Emerging and Re-emerging Respiratory Viruses (SARS-CoV-1, SARS-CoV-2, MERS-CoV, Avian Influenza, Hantavirus)

University of Jordan

Malik Sallam, M.D., Ph.D.

School of Medicine

Department of Pathology, Microbiology and Forensic Medicine

What do “emerging” and “re-emerging” mean?

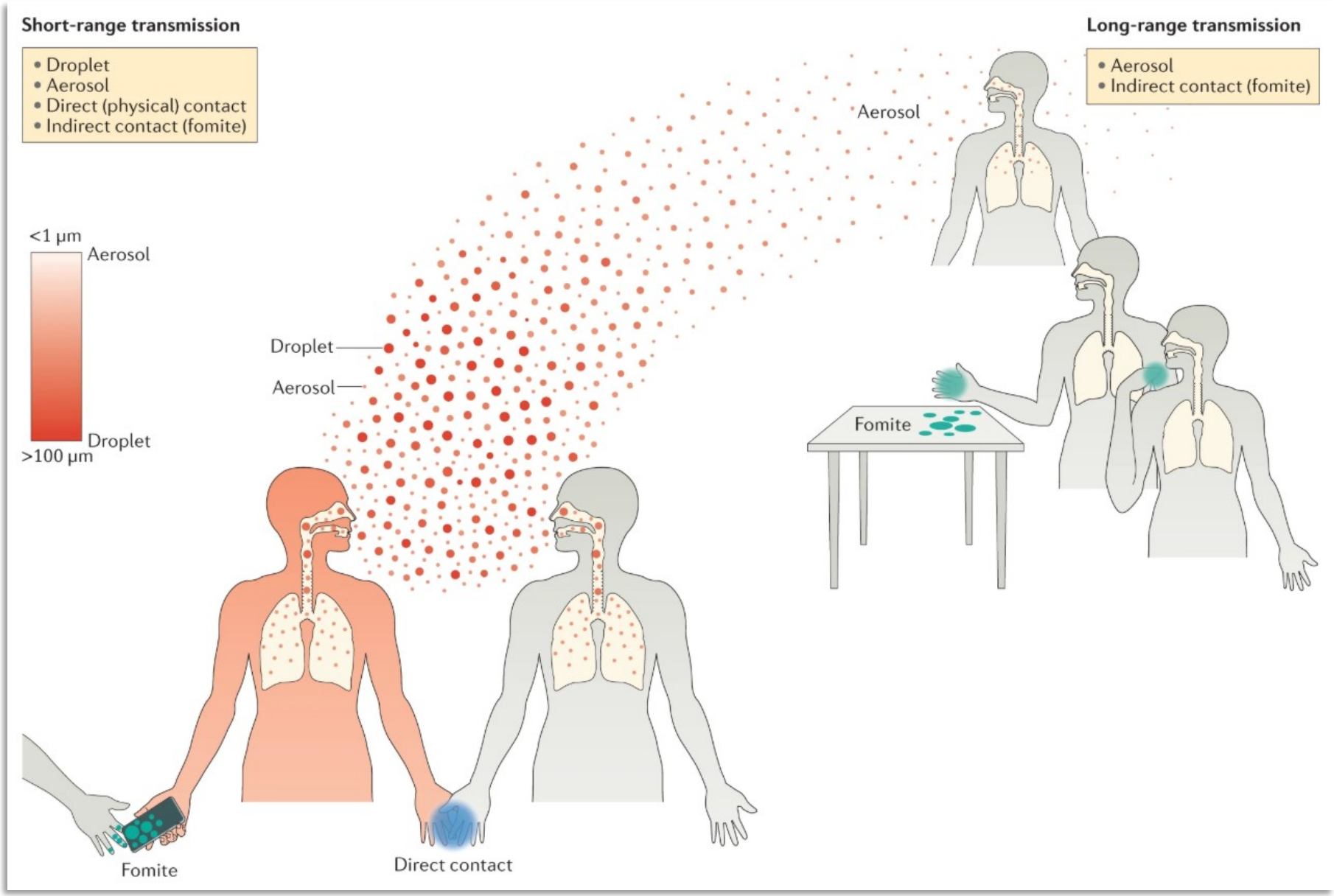
- **Emerging virus:** newly recognized or newly introduced into humans (first successful contact between the virus and humans)
- **Re-emerging virus:** known virus with renewed clinical impact (increased incidence, severity, or geographic spread) due to failed control or virus evolution.
- **Most feared examples are respiratory. Why?**
  - Large exposed surface area with constant exposure to inhaled air
  - Direct access to the environment
  - Aerosol (travel beyond close contact) and droplet transmission (efficient at short range) especially in in poorly ventilated spaces
  - Lower airway involvement means higher severity (pneumonia, hypoxia, ARDS)

Table. Outbreaks of emerging and reemerging respiratory viral infections.

Virus	Year	Region
Spanish Flu H1N1	1918	Spain [25]
Asian flu H2N2	1956	East Asia [28]
HCoV-229E HCoV-OC43	1960	The different part of the World [29]
Hong Kong Flu H3N2	1968	Hong Kong [28]
Hantavirus pulmonary syndrome	1993	USA [16]
Influenza A H5N1	1997	Hong Kong [28]
Influenza A H9N2	1999	Hong Kong [28]
Human metapneumovirus	2001	Netherlands [18]
SARS CoV	2002–2003	Guangdong, China [22]
Human CoV NL63	2004	Netherlands [20]
Influenza A H7N7	2004	Netherlands [28]
Human CoV HKU1	2005	China [20]
Triple reassortant H3N2 Influenza A	2005	Canada [28]
Bocavirus	2005	Sweden [19]
Influenza A H1N1 pmd09	2009	Mexico [28]
Adenovirus 14	2010	USA [30]
Influenza (H3N2)v	2011	USA [9]
MERS-CoV	2012	Saudi Arabia [23]
Influenza A H7N9	2013	China [28]
Influenza A H10N7	2014	China [28]
SARS-CoV-2	2019	China [26]

Source: Çelik, Ilhami et al. “Emerging and reemerging respiratory viral infections up to Covid-19.” Turkish journal of medical sciences vol. 50,SI-1 557-562. 21 Apr. 2020

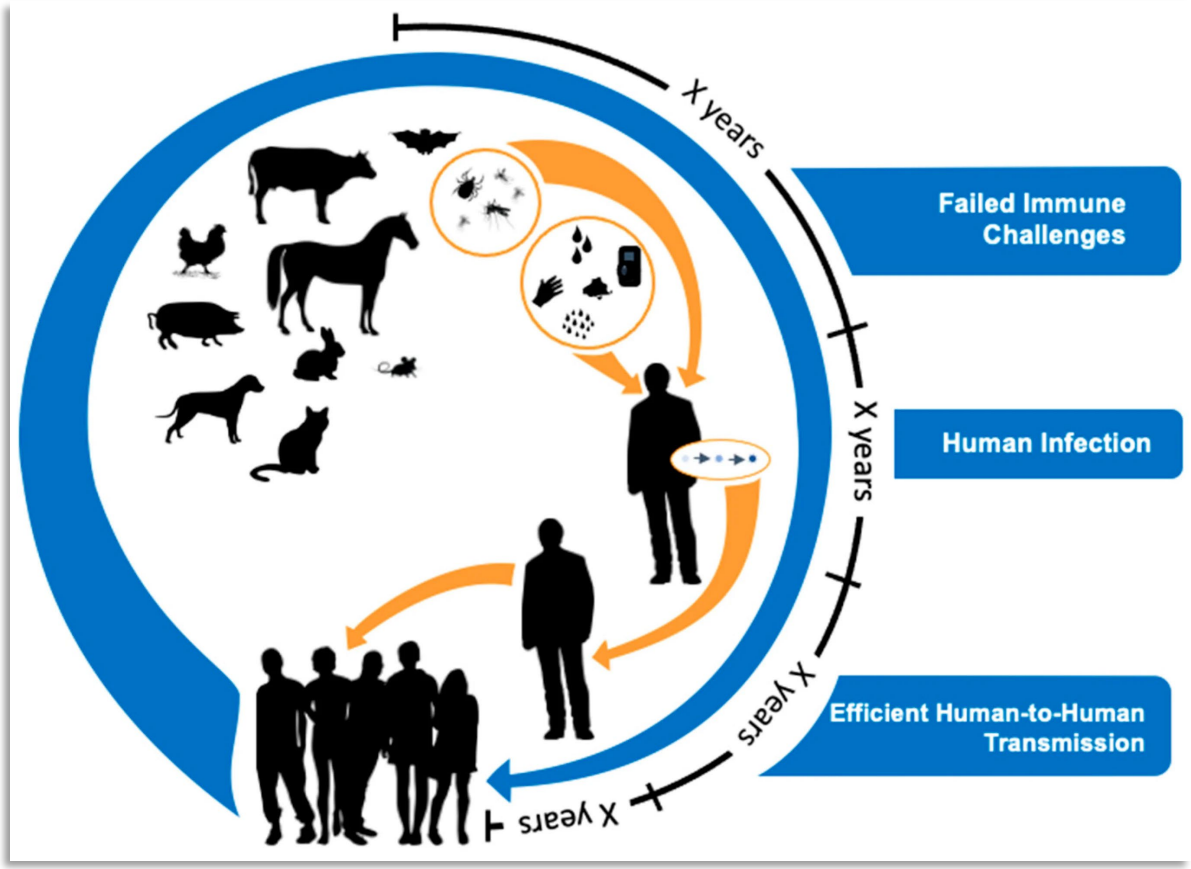
Emerging and re-emerging respiratory viruses are feared



