

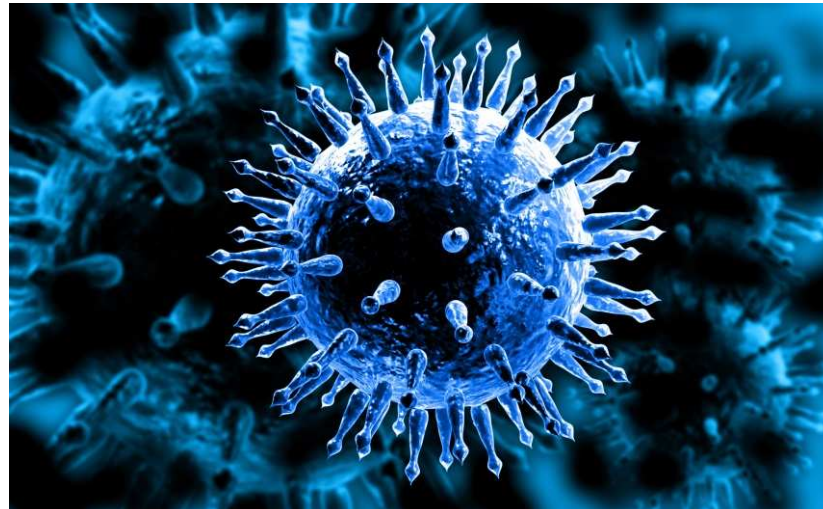
Influenza

Avian influenza

Tomáš Gergel

Influenza

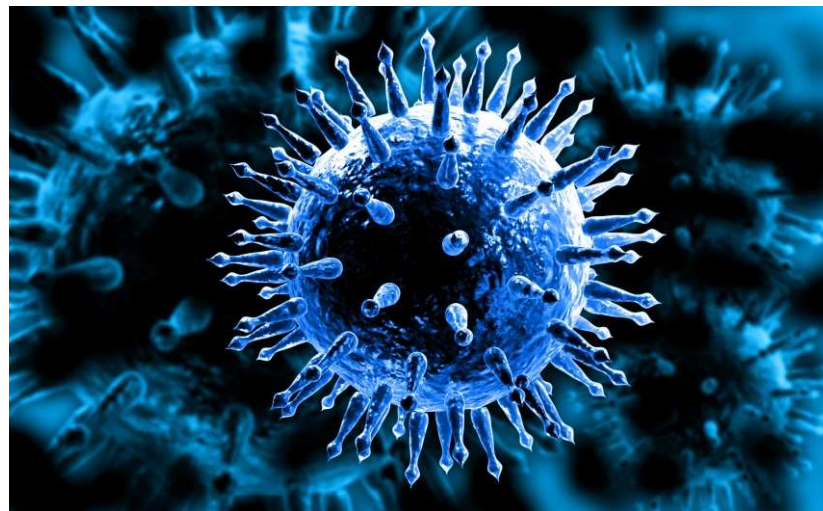
- segmented RNA viruses, family *Orthomyxoviridae*
- **Influenzavirus A** - seasonal epidemics and pandemics
- **Influenzavirus B** - milder, small epidemics
- Influenzavirus C - pigs, dogs, less common, „common cold“
- Influenzavirus D - pigs, cattle, no human infection was reported

