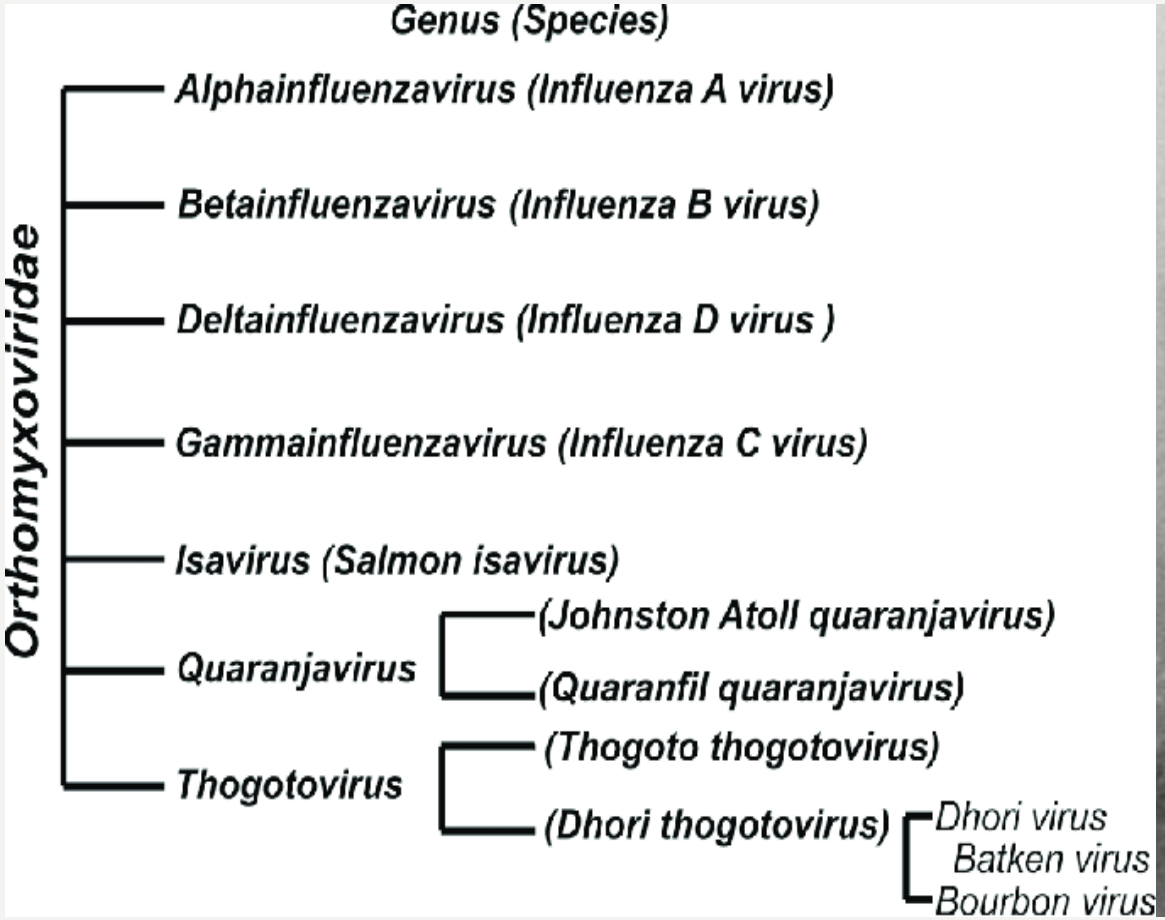
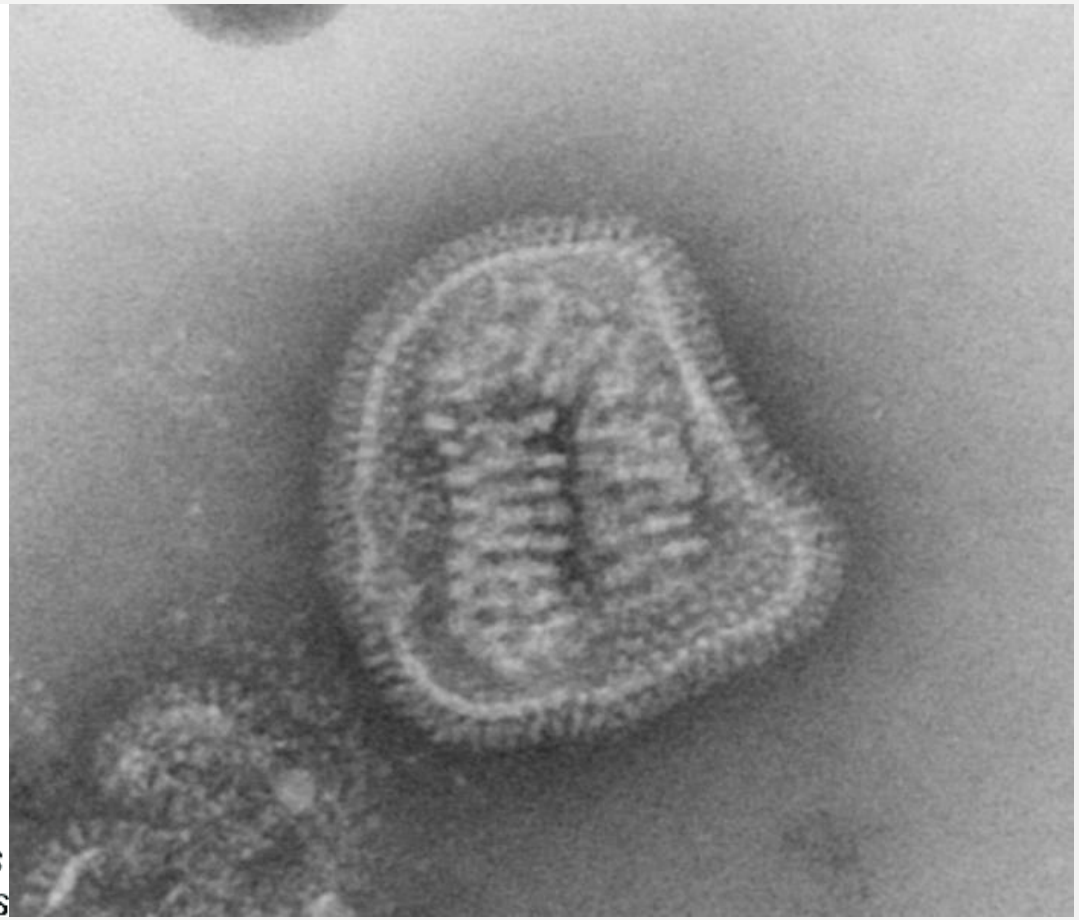
INFLUENZA VIRUS

