بسم الله الرحمن الرحیم

Immunopathological similarities of FLU and COVID-19

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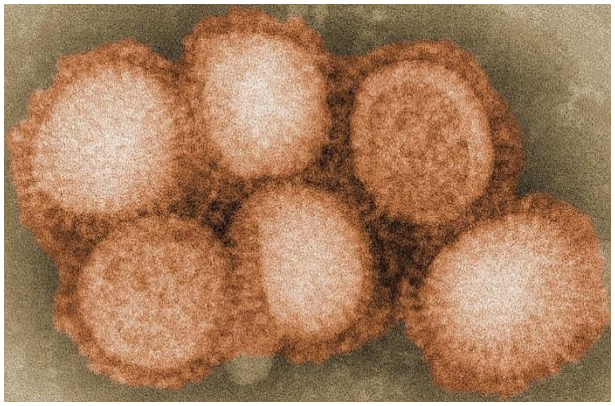
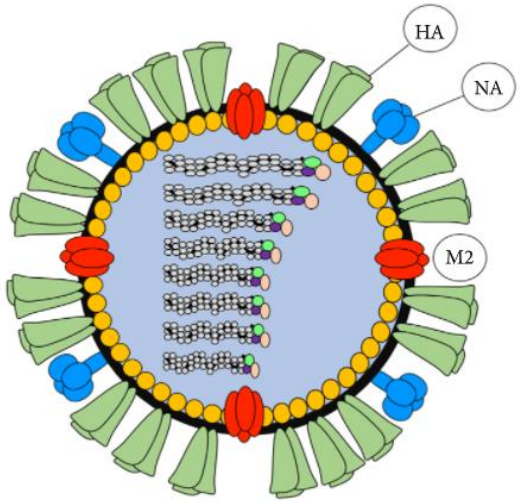
1400.10.5

Last century: FLU and COVID-19

- Two deadly viral infections in the last century was Influenza and COVID-19
  - Spanish flu (caused by H1N1 influenza A virus), which infected one-third of the population in 1918 and killed about 50 million people
  - FLU pandemics was repeated in1957 (H2N2 or Asian Flu), 1968 (H3N2 or Hong Kong flu) and 2009 (H1N1 swine flue)

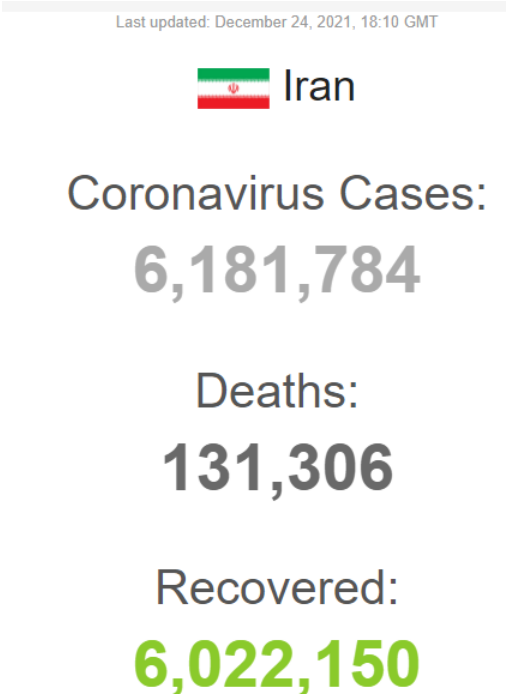




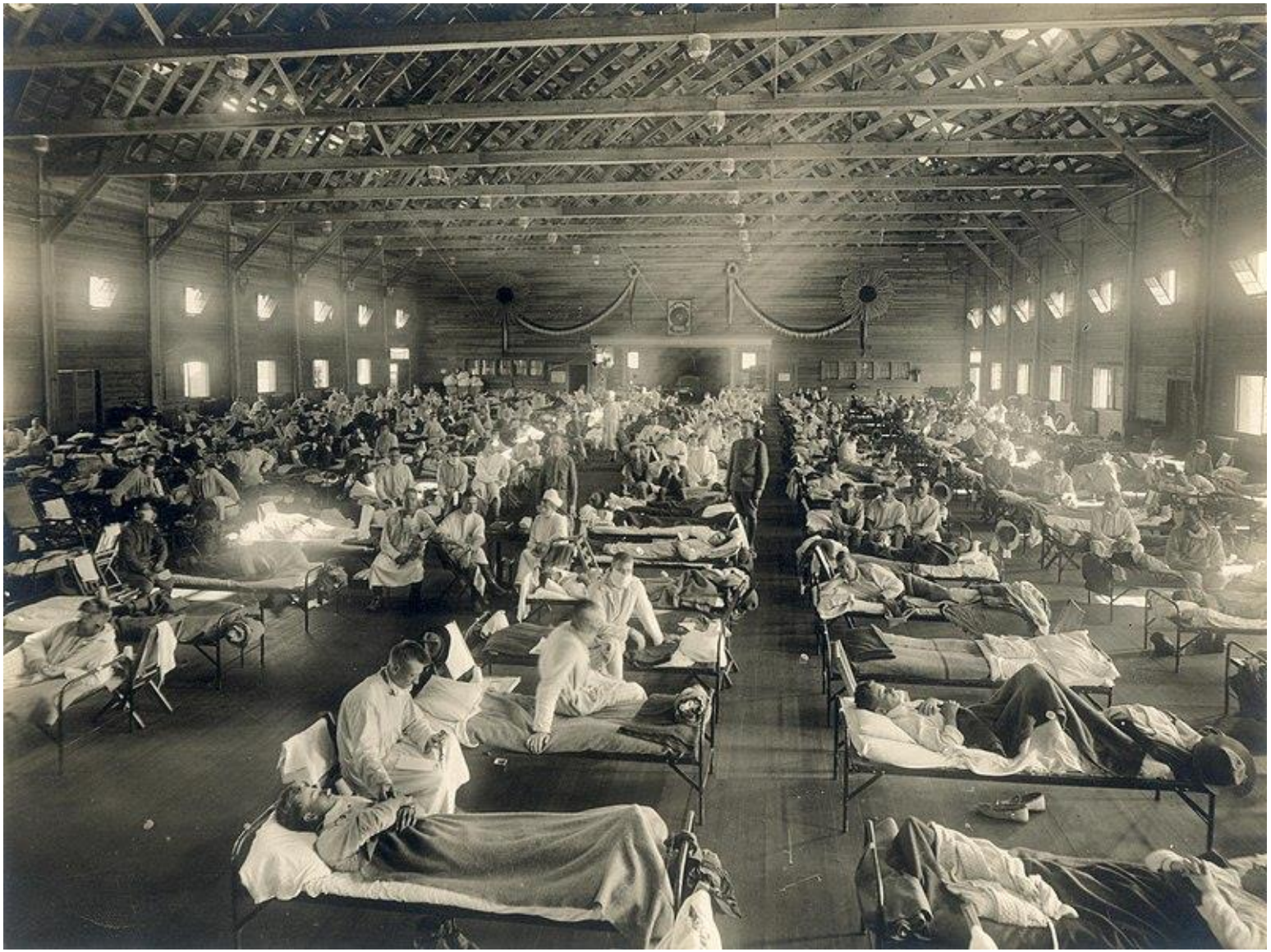
Last century: FLU and COVID-19

- Two deadly viral infections in the last century was Influenza and COVID-19
  - COVID-19 (caused by SARS-COV2), which infected at least 280 milion peple and killed 5.4 milion people.

