



Common Viral Respiratory Pathogens

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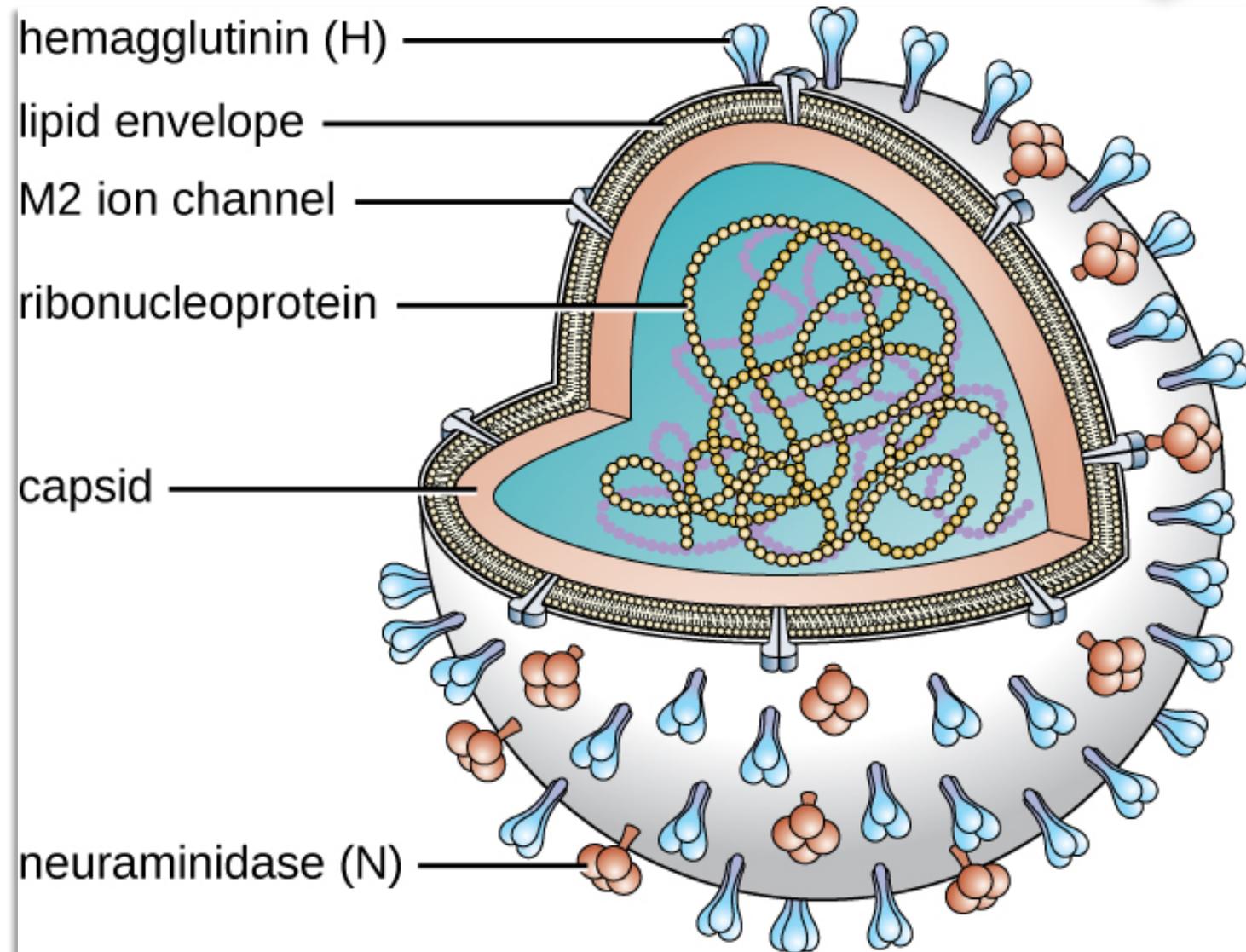
Overview of RTI-causing virus families

Virus	Family	Genome	Envelope
Influenza A/B/C	<i>Orthomyxoviridae</i>	Segmented (–) ssRNA	Enveloped
Parainfluenza virus (1-4)	<i>Paramyxoviridae</i>	Non-segmented (–) ssRNA	Enveloped
Respiratory syncytial virus	<i>Pneumoviridae</i>	Non-segmented (–) ssRNA	Enveloped
Human metapneumovirus	<i>Pneumoviridae</i>	Non-segmented (–) ssRNA	Enveloped
Adenovirus	<i>Adenoviridae</i>	Linear dsDNA	Non-enveloped
Rhinovirus	<i>Picornaviridae</i>	(+) ssRNA	Non-enveloped
Coronaviruses	<i>Coronaviridae</i>	(+) ssRNA	Enveloped
SARS-CoV-2	<i>Coronaviridae</i>	(+) ssRNA	Enveloped
Measles virus	<i>Paramyxoviridae</i>	Non-segmented (–) ssRNA	Enveloped
Human bocavirus	<i>Parvoviridae</i>	ssDNA	Non-enveloped
Enteroviruses	<i>Picornaviridae</i>	(+) ssRNA	Non-enveloped



Influenza virus structure

- Segmented negative-sense single-stranded RNA genome with 8 segments (A and B).
- Enveloped virus.
- Two key surface glycoproteins:
 - Hemagglutinin (HA): viral attachment
 - Neuraminidase (NA): viral release