MARYAM VAEZJALALI

ASSOCIATE PROFESSOR OF MEDICAL VIROLOGY, SHAHID BEHESHTI UNIVERSITY OF MEDICAL SCIENCES

ORTHOMYXOVIRIDAE





ORTHOMYXOVIRIDAE

- Viruses in the first four genera, which are identified by antigenic differences in their nucleoprotein (NP) and matrix (M) proteins, cause influenza disease in vertebrates, including birds, humans, and other mammalian species.
- Alphainfluenzavirus (Influenzavirus A, IAV), Betainfluenzavirus (Influenzavirus B, IBV), and Gammainfluenzavirus (Influenzavirus C, ICV). Influenza D virus (IDV) belongs to genus Deltainfluenzavirus.
- Influenza viruses of distinct types (A, B, C, or D) exhibit variations in genome structure, properties of surface glycoproteins, and the antigenicity of the viral nucleoprotein and matrix protein.

THE VIRUS

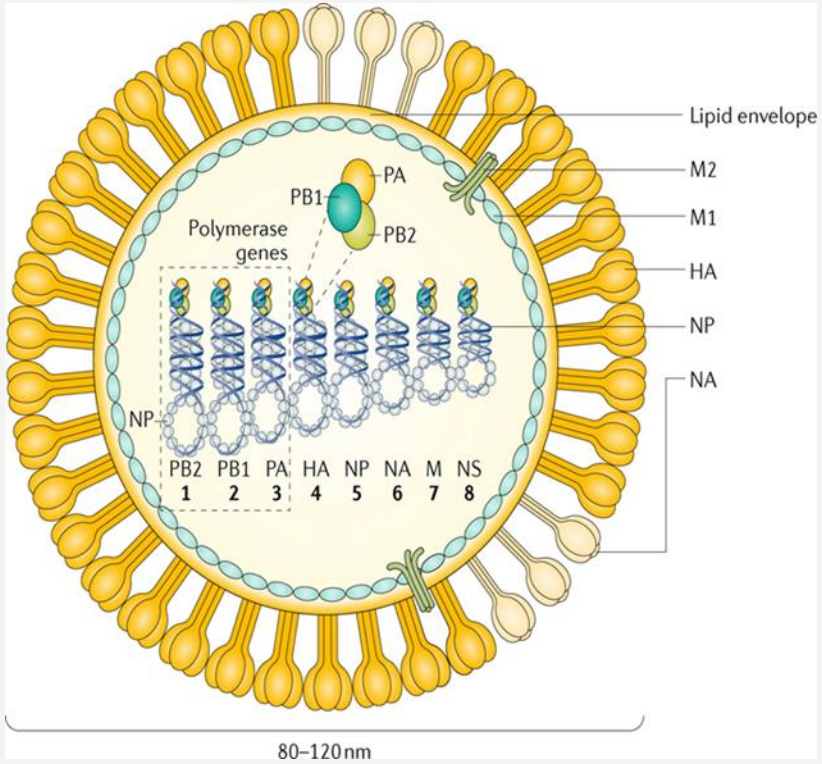
- Influenza viruses are spherical and 80 to 120 nm in diameter, although filamentous forms may also occur.

- The antisense RNA genome occurs in eight separate segments containing 10 genes. The segments are complexed with nucleoprotein to form a nucleocapsid with helical symmetry. The nucleocapsid is enclosed in an envelope consisting of a lipid bilayer and two surface glycoproteins, a hemagglutinin and a neuraminidase.