COVID1-19 morbidity and mortality



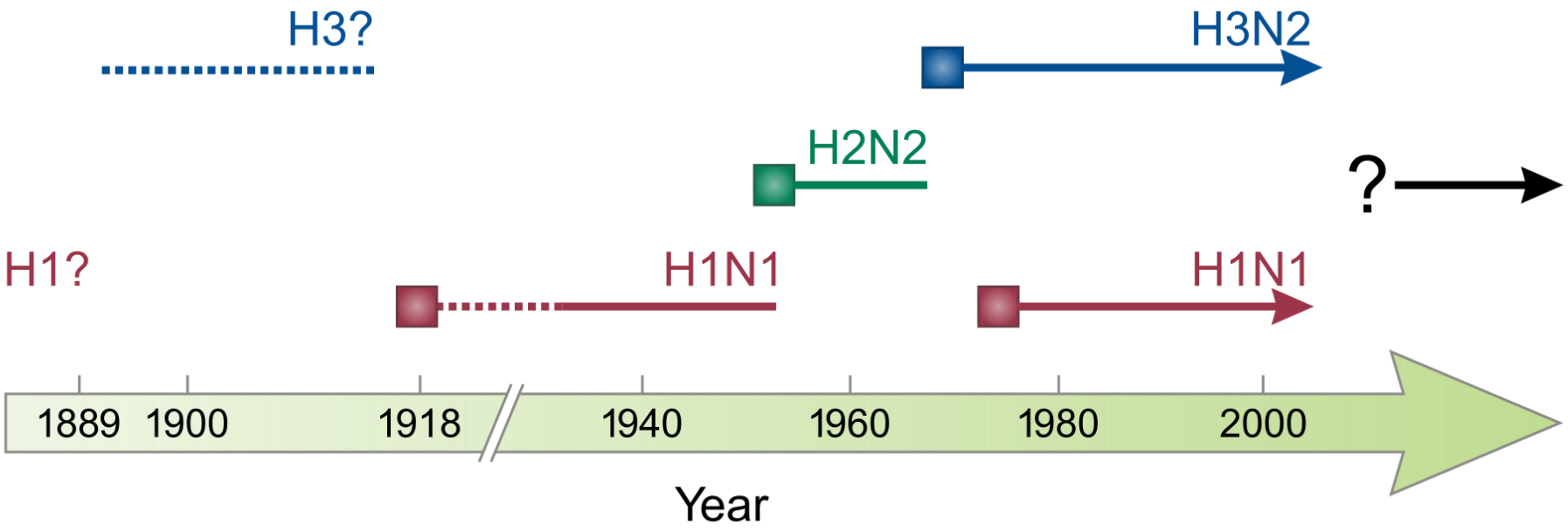
H1N1 FLU was the mother of all pandemics with three peaks in 1918



FLU and famine during 1918 in Iran

- During world war I, from 1917-19 about **8-10** million Iranian died due to famine, influenza, cholera, plaque and typhus

Main influenza A subtypes in humans



Nature Medicine 10 (2004)

Major FLU pandemics

Name	Date	World population	Subtype	Infected (est.)	Deaths worldwide	Fatality rate	Pandemic severity
1889–90 flu	1889–90	1.53 billion	H3N8 or H2N2	20–60% (300–900 million)	1 million	0.10–0.28%	2
Spanish flu	1918–20	1.80 billion	H1N1	33-56% (500 million->1 billion)	17-100 million	2- 10%	5
Asian flu	1957–8	2.90 billion	H2N2	>17% (>500 million)	1–4 million	<0.2%	2
Hong Kong flu	1968–9	3.53 billion	H3N2	>14% (>500 million)	1–4 million	<0.2%	2
1977 Russian flu	1977–9	4.21 billion	H1N1	?	0.7 million	<0.1%	?
2009 swine flu	2009–10	6.85 billion	H1N1/09	11–21% (0.7–1.4 billion)	152,000–575,000	0.01%	1
Typical seasonal flu	Every year	7.75 billion	A/H3N2, A/H1N1, B, ...	5–20% (240 million-1.6 billion)	290,000–650,000/year	<0.1%	1

Seasonal FLU and CDC reports (2020)

- In USA, seasonal FLU infected 38–54 million in 2019–2020, with 400,000–730,000 severe cases and 24,000–62,000 deaths.
- In the Middle-East; however, influenza prevalence varies between 5% in Qatar to 70% in Syria, with the mean of 10%.
- Iran has a prevalence of 18.5%, among which the healthcare workers, children(<6 y old), and Hajj pilgrims are more prone to seasonal FLU.

COVID-19 compared to 2009 FLU

- Influenza and COVID-19 show similar clinical symptoms.
- Hospitalized COVID-19 patients were older than those hospitalized during the 2009 influenza pandemic.
- There were similar patterns of symptoms, with distinct rates between COVID-19 and influenza patients.
- There was a high incidence of cardiovascular disease, hypertension and diabetes in COVID-19 patients.
- There was a similar disease burden in hospitalized COVID-19 and 2009 influenza pandemic patients.

Pengfei et al 2021

COVID-19 compared to 2009 FLU

- The incidence rates of fever, cough, shortness of breath, sore throat, rhinorrhea, myalgia and vomiting were significantly higher in influenza patients compared to COVID-19 patients.
- The incidence rates of comorbidities, including cardiovascular disease, hypertension and diabetes were significantly higher in COVID-19 compared to influenza.