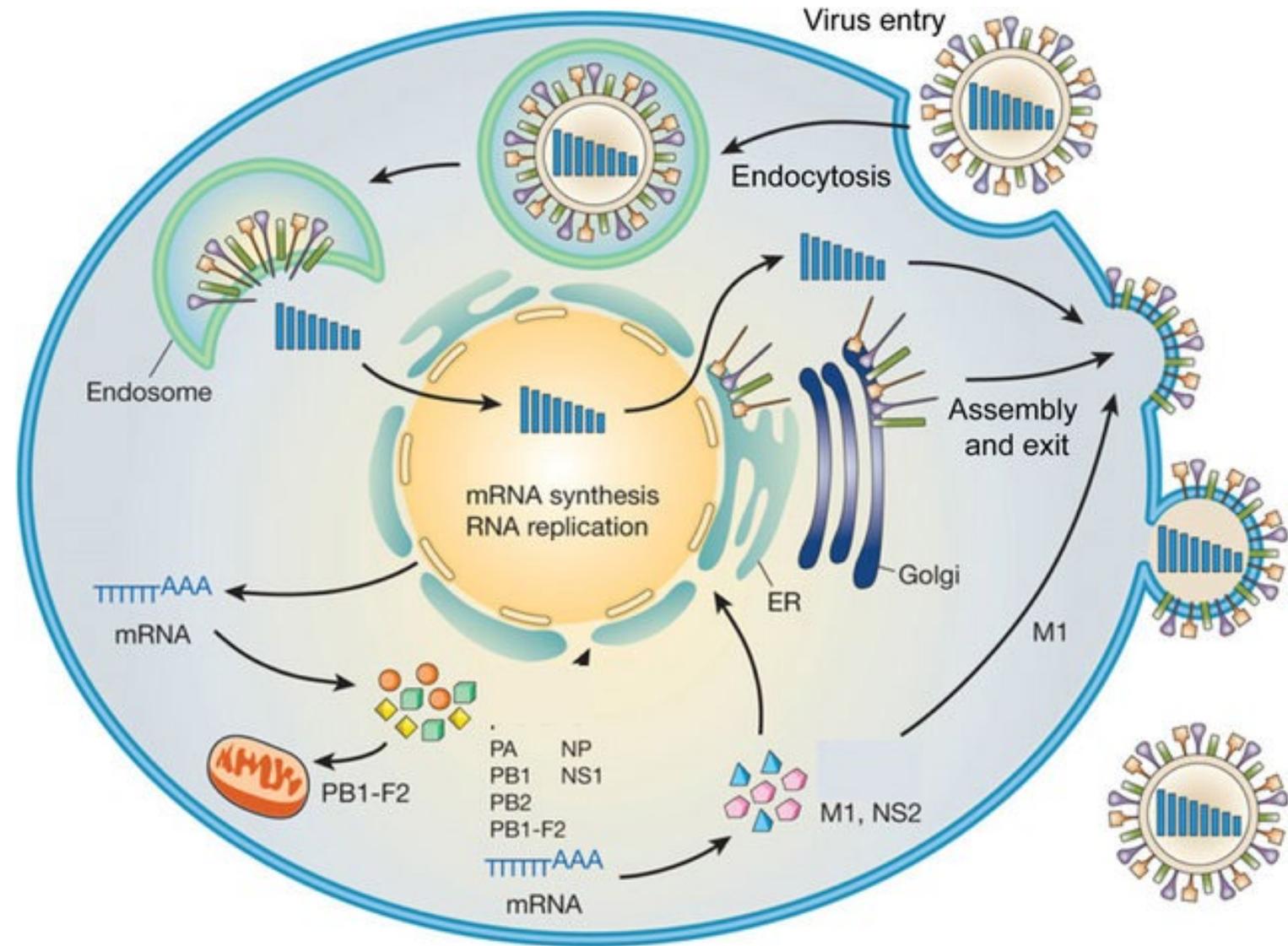




Influenza virus structure and replication

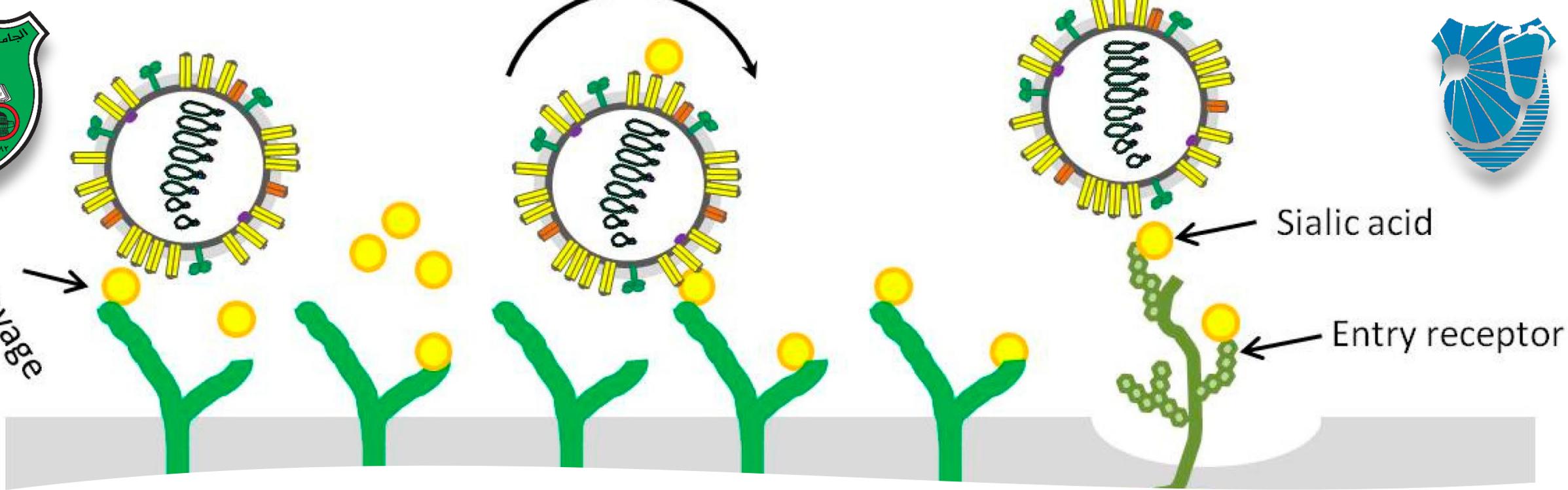


- HA binds sialic acid on respiratory epithelial cells allowing viral entry
- NA cleaves sialic acid causing release of newly formed virions and prevents viral clumping which facilitates spread





NA cleavage



- Primary target cells are the ciliated columnar epithelial cells in the URT (nasal mucosa, trachea), LRT (bronchi, bronchioles). Type I and type II pneumocytes (in severe disease) especially in viral pneumonia.
- Receptor specificity: Viral hemagglutinin (HA) binds sialic acid receptors.
- Viral replication inside epithelial cells causes apoptosis and necrosis, loss of ciliated cells which results in impaired mucociliary clearance, and exposure of basement membrane. This mechanical damage explains cough and predisposition to bacterial infection

Influenza: Pathogenesis



Influenza immunopathogenesis

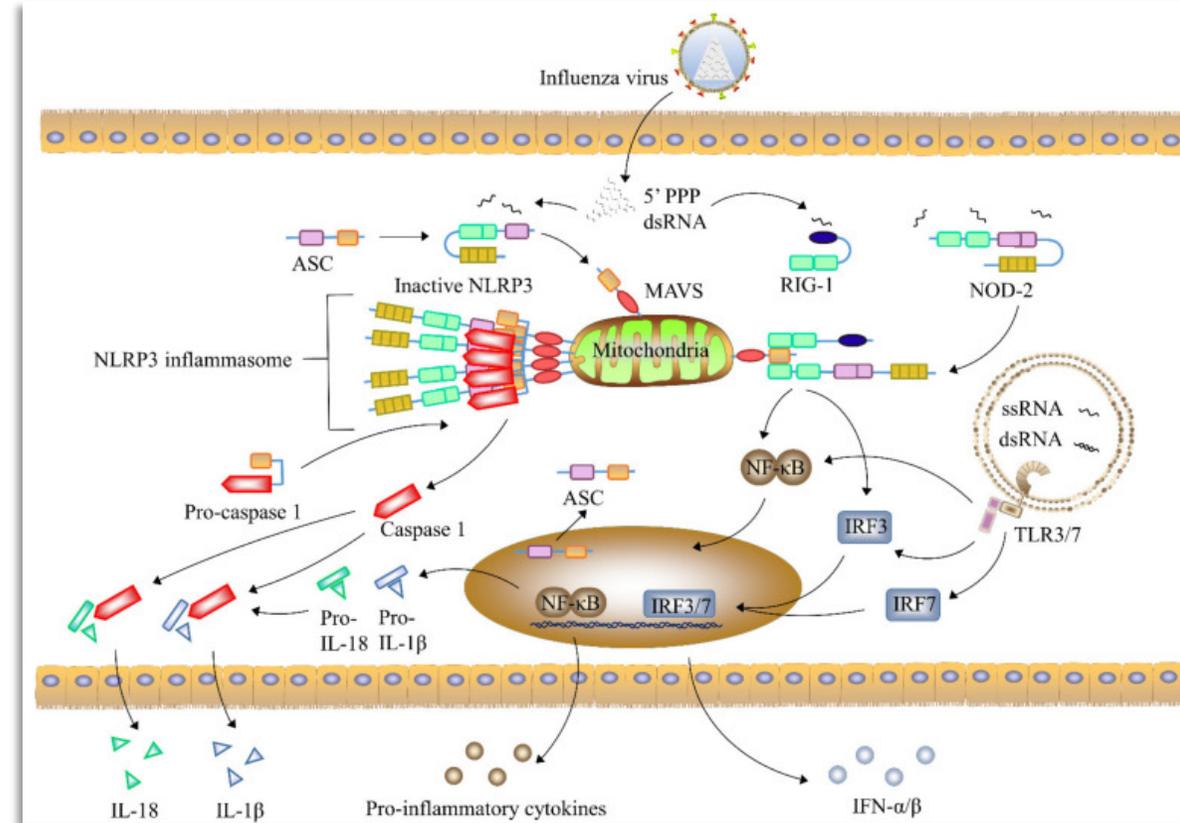


- Viral RNA is detected by TLR3, TLR7. IFN- α , IFN- β are released resulting in antiviral state, fever, malaise. IL-1, IL-6, TNF- α cause fever, myalgia, fatigue.

- **Cytokine storm** result from high levels of TNF- α , IL-6, IFN- γ , leading to capillary leak, pulmonary edema and ARDS.

- CD8+ T cells kill infected epithelial cells resulting in viral clearance but contribute to lung tissue damage. CD4+ T cells support B-cell antibody.

Secondary bacterial pneumonia occurs due to loss of cilia and impaired clearance with exposed epithelial receptors. Common pathogens include *S. aureus*, *S. pneumoniae*, *H. influenzae*



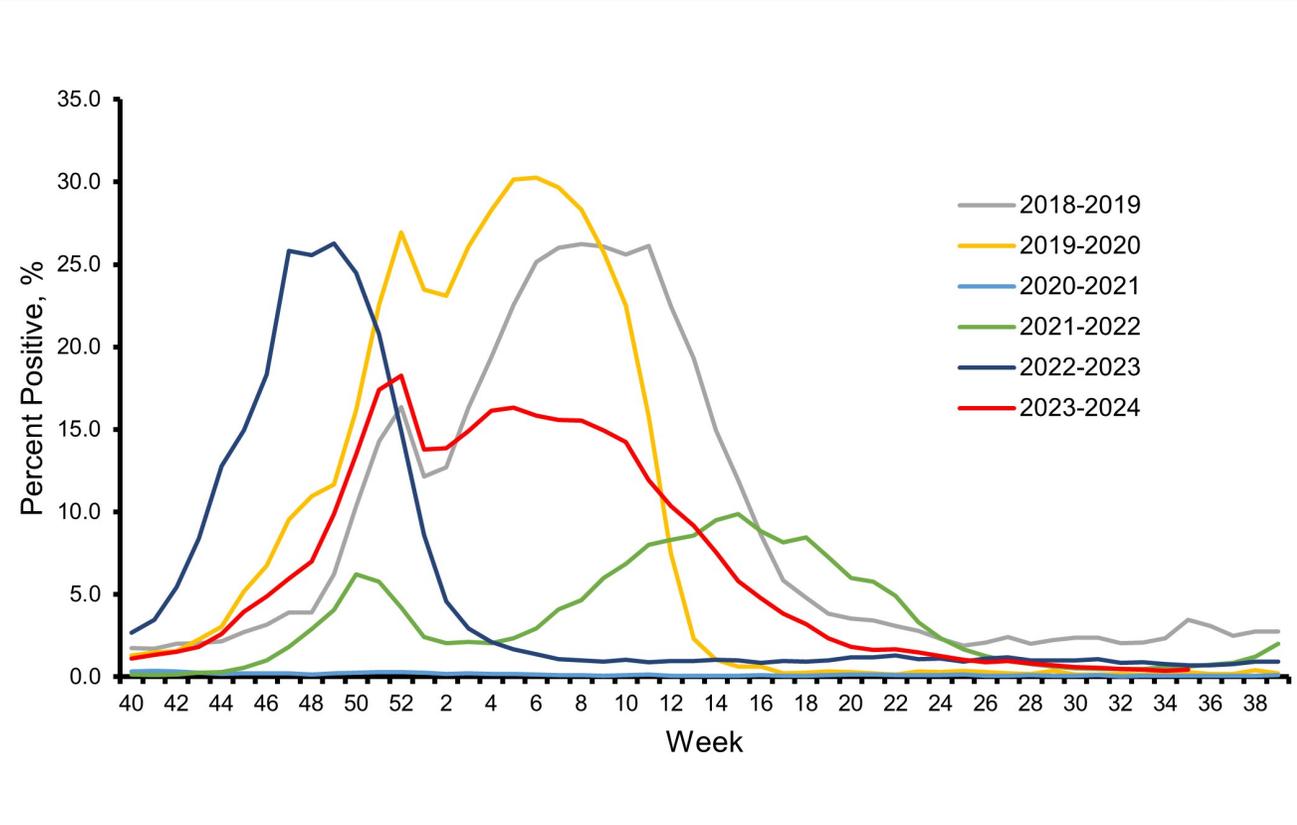
Source: Gu, Yinuo et al. "The Mechanism behind Influenza Virus Cytokine Storm." *Viruses* vol. 13,7 1362. 14 Jul. 2021



Influenza epidemiology and seasonality



- Flu peaks in winter months in temperate climates since cold, dry air enhances viral stability, impairs mucociliary clearance, and increases indoor crowding. In tropics, flu has year-round transmission
- Spread via respiratory droplets, aerosols, and fomites. The incubation period: 1-4 days, while the infectious period is 1 day before symptoms to 5-7 days after.
- Highest morbidity/mortality among elderly, pregnant women, infants, chronic cardiopulmonary disease, immunocompromised.
- There are around a billion cases of seasonal influenza annually, including 3-5 million cases of severe illness. It causes 290,000 to 650,000 respiratory deaths annually.