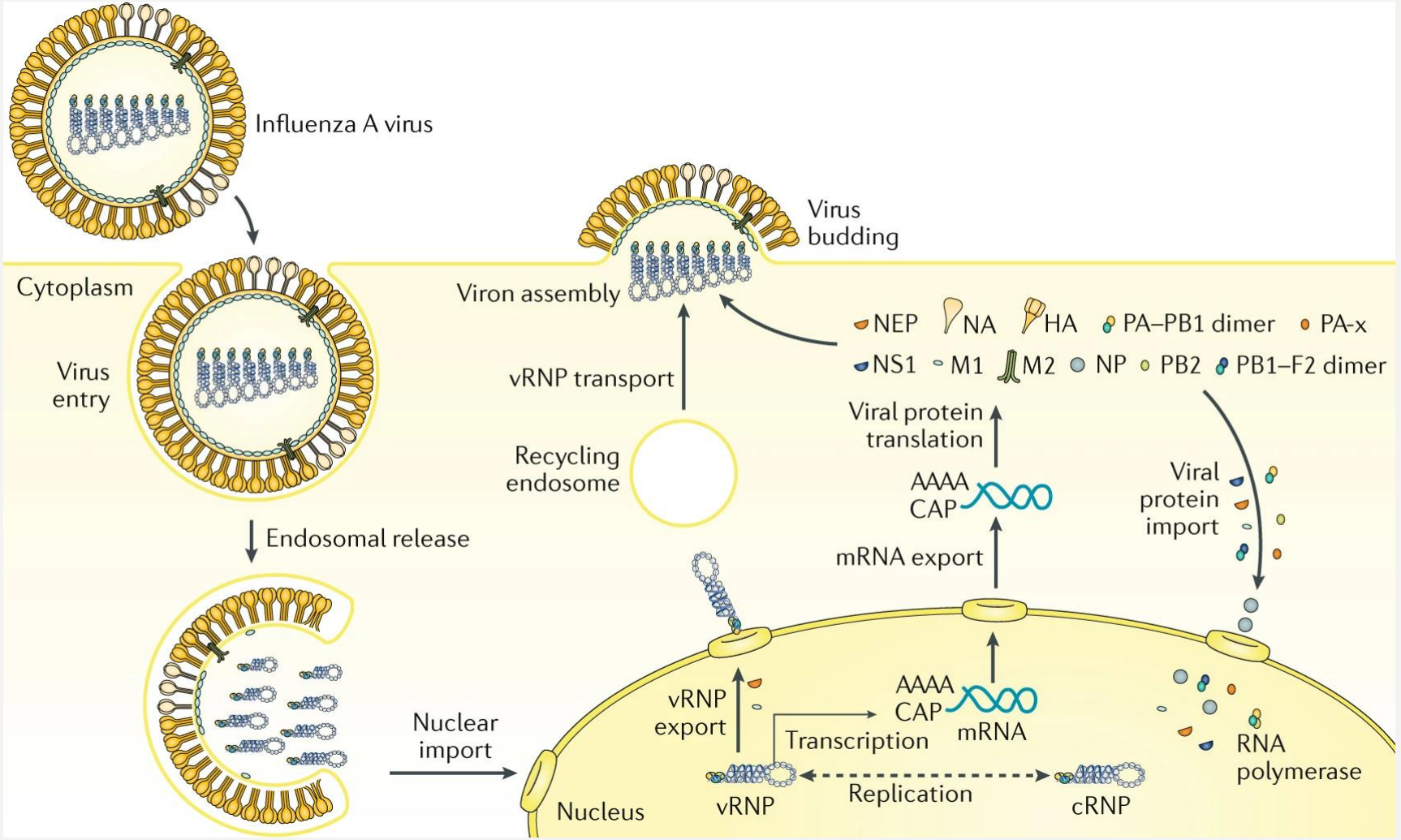
STRUCTURE

- enveloped
- negative-sense single-strand RNA viruses with a segmented genome.
  - Influenza A and influenza B viruses contain eight RNA segments,
  - Influenza C and influenza D viruses contain seven RNA segments

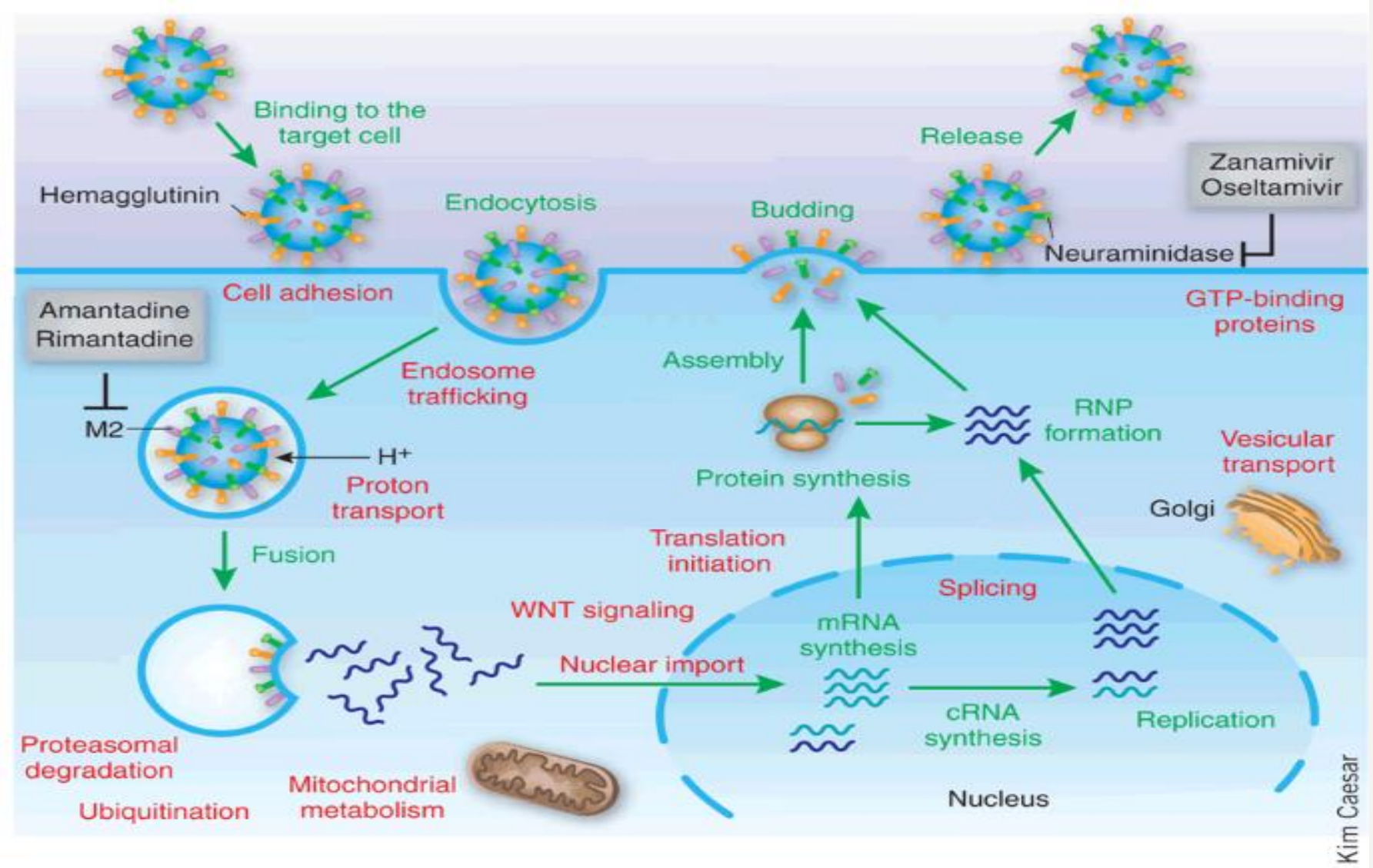
- Gene products:
  - RNA polymerase subunits,
  - viral glycoproteins (namely, haemagglutinin (HA), with its distinct globular 'head' and 'stalk' structures, which facilitate viral entry,
  - neuraminidase (NA), which facilitates viral release),
  - viral nucleoprotein (NP),
  - matrix protein (M1)
  - membrane protein (M2),
  - nonstructural protein NS1.