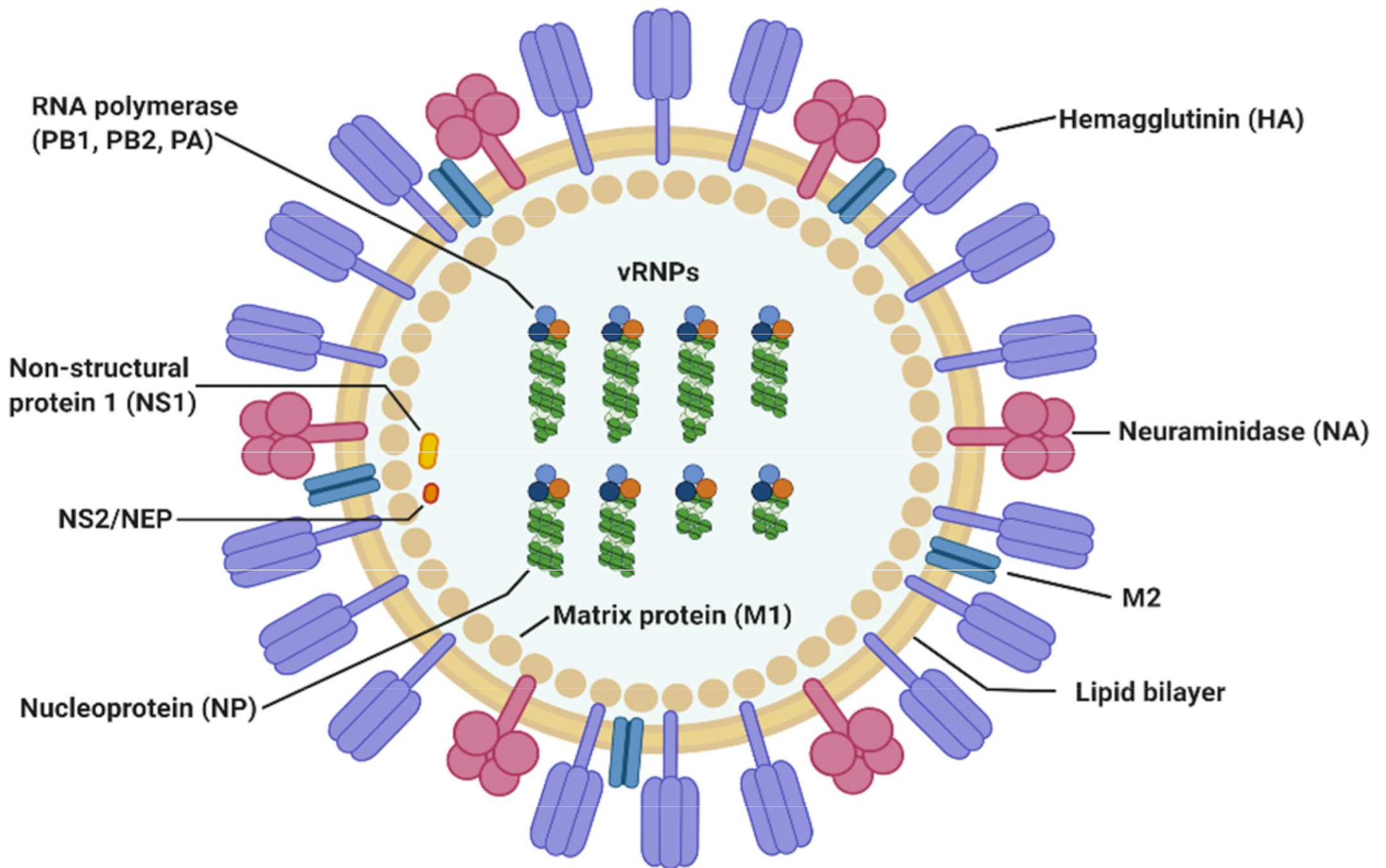


Epidemiology

- the illness occurs in outbreaks and epidemics worldwide
- mainly during the winter season
- self-limited infection in the general population
- associated with increased morbidity and mortality in certain high-risk populations (cardiovascular illnesses, chronic respiratory tract illnesses, immunocompromised patients,...)
- CDC + WHO track influenza virus isolates throughout the world → monitor disease activity → predict the appropriate components for the annual influenza vaccine

- infected >10% world population annually
- 5 millions of severe cases / year
- 0,5 million deaths / year
- in Czech republic 3000 deaths / year





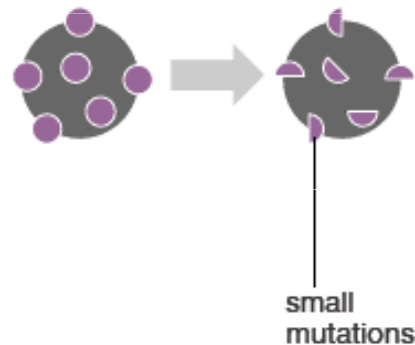
- 2 large surface antigens - glycoproteins
 - **Hemagglutinin - HA** (H1-H18, humans only H1-H3)
 - binding the viral particle to the host cell
 - **Neuraminidase - NA** (N1-N11, humans only N1-N2)
 - **internalization** of particle **into** the host cell, **release** the new particles **from** the cell

Subtype f.e. : H1N1

Antigenic drift

- minor antigenical change
- occurs almost annually
- results in outbreaks of variable extent and severity
- outbreaks less extensive and severe than the epidemics or pandemics associated with antigenic shifts
- point mutations in the RNA gene segments that code for the hemagglutinin or the neuraminidase

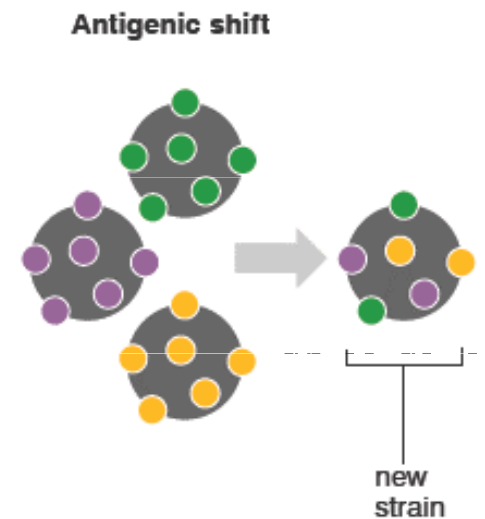
Mutation
Antigenic drift



Antigenic shift

- major antigenical change
- segmented genome can be reassorted among viruses coinfected the same cell
- reassortment between animal and human viruses - may result in the emergence of pandemic strains
- caused the pandemics of 1957, 1968 and 2009