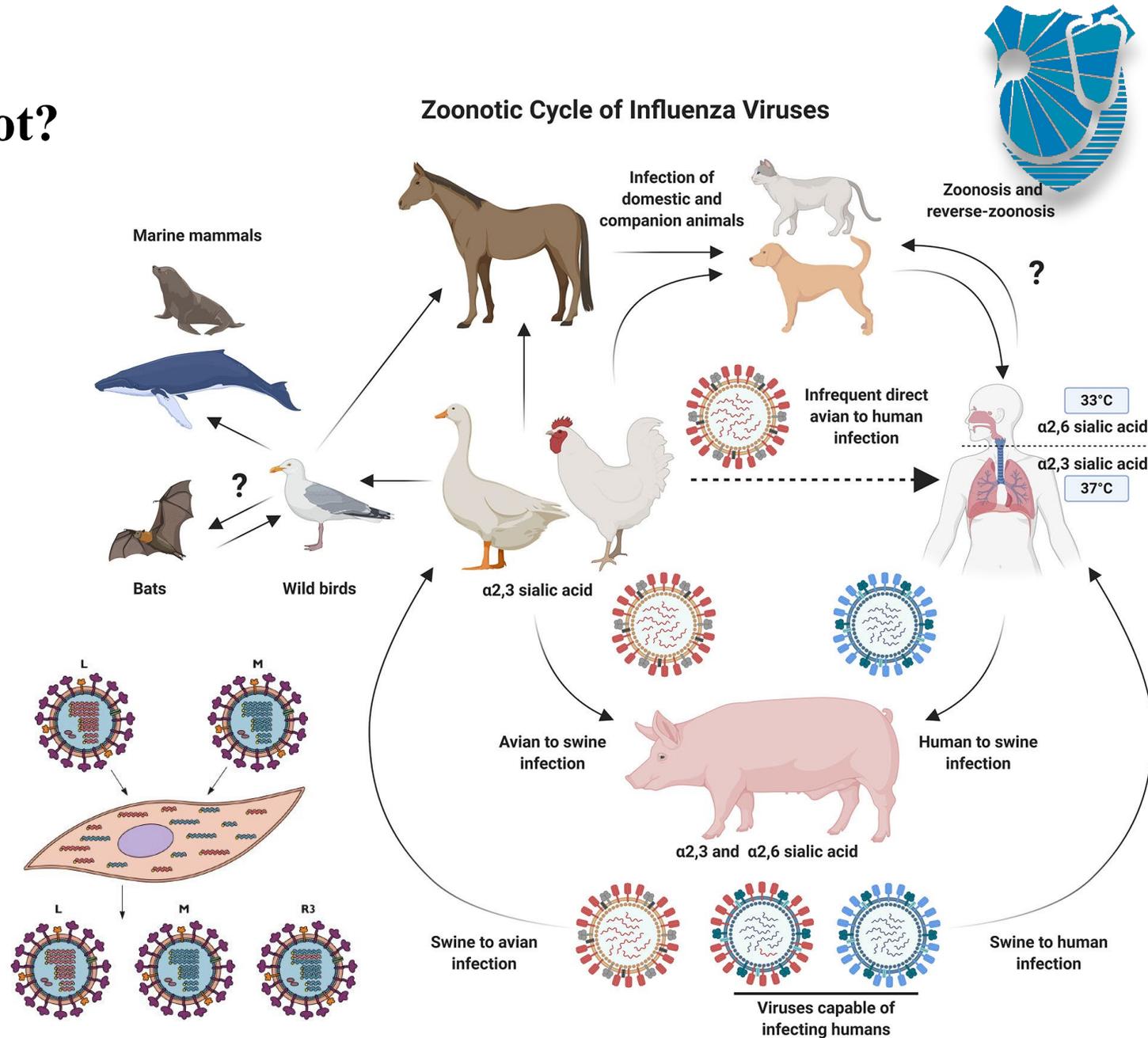


Source: Influenza Positive Test Results Reported by Clinical Laboratories to CDC, National Summary by MMWR week and Influenza Season — United States, 2018–2019 to 2023–2024 Seasons



Why does Influenza A cause pandemics, but B and C do not?

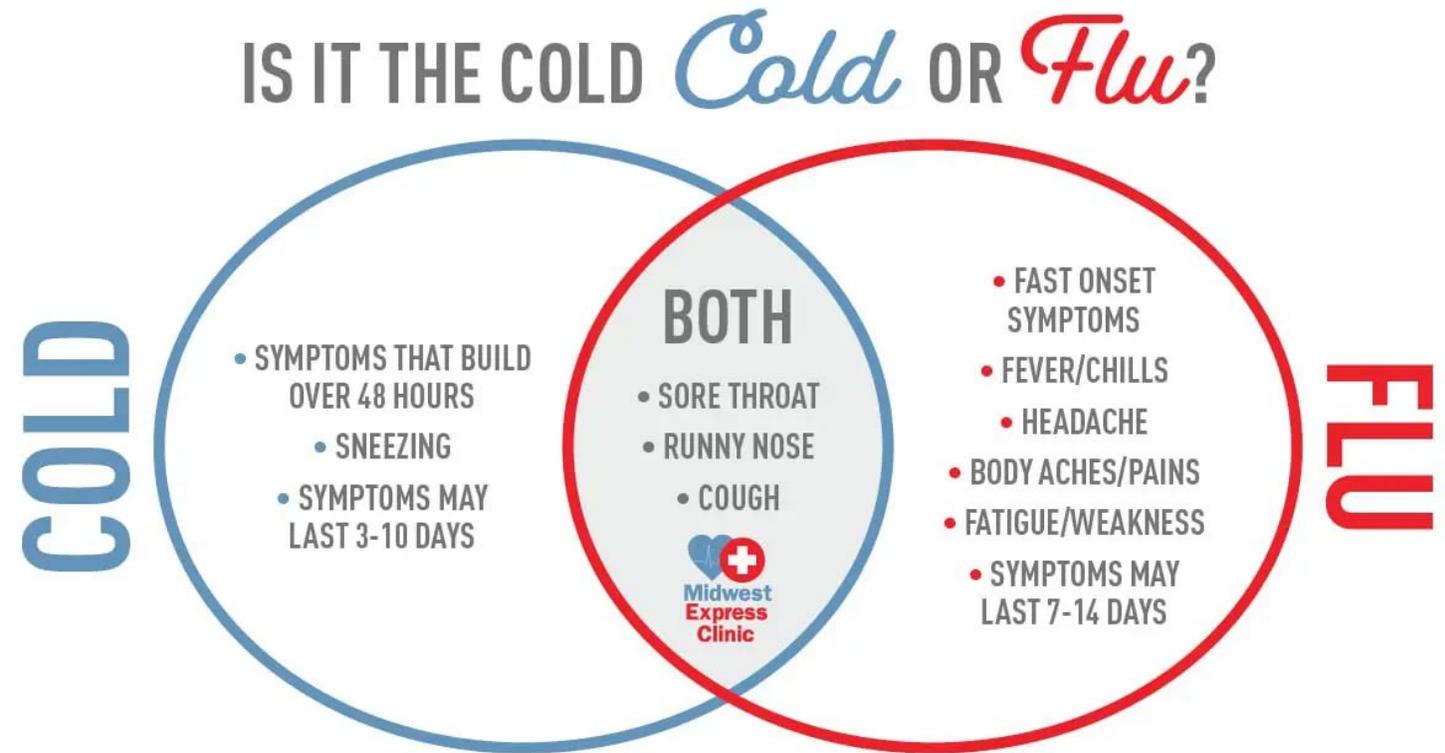
- Flu A has multiple animal reservoirs: birds, pigs, humans. Genome is segmented and undergo **reassortment** when two different strains infect the same cell. This leads to **antigenic shift** with new combinations to which humans have no pre-existing immunity resulting in pandemics
- Flu B almost exclusively human virus without significant animal reservoir. Antigenic drift only causing seasonal epidemics, not pandemics
- Flu C infects URT only with limited replication efficiency and weak innate immune activation resulting in common cold





Flu vs. coryza

Feature	Flu	Coryza (common cold)
Onset	Sudden	Gradual
Fever	High, common	Rare / low
Myalgia	Prominent	Mild / absent
Fatigue	Severe	Mild
Headache	Common	Uncommon
Nasal symptoms	Mild	Prominent
Sneezing	Rare	Common
Severity	Moderate–severe	Mild