INFLUENZA VIRUS REPLICATION

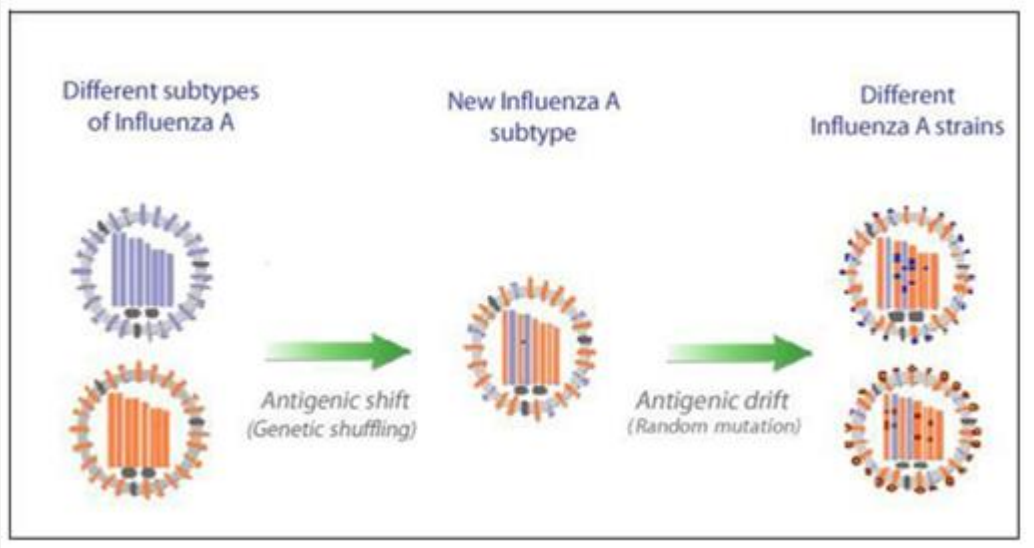


INFLUENZA VIRUS REPLICATION



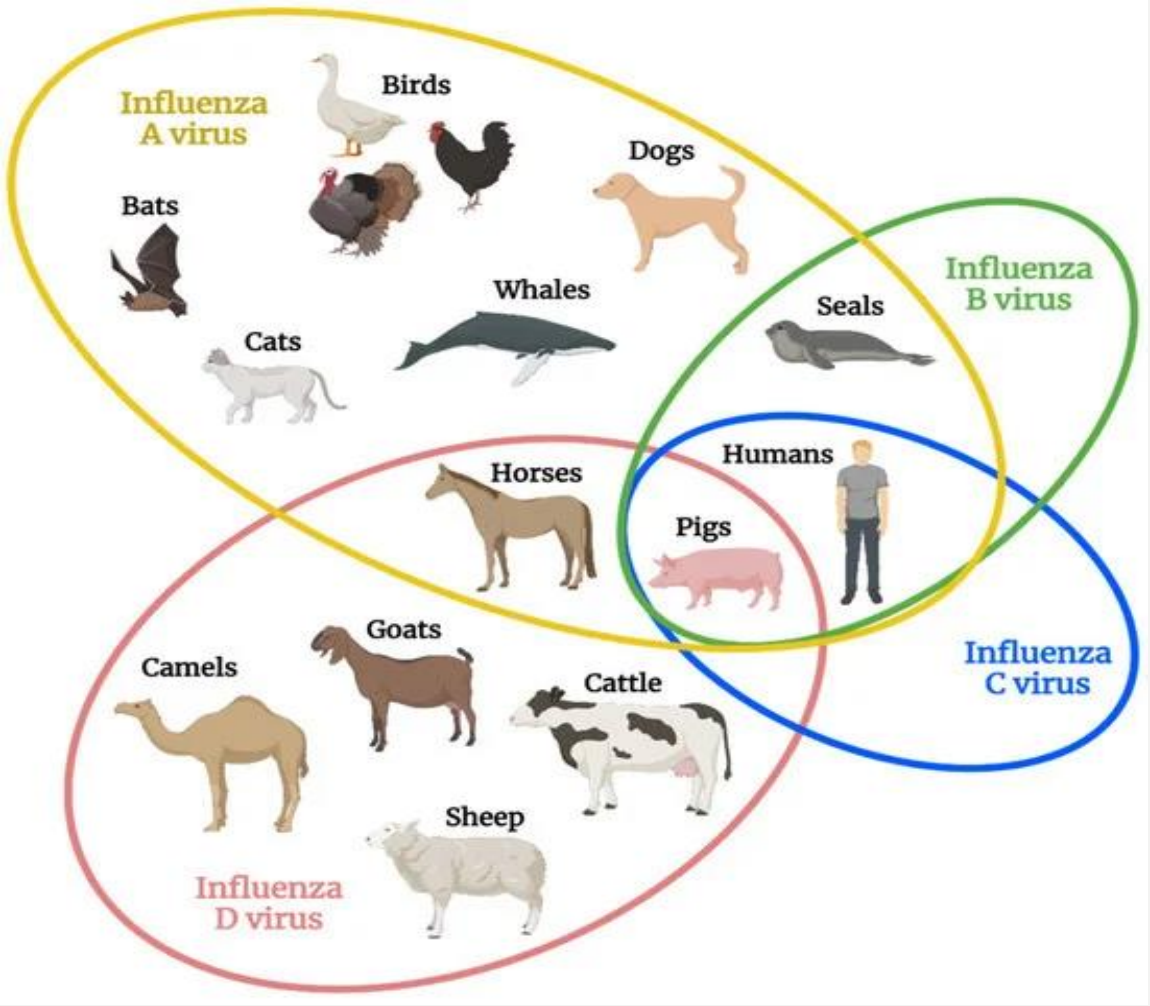
ANTIGENIC SHIFT & DRIFT

- Eight segmented pieces of RNA, a structure that permits the introduction of new RNA. This is called genetic reassortment. This is called antigenic shift.
- The hemagglutinin spikes which provide viral attachment to cell membranes. They are strain specific antigens that mutate frequently because of inefficient proofreading by RNA polymerase. This is called antigenic drift.
- Antigenic shifts are associated with the epidemics and pandemics of influenza A, whereas antigenic drifts are responsible for more localized outbreaks of varying extent.



DIFFERENT TYPES OF INFLUENZA VIRUSES

Influenza viruses belonging to different types also display differing host ranges.