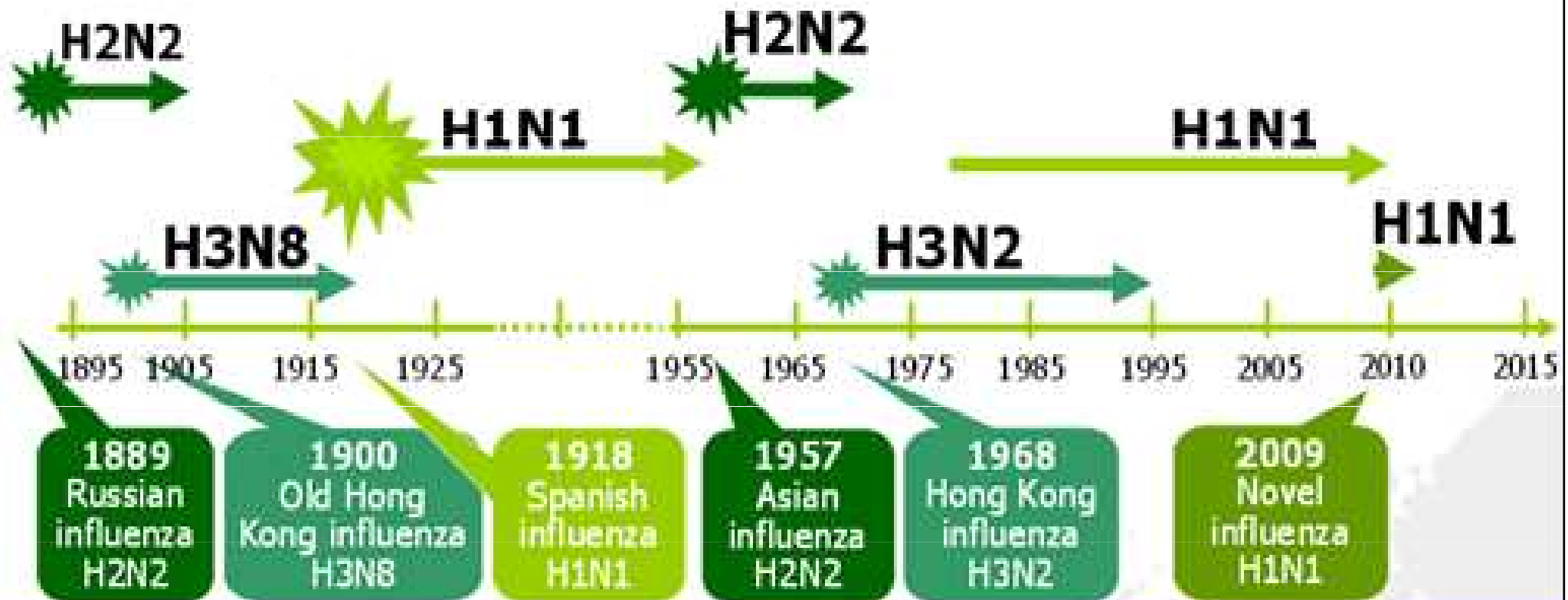
- reassortment, switching the genom segments, among viruses coinfected the same cell
- great role of pig and bird (avian) influenzaviruses



Pandemics of influenza



Recorded human pandemic influenza (early sub-types inferred)



Recorded new avian influenzas



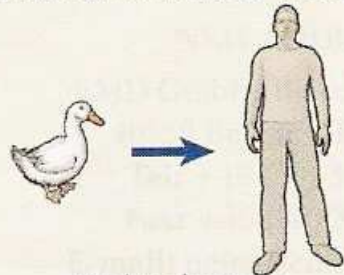
1918 "Spanish influenza"

1957 "Asian influenza"

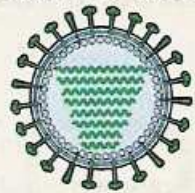
1968 "Hong Kong influenza"