Source: Leung, N.H.L. Transmissibility and transmission of respiratory viruses. Nat Rev Microbiol 19, 528–545 (2021).

Shared features of emerging and re-emerging respiratory viruses

- Zoonotic origin (cross-species transmission): The species barrier is the sum of all the things that usually prevent animal viruses from infecting humans due to different receptors. different body temperature, different immune responses, different cell machinery. Only a tiny fraction ever infect a human
- RNA genomes and high adaptability (RNA replication is error-prone and accumulate adaptive mutations over time also through recombination or re-assortment
- Efficient respiratory spread (breathing, speaking, coughing, fomites)
- Limited or absent population immunity (most people have no prior immunity when the virus appears). The result is rapid geographic spread and recurrent waves of infection until immunity accumulates



Source: Gray, G.C.; Robie, E.R.; Studstill, C.J.; Nunn, C.L. Mitigating Future Respiratory Virus Pandemics: New Threats and Approaches to Consider. Viruses 2021, 13, 637

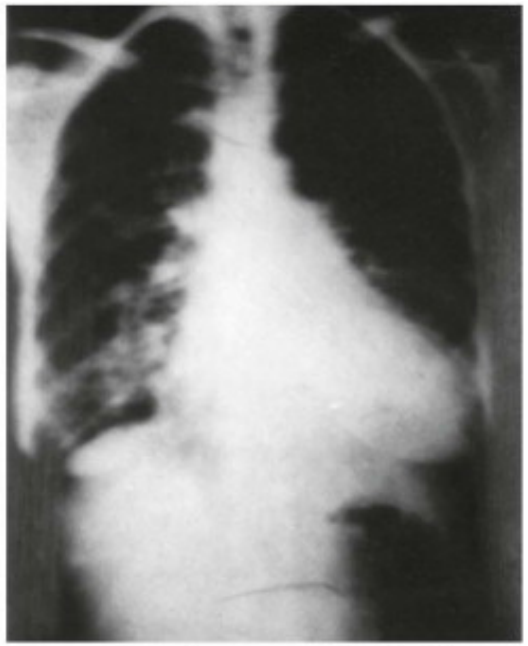
Zoonotic spillover is the common starting point

- Animal reservoirs (birds, bats, rodents)
- Human exposure at the animal-human interface (e.g., live animal markets, farming, rodent-infested environments)
- Spillover rarely causes pandemic (human infection is easy but sustained human transmission is hard). Thus, most spillovers fail
- Laboratory-associated exposure is a rare but biologically plausible route that must be evaluated using evidence, not assumption

SARS-CoV-1 (2002-2004)

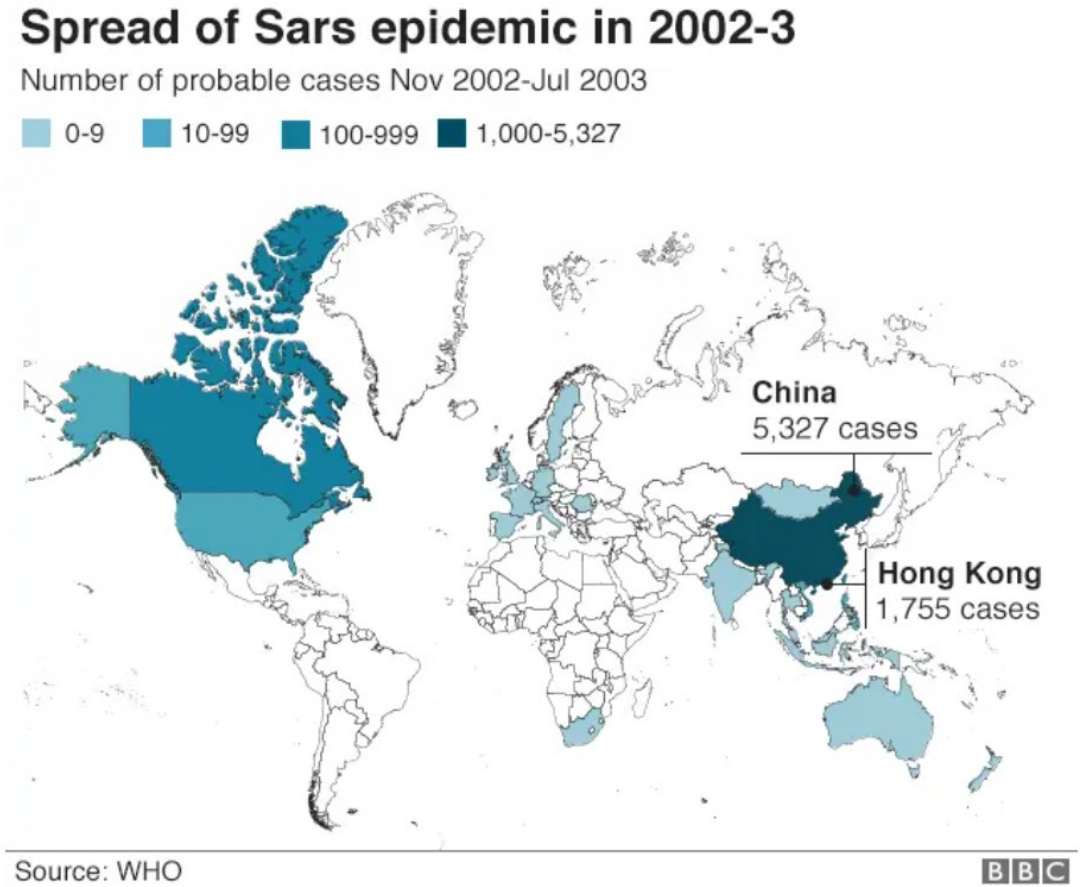
Betacoronavirus utilizing ACE2 receptor. Predominant LRTI with severe clinical disease (viral pneumonia, ARDS). Transmission mainly after symptom onset and limited community spread. Effectively controlled by isolation and infection control

Early SARS symptoms are similar to other respiratory infections and include headache, chills, myalgia, and fever, typically seen in the first week following onset. This is followed by cough and shortness of breath, which typically appear in the second week



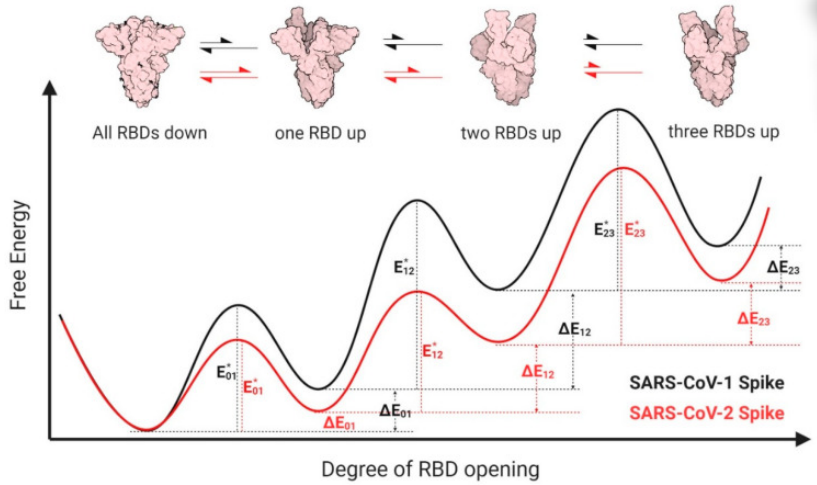
Chest radiographs can provide valuable information. Typical early findings include a ground glass appearance and focal opacities or consolidations in the peripheral lower lung fields, which often progress to bilateral patchy consolidations

Source: Schneider, Eileen. "Severe Acute Respiratory Syndrome (SARS)." Netter's Infectious Diseases (2012): 537–543.