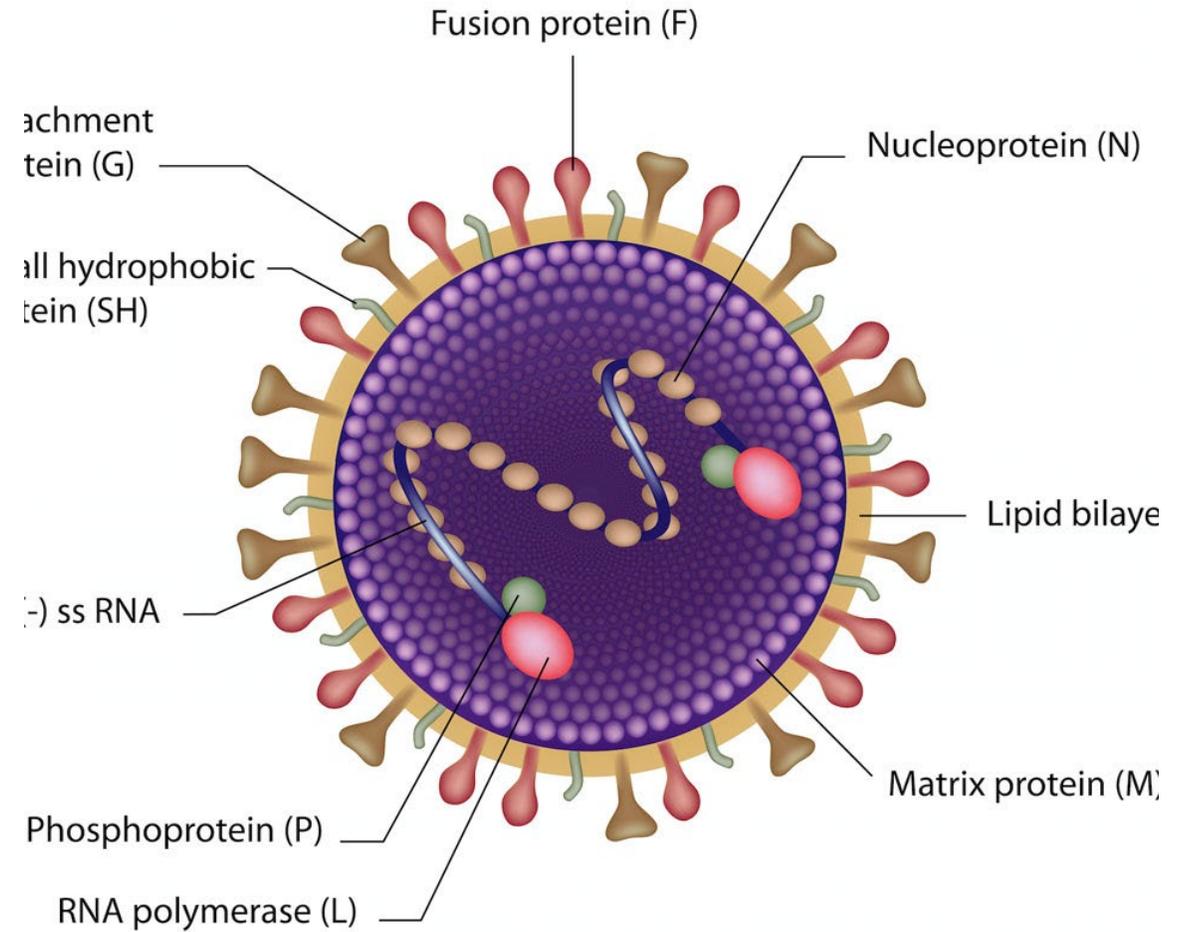




Respiratory Syncytial Virus (RSV)

- Enveloped negative-sense single-stranded non-segmented RNA virus
- Part of the *Paramyxoviridae* family with a F (fusion) protein that causes cell fusion and syncytia formation
- Two major subtypes: A and B
- Leading cause of bronchiolitis and pneumonia in infants
- Causes severe disease in elderly and immunocompromised
- Major cause of hospitalization in infants <1 year

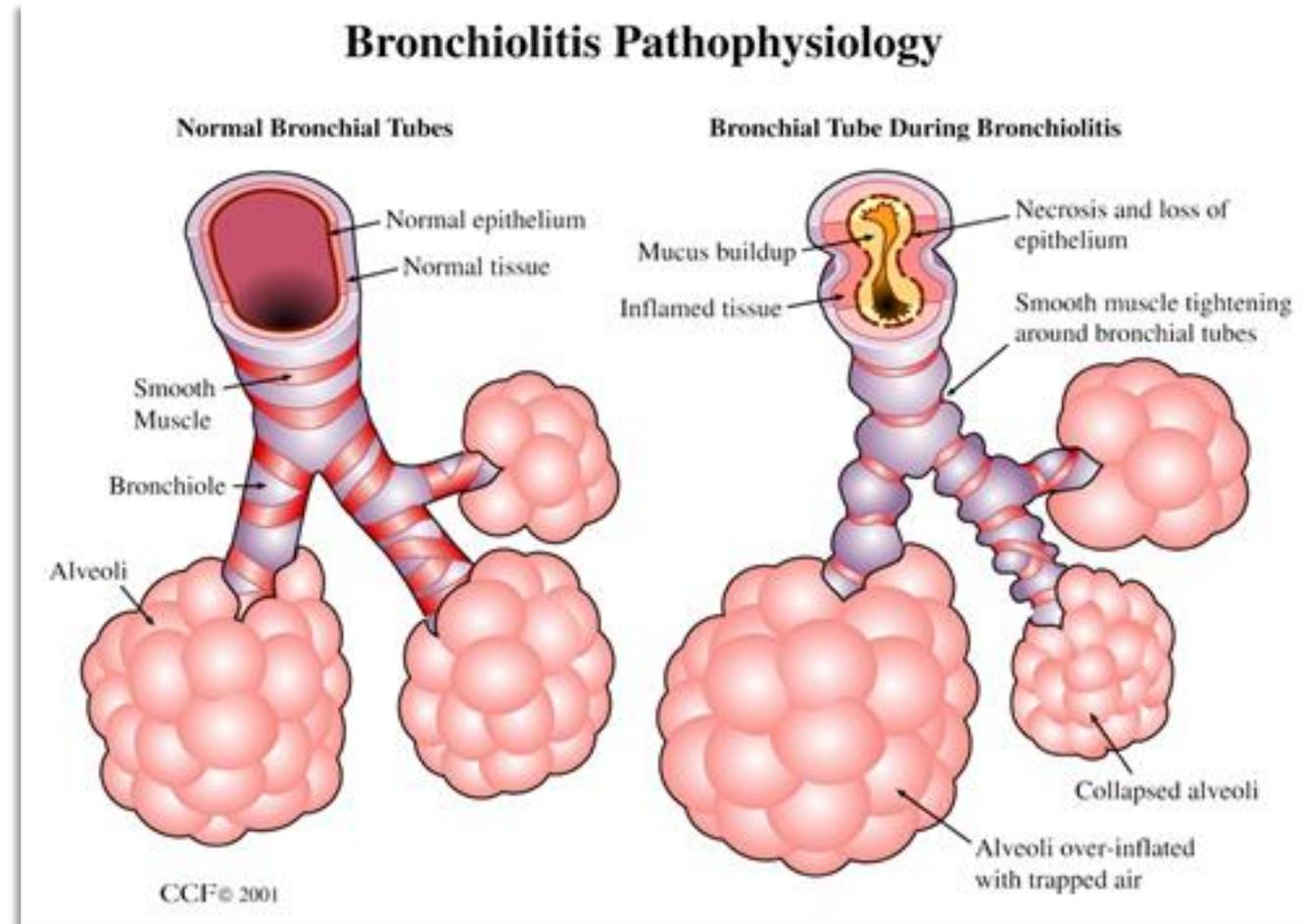
Respiratory Syncytial Virus





RSV pathogenesis

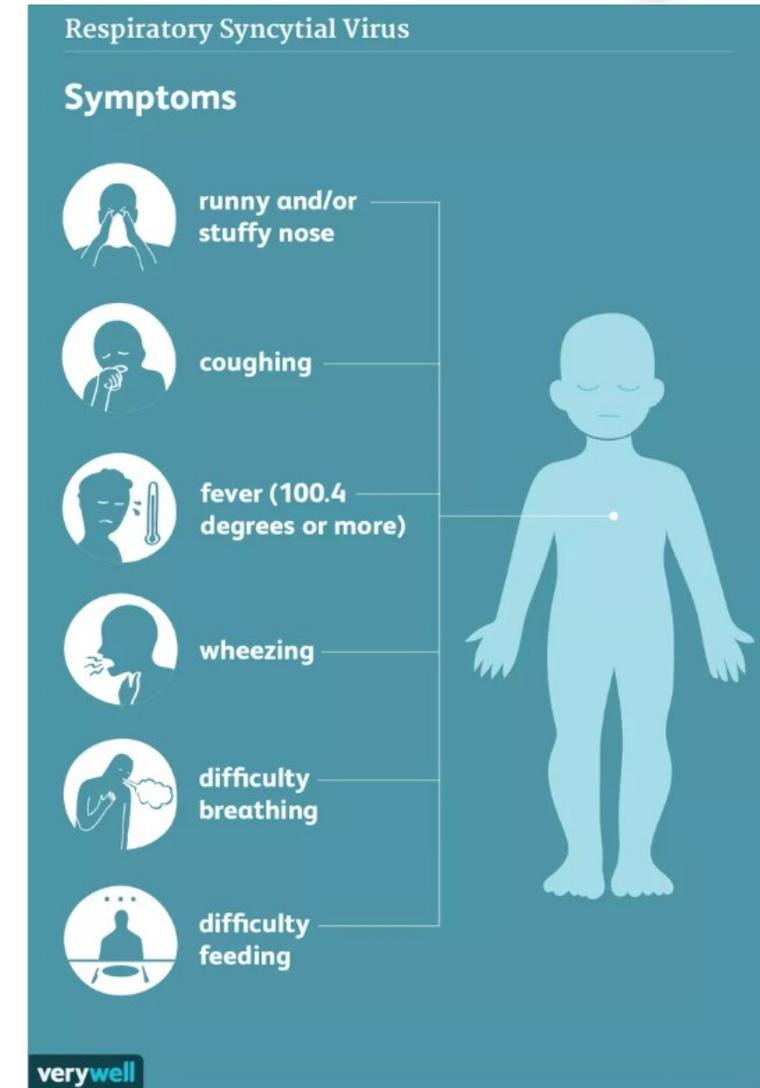
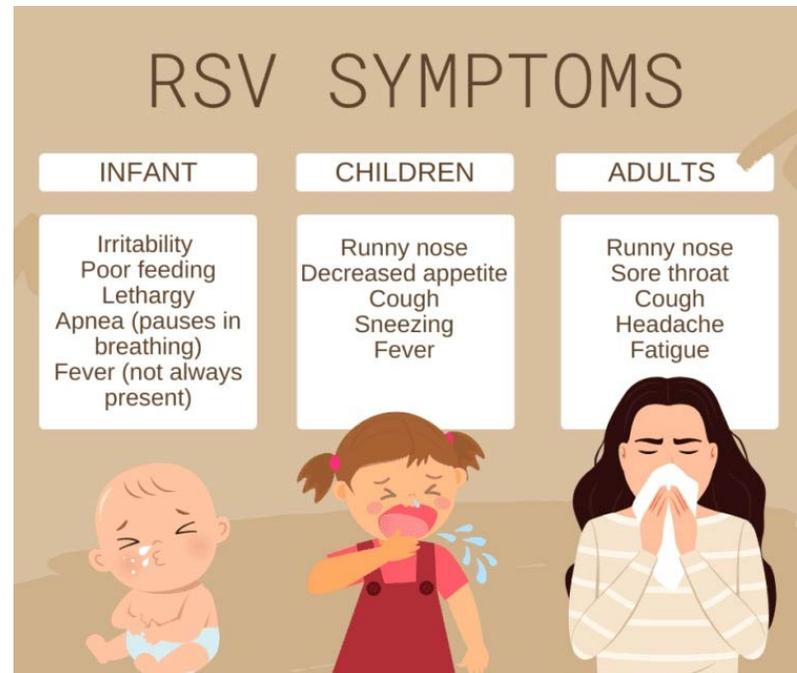
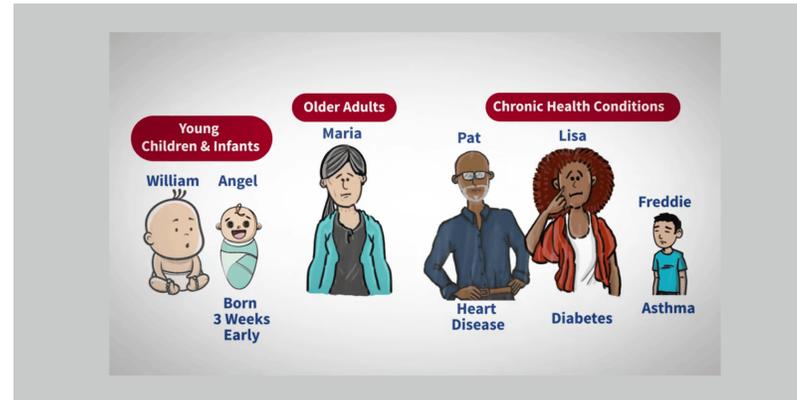
- RSV infects bronchiolar epithelial cells causing cell necrosis and sloughing.
- Inflammation, edema, and increased mucus production leads to narrowed small airways, air trapping leading to atelectasis and V/Q mismatch and finally hypoxia.
- This is most severe in infants with small airway diameter.





