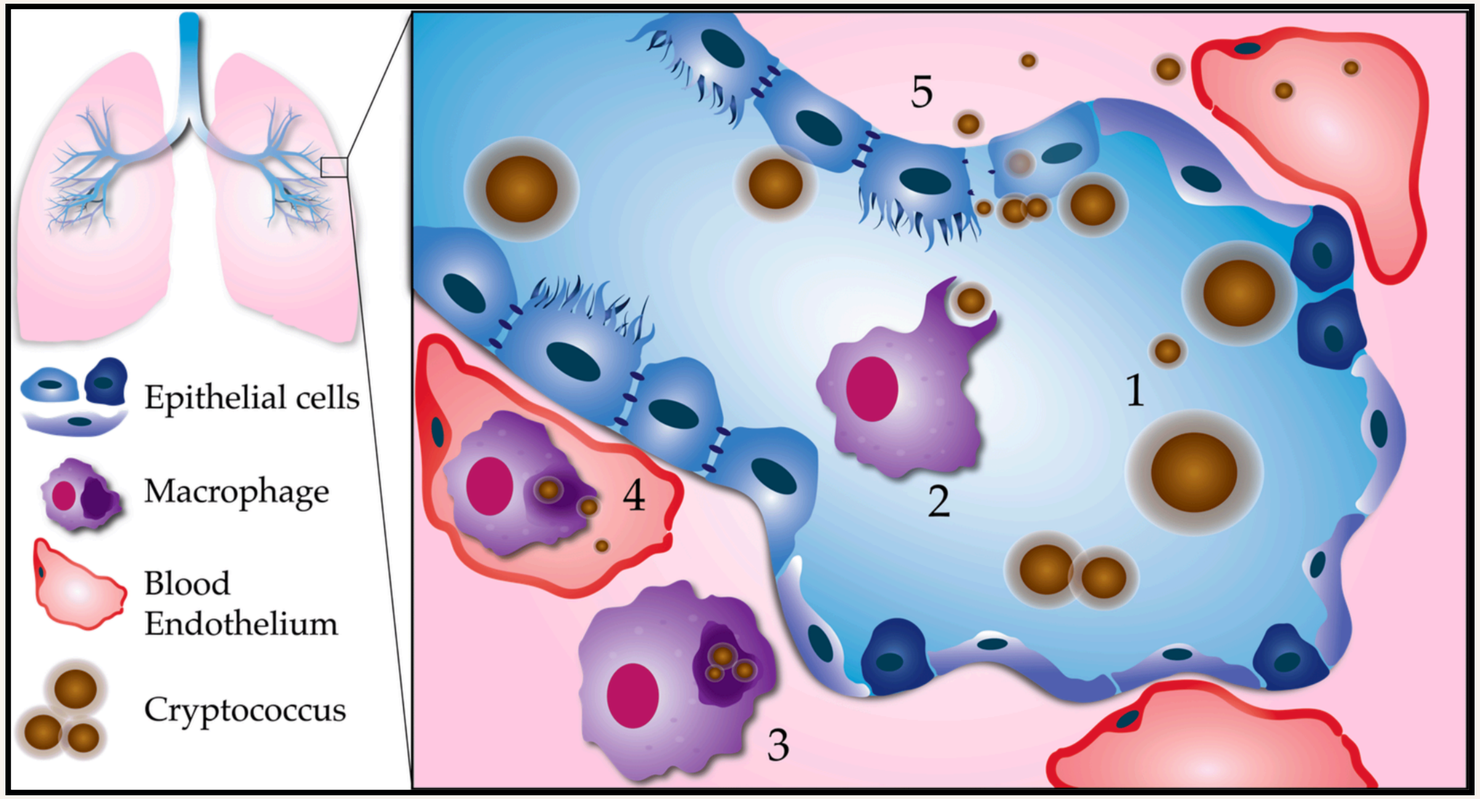
First morphological changes in Cryptococcus spp. inside the host and its dissemination mechanisms through the respiratory and blood–brain epithelial barriers.

Immunological Response

Immune response against Cryptococcus spp. and its capsular polysaccharides immunomodulatory effects.



ARDS



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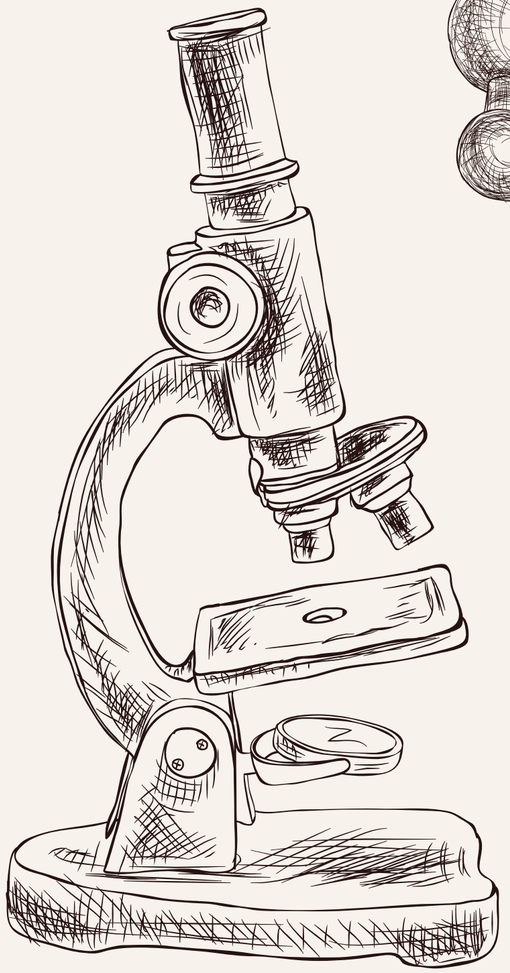

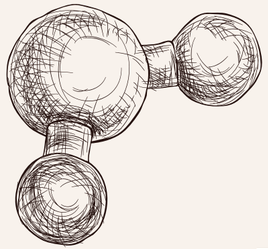

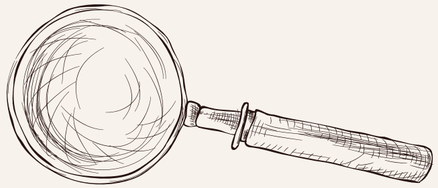

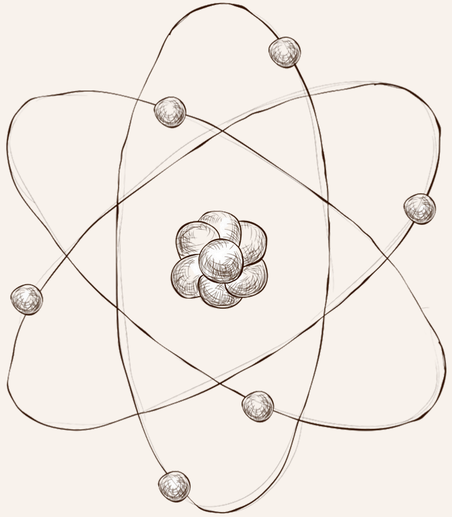

Thank you!

Do you have any questions?