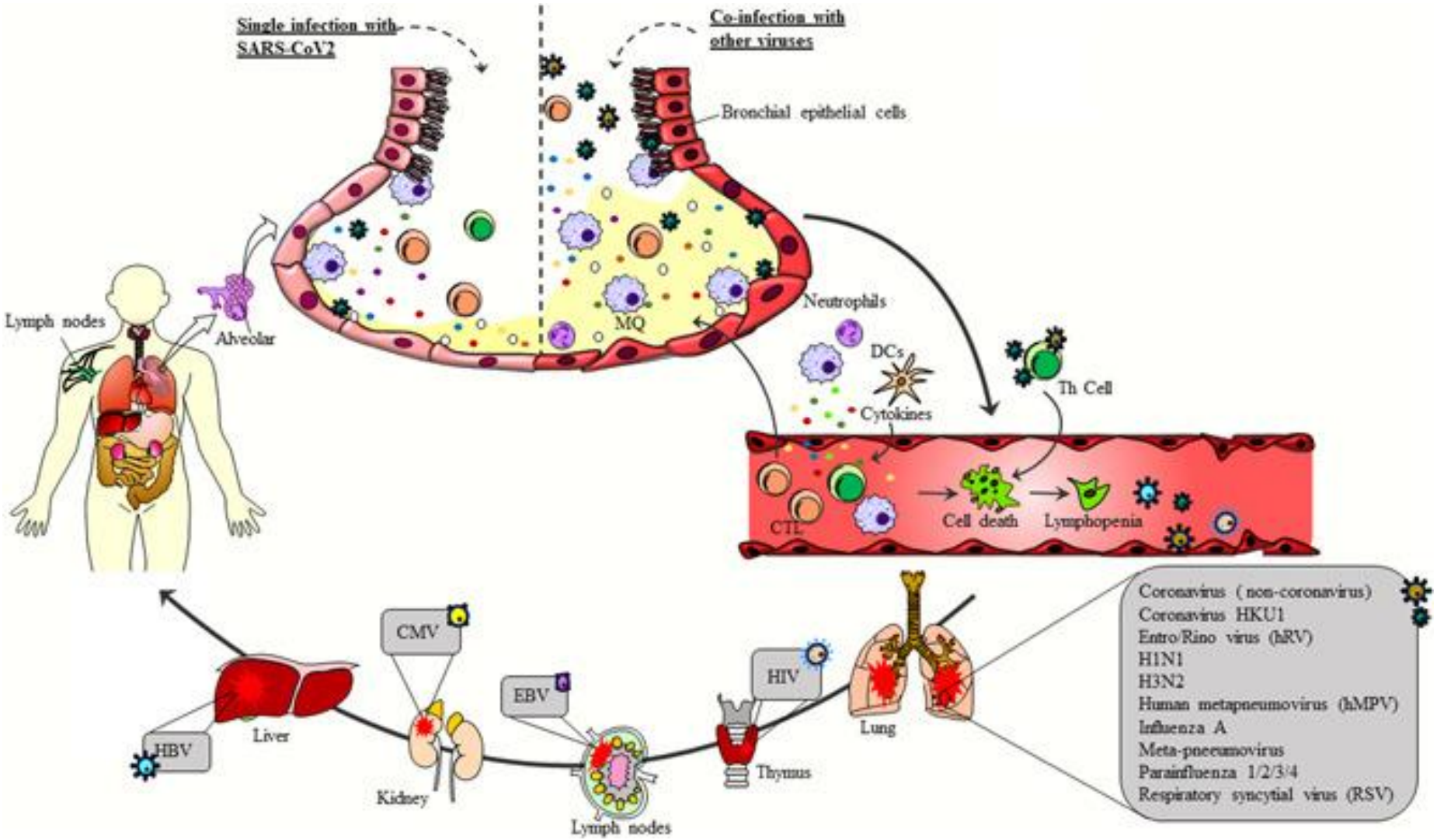
Pengfei et al 2021

COVID-19 compared to 2009 FLU

- In contrast, comorbidities such as asthma, chronic obstructive pulmonary disease, and immunocompromised conditions were significantly more common in influenza compared with COVID-19 patients.
- Unexpectedly, the estimated rates of intensive care unit admission, treatment with extracorporeal membrane oxygenation, treatment with antibiotics, and fatality were comparable between hospitalized COVID-19 and 2009 influenza pandemic patients.

Pengfei et al 2021

Viral coinfections in COVID-19



Aghbash et al 2021

Co-infection of COVID-19 and FLU

- Influenza and COVID-19 show similar symptoms.
- Co-infection of COVID-19 and influenza can increase the severity of the symptoms, specially in pregnant women, elderly, and children.
- This co-infection rate is high in children. Thus, COVID-19 screening during the prevalence of seasonal influenza is recommended.