RSV clinical features

- Clinical features include rhinorrhea, cough, low-grade fever tachypnea, wheezing, chest retractions, nasal flaring
- In young infants apnea, poor feeding, dehydration. Markers of severe disease include hypoxia, cyanosis, respiratory failure.
- High-risk groups: Premature infants, congenital heart disease, chronic lung disease, and immunocompromised.





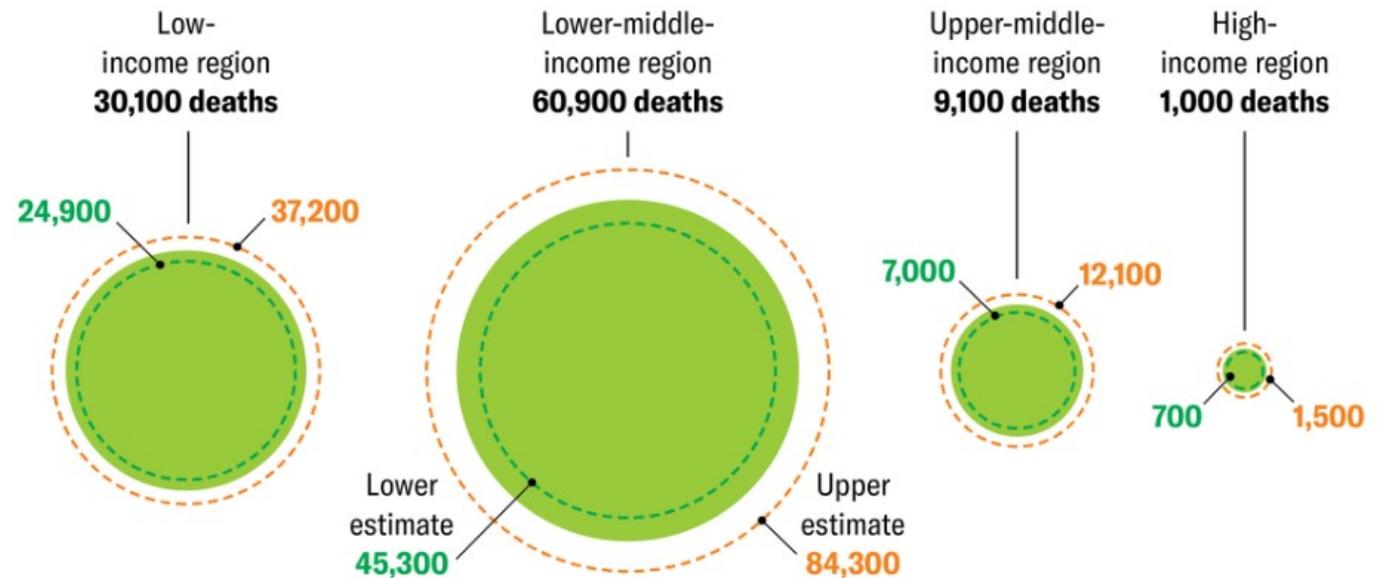
RSV Epidemiology based on the WHO



- RSV is one of the most common causes of acute LRTIs in children globally with substantial burden of severe respiratory disease among elderly persons.
- Each year RSV causes over 3.6 million hospitalizations and about 100,000 deaths in children under 5 years of age. Most pediatric RSV deaths (97%) occur in low- and middle-income countries where there is limited access to supportive medical care.
- Reinfection is common throughout life due to incomplete and short-lived immunity

Deaths Attributable to RSV in Children under Age Five

RSV kills around 100,000 children under age five globally each year. Of these deaths, 90 percent are in low- or lower-middle-income countries. Data below are from 2019, broken down by World Bank income region. Numbers are rounded to the nearest hundred.



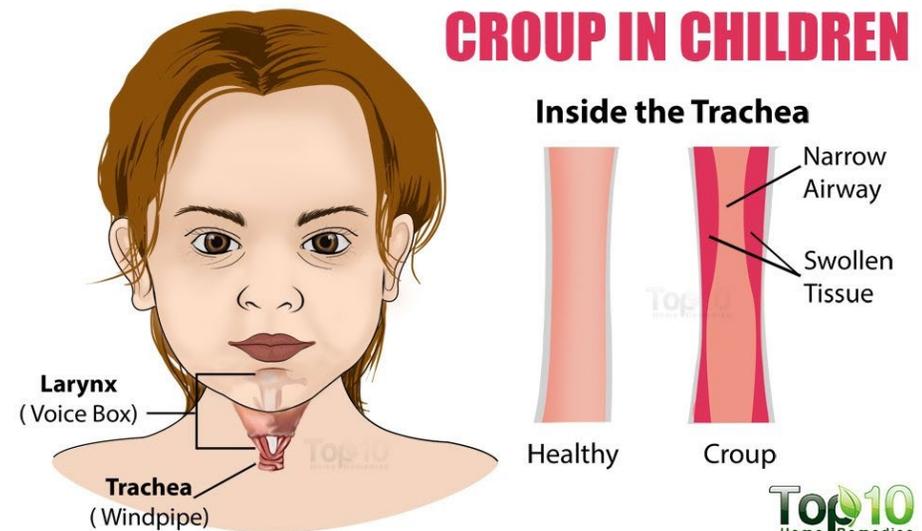
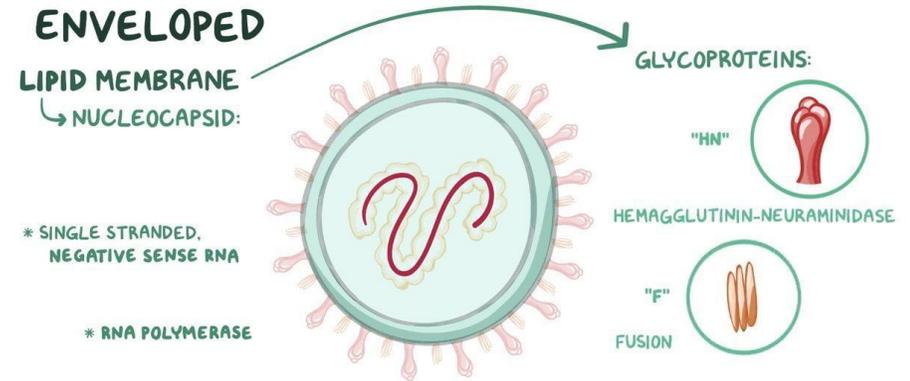
Miriam Quick and Jen Christiansen; Source: "Global, Regional, and National Disease Burden Estimates of Acute Lower Respiratory Infections Due to Respiratory Syncytial Virus in Children Younger Than 5 Years in 2019: A Systematic Analysis," by You Li et al., in *Lancet*, Vol. 399, No. 10340; May 28, 2022 (data)



Parainfluenza viruses (PIVs)