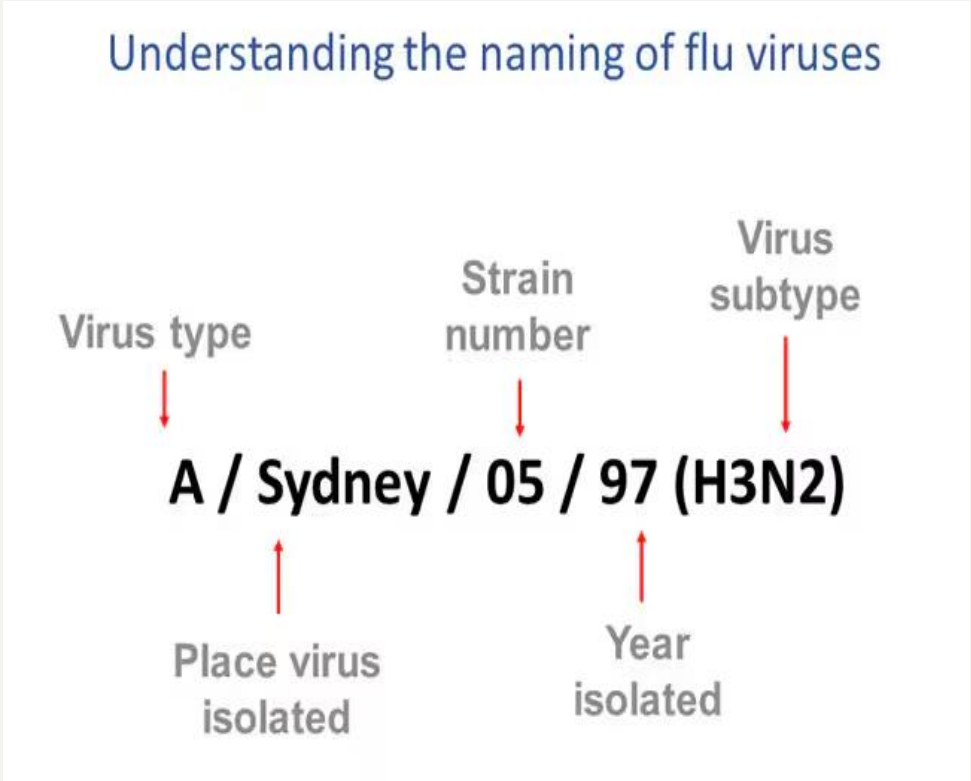


DIFFERENT TYPES OF INFLUENZA VIRUS

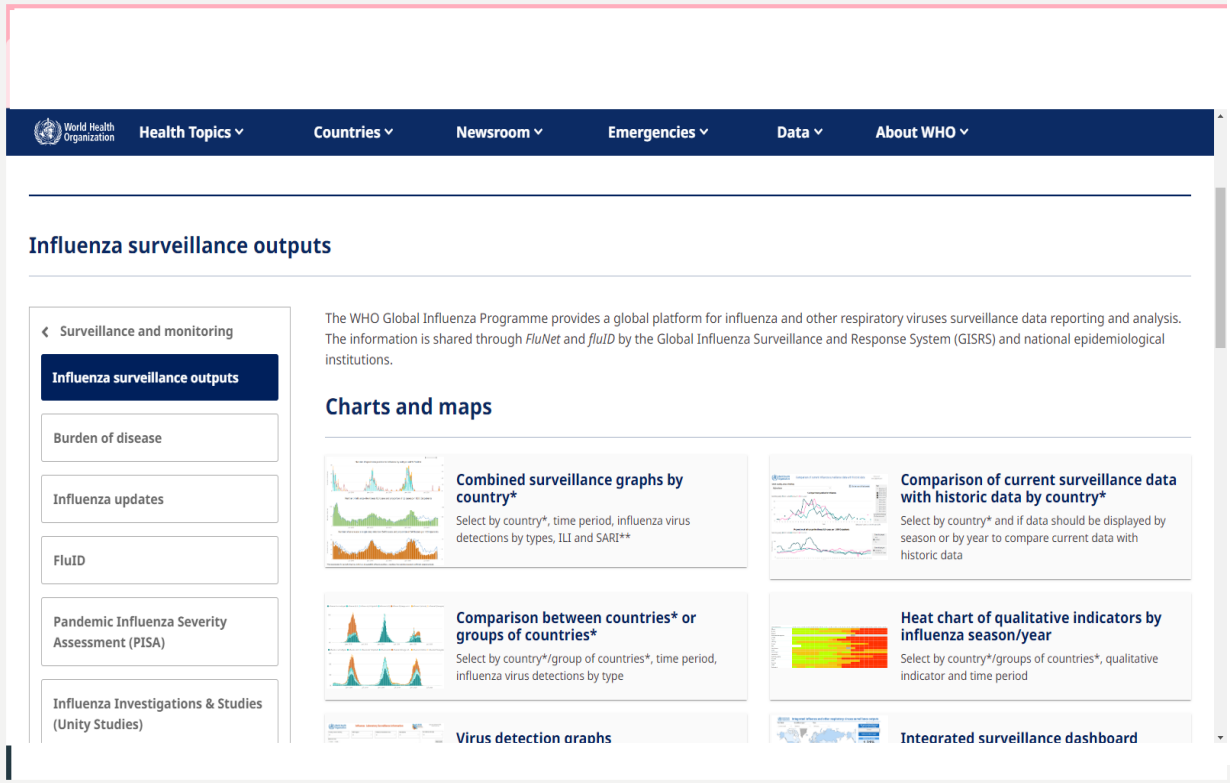
- For influenza type A, at least 18 highly variable hemagglutinins (H1 to H18) and 11 distinct NAs (N1 to N11) have been recognized so far. With the aid of these different antigens, the influenza type A virus is further subdivided into subtypes on the basis of variable combination patterns of their own specific H or N proteins (e.g., H1N1 or H3N2). Nonetheless, in the nomenclature of the viruses, other variables such as the place of initial isolation and the year of isolation are included.
- influenza B are mostly restricted to the human host, but they can also infect pigs and seals.
- Humans and pigs are the only known hosts for ICV.
- Influenza D virus naturally infects cattle, pigs, horses, and other ruminants around the world such as camels, goats, and sheep.