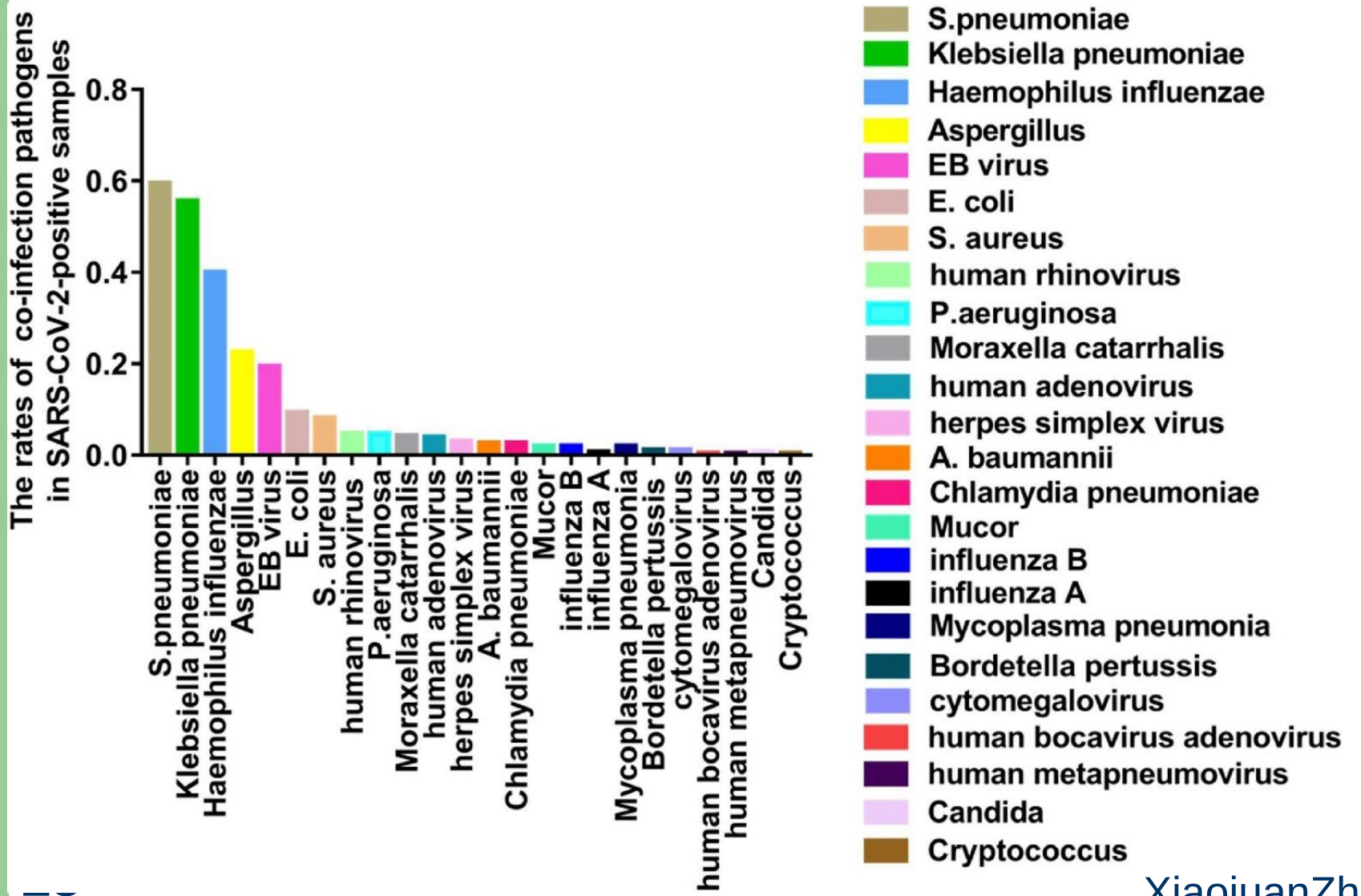
Azekawa, et al. 2020

Respiratory co-infection with SARS-CoV2

- Bacterial co-infections is dominant in COVID-19, similar to other viral infections.
- *Streptococcus pneumoniae* *Klebsiella pneumoniae* and *Haemophilus influenzae* are the most common co-infecting pathogens.
- The highest and lowest rates of co-infections occur in patients aged 15-44 and below 15, respectively.
- Most co-infections occur within 1-4 days of COVID-19 onset.
- Sever COVID-19 cases show more co-infections.