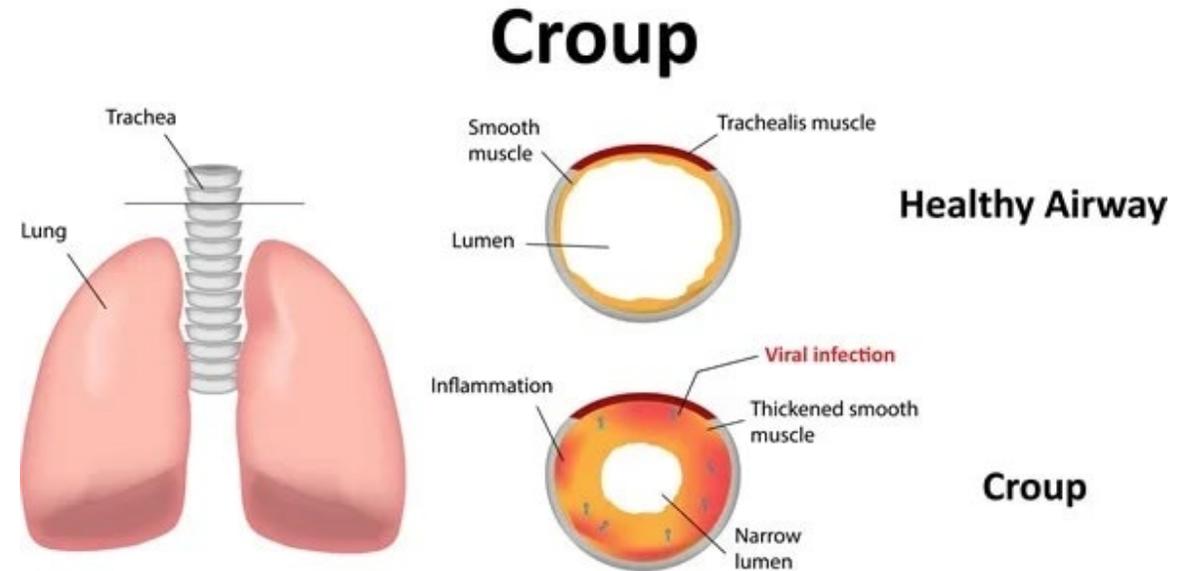
- *Paramyxoviridae* family member (i.e., enveloped, non-segmented negative-sense ssRNA)
- HN glycoprotein combines hemagglutinin and neuraminidase
- PIV-1: Croup (most common cause)
- PIV-2: Croup
- PIV-3: Bronchiolitis & pneumonia
- PIV-4: Mild URTI
- Croup: barking cough, **hoarseness, inspiratory stridor**. Mainly affects infants and young children. Usually self-limited, but may cause hospitalization



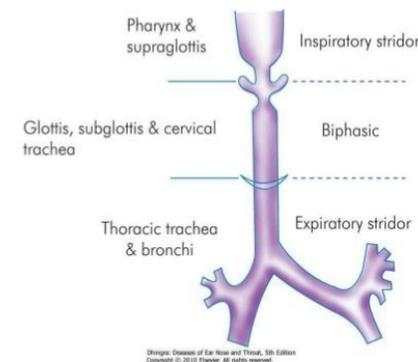


PIVs pathogenesis

- PIVs infects upper airway epithelium in the larynx, trachea, bronchi and causes mucosal inflammation and edema. Narrow pediatric airway leads to critical airflow limitation and leads to laryngotracheobronchitis (croup)
- Croup (PIV-1 and PIV-2): Barking cough, **inspiratory stridor**, **hoarseness**. Worse at night; improves with humidified air



TYPES OF STRIDOR





Adenoviruses

- Non-enveloped, ds DNA virus.
- Very stable in the environment (i.e., adenoviruses survive on surfaces for a long time)
- >50 serotypes with a wide range of clinical syndromes
- Transmitted by respiratory droplets, fomites
- Causes pharyngitis, pharyngoconjunctival fever, and pneumonia classically in military recruits which can be severe.

Table 1 Adenoviral respiratory clinical syndromes and associated serotypes

Clinical syndrome	Frequently isolated adenovirus serotype ^a
Upper respiratory tract infection	1, 2, 3, 5, 7
Lower respiratory tract infection	3, 4, 7, 14, 21, 35
Pharyngoconjunctival fever	2, 3, 4, 7, 14
Epidemic keratoconjunctivitis	3, 8, 19, 37

^a All serotypes listed are those that have been identified in each clinical syndrome; serotypes in **bold** are the most commonly isolated serotypes

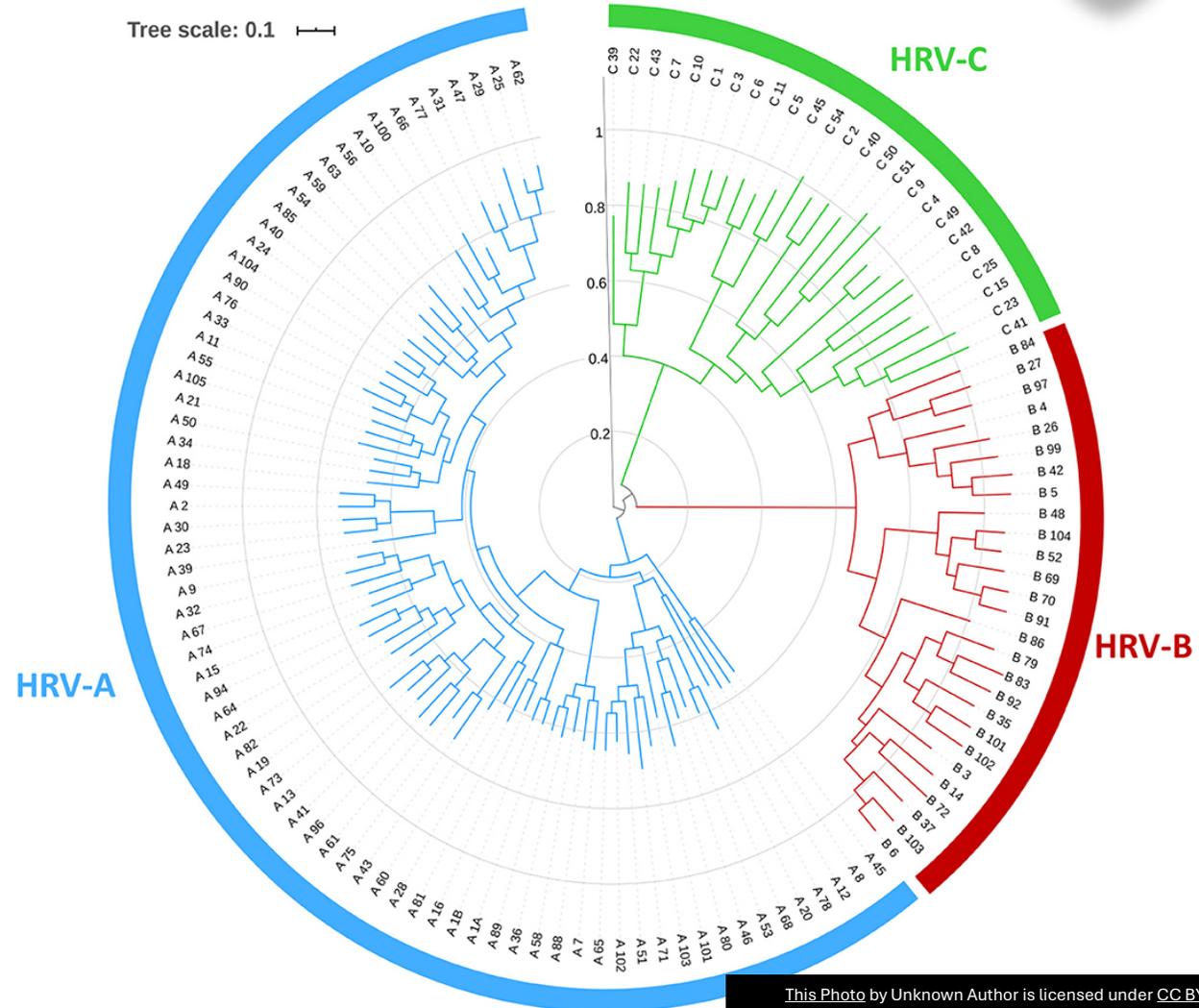
Source: Kunz, Anjali N, and Martin Ottolini. "The role of adenovirus in respiratory tract infections." Current infectious disease reports vol. 12,2 (2010): 81-7.



Rhinoviruses



- Members of the *Picornaviridae* family. Non-enveloped, positive-sense ssRNA virus >150 serotypes explaining why reinfection is common. Optimal replication at 33-35 °C explaining URT tropism
- Most common cause of the common cold (coryza). Symptoms include nasal congestion, rhinorrhea, sneezing, mild sore throat.
- Major trigger of asthma exacerbations and can worsen COPD



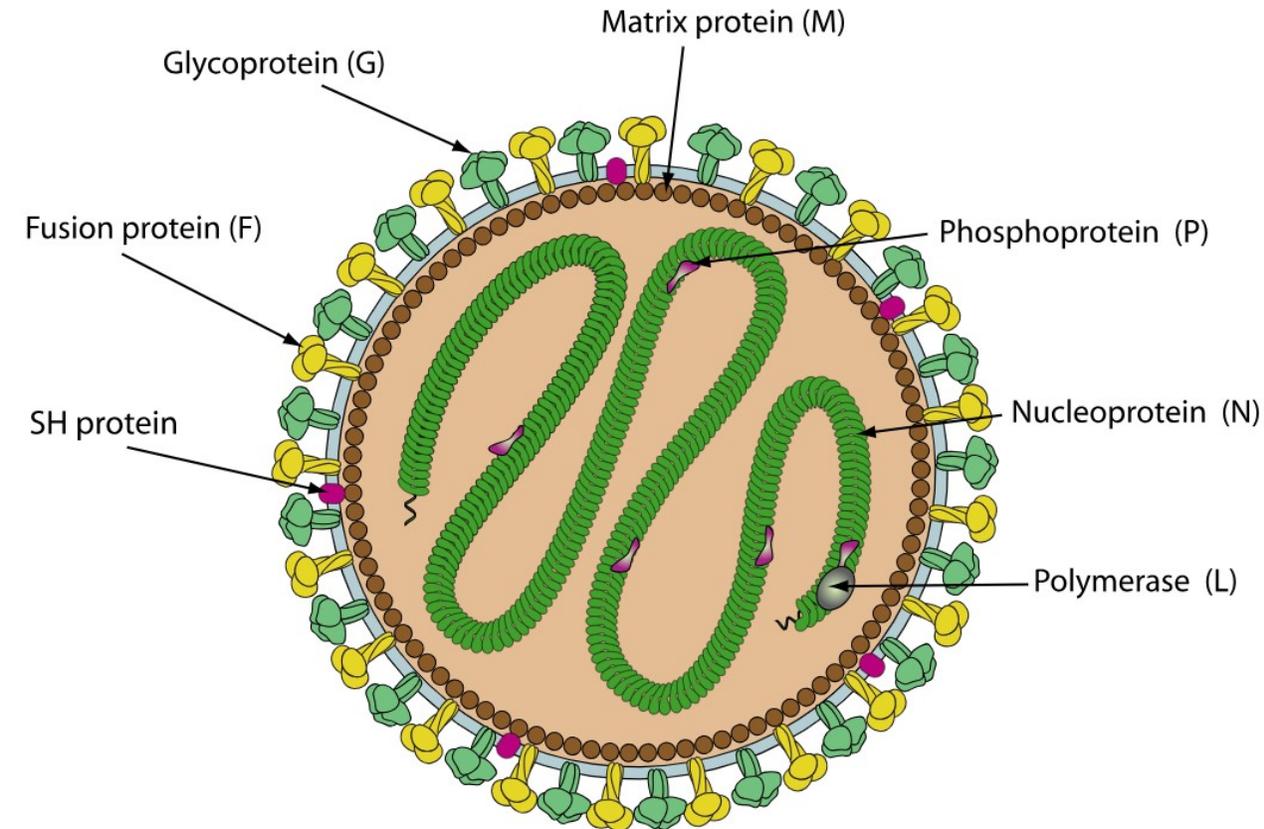


Human Metapneumovirus (hMPV)