Next pandemic influenza

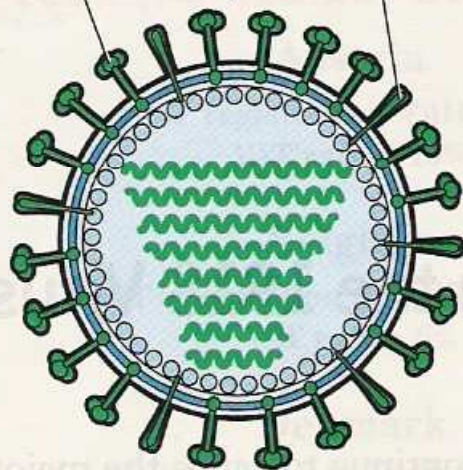
H1N1 influenza virus



Bird-to-human transmission of H1N1 virus

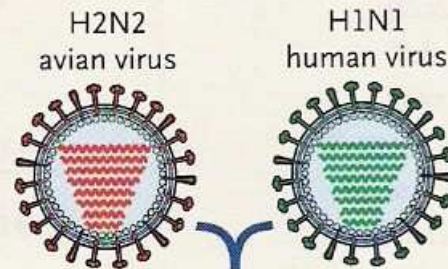


Hemagglutinin Neuraminidase

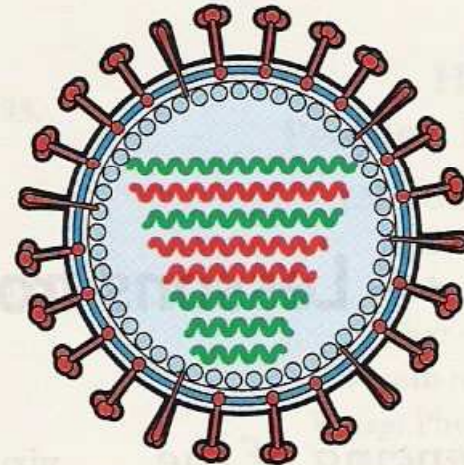


All 8 genetic segments thought to have originated from avian influenza virus

H2N2 influenza virus

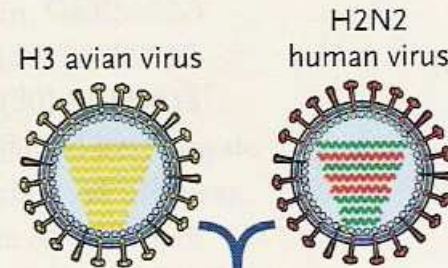


Reassortment

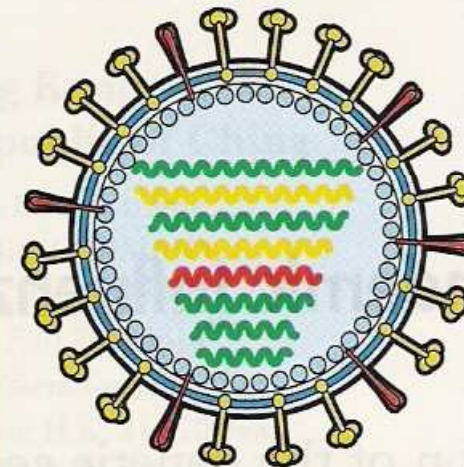


3 new genetic segments from avian influenza virus introduced (HA, NA, PB1); contained 5 RNA segments from 1918

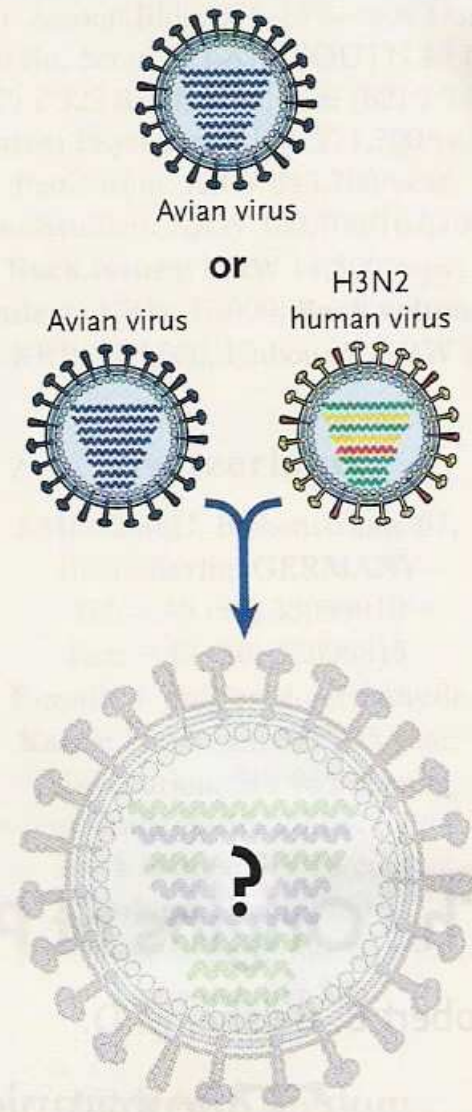
H3N2 influenza virus



Reassortment



2 new genetic segments from avian influenza virus introduced (HA, PB1); contained 5 RNA segments from 1918



All 8 genes new or further derivative of 1918 virus

Outbreak characteristics

- 2-3 different strains circulate in a influenza season, 1 dominant
- **Seasonality** — exclusively during the winter months in the Northern and Southern hemispheres (occur at different times of the year)
 - !!! traveling to tropical regions
 - persistence between outbreaks - poorly understood - import from geographically distant sites ??
- **Factors determining the severity of an outbreak**
 - not fully understood
 - the susceptibility of the population = prevalence of antibodies to circulating virus = major role.