XiaojuanZhu et al

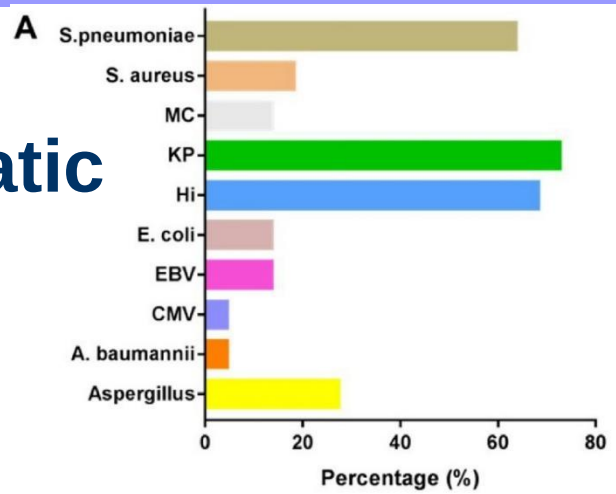
Respiratory co-infection with SARS-CoV2



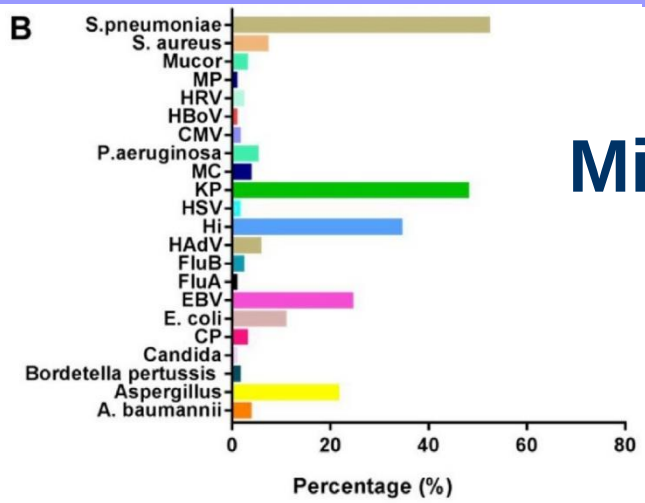
XiaojuanZhu et al

Respiratory co-infection with SARS-CoV2

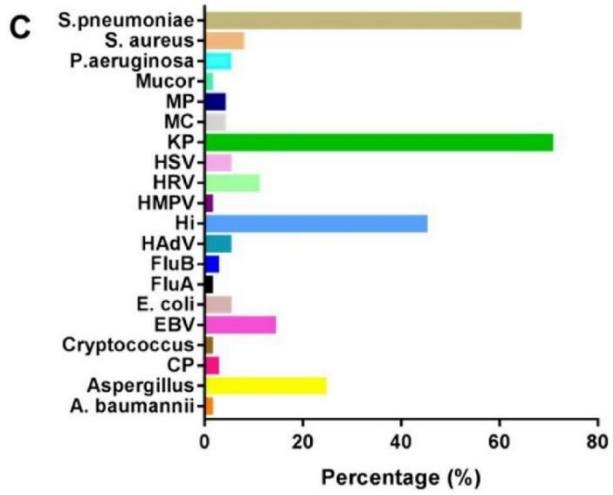
Symptomatic



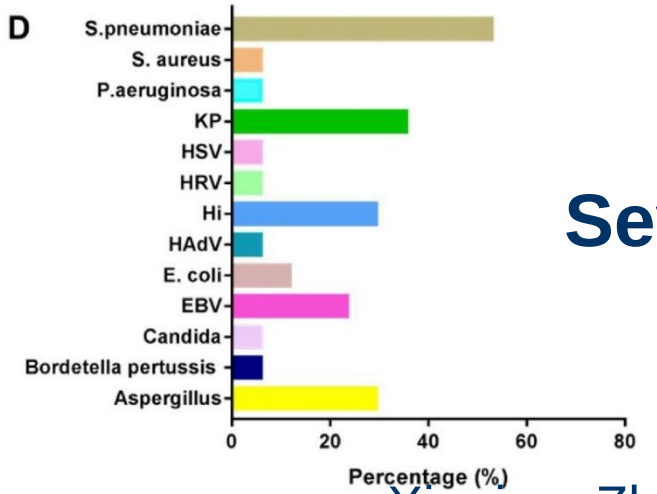
Mild



Moderate



Sever



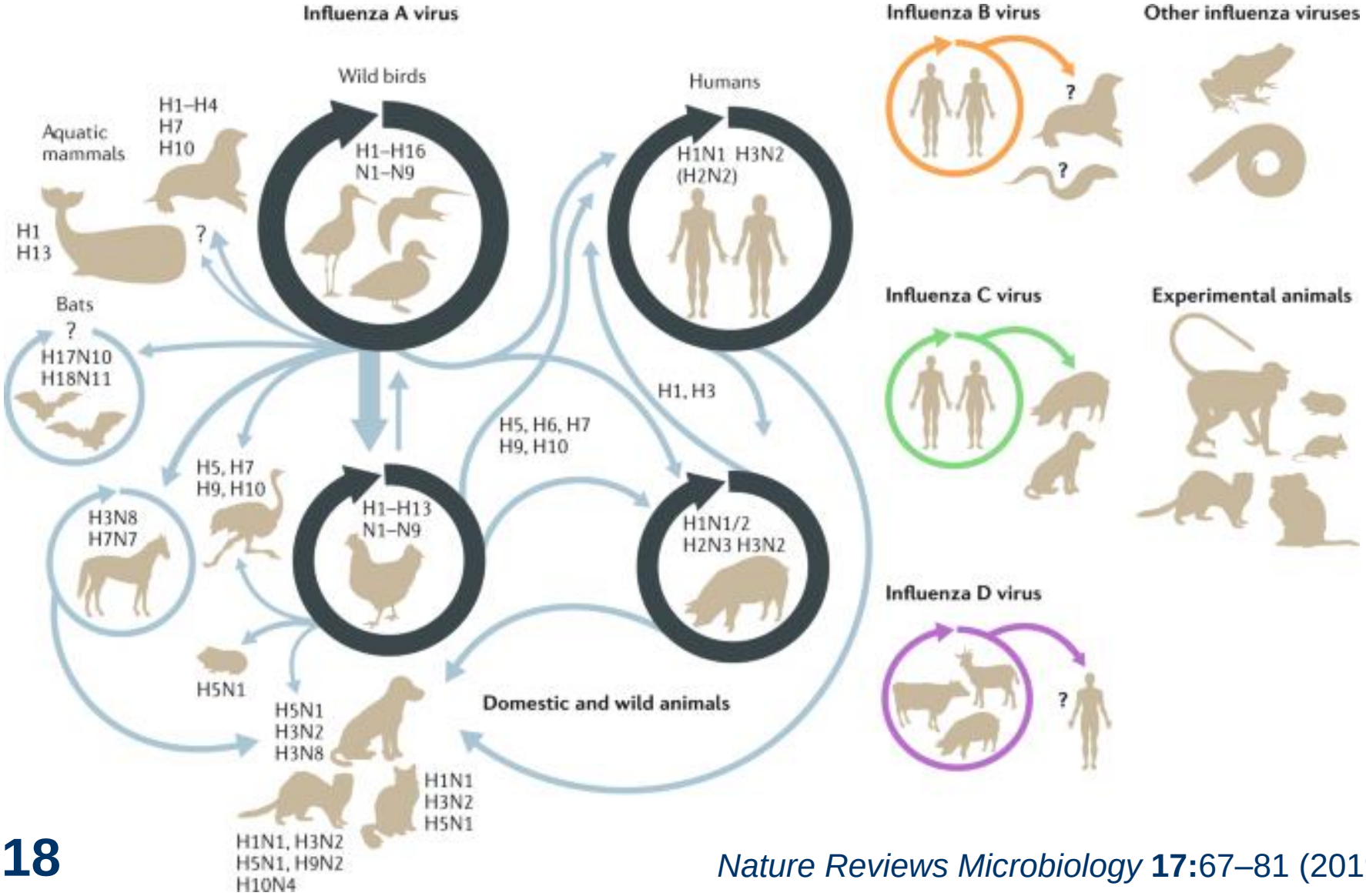
XiaojuanZhu et al

Ecology of influenza viruses

- Enveloped, negative single-stranded RNA virus from Orthomyxoviridae family
- Comprised of subtypes A, B, C, and D.
- Influenza A can infect many species
- Primary host of influenza B and C is human
- Influenza D infects cattle, goat and pig.

Long et al 2019

Ecology of influenza viruses



Nature Reviews Microbiology **17:**67–81 (2019)

Influenza virus RNA and proteins

- Influenza A and B contain eight RNA segments and encodes 18 different proteins.
- The fourth segment encodes hemagglutinin (HA)
- The fifth segment encodes neuraminidase (NA).
- Other genes encode basic and acidic polymerases, nucleoprotein, major matrix protein (M1), ion-channel matrix protein (M2), and non-structural proteins.

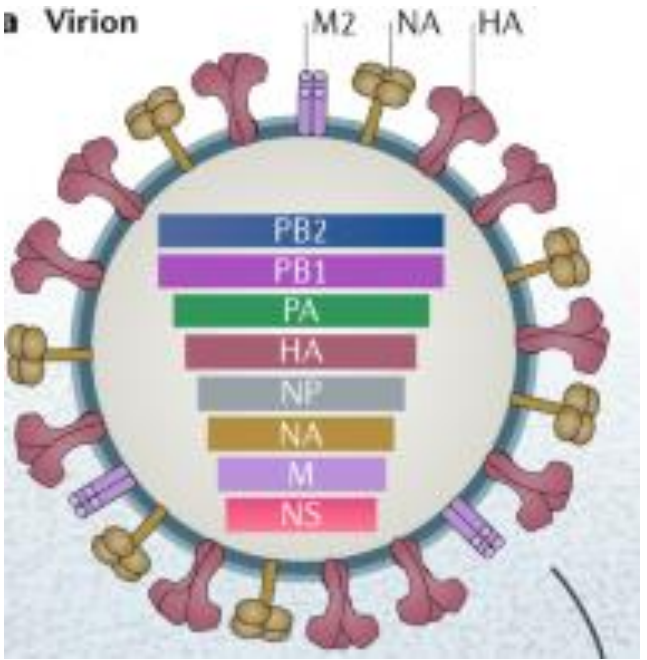
Long et al 2019
Vasin et al 2014

Influenza virus RNA and proteins

- Replication of the negative-sense RNAs of the virus requires RNA polymerases, which are carried with the virus into the host nucleus. Budding and release of newly assembled virions is facilitated by NA, M1 and M2 proteins.
- Nucleoprotein encapsidates the genetic content of virus, and non-structural proteins are mainly involved in host immune suppression and viral translation enhancement.

Influenza virus subtypes

- Influenza A viruses are categorized by surface glycoproteins on virus envelope including HA, (H1-18) and NA (N1-11).
- HA and NA play crucial role in viral attachment to cells and pathogenesis and is the primary target for neutralizing antibodies.