SARS-CoV-1 (2002-2004)

- SARS-CoV-1 spike protein binds ACE2. The ACE2 expression is higher in LRT epithelium (type II pneumocytes). Binding affinity was sufficient for infection but not optimized for nasal epithelium (same receptor as SARS-CoV-2, very different biology). Thus, SARS-CoV-1 replication occurred mainly in bronchioles and alveoli with minimal early replication in URT.
- Clinical consequences meant that early symptoms were severe and patients sought care quickly. The viral load peaked late (transmission late)
- Clinical features included high fever, dyspnea, viral pneumonia with frequent progression to ARDS. The CFR was about 10% with overall higher CFR in elderly and comorbid patients. Most transmission occurred in households and in healthcare settings
- Control succeeded because patients were visibly ill and the transmission was late. Standard public health tools worked such as isolation, PPE, contact tracing and travel restrictions



Source: Wrobel, Antoni G. "Mechanism and evolution of human ACE2 binding by SARS-CoV-2 spike." Current opinion in structural biology vol. 81 (2023): 102619.

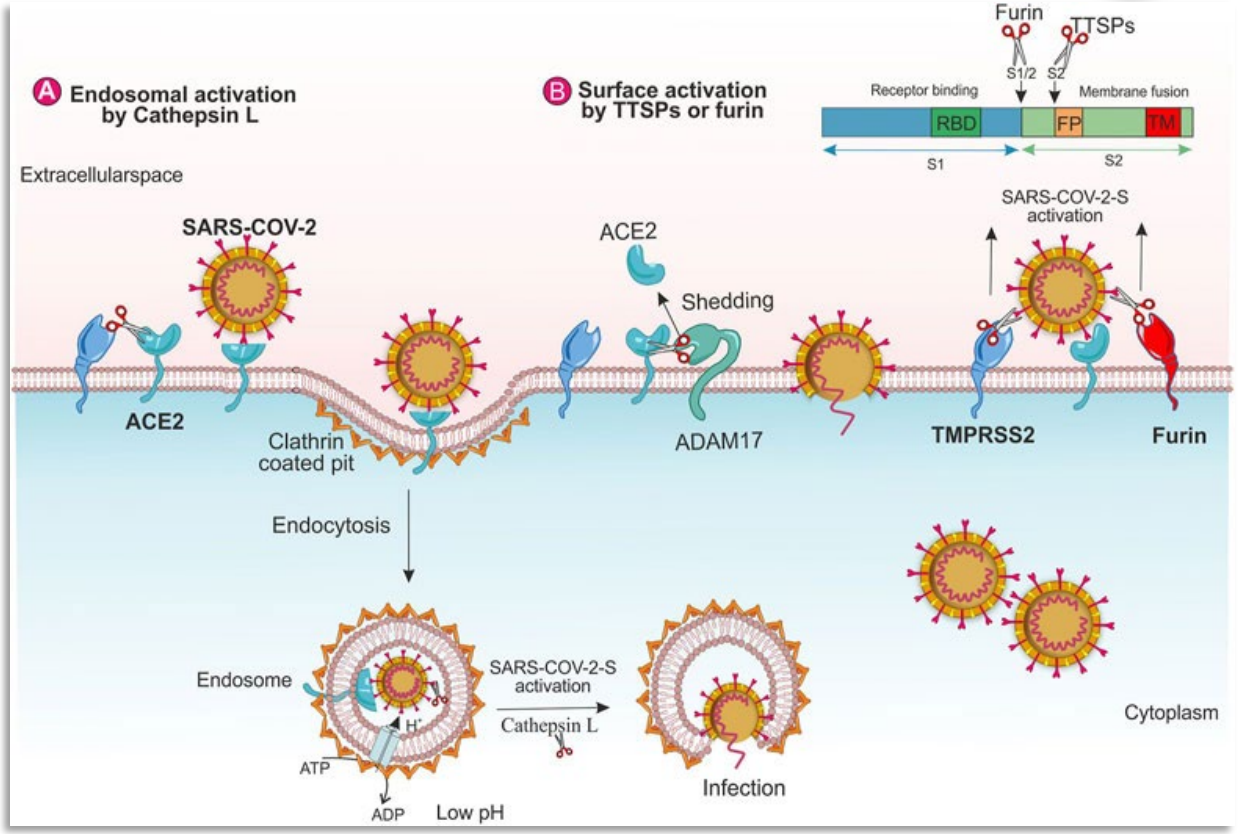
Table 1 Clinical features of SARS on presentation[3–6]

Symptom	% of patients with symptom
Persistent fever > 38C	99–100
Non-productive cough	57–75
Myalgia	45–61
Chills/rigor	15–73
Headache	20–56
Dyspnoea	40–42
Malaise	31–45
Nausea and vomiting	20–35
Diarrhoea	20–25
Sore throat	13–25
Dizziness	4.2–43
Sputum production	4.9–29
Rhinorrhoea	2.1–23
Arthralgia	10.4

Source: Hui, David Shu-Cheong et al. "SARS: clinical features and diagnosis." Respirology (Carlton, Vic.) vol. 8 Suppl,Suppl 1 (2003): S20-4.

SARS-CoV-2 and COVID-19

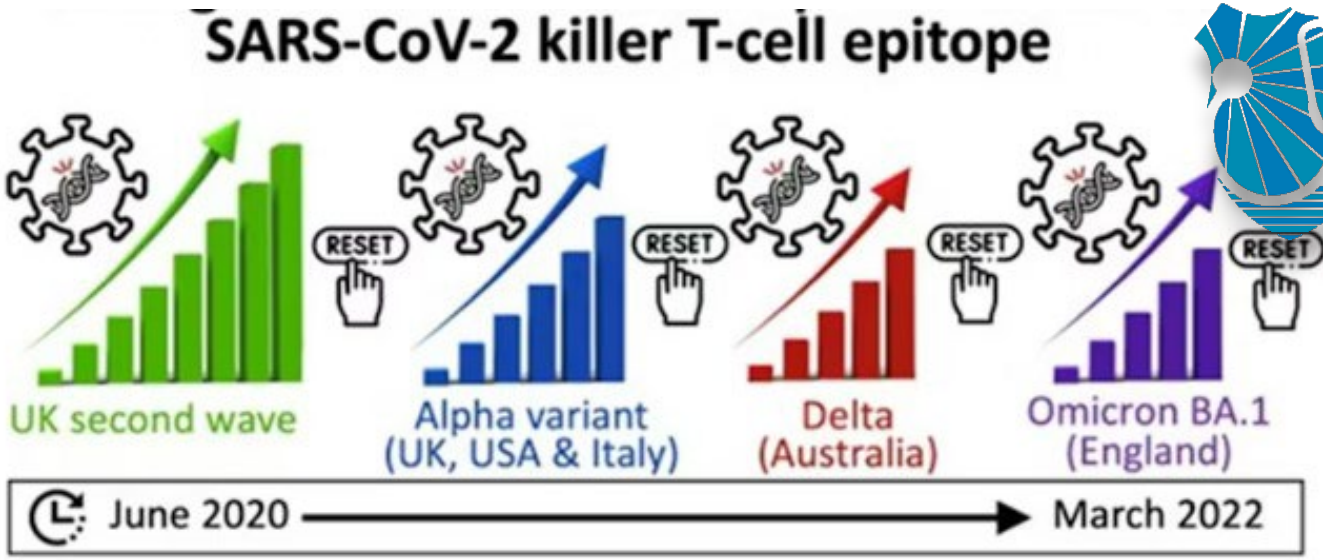
- Same receptor (ACE2) as SARS-CoV-1, but different biology.
- Efficient replication in the URT, early, pre-symptomatic, and asymptomatic transmission. Progressive immune escape through viral evolution. This led to sustained global transmission and a pandemic.
- Much higher binding affinity of S to ACE2 and more efficient S cleavage (furin cleavage site). Broader cellular tropism across RT epithelium.
- High viral loads in URT and early in infection. The result is mild or no early symptoms with talking, breathing, socializing while infectious with subsequent explosive spread of SARS-CoV-2



Source: Rahbar Saadat Y, Hosseiniyan Khatibi SM, Zununi Vahed S and Ardalan M (2021) Host Serine Proteases: A Potential Targeted Therapy for COVID-19 and Influenza. Front. Mol. Biosci. 8:725528

SARS-CoV-2 and COVID-19

- SARS-CoV-2 escaped immunity repeatedly through accumulation of S mutations mediated by antigenic drift under natural infection pressure and later on through vaccine-induced immunity.
- Thus, there was selection for variants with antibody evasion and maintained or increased transmissibility.