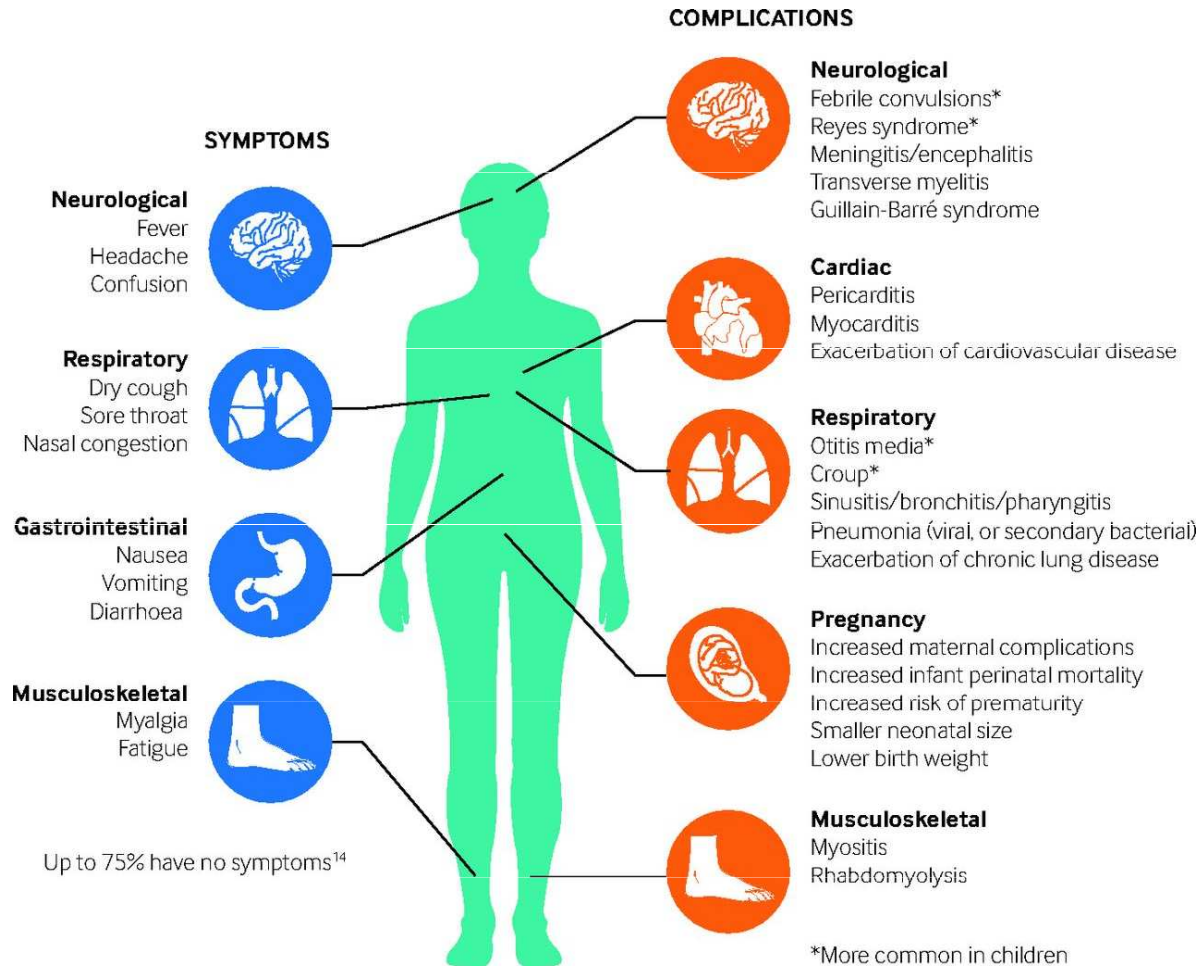
Outbreak characteristics

- **Time course of an outbreak**
 - begin abruptly
 - peak over 2-3 weeks
 - last for 2-3 months
 - earliest indicator of outbreak = increase in febrile respiratory illnesses in children → increases in influenza-like illnesses in adults
 - **outbreaks attack rates** = 10-20% in the general population, >50 % in pandemics, extraordinarily high attack rates in institutionalized and semiclosed populations.