NAMING INFLUENZA VIRUSES

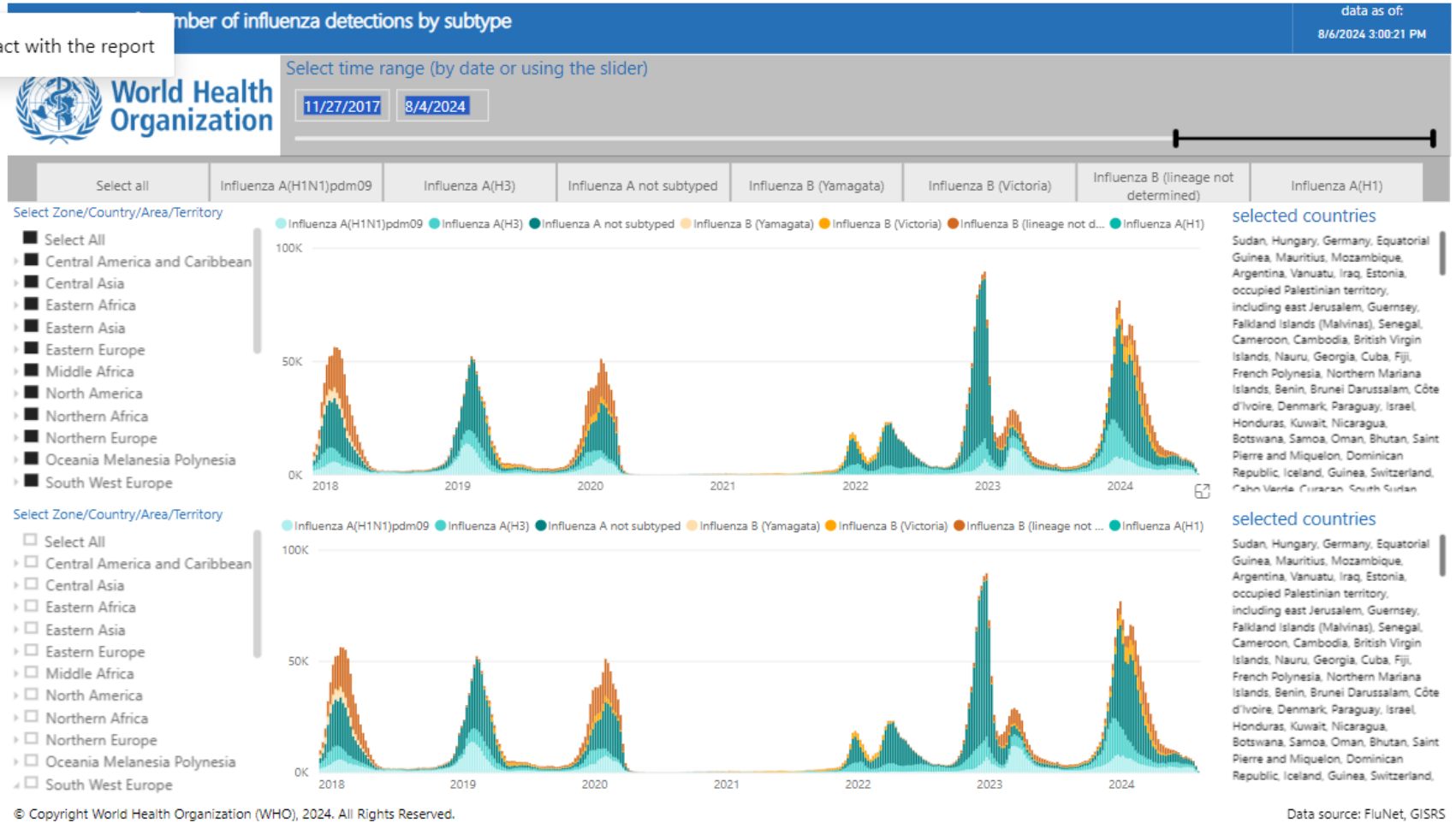
- The HA and NA viral proteins are the most antigenically variable, and in the case of influenza A virus, they are classified into antigenically diverse subtypes.



GLOBAL INFLUENZA PROGRAMME



Press Ctrl + Enter to interact with the report



EPIDEMIOLOGY

- Influenza A viruses
  - Common pathogens of horses, swine, humans, and domestic poultry throughout much of the world, but they also are the cause of sporadic or geographically limited infections and disease in mink, seals, whales, and dogs.
  - The main subtypes of influenza based on pathogenesis and epidemiology aspects include H1N1, H5N1, H3N2, H7N7 and H9N2.
  - Currently circulating influenza A(H1N1) viruses are related to the pandemic 2009 H1N1 virus that emerged in the spring of 2009 and caused a flu pandemic. Of all the influenza viruses that routinely circulate and cause illness in people, influenza A(H3N2) viruses tend to change more rapidly, both genetically and antigenically.
  - Influenza A(H3N2) viruses have formed many separate, genetically different clades in recent years that continue to co-circulate.

EPIDEMIOLOGY

- Influenza A viruses
  - In 2019, 2977 patients from Mashahd (3% outpatients vs. 97% hospitalized) with flu like syndrome were tested by RT-PCR for influenza. Out of 84 outpatients, only two cases were positive for influenza. Among hospitalized patients, 80 cases (51% male vs. 49% female; age range: 1 - 87 years) had a positive RT-PCR test, and influenza type A was seen in 95% of cases.
    - Pneumonia was the most common complication. Death happened in 29 (35.36%) patients and three (33.33%) cases with risk factors. The highest number of influenza patients had been reported from crowded place and near the holy shrine.
    - The results showed a high prevalence of complication and death among hospitalized patients, especially among those who did not have a risk factor for influenza viruses. Comprehensive vaccination programs and promotion of knowledge about transmission routes are two important measures for disease prevention and lower death rates.

EPIDEMIOLOGY

- Influenza A viruses
  - Among 204 positive results in Fars Province (2015–2019), 191 (15.05%) were influenza type A, and 8 (0.63%) influenza type B. Among patients with definite influenza type A, 34 (2.68%) had H1N1/p subtype, 58 (4.57%) H3N2, and one (0.08%) had other subtypes; however, subtypes were not identified in 7.72% of patients.
  - The incidence of influenza at the two ends of the age range may be due to a weak immune system; these two age groups need more surveillance and follow-up during an outbreak.
  - From August 2022 to December 2022, Hormozgan province in the south of Iran witnessed an influenza peak with an increase in the prevalence of H1N1 and H3N2 subtypes.

EPIDEMIOLOGY

- Influenza A viruses
  - In a Systematic Review of Influenza Epidemiology and Surveillance in the Eastern Mediterranean and North African Region:
    - The predominantly identified influenza strain was strain A; H1N1 was the most prominent circulating subtype.
    - Data on those considered most at risk for influenza complications were collected in 21% of studies, highlighting a regional gap for these data.
    - They reveals existing gaps in regional estimates of influenza health and economic burden, hospitalisation rates and duration, and highlights the need for robust and high-quality epidemiology data to help inform public health interventions. Furthermore, data on mortality were reported in less than 24% of the studies identified.
    - Morbidity and mortality data are important to provide a complete overview of the health burden of disease, which, in turn, is critical to understanding the impact of influenza infections on public health. A lack of knowledge on influenza and its impact with respect to morbidity and mortality has been cited as a major barrier to attaining higher vaccination coverage in the region.