Source: https://www.cardiff.ac.uk/news/view/2642425-study-pinpoints-sars-cov-2-spike-mutation-that-escapes-killer-t-cells-generated-by-infection-and-vaccination

CellPress

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Heliyon

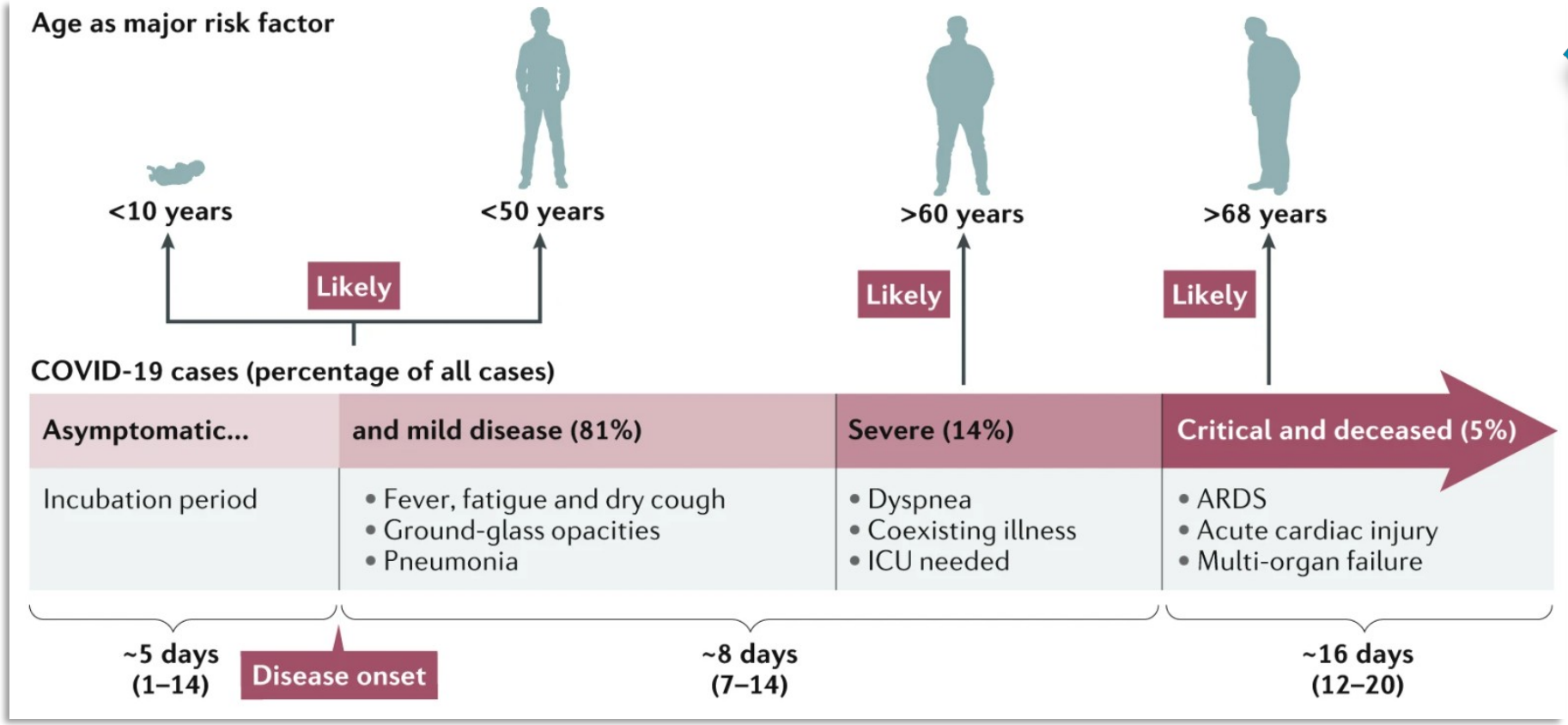
Research article

Temporal increase in D614G mutation of SARS-CoV-2 in the Middle East and North Africa

Malik Sallam [a,b,c,*], Nidaa A. Ababneh [d], Deema Dababseh [e], Faris G. Bakri [f,g,h], Azmi Mahafzah [a,b]

[a] Department of Pathology, Microbiology and Forensic Medicine, School of Medicine, The University of Jordan, Amman, Jordan
[b] Department of Clinical Laboratories and Forensic Medicine, Jordan University Hospital, Amman, Jordan
[c] Department of Translational Medicine, Faculty of Medicine, Lund University, Malmö, Sweden
[d] Cell Therapy Center (CTC), The University of Jordan, Amman, Jordan
[e] School of Dentistry, The University of Jordan, Amman, Jordan
[f] Department of Internal Medicine, School of Medicine, The University of Jordan, Amman, Jordan
[g] Department of Internal Medicine, Jordan University Hospital, Amman, Jordan
[h] Infectious Diseases and Vaccine Center, University of Jordan, Amman, Jordan

COVID-19



Source: Hu, B., Guo, H., Zhou, P. et al. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 19, 141–154 (2021)

- Incubation period: Median is 5 days with a range of 2-14 day. The majority developed symptoms by day 7-10. Long enough to allow travel, social interaction and silent spread
- Early/mild disease (URTI): Fever, dry cough, sore throat, nasal congestion, anosmia, ageusia, malaise, myalgia.
- Moderate disease (LRTI): Dyspnea, persistent cough, chest tightness, and hypoxemia. Viral pneumonia with increased oxygen requirement.
- Severe/critical disease: Severe hypoxemic respiratory failure, ARDS, shock, multi-organ dysfunction. ICU-level disease dominated by host inflammatory response

COVID-19

- Lung injury in severe disease occurs due to diffuse alveolar damage, endothelial injury, microvascular thrombosis, loss of surfactant and impaired gas exchange.

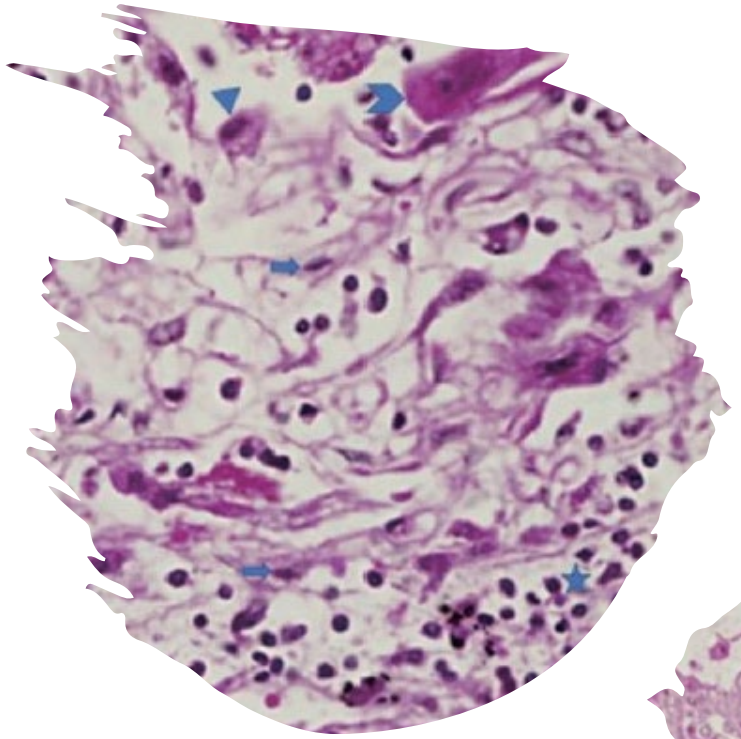
- "*Another important cause of bias, which was noticed in this study, is the overestimation of fatalities due to COVID-19. This can happen as a result of reporting any death with a positive SARS-CoV-2 testing result as a COVID-19 case, even in the absence of sufficient evidence that the individual died as a result of virus infection, which might be present as an incidental finding*"