Transmission

- large amounts of influenza virus in respiratory secretions → cough, sneezing
 - large droplets (>5um) - small distance (up to 2 m/6 feet)
 - small particle aerosols - long distances
 - contact with contaminated surface
 - respiratory tract
 - (ocular mucousa)
- **Incubation period:** 1-4 days
- **Duration of shedding:** detected 24 to 48 hours before illness onset, 5 days after onset of symptoms in average

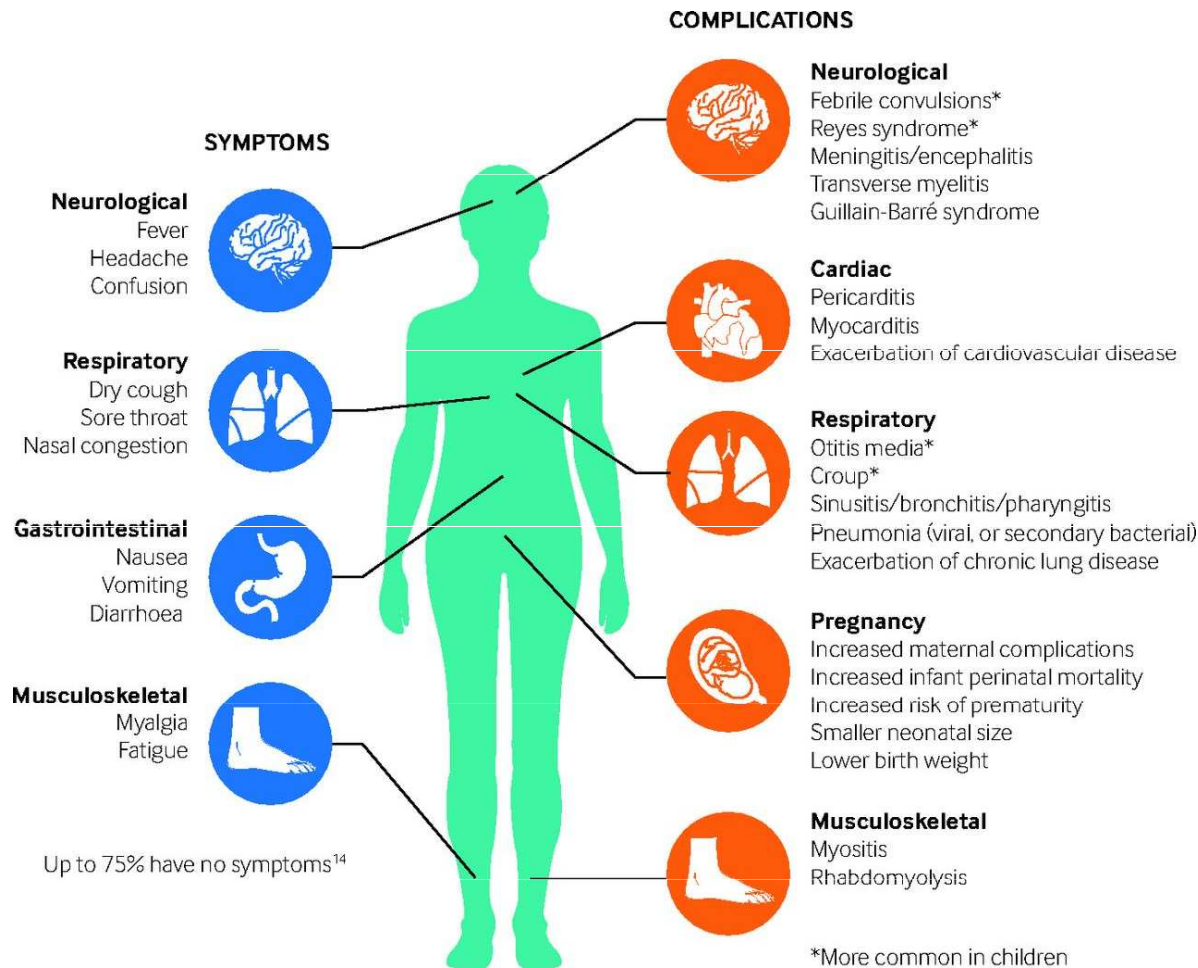
Clinical manifestation



Uncomplicated influenza

- abrupt onset of fever (37.8-40.0°C), headache, myalgia, and malaise
- respiratory tract illness - nonproductive cough, sore throat, and nasal discharge
- GIT - vomiting, diarrhea (usually children)
- patient appears hot and flushed
- oropharyngeal hyperemia, mild cervical lymphadenopathy
- physical examination is unremarkable
- Lab: unspecific, leukocyte normal, leukopenia in the early state, >15,000 cells/microL suggest bacterial superinfection
- improvement usually 2-5 days
- postinfluenza asthenia - persistent symptoms of weakness, fatigability, last for several weeks