EPIDEMIOLOGY

- Influenza B viruses
  - Pathogens of humans, but there are reports of influenza B infection in pigs and seals.
  - They are not divided into subtypes, but instead are further classified into two lineages: B/Yamagata and B/Victoria.
  - Seasonal influenza epidemics are caused by influenza A viruses of the H3N2 (A/H3N2) and H1N1 (A/H1N1) subtype, and influenza B viruses of both lineages.
  - The limitation for zoonotic transmission influenza B viruses leads to low risk of pandemic outbreaks.
  - The continuous co-circulation of influenza B viruses with influenza A/H3N2 and A/ H1N1 viruses during the seasonal epidemics and its significant contribution to influenza-related morbidity and mortality have increased the interest in influenza B viruses. Although influenza B viruses are included in currently used trivalent seasonal vaccines.

EPIDEMIOLOGY

- Influenza B viruses have attracted relatively little attention. However, influenza B viruses are an important cause of morbidity and mortality in the human population.
- Influenza B viruses have lower receptor-binding affinities than human influenza A viruses.
- Critical difference between the HA molecules of influenza viruses could explain the limited host range of influenza B viruses.
- In 2018 the proportion of influenza A cases that were subtyped was 85.9%, while only 4.4% of influenza B cases were characterized in the Middle East and North Africa regions.
- In Iran (Fars) among the positive results, 191 (15.05%) were influenza type A, and 8 (0.63%) were influenza type B. (2021)
- A Systematic Review of Influenza Epidemiology and Surveillance in the Eastern Mediterranean and North African Region in 2022 showed influenza B accounted for a similar proportion of positive cases in their study 23.8% as that reported in Caini et al. 23.5% of all influenza cases.

EPIDEMIOLOGY

- Influenza C viruses
  - Infect humans and swine, and reassortants have been detected, but influenza C viruses rarely cause serious disease in either species.
  - First serological survey of influenza C virus in Iran (March 1997-May 1998) showed presence of antibodies against influenza C virus (C/Paris/1/67) by haemagglutination inhibition (HI) test. 43.7% of people tested in Tehran and 40.7% of people tested from other provinces had protective antibodies against influenza C virus.
  - Distribution of seropositives in various age groups had a somewhat similar pattern as what has been reported from other countries. The results of this study indicates that the lowest level of protective antibody titer is found at childhood and the level increases with age.
  - The protective antibody titer level off for 20-30 years old age group and decreases in older age groups. These results indicates a primary contact in childhood, reinfection in adulthood. The influenza C virus is simultaneously circulating in Iran with other types of influenza viruses (types A and B).

EPIDEMIOLOGY

- Influenza C virus
  - ICV is an important respiratory pathogen of childhood, though there are wide variations in prevalence from year to year and in different regions.
  - While the most common manifestation of ICV infection is upper respiratory infection, severe lower respiratory infection does occur.
  - Co-infection with other viral and bacterial pathogens is frequent, making the causal role of ICV in these cases uncertainty.
  - Larger scale studies describing year-to-year prevalence, clinical characteristics, and strain type are needed.
  - ICV exhibits minimal antigenic drift over time, suggesting that a monovalent vaccine could be effective against childhood infection.

EPIDEMIOLOGY

- ICV infection is more commonly associated with hospitalization and lower respiratory disease in young children. ICV-associated hospitalization occurs most often among children <3 years of age and cases of Intensive Care Unit admission among infants with prematurity and congenital heart disease have been described, as well as otherwise healthy young children.
- Among children hospitalized for ICV infection, co-morbidity is reported in 58–80% of cases. Prematurity is the most common comorbidity present in ICV-associated hospitalization; however, asthma, IgG deficiency, acute lymphoblastic leukemia, cystic fibrosis, and congenital heart disease have also been described.
- The possible role of ICV in bacterial–viral or viral–viral respiratory co-infection is of interest but is not well understood.

Summary of co-infections seen in patients with influenza C virus (ICV) infection.

Pathogen	N
Rhinovirus/Enterovirus	20
Respiratory syncytial virus	16
Adenovirus	11
Influenza A virus	6
Influenza B virus	4
Parainfluenza virus (1–4)	9
Human metapneumovirus	6
Coronavirus (229E, NL63)	3
Rotavirus	2
Chlamydia pneumoniae	1
Moraxella catarrhalis	1
Bordetella parapertussis	1
Mumps virus	1
Rubella virus	1
Herpes simplex virus	1
Total ICV (+)	278

EPIDEMIOLOGY

- Influenza D virus
  - Interestingly, humans can become seropositive for IDV, despite the absence of clinical symptoms. This suggesting that IDV is capable of inducing adaptive immunity in humans that have high exposure rates.
  - In the absence of clinical cases of IDV, it is assumed that these infections are associated with either mild symptoms or asymptomatic illness.
  - The incidence of seropositivity increases in individuals that are at high risk for exposure to this virus, including those in close contact with cattle.
  - With little known about the host–pathogen interactions with IDV, this virus presents an exciting opportunity to evaluate host responses against a virus that does not cause illness in humans.
  - Since IAV and IBV remain the most aggressive influenza viruses in the human host, there has been a lot of research into the host–pathogen interactions induced by these viruses. Using this information to begin understanding host–pathogen interactions with IDV will allow us to determine what causes the lack of illness associated with IDV in the human host.

INFLUENZA PATHOGENESIS

- Host factors
  - T and B cell immunity against IAV is a key factor in protection from infection and disease. However, other host factors, such as age, sex, and genetic variation, also modulate the clinical course and outcome of the disease.
    - B cells produce non-neutralizing Abs that target the NA or matrix 2 (M2) protein. These Abs promote uptake of virus particles or virus-infected cells by macrophages and neutrophils and induce Ab dependent cellular toxicity.
    - The increase in Influenza A virus disease in female mice strongly correlates with increased cytokine and chemokine production.
    - A reduction in the numbers and activity of virus-specific CD8T cells in aged mice is one of the factors that contribute to a higher virus load and severe disease.