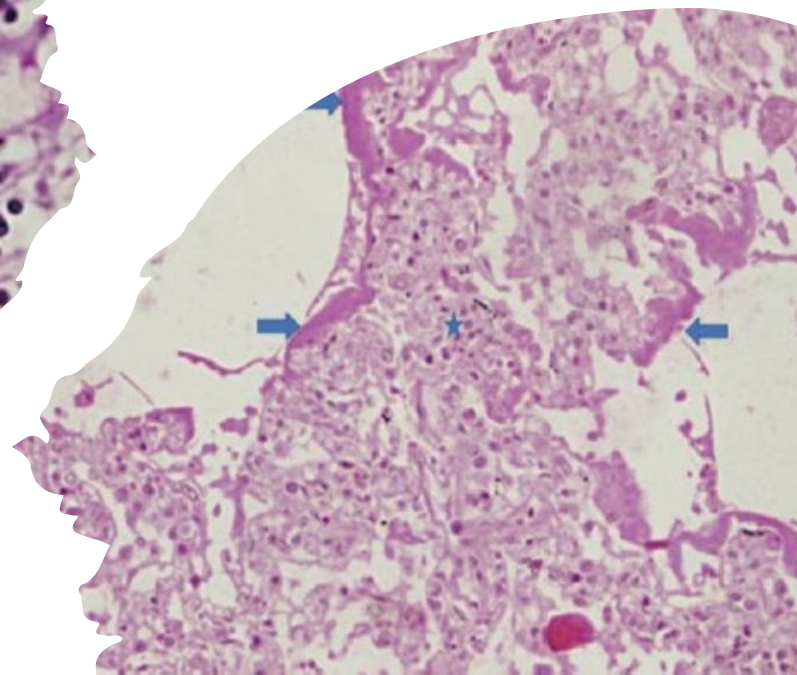
JPTM
Journal of Pathology and Translational Medicine 2023; 57: 102-112
https://doi.org/10.4132/jptm.2023.01.30

ORIGINAL ARTICLE

Postmortem lung and heart examination of COVID-19 patients in a case series from Jordan

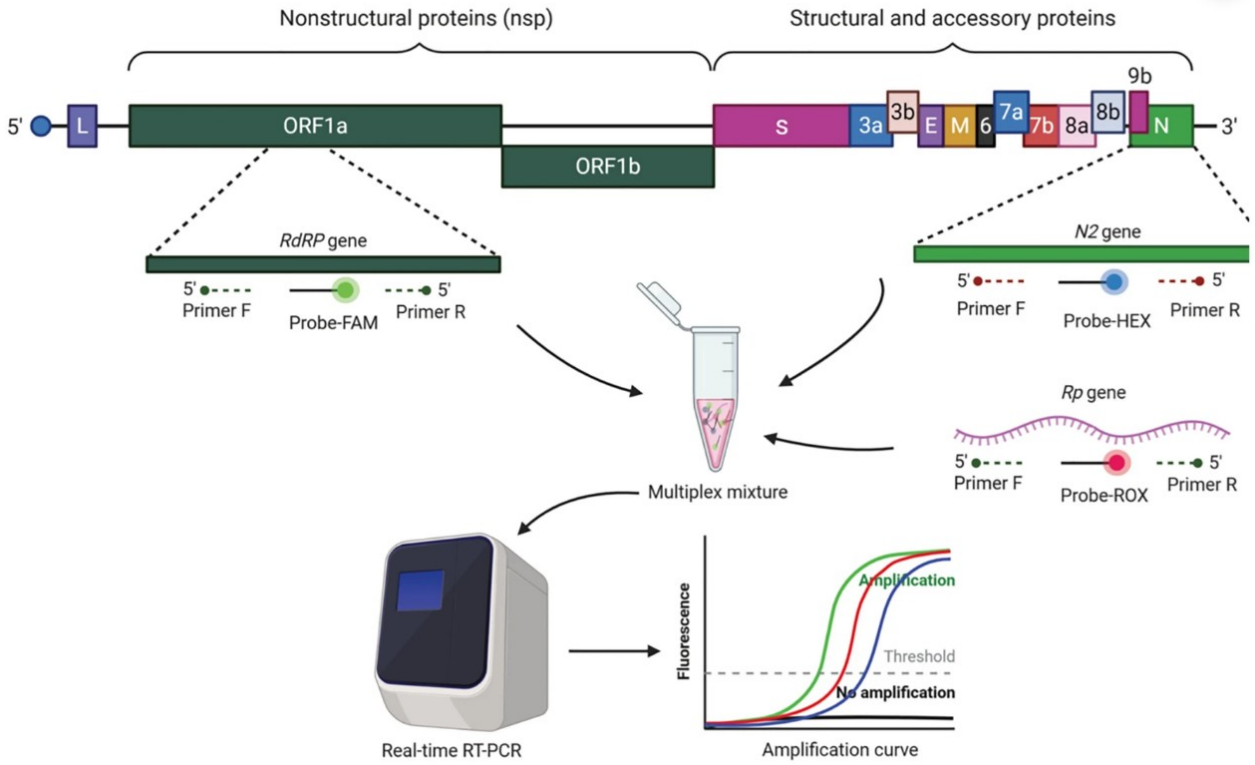
Maram Abdaljaleel[1,2], Isra Tawalbeh[3], Malik Sallam[1,2,4], Amjad Bani Hani[5], Imad M. Al-Abdallat[1,2], Baheth Al Omari[1,2], Sahar Al-Mustafa[1,2], Hasan Abder-Rahman[1,2], Adnan Said Abbas[3], Mahmoud Zureigat[3], Mousa A. Al-Abbadi[1,2]





COVID-19 diagnosis

- Clinical in epidemic situation
- Molecular testing by RT-PCR
- Antigen tests: Rapid and is best used when viral load is high
- Serology
- Laboratory findings in severe and critical disease: Lymphopenia, elevated CRP, ferritin, elevated D-dimer, elevated IL-6 and it signals thrombo-inflammatory disease.
- Imaging (adjunctive) Chest X-ray, CT chest.



Source: Tombuloglu, H., Sabit, H., Al-Khallaf, H. et al. Multiplex real-time RT-PCR method for the diagnosis of SARS-CoV-2 by targeting viral N, RdRP and human RP genes. Sci Rep 12, 2853 (2022).

COVID-19 management

- Mild disease: Supportive care through anti-pyretics, hydration
- Moderate disease (hypoxia): Oxygen therapy, anti-viral therapy
- Severe disease: Corticosteroids (e.g., dexamethasone), oxygen escalation. High-flow nasal cannula. Non-invasive ventilation. Mechanical ventilation.