- Enveloped, negative-sense single-stranded RNA virus (*Paramyxoviridae* family; *Pneumovirinae* subfamily).
- Seasonal (late winter-spring); most children infected by age 5
- Mild URTI: coryza
- Severe LRTI: bronchiolitis, pneumonia (especially infants, elderly, immunocompromised). Clinically indistinguishable from RSV

VIRION

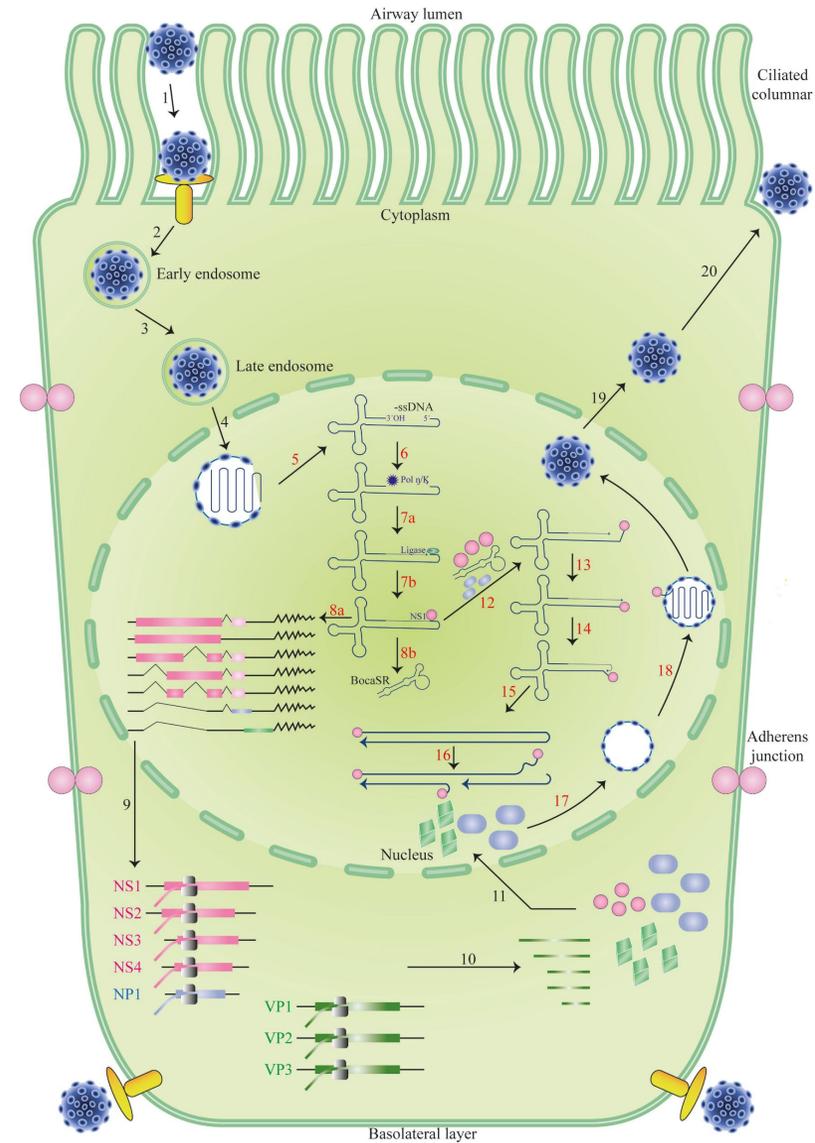


Source: ViralZone is operated by the Swiss-Prot group of the SIB Swiss Institute of Bioinformatics



Human Bocavirus (HBoV)

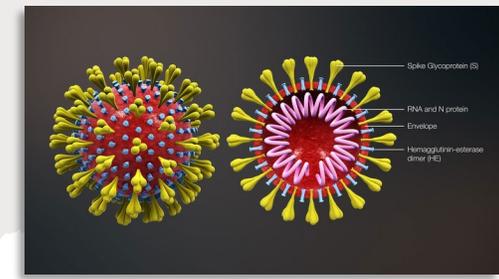
- Small, non-enveloped, single-stranded DNA virus (*Parvoviridae* family; *Bocaparvovirus* genus)
- URTI: coryza
- LRTI: bronchiolitis, pneumonia, asthma exacerbations
- Infects respiratory epithelium; prolonged viral shedding; therefore, the detection of HBoV does not always imply causation with frequent co-detection with RSV, hMPV, adenovirus



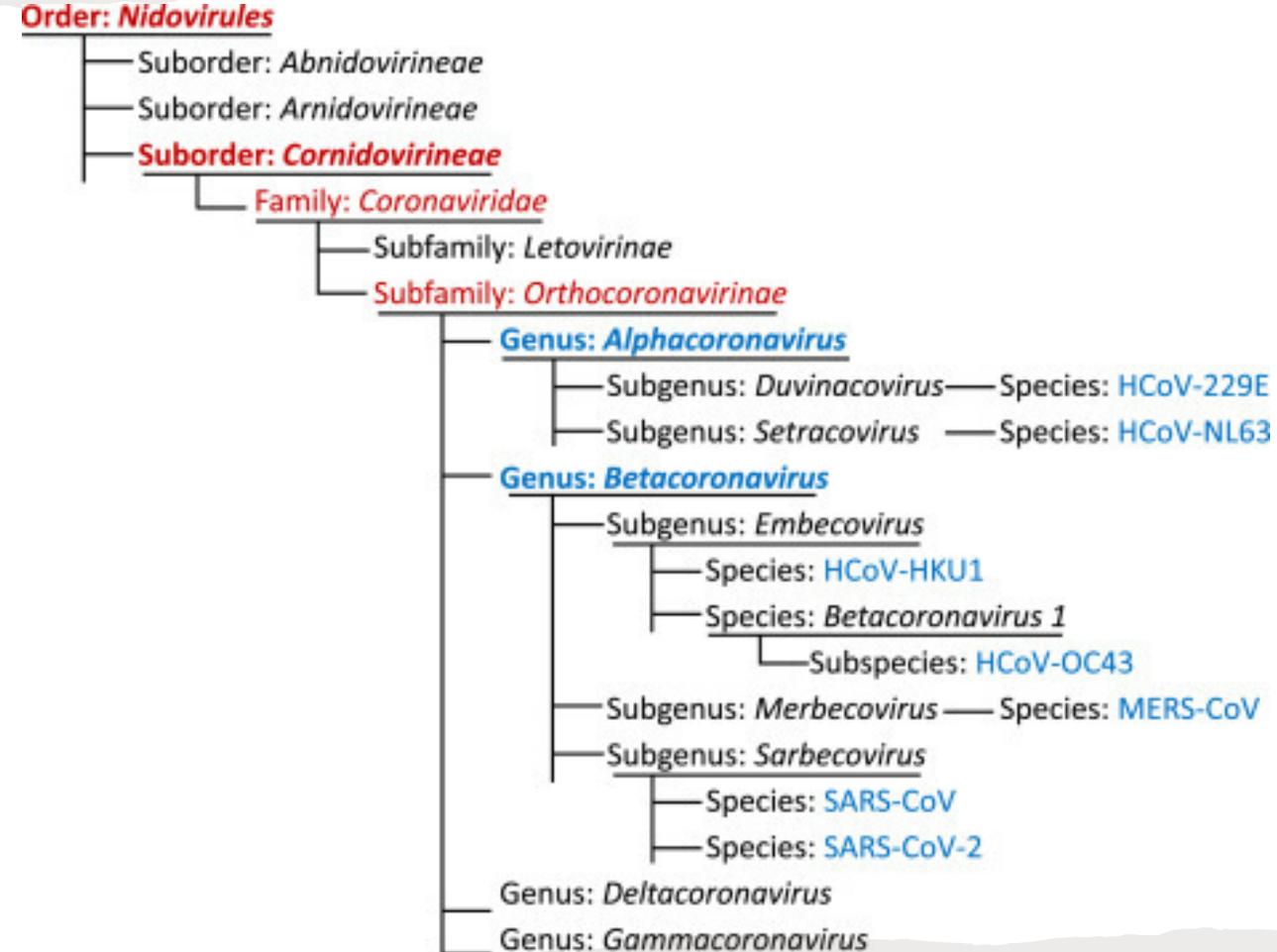
Source: Mohammadi M (2023) HBoV-1: virus structure, genomic features, life cycle, pathogenesis, epidemiology, diagnosis and clinical manifestations. *Front. Cell. Infect. Microbiol.* 13:1198127.