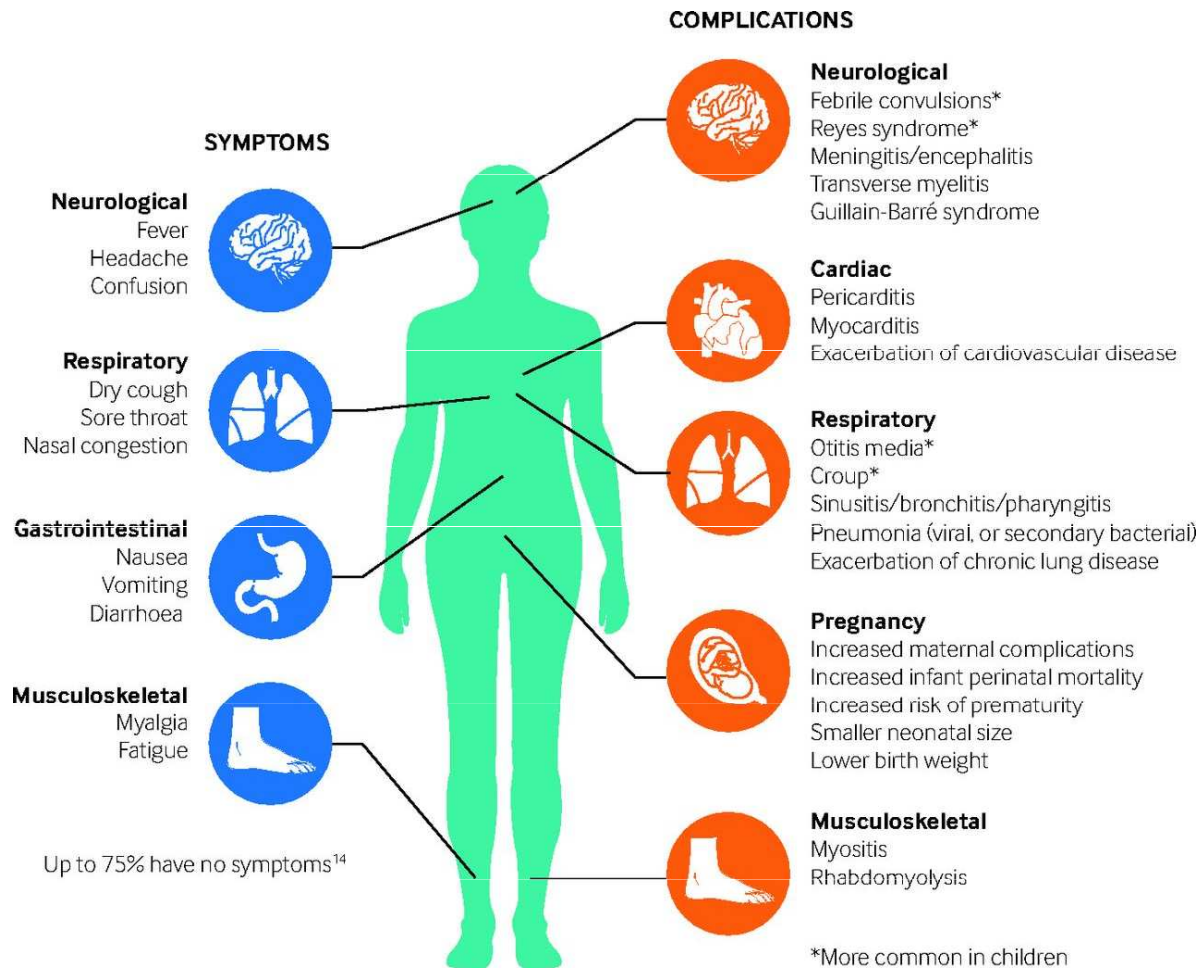
Clinical manifestation



Complicated influenza

- **Pneumonia** - most common complication of influenza
- **Primary influenza pneumonia**
 - severe pneumonia
 - symptoms persist and increase instead of resolving
 - high fever, dyspnea, cyanosis
 - X-ray, CT
- **Secondary bacterial pneumonia**
 - ↑ morbidity and mortality ≥65 years
 - exacerbation symptoms after initial improvement, production of purulent sputum, pulmonary infiltrates
 - bacterial pathogens: ***S. pneumoniae*, *S.aureus*, (*S.pyogenes*, *P.aeruginosa*, *H.influenzae*, *K.pneumoniae*, *M.catarrhalis*, *E.coli***
- **Mixed viral and bacterial pneumonia**

Clinical manifestation



Complicated influenza

- **Acute respiratory distress syndrome (ARDS) and multisystem organ failure (MOF)**
- **Myositis and rhabdomyolysis**
 - most frequently in children
 - extreme tenderness of affected muscles (legs)
 - elevated serum creatine phosphokinase, myoglobinuria with associated renal failure
- **Cardiac**
 - ↑risk acute coronary syndrome, myocarditis and pericarditis
- **Central nervous system**
 - encephalopathy, encephalitis, transverse myelitis, aseptic meningitis and Guillain-Barré syndrome

Diagnosis

- during season/outbreak
- **clinical dg.**
 - uncomplicated acute respiratory illness
 - not requiring hospitalization
 - ↓risk of complications

