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TU 02 : Viral respiratory infections

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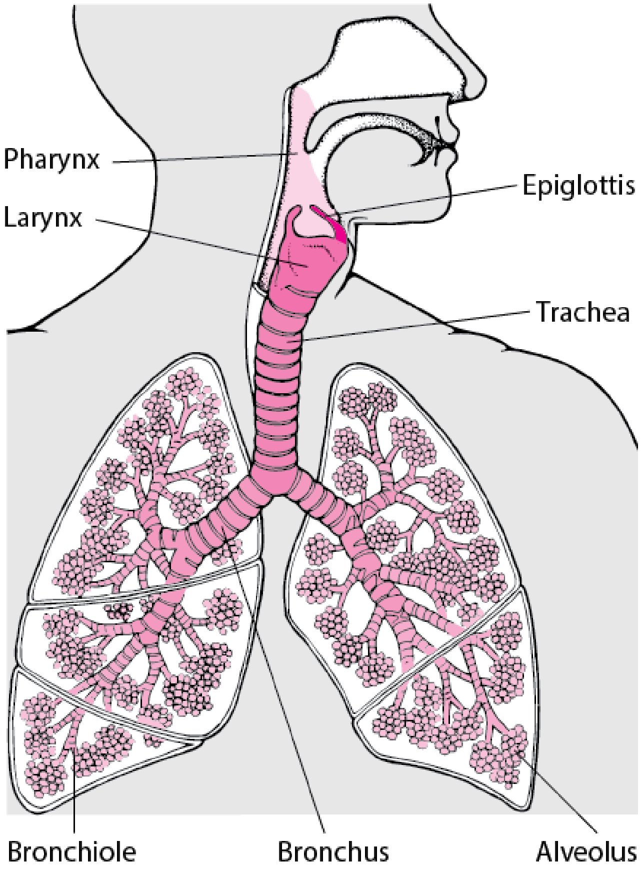
Respiratory syndroma