VIRAL FACTORS

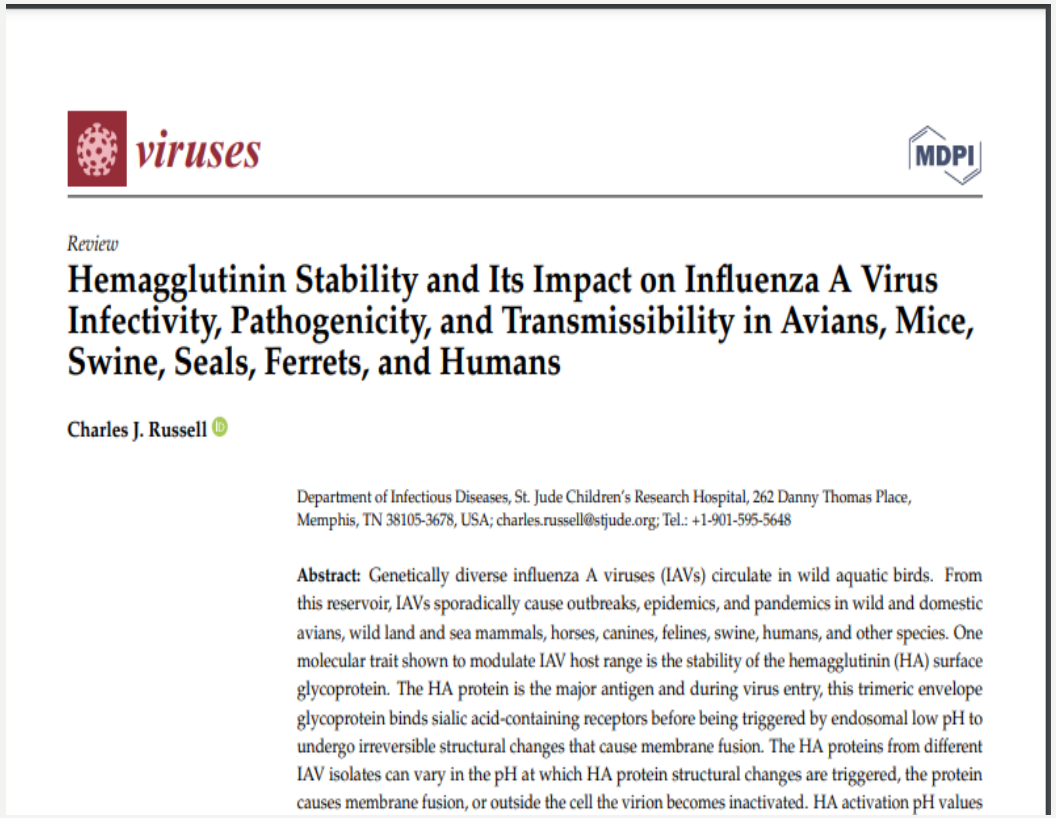
The influenza viral proteins play a role in the lung pathology of humans. Among these proteins, HA is responsible for targeting cells for infection.

Table 1

Mutations in viral proteins that influence viral pathogenicity.

Protein	Virus	Mutation	Pathogenic effect	Reference
HA	H7N7	A143T	Increased attachment to bronchial epithelial cells and alveolar macrophages in humans	[9]
HA	1918 virus	D190E, D225G	From α2,6 to α2,3 (loss of transmission ability)	[10]
HA	Pandemic A(H1N1) 2009	D222G	From α2,6 to α2,3 Infection of ciliated bronchial epithelial cells	[11]
NA	H3N2	R292K, E119V, N294S	Oseltamivir-resistant (R292K, loss of transmission ability)	[62,63]
NA	H5N1	H274Y	Oseltamivir-resistant	[64]
PB1-F2	1918 virus	N66S	Delay of innate immune responses	[28]
PB2	H5N1	T271A	Increased polymerase activity in mammalian cells	[18]
PB2	H5N1, H7N7	E627K	Increased replication in mammalian respiratory tract	[19,20]
PB2	H5N1	D701N	Increased ability to replicate in mice	[21]
PA	H5N2	T97I	Adaptation in mice	[22]
NS1	H5N1	P42S	Increase in IFN antagonism	[33]
NS1	H5N1	Deletion from 85-94	Impaired inhibition of IFN production	[34]
NS1	H3N8 (duck), WSN	R127K, V205I, N209D	Increased replication and lethality in mice (R127K, loss of PKR binding)	[35,36]
NS1	H5N1	D92E	Low sensitivity to IFN and TNFa	[37]

VIRAL FACTORS



viruses

MDPI

Review

Hemagglutinin Stability and Its Impact on Influenza A Virus Infectivity, Pathogenicity, and Transmissibility in Avians, Mice, Swine, Seals, Ferrets, and Humans

Charles J. Russell

Department of Infectious Diseases, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678, USA; charles.russell@stjude.org; Tel.: +1-901-595-5648

Abstract: Genetically diverse influenza A viruses (IAVs) circulate in wild aquatic birds. From this reservoir, IAVs sporadically cause outbreaks, epidemics, and pandemics in wild and domestic avians, wild land and sea mammals, horses, canines, felines, swine, humans, and other species. One molecular trait shown to modulate IAV host range is the stability of the hemagglutinin (HA) surface glycoprotein. The HA protein is the major antigen and during virus entry, this trimeric envelope glycoprotein binds sialic acid-containing receptors before being triggered by endosomal low pH to undergo irreversible structural changes that cause membrane fusion. The HA proteins from different IAV isolates can vary in the pH at which HA protein structural changes are triggered, the protein causes membrane fusion, or outside the cell the virion becomes inactivated. HA activation pH values

- Shift and antigenic drift
- HA2 E47K substitution in hemagglutinin (HA) of the 2009 pH1N1 IAV reduces the pH threshold for membrane fusion, conferring the virus with thermal stability and infectivity, which partially explains its rapid spread and adaptation to humans.
- M2 protein channel activity enhanced 2009 pH1N1 IAV infectivity by protecting against premature HA cleavage and preserving membrane fusion competence.
- Seasonal, as well as pandemic, strains show specificity for 2,6-linked sialic acids that are prominently expressed in the human trachea, whereas the avian viruses preferentially bind to the 2,3-linked sialic acids that are expressed in alveolar type II cells.
- The NS1 Protein of a Human Influenza Virus Inhibits Type I Interferon Production and the Induction of Antiviral Responses


Thank you!