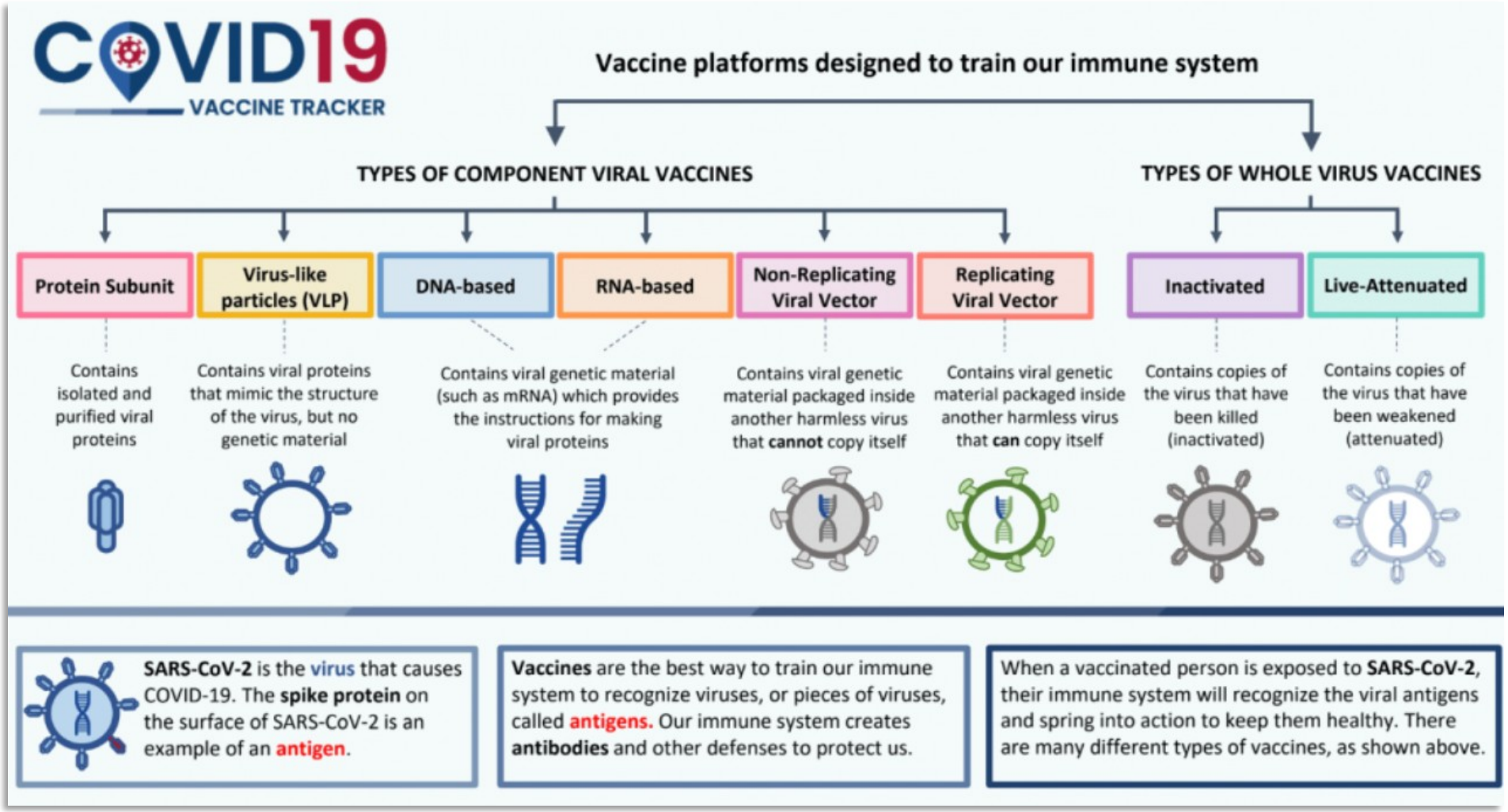
Table 1 | COVID-19 management strategies

Patient status	Antiviral	Immunomodulator
Outpatient with mild to moderate COVID-19 (not requiring supplemental oxygen)		
No risk factors	None	None, steroids may cause harm (RECOVERY study)[15]
More than one high-risk factor(s)[a]	Nirmatrelvir–ritonavir (NMV–r)[b] (within 5 days of symptom onset)[97] or intravenous remdesivir[c] (within 7 days of symptom onset)[78]	None, steroids may cause harm[15]
Inpatient		
Not requiring supplemental oxygen, more than one high-risk factor(s)	Consider remdesivir if within 7 days of symptom onset[78]	None[15]
Stable and minimal supplemental oxygen (2 l nasal cannula)	Remdesivir recommended if initiated within 7 days of symptom onset[74,77,79,80]	None[15]
Worsening respiratory status while on 2–4 l nasal cannula	Remdesivir recommended if initiated within 7 days of symptom onset[74,77,79,80]	Dexamethasone[d][15]
HFNC, non-invasive ventilation or invasive ventilation (within 24 h)	Remdesivir may be considered if initiated within 7 days of symptom onset[74,77,79,80]	Dexamethasone[15] plus tocilizumab (RECOVERY-TOCI study)[109,117–120], or baricitinib[143,144]
HFNC, non-invasive ventilation or invasive ventilation (after 24–48 h of requiring this level of support)	Remdesivir may be considered if initiated within 7 days of symptom onset but is not routinely recommended[74,77,79,80]	Dexamethasone[15] Consider tocilizumab[e],[110,118–121] or baricitinib[f] if within 72 h of admission[143,144]
Mechanical ventilation or ECMO (within 24–48 h)	Remdesivir may be considered if initiated within 7 days of symptom onset but is not routinely recommended[74,77,79,80]	Dexamethasone[15] Consider tocilizumab[109,117–120] or baricitinib if within 72 h of admission[143,144]
Pregnant	Consider intravenous remdesivir if initiated within 7 days of symptom onset[74,142] or NMV–r if initiated within 5 days of symptom onset[90,143,144] when meets eligibility criteria	Dexamethasone in some countries, for example the United States[147] Prednisolone or hydrocortisone is preferred over dexamethasone in some countries, for example the United Kingdom[165] Dexamethasone, when early delivery is planned[165] Tocilizumab, when meets eligibility criteria[168] Baricitinib is contraindicated[169]

Source: Meyerowitz, E.A., Scott, J., Richterman, A. et al. Clinical course and management of COVID-19 in the era of widespread population immunity. Nat Rev Microbiol 22, 75–88 (2024).

COVID-19 prevention

Vaccination: Vaccines prevent severe disease and reduce hospitalization and death. Vaccines do not fully prevent infection