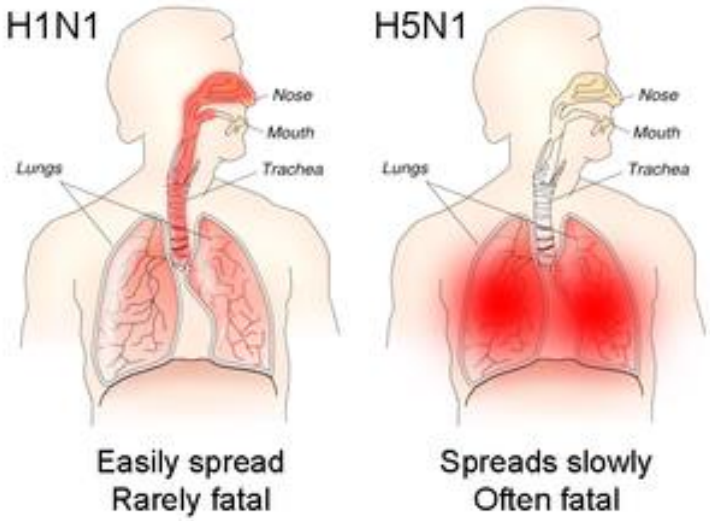
Hemagglutinin (HA)

- HA binds to the terminal glycosides of sialic acid on the surface of cells
  - Columnar epithelial cells in the upper respiratory tract (in human influenza types)
  - Alveolar type II cells and ocular epithelium (in avian influenza types).
- Virus binding by HA glycoprotein is facilitated by M1 protein, which help fusion of the virion with the endoplasmic membrane and endocytosis.
- Virus entry into cell nucleus occurs by M2 protein.

Long et al 2019
Vasin et al 2014

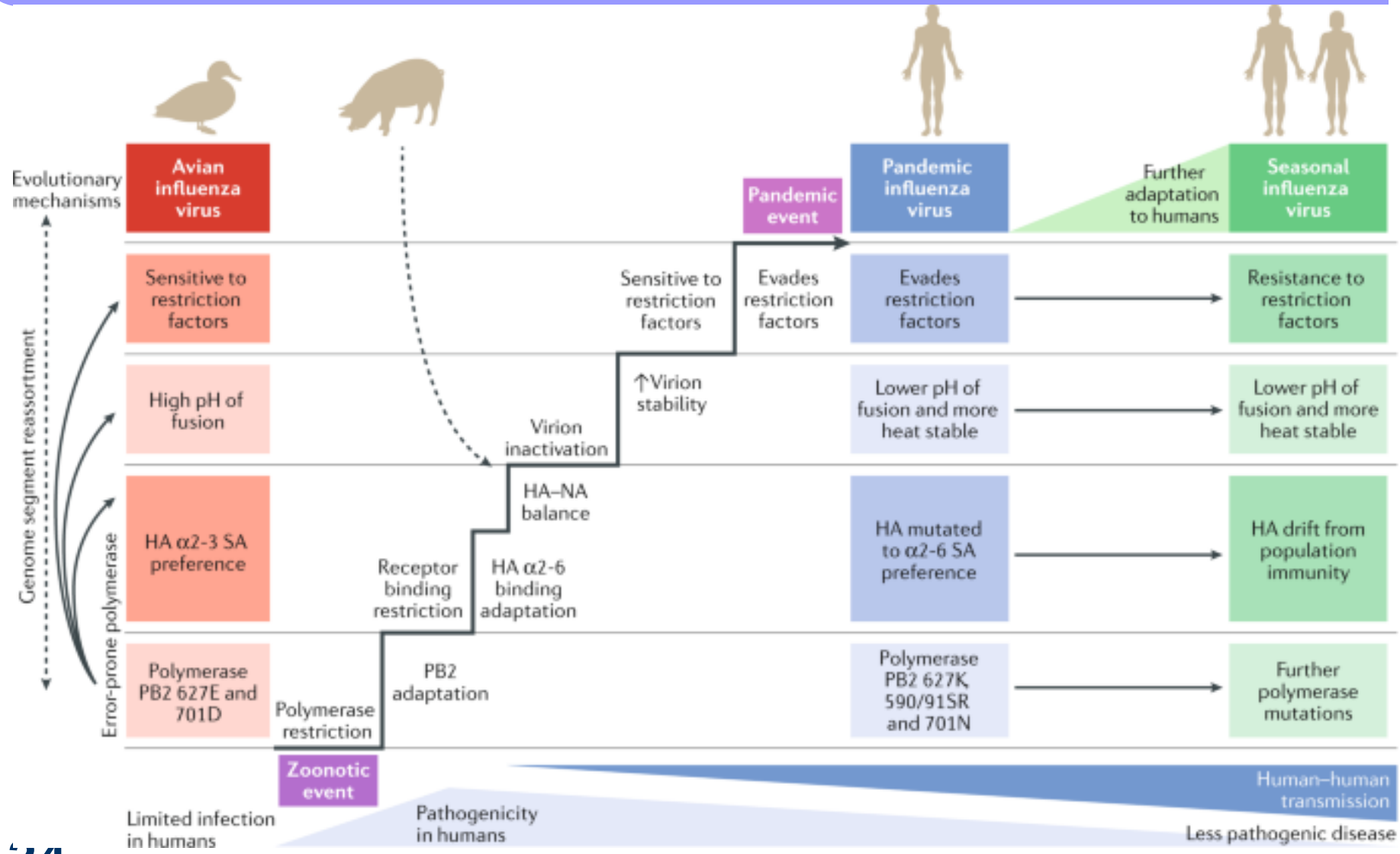
Variants and severity

- Upper respiratory tract infecting variants (e.g. H1N1) have high transmission capability but low virulence severity.
- Lower respiratory tract infecting variants (e.g., H5N1 and H7N9) causes more severe inflammation and complications, despite their lower contagious features.