Diagnosis

- **whom to test:**
 - symptomatic immunocompromised patients / patients at ↑risk
 - patients requiring hospitalization with acute respiratory illness, including pneumonia, with or without fever
 - patients requiring hospitalization with acute worsening of chronic cardiopulmonary disease (eg, COPD, asthma, coronary artery disease, or congestive heart failure)
 - acute onset of respiratory symptoms with or without fever, or respiratory distress, after hospital admission

Diagnosis

- **RT-PCR**

- golden standard, genome identification
- most sensitive and specific
- rapid results (1-8 hours)
- differentiates between influenza types and subtypes
- nasopharyngeal aspirates, bronchoalveolar lavage fluid, nasal and throat swabs

- **Rapid antigen tests**

- influenza A and B viral nucleoprotein antigens in respiratory specimens
- qualitative results (+/-)
- results in approximately 15 minutes or less
- but **much lower sensitivity** than RT-PCR

Diagnosis

- **Viral culture**

- nasal washes, throat swabs, sputum, bronchoalveolar lavage specimens
- results available in 48-72 hours

- **Serologic testing**

- useful primarily for research purposes
- not useful for the diagnosis of acute illness - paired acute and convalescent are required
- to establish the diagnosis of influenza retrospectively

Treatment

- **Nonspecific**
 - fluids
 - vitamins
 - antipyretics/analgetics
 - antitussives...

Treatment

- **Antivirals:**

- **neuraminidase inhibitors:** **zanamivir** (inhalation 10 mg 1-0-1, 5 days), **oseltamivir** (p.o. 75 mg 1-0-1, 5 days), **peramivir** (i.v. 600 mg 1xdaily)
 - active against both influenza A and B
- **inhibitor of influenza cap-dependent endonuclease:** **baloxavir**
 - active against influenza A and B
- **adamantanes:** **amantadine, rimantadine**
 - only active against influenza A
 - increase in resistant isolates, adverse effects → ↓ **of use**

Prevention

- Preexposing measures
 - hand washing, aerosols (masks)
- Vaccination
- Prophylactic drug use
 - Oseltamivir (75 mg 1xdaily)
 - Zanamivir (5 mg 1-0-1)



Prevention

Vaccination

- most effective prevention
- against hemagglutinine
- every year due to antigenic drifts
 - i.m. - inactivated vac., recombinant vac.
 - nasaly - live attenuated vac. (not available in CR)
 - quadrivalent vac. - influenza A Ag x2 + influenza B Ag x2
 - trivalent vac. - influenza A Ag x2 + influenza B Ag x1
- elderly, chronically ill, healthcare workers, long term facility workers, ...

Avian influenza

- influenza viruses adapted to birds
- mostly influenza A virus
- high pathogenic avian influenza (HPAI), low pathogenic avian influenza (LPAI)
- H1-16, N1-9 = many subtypes
 - only H5N1, H7N3, H7N7, H7N9, H9N2 were confirmed in human
- new strains typically emerge in Southeast Asia (close contact of human, bird and swine)
- ↑ pandemic potential, ↑ case fatality rate



Transmission

- **Bird-to-human**

- handling dead infected birds
- contact with infected (animal) fluids
- contaminated surfaces and droppings
- close contact, ↓hygiene

- **Human-to-human**

- rare, only prolonged contact
- spreading after mutation is ↑concern

- **Role of pigs**

- infected by avian and human strains → reassortement → new strain

Why so dangerous ?

- avian influenza viruses attach cells via different receptors than human strains
→ these receptors are in lower respiratory tract in human → severe pneumonia with ARDS
- ↓ effect of host antiviral cytokines, ↑ proinflammatory mediators → SIRS
→ ARDS
- predominance of children and young adults

Clinical manifestation

- **Incubation period:** 2-5 days
 - respiratory illness
 - GIT
 - CNS
- **Complications:** pneumonia, MOF, renal dysfunction, cardiac compromise, pulmonary hemorrhage, pneumothorax, pancytopenia
- **Lab:** leukopenia, neutropenia, lymphopenia, thrombocytopenia, ↑ aminotransferases (AST>ALT), ↑LDH, ↑ CK, ↓ albumin

Diagnosis, treatment

DG:

- PCR
- antigen detection
- serology
- viral isolation

Treatment

- nonspecific
- only oseltamivir is recommended in specific treatment of avian flu

Prevention

- **Infection control measures**
 - appropriate biosafety precautions when handling suspected specimen
 - higher level of infection control than for seasonal influenza viruses - eye protection and respirators (eg, N95 masks, FFP2) in addition
 - patients in airborne infection isolation rooms
- **postexposure prophylaxis** – oseltamivir, zanamivir
- **vaccine** against H5N1 is available - ??? Efficiency after 10 years ???

Thank you for your attention !



COVID-19 pandemic, 1.wave