Very frequent infections, most of the time asymptomatic or pauci symptomatic

Benign infections are mostly viral

Involvement of asymptomatic infections in transmission



- **Upper respiratory tract infections**

Rhinitis

Pharyngitis

mostly viral

Laryngitis, epiglottitis, tracheitis

- **Lower respiratory tract infections**

Bronchiolitis

Bronchitis

Pneumonia

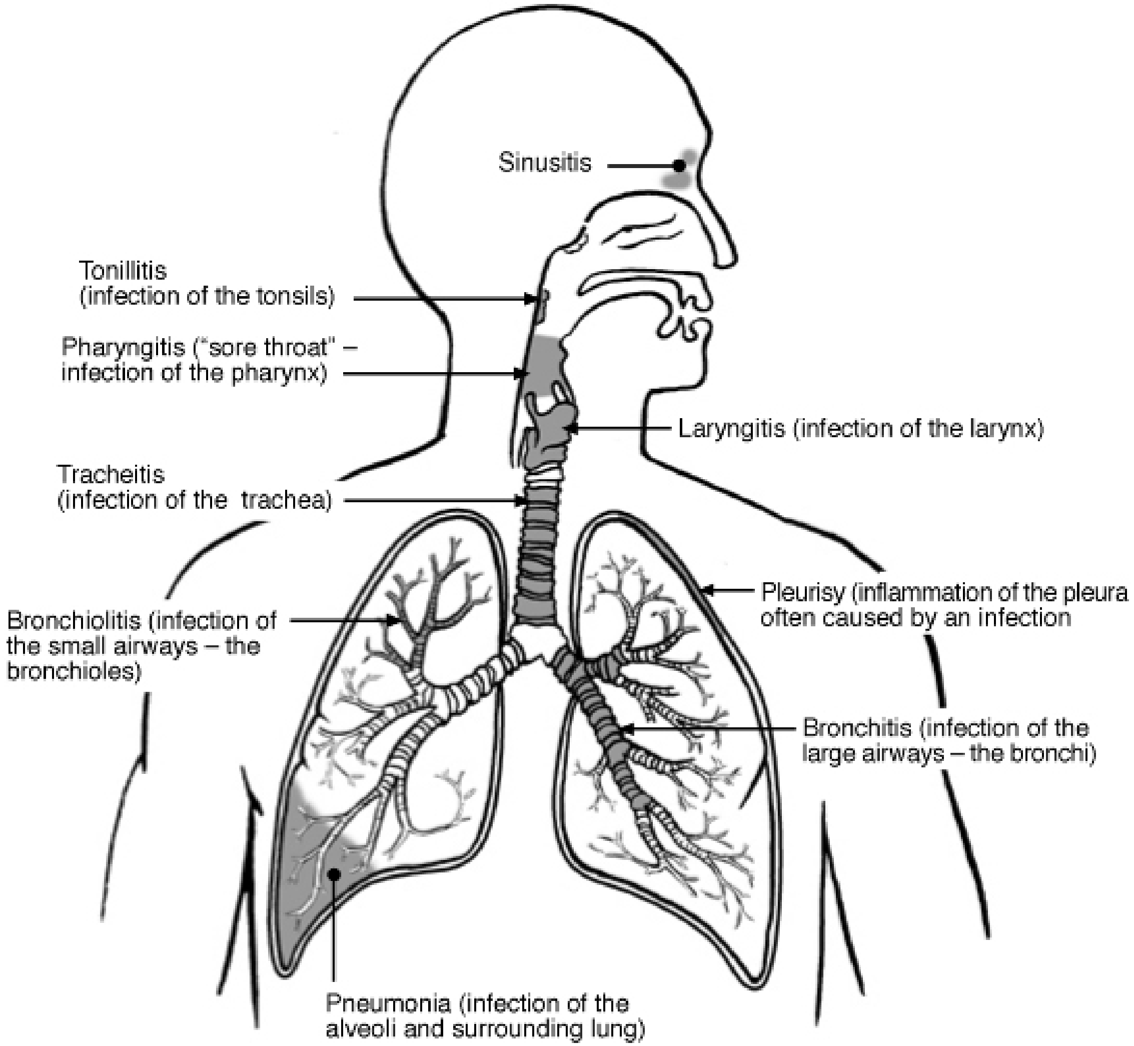
Bronchiolitis always viral infection and affect young children

Viral respiratory infections

- Are important by
  - The **frequency** of some diseases : Common cold, Flu, Bronchiolitis
  - The **gravity** of some diseases in specific population
    - Bronchiolitis in newborns
    - Influenza in elderly people
    - Viral pneumonia in immunocompromised patient
    - COVID-19 in elderly people / co-morbidity
- Community and/or nosocomial infections
- Most are epidemic
- Acute infections (exceptionally chronic)
- Can lead to bacterial superinfections

Numerous viruses involved in human infections

- Influenza virus A, B
- Respiratory syncytial Virus (RSV) A, B
- Rhinovirus A, B, C
- Parainfluenza Virus 1, 2, 3, 4
- Metapneumovirus
- Adenovirus A-F
- Enterovirus
- Coronavirus, SARS-CoV-2, HCoV-OC43, HCoV-229E, HCoV-NL63 et HCoV-HKU 1, SARS-CoV-1, MERS-CoV
- Polyomavirus KI, WU



Infections of the respiratory tract

Causes of respiratory infections

Syndroma	Causative virus
Rhinitis, Rhino pharyngitis Pharyngitis Laryngitis, epiglottitis	Rhinovirus, Enterovirus Coronavirus Adenovirus, HSV, EBV Virus Para-influenza Influenza Virus …
Bronchitis Bronchiolitis	Para-influenza Virus VRS, rhinovirus, metapneumovirus, adenovirus, coronavirus …
Pneumopathy ID	Para-influenza Virus Influenza Virus Coronavirus (SARS-CoV-2) Adenovirus Rhinovirus…
Special Pneumonia	Measles, Chicken Pox Cytomegalovirus, Hantavirus

Measles virus and VZV are responsable of pneumopathies in adults

Transmission

- Direct inter human transmission
- Essentially respiratory via respiratory droplets
- Persistence on the hands, on surfaces and objects for a few hours, even for enveloped viruses
- Higher resistance in the environment for naked viruses (Adenovirus, Rhinovirus)

→ Important hygiene rules to follow :
wash hands regularly with soap and water, cover mouth and nose when coughing or sneezing, wear a mask when ill, use tissues, limit contact...