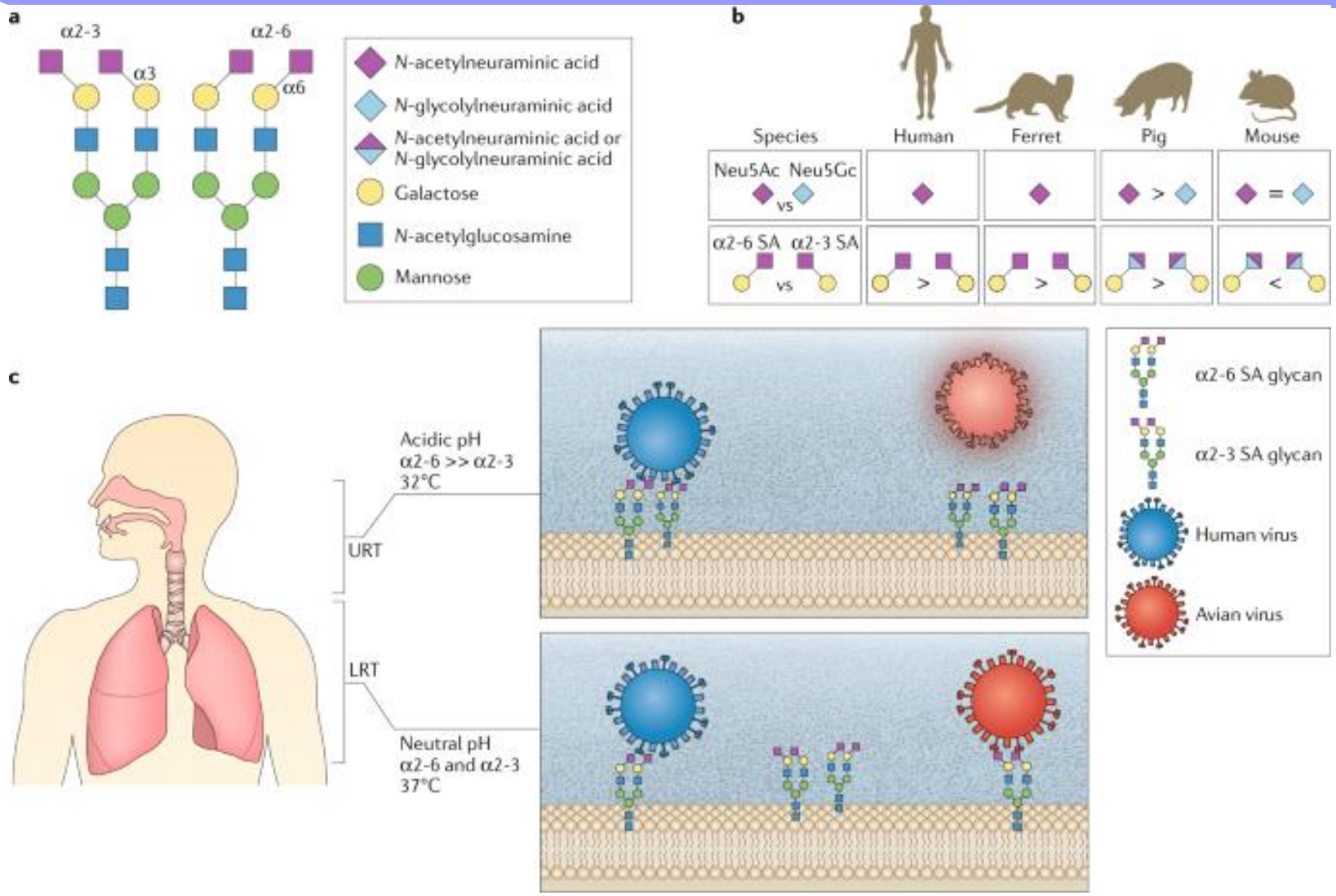
Long et al 2019
Vasin et al 2014

Cumulative influenza adaptations required to overcome species restriction and initiate a new pandemic



Nature Reviews Microbiology **17**:67–81 (2019)

Host sialic acid presentation and physiology drives HA adaptation



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Influenza virus antigenic changes

- Cumulative mutations of the influenza virus cause minor changes in NA and HA glycoproteins, a phenomenon known as antigenic drift, that occurs in all influenza subtypes.
- Furthermore, the antigenic shift is due to gene rearrangement.
- Pandemic usually occurs following a lot of mutations in viruses to spread from one species to another.

Vasin et al, 2014

Influenza virus antigenic changes

- Antigenic drift does not generally cause pandemics because the population's immunity plays a selective role.
- Susceptibility to a specific type of influenza virus depends on the virus binding ability to the host cell, virus genome replication, and escape from the host immune response.
- Due to antigenic changes and ability of swine and avian subtypes to infect humans, possibility of a new epidemic or pandemic of influenza is still high.

Vasin et al, 2014

Similarities between COVID-19 and FLU

- Both are respiratory diseases and show similar symptoms, including cough, runny nose, sore throat, fever, headache and fatigue.
- Both can be fatal.
- Both spread in similar ways by droplets and aerosols
- Similar groups are at high risk for severe infection
- The same protective measures are effective against COVID-19 and influenza

People at high risk of COVID-19 & FLU

- All age groups can be infected with both COVID-19 and influenza, but some people are at higher risk for severe disease and death:
- Elderly and healthcare workers
- Pregnant and those who have recently given birth
- People with chronic medical conditions (such as chronic cardiac, pulmonary, renal, metabolic, neurologic, liver or hematologic diseases)
- People with immunosuppressive conditions (such as AIDS, malignancy, chemotherapy, steroid therapy)

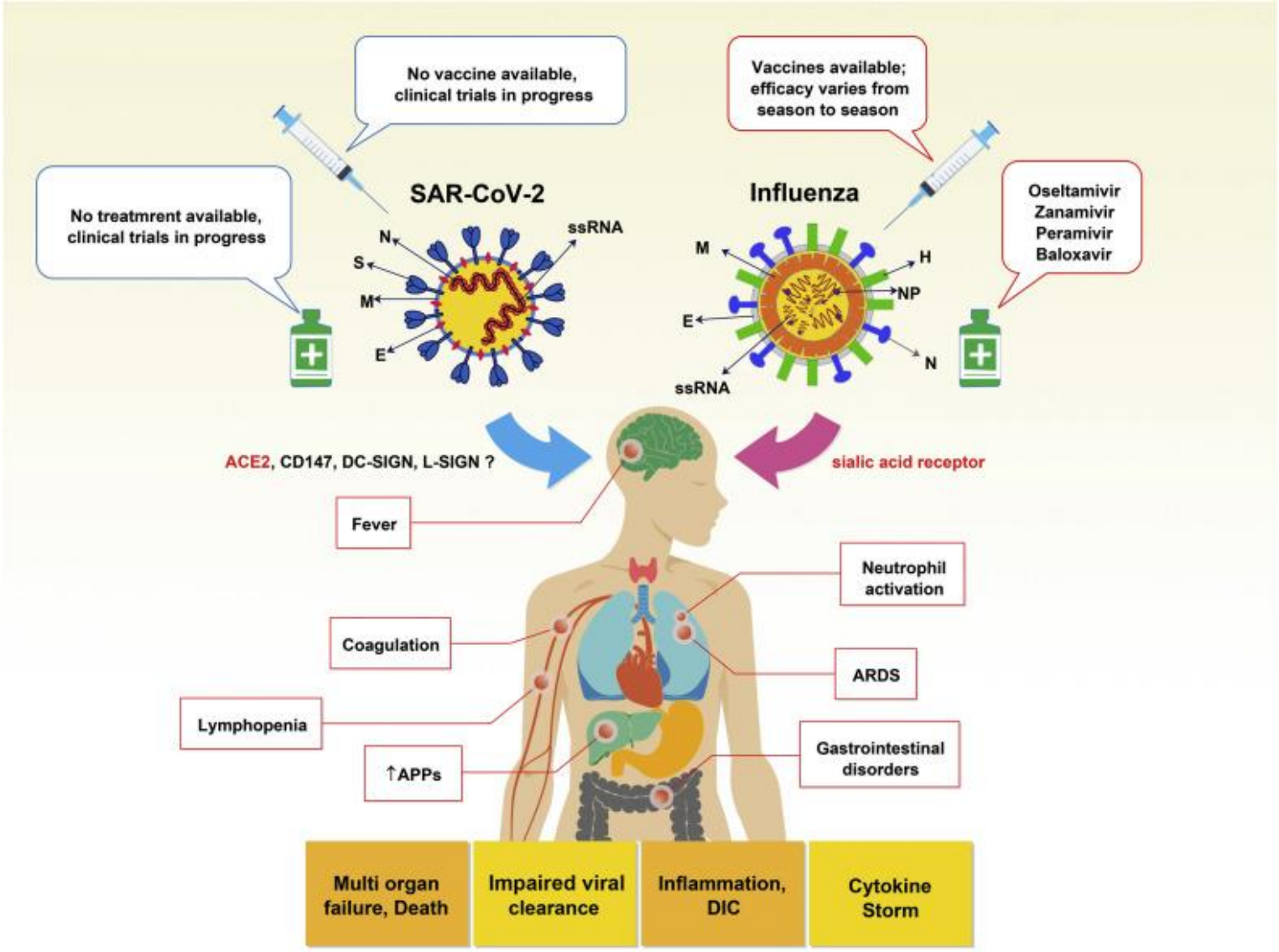
Comparison of clinical symptoms in COVID-19 and FLU