Human Coronaviruses



- Enveloped, (+) ssRNA viruses that belong to *Coronaviridae* family
- Main human strains: 229E, NL63, OC43, and HKU1
- Worldwide distribution with seasonal peaks during winter. Reinfections are common due to short-lived immunity
- The second most common cause of common cold / mild URTI



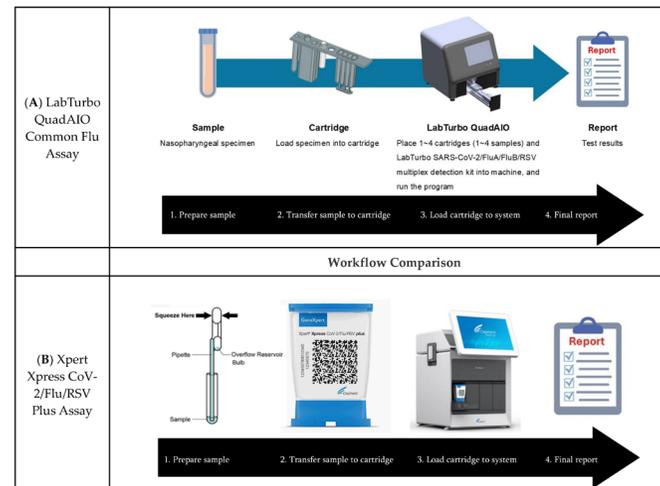
Source: Liu, Ding X. et al. "Human Coronavirus-229E, -OC43, -NL63, and -HKU1 (Coronaviridae)." Encyclopedia of Virology (2021): 428–440.



Diagnosis of viral RTIs

- Molecular testing by multiplex-PCR can yield definitive diagnosis
- Widely used in hospital settings with rapid turnaround
- Antigen detection such as rapid influenza antigen tests. Fast but variable sensitivity. RSV antigen tests: Useful in infants and young children
- **During epidemics, clinical diagnosis alone may be sufficient**

Source: Tai C-S, Jian M-J, Lin T-H, Chung H-Y, Chang C-K, Perng C-L, Hsieh P-S, Shang H-S. Diagnostic Accuracy of the LabTurbo QuadAIO Common Flu Assay for Detecting Influenza A Virus, Influenza B Virus, RSV, and SARS-CoV-2. *Diagnostics*. 2024; 14(19):2200.



Accuracy Data for the BioFire RP2.1 Test Extrapolated From 2018 and 2022 Multicenter Clinical Studies

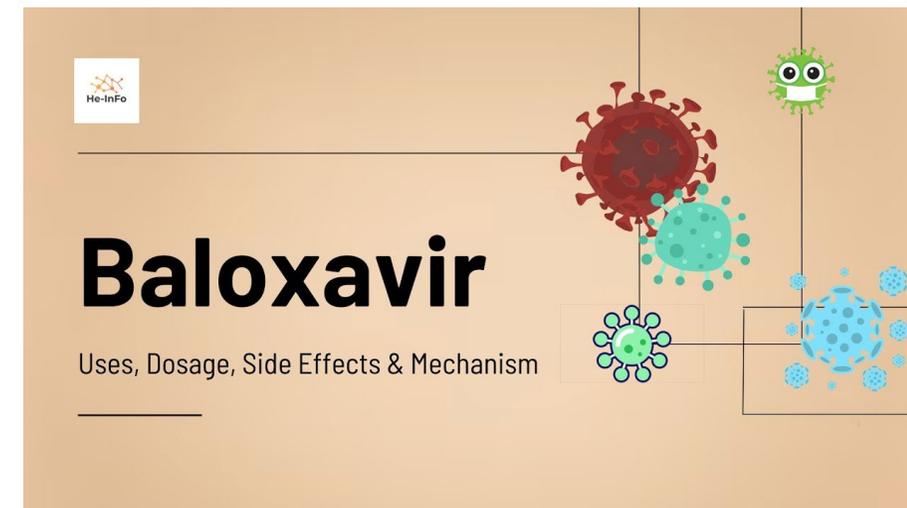
Pathogen	No. detected	Sensitivity (%)	Specificity (%)	LR+	LR-
Viruses					
Adenovirus	118	94.6	96.9	30.5	0.06
Coronavirus HKU1	16	100	99.2	125.0	0.00
Coronavirus NL63	50	100	99.4	166.7	0.00
Coronavirus 229E	16	91.7	99.7	305.7	0.08
Coronavirus OC43	38	80.5	99.7	268.3	0.20
MERS-CoV	0	NA	100	NA	NA
SARS-CoV-2	524	98.4	98.9	0.0	0.00
Human metapneumovirus	81	97.3	99.5	194.6	0.03
Human rhinovirus/enterovirus	502	97.5	93.5	15.0	0.03
Influenza A	78	100	100	NA	0.00
Influenza A/H1	0	NA	100	NA	NA
Influenza A/H3	4	100	100	NA	0.00
Influenza A/H1-2009	74	100	100	NA	0.00
Influenza B	16	100	99.9	1000.0	0.00
Parainfluenza virus 1	10	100	99.9	1000.0	0.00
Parainfluenza virus 2	54	97.9	99.5	195.8	0.02
Parainfluenza virus 3	53	95.6	99.4	159.3	0.04
Parainfluenza virus 4	16	100	99.6	250.0	0.00
Respiratory syncytial virus	199	99.4	98.3	58.5	0.01

Bacteria					
<i>Bordetella pertussis</i>	3	66.7	99.9	667.0	0.33
<i>B. parapertussis</i>	6	85.7	100	NA	0.14
<i>Chlamydia pneumoniae</i>	6	100	99.9	1000.0	0.00
<i>Mycoplasma pneumoniae</i>	28	95.8	99.7	319.3	0.04



Management of Viral RTIs

- **Supportive care is the cornerstone.**
- Oxygen (if hypoxic), adequate hydration, anti-pyretics / analgesics, respiratory support as needed.
- Antibiotics are not indicated unless bacterial superinfection suspected
- Antivirals for influenza which are indicated for severe or progressive illness and for high-risk patients
- Neuraminidase inhibitors: Oseltamivir, Zanamivir
- Cap-dependent endonuclease inhibitor: Baloxavir





Prevention of Viral RTIs

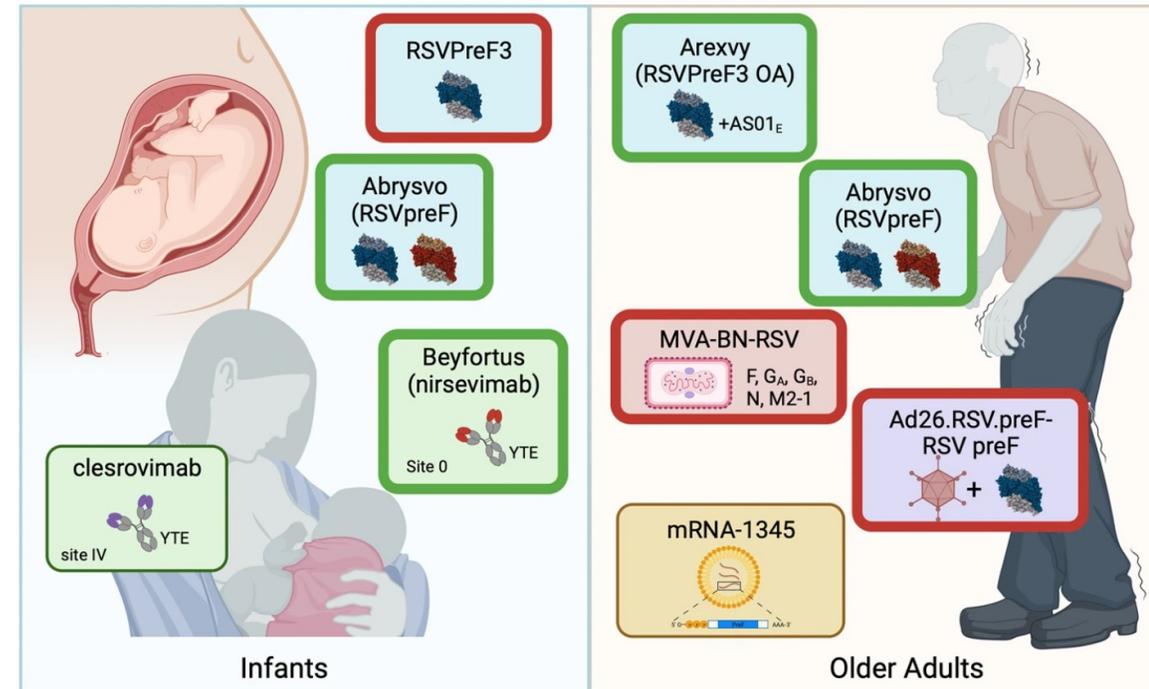


- **Influenza**

- Inactivated influenza vaccine (IIV). Live attenuated influenza vaccine (LAIV) (nasal). Updated annually to match circulating HA/NA strains. The primary strategy for prevention & reduction of complications

- **RSV**

- Maternal RSV immunization (protects newborns). Adult RSV vaccines now licensed.
- Monoclonal antibodies: Nirsevimab and Palivizumab are given to high-risk infants (prematurity, congenital heart disease, chronic lung disease)



Source: Ruckwardt, T.J. The road to approved vaccines for respiratory syncytial virus. npj Vaccines 8, 138 (2023).



Prevention of Viral RTIs



- The live oral adenovirus vaccine for types 4 and 7 is only available for U.S. military personnel and is not available to the general public. It is specifically used to prevent acute respiratory disease outbreaks in military training environments It is a live, oral vaccine.

- **General preventive measures**

- Hand hygiene
- Avoid close contact during outbreaks
- Environmental disinfection
- Droplet and contact precautions in healthcare settings



Article

Live Oral Adenovirus Type 4 and Type 7 Vaccine Induces Durable Antibody Response

Natalie D. Collins ^{1,*}, Anima Adhikari ¹, Yu Yang ¹, Robert A. Kuschner ¹, Nicos Karasavvas ¹, Leonard N. Binn ¹, Shannon D. Walls ¹, Paul C. F. Graf ^{2,3}, Christopher A. Myers ², Richard G. Jarman ¹ and Jun Hang ¹





Thank You!
Wishing you all
the best!
It was a huge
pleasure 😊