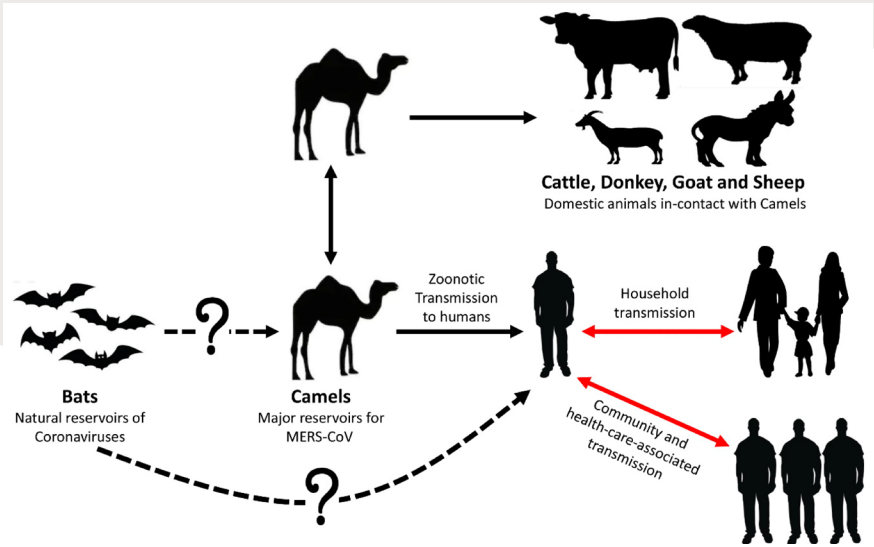


COVID-19 prevention

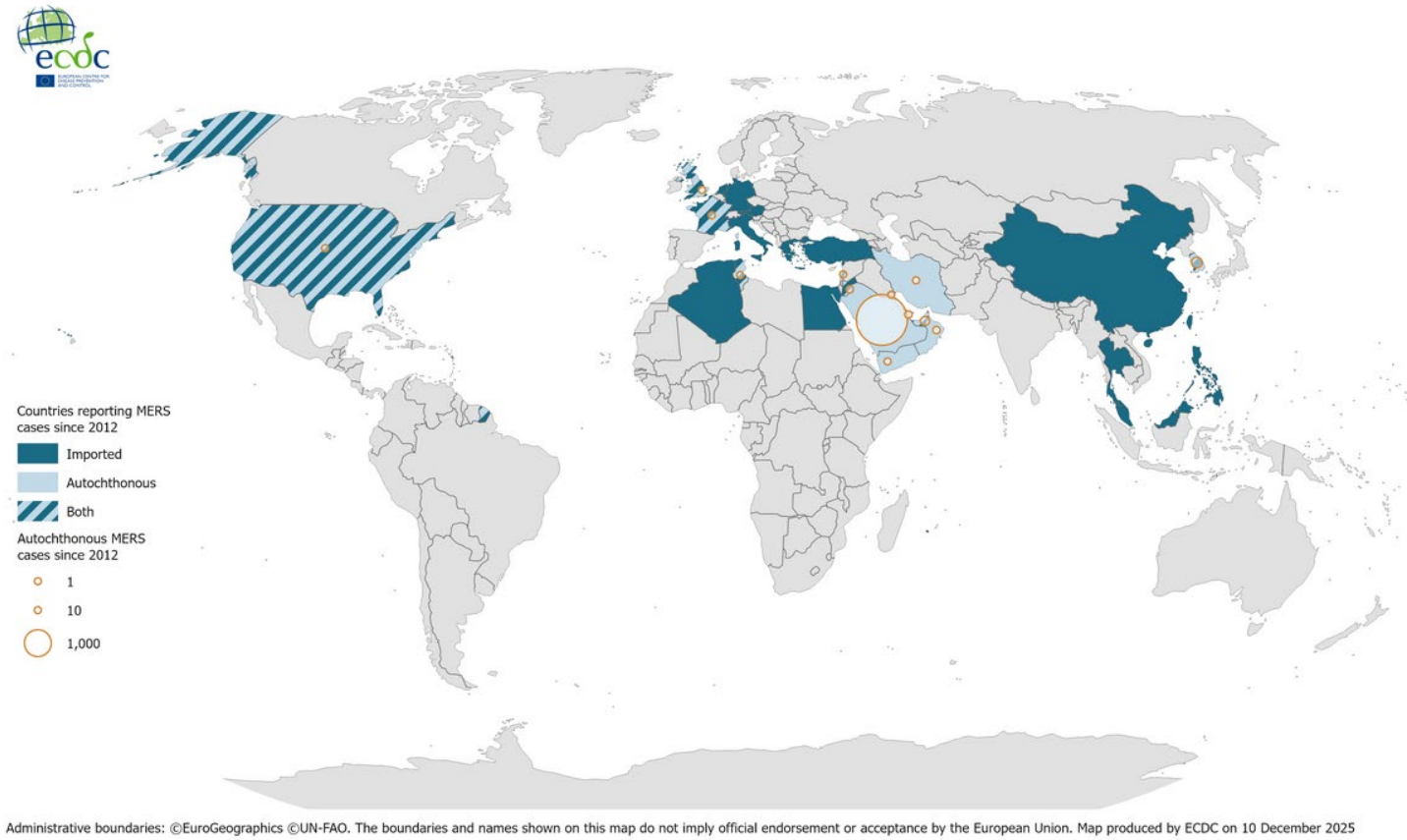
Non-pharmaceutical interventions (NPIs)

MERS-CoV

Source: Mostafa, A.; Kandeil, A.; Shehata, M.; El Shesheny, R.; Samy, A.M.; Kayali, G.; Ali, M.A. Middle East Respiratory Syndrome Coronavirus (MERS-CoV): State of the Science. Microorganisms 2020, 8, 991.

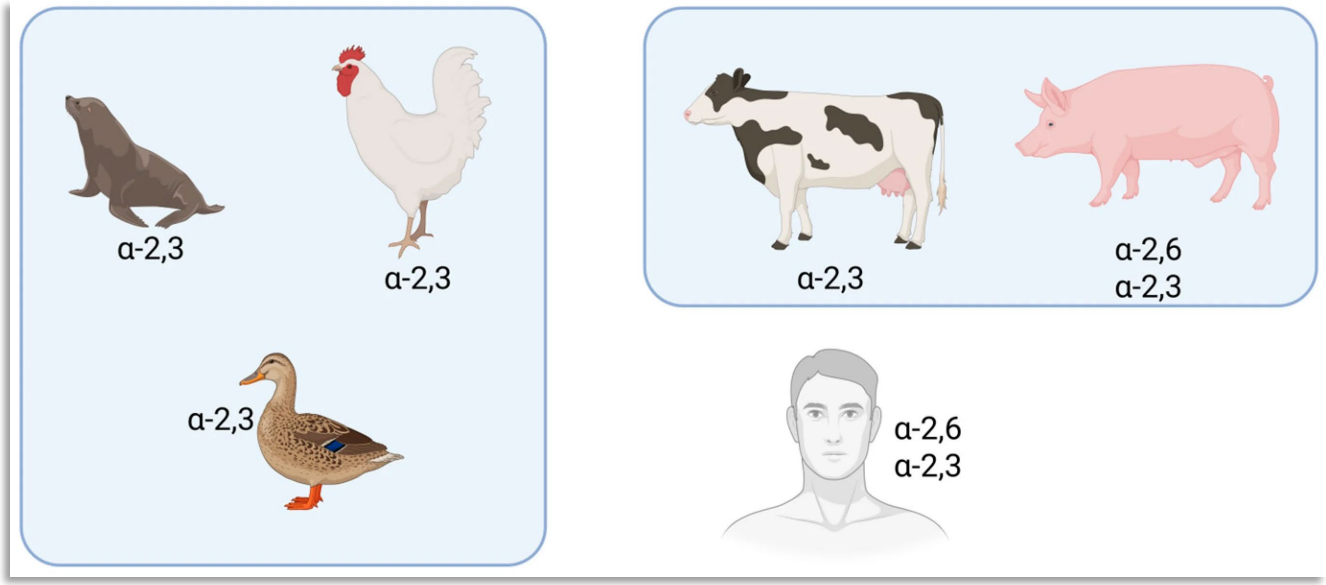


- Uses dipeptidyl peptidase-4 (DPP4/CD26) receptor (not ACE2). DPP4 is expressed predominantly in the LRT, kidneys, and immune cells which explains severe pneumonia and extra-pulmonary manifestations
- Dromedary camels are the established reservoir and humans acquire infection through repeated zoonotic introductions. No sustained adaptation for efficient community spread
- Limited human-to-human transmission with spread occurring mainly in healthcare settings.
- CFR can reach 37% due to severe LRTI. Frequent complications include ARDS and acute kidney injury



Avian Influenza

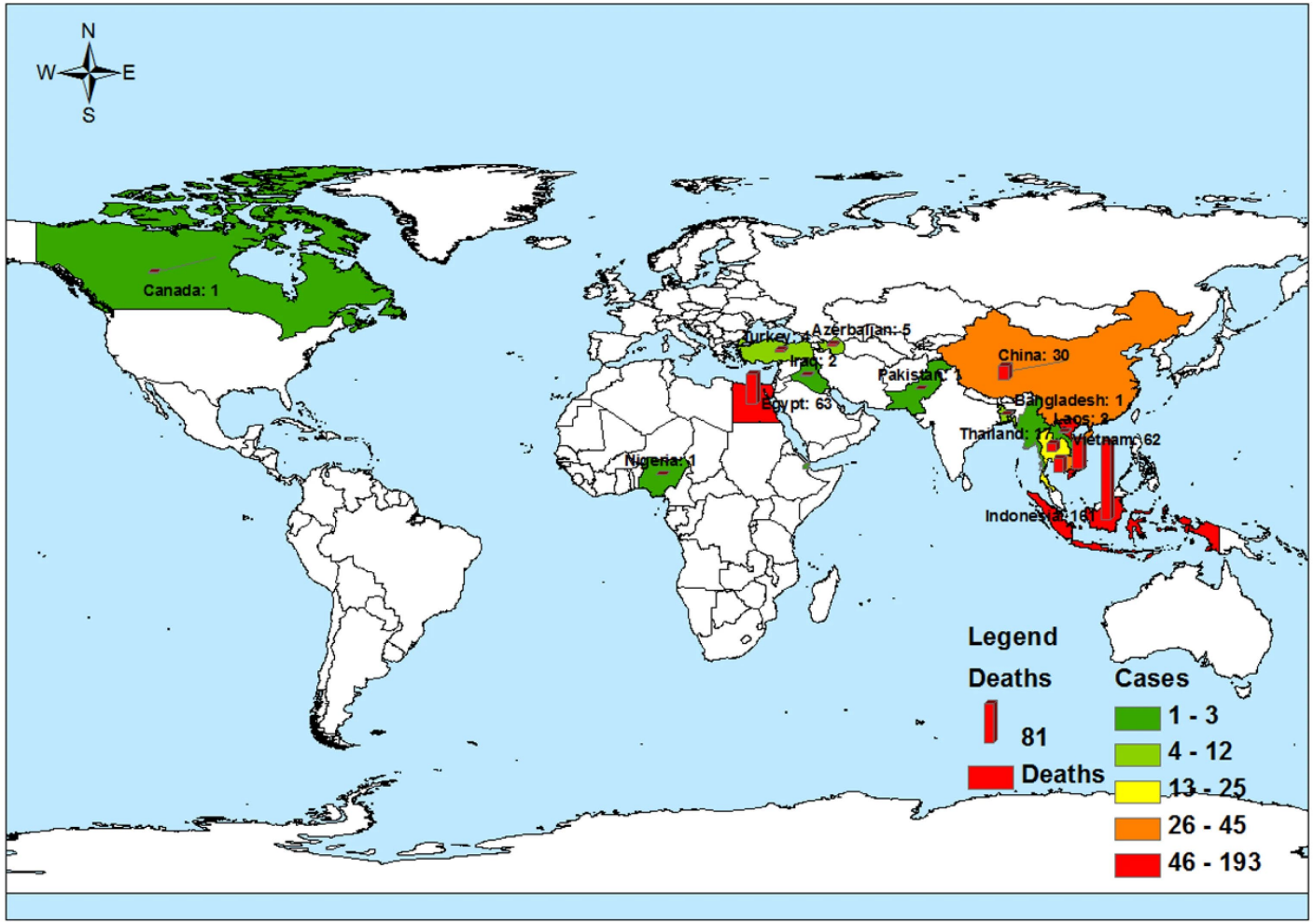
- Influenza A viruses are the only influenza type with pandemic potential since it has a broad host range including birds, humans, swine, other mammals. It has segmented - ssRNA genome (8 segments) which allows genetic reassortment when two strains co-infect the same cell producing antigenic shift which result in sudden emergence of novel viruses.
- Natural reservoir: Wild aquatic birds. Long-term viral evolution occurs silently in birds. Humans are accidental, maladapted hosts Poultry acts as an amplifier at the animal-human interface. Avian viruses bind α-2,3 sialic acid (LRT) while human viruses bind α-2,6 sialic acid (URT). Limited human-to-human transmission unless adaptation occurs