Influenza	*COVID-19*	*Similarities*	*Differences*
•Fever or feeling feverish/chills •Cough •Sore throat •Runny or stuffy nose •Muscle or body aches •Headaches •Fatigue (tiredness) •Vomiting and diarrhea	•Fever or feeling feverish/chills •Dry cough •Sore throat •Runny or stuffy nose •Muscle or body aches •Headaches •Fatigue (tiredness) •Vomiting and diarrhea •Skin rash or discoloration of toes or fingers	•Fever or feeling feverish/chills •Cough •Shortness of breath or difficulty breathing •Fatigue (tiredness) •Sore throat •Runny or stuffy nose •Muscle pain or body aches •Headache •Vomiting and diarrhea	•Non-productive dry cough in SARS-CoV-2 infection •Change in or loss of taste or smell in SARS-CoV-2 infection •Skin rash or discoloration of toes or fingers in SARS-CoV-2 infection

Treatments
Vaccines

Khorramdelazad et al, Microbial Pathogenesis 2021

Immunopathological similarities between COVID-19 and FLU



Fever

- Increased inflammatory cytokine levels following innate immune responses mediate fever development.
- Cytokines can cross the blood-brain barrier and also react with peripheral vagus nerve terminals, sending signals to the body's temperature control center in the hypothalamus, which raises body temperature to control infection and results contraction of the skin and blood vessels.

Cytokine storm

- Occur due to production of high amounts of pro-inflammatory cytokines including IL-1β, IL-4, IL-6, IL-10, IL-18, IL-33, TNF-α, and IFN-γ; usually after infection with pathogens with super-antigens.
- IL-6 is responsible for most of complications and triggers several downstream signaling pathways, including JAK-STAT, MAPK, PI3K, and NOTCH.
- IL-6R blockers, JAK-STAT inhibitors and glucocorticoids are beneficial in control of over-reaction of immune responses in cytokine storm.

Cytokine storm

- TNF-α and IL-1 family provoke an amplification loop through NF-κB activation and production of pro-inflammatory mediators.
- NLRP3 inflammasome activatition results incresedd IL-1β and IL-18, which stimulate pyroptosis as an inflammatory programmed cell death process.

Cytokine storm

- Cytokine storm can lead to ARDS due to increased vascular permeability and perfusion of fluid and blood components into the alveoli.
- Cytokine storm may cause hyperinflammatory syndrome called secondary hemophagocytic lymphohistiocytosis (sHLH), leading to fatal multi-organ failure and death. So, they need intensive care.

Tissue damage

- Death in most people with influenza is due to dysregulated immune system responses and defects in virus clearance.
- There is a relationship between the viral load and ARDS and lung injury in COVID-19, too.
- Neutrophils play role in lung injury.
- Inhibiting chemotactic factors (e.g. CXCL2 and CXCL10) can reduce locomotion of neutrophils in lungs resulting significant reduction of lung tissue damage.

Tissue damage

- Complete neutrophil depletion can worsen the condition of influenza patients, and impair the clearance of the virus.
- Thus, neutrophils play a dual role in this disease:
  - In clearance and reduction of viral infection
  - Tissue damage in these patients.

Tissue damage

- Cytokine could result multi-organ dysfunction and tissue damage in the heart, lungs, kidneys, and liver in COVID-19 patients.
- They recruit neutrophils and macrophages to the lung tissue resulting in hyaline membranes formation and diffuse alveolar damage.
- Spleen atrophy and necrosis of lymph nodes can ultimately disrupt adaptive immune responses and reduce lymphocyte count.

Lymphopenia

- In influenza a monocytosis along with slight lymphopenia and leukopenia is observed.
- Decrease of T cells is more prominent.
- However, lymphocyte functionality is preserved and 90% of patients show seroconversion.
- Lymphopenia is due to:
  - Cell migration from the circulation
  - Cell death via necrosis or apoptosis
  - Suppression of hematopoiesis

Lymphopenia

- In COVID-19 lymphopenia is more prominent and several mechanisms are involved:
  - Pro-inflammatory cytokines such as IL-6
  - Low expression of MHC II on monocytes by IL-6
  - Injury in spleen and lymph nodes
  - FAS expression on infected cells
  - Infection of ACE2+CD68+CD169+ macrophages

Dysregulated coagulation

- IL-1β and TNF-α play an anti-coagulation role during viral infection, whereas IL-6 can initiate coagulation.
- Dysregulated coagulation play role in pathogenesis of influenza, which is characterized by stimulation of lung endothelial, leakage of vessels, diffused intravascular coagulation and blockage in pulmonary arteries (micro-embolism), it also results increased viral replication and reduced immune responses.

Dysregulated coagulation

- Influenza infections increase the risk of venous thrombosis and atherothrombotic disorders through amplification in thrombin production and reduced C protein expression.
- Thrombin, through the proteinase-activated receptor-1 (PAR-1), can participate in coagulation and inflammation.
- In a homeostatic mechanism, anticoagulant molecules such as protein C and antithrombin III regulate the production of thrombin.

Dysregulated coagulation

- Heparin therapy could be helpful for this prothrombotic state.
- During a viral infection such as SARS-CoV-2 or influenza, these molecules become defective due to uncontrolled inflammation, and eventually, coagulation and inflammatory pathways are stimulated, resulting in diffused intravascular coagulation (DIC), micro thrombosis and multi-organ failure.

Summary

- SARS-CoV2 mimics the influenza virus regarding methods and modes of transmission, clinical features, related immune responses, and seasonal coincidence.
- Accordingly, coinfection by these viruses is possible and some studies have reported several cases with SARS-CoV-2 and influenza virus co-infection.

Summary

- Due to the importance of the mentioned co-infection and the coming influenza season, it is essential to consider the similarities and differences between the symptoms, immunopathogenesis and treatment of SARS-CoV2 and influenza virus.

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Thanks for your attention