Source: Li, H.; Ren, R.; Bai, W.; Li, Z.; Zhang, J.; Liu, Y.; Sun, R.; Wang, F.; Li, D.; Li, C.; et al. A Review of Avian Influenza Virus Exposure Patterns and Risks Among Occupational Populations. Vet. Sci. 2025, 12, 704

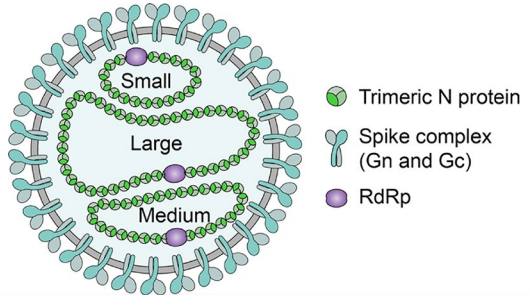
Avian Influenza

- H5N1 causes viral replication deep in the lungs resulting in severe viral pneumonia, ARDS and high cytokine release and tissue damage. Very high CFR 50-60%.
- Seasonal influenza vaccines are designed against circulating human influenza A and B strains Typically H1N1, H3N2, and influenza B lineages.
- Avian influenza viruses (e.g., H5N1, H7N9) are antigenically distinct and not included in routine seasonal vaccines. Neutralizing antibodies generated by seasonal vaccines do not effectively bind avian HA proteins
- Avian influenza is controlled in farms, markets, and surveillance systems.



Wu, Z.-Q.; Zhang, Y.; Zhao, N.; Yu, Z.; Pan, H.; Chan, T.-C.; Zhang, Z.-R.; Liu, S.-L. Comparative Epidemiology of Human Fatal Infections with Novel, High (H5N6 and H5N1) and Low (H7N9 and H9N2) Pathogenicity Avian Influenza A Viruses. Int. J. Environ. Res. Public Health 2017, 14, 263

Hantavirus Pulmonary Syndrome (HPS)



- Hantaviruses are enveloped, negative sense RNA viruses with segmented genome belonging to *Bunyavirales* with reservoir in wild rodents. Humans are dead-end hosts. Transmitted by inhalation of aerosolized rodent excreta such as urine, feces, saliva.
- Hantavirus infects endothelial cells with the disease driven by immune-mediated capillary leak with subsequent pulmonary edema and rapid respiratory failure. Clinically, HPS starts with a prodromal phase (3-5 days) with fever, myalgia, headache, GI symptoms. The cardiopulmonary phase follows with sudden dyspnea, hypoxemia and pulmonary edema. CFR can reach 40%
- Supportive care is critical such as early ICU admission, mechanical ventilation

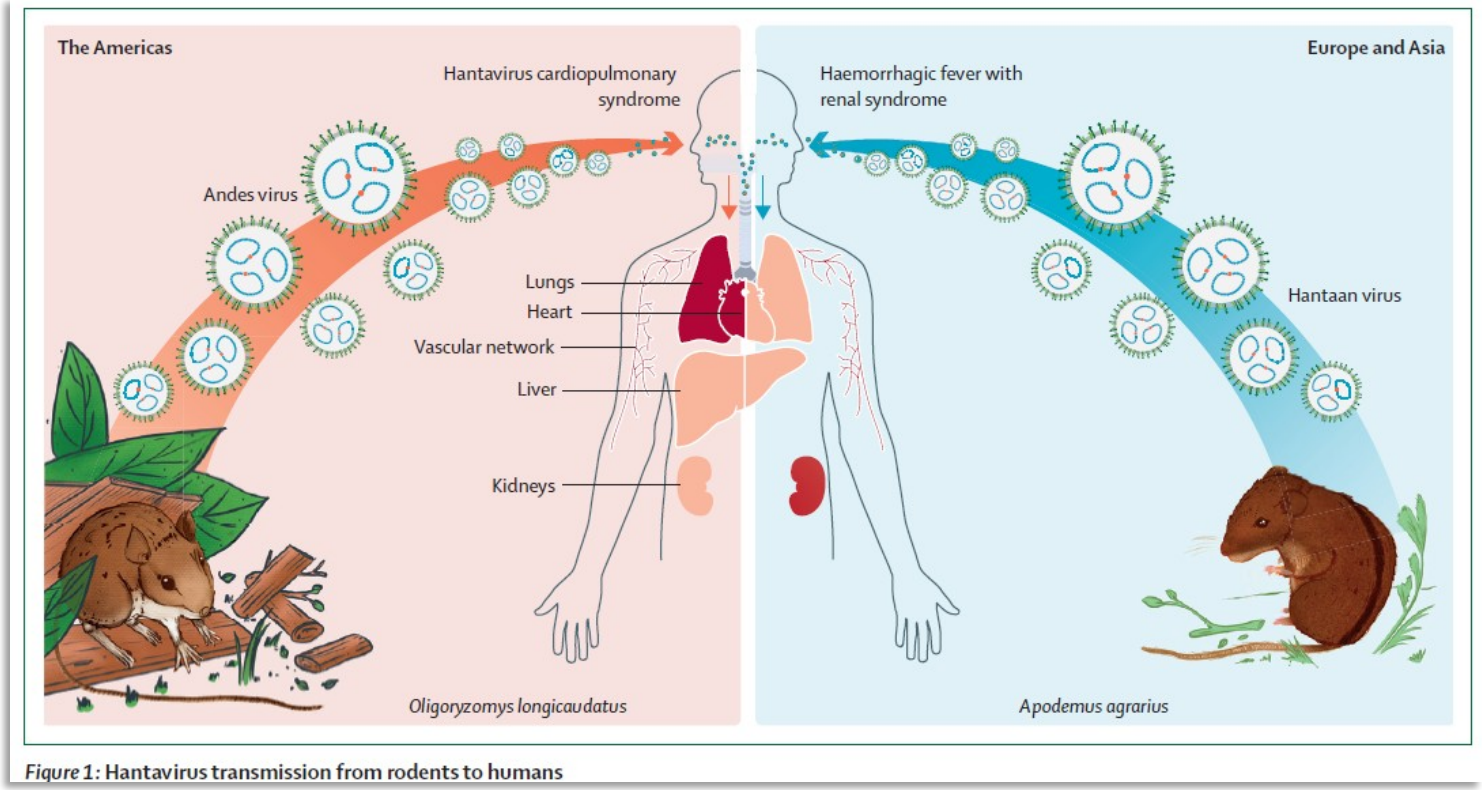


Figure 1: Hantavirus transmission from rodents to humans

Source: Vial PA, Ferrés M, Vial C, Klingström J, Ahlm C, López R, Le Corre N, Mertz GJ. Hantavirus in humans: a review of clinical aspects and management. Lancet Infect Dis. 2023 Sep;23(9):e371-e382. doi: 10.1016/S1473-3099(23)00128-7. Epub 2023 Apr 24. PMID: 37105214.

Thank You!
Wishing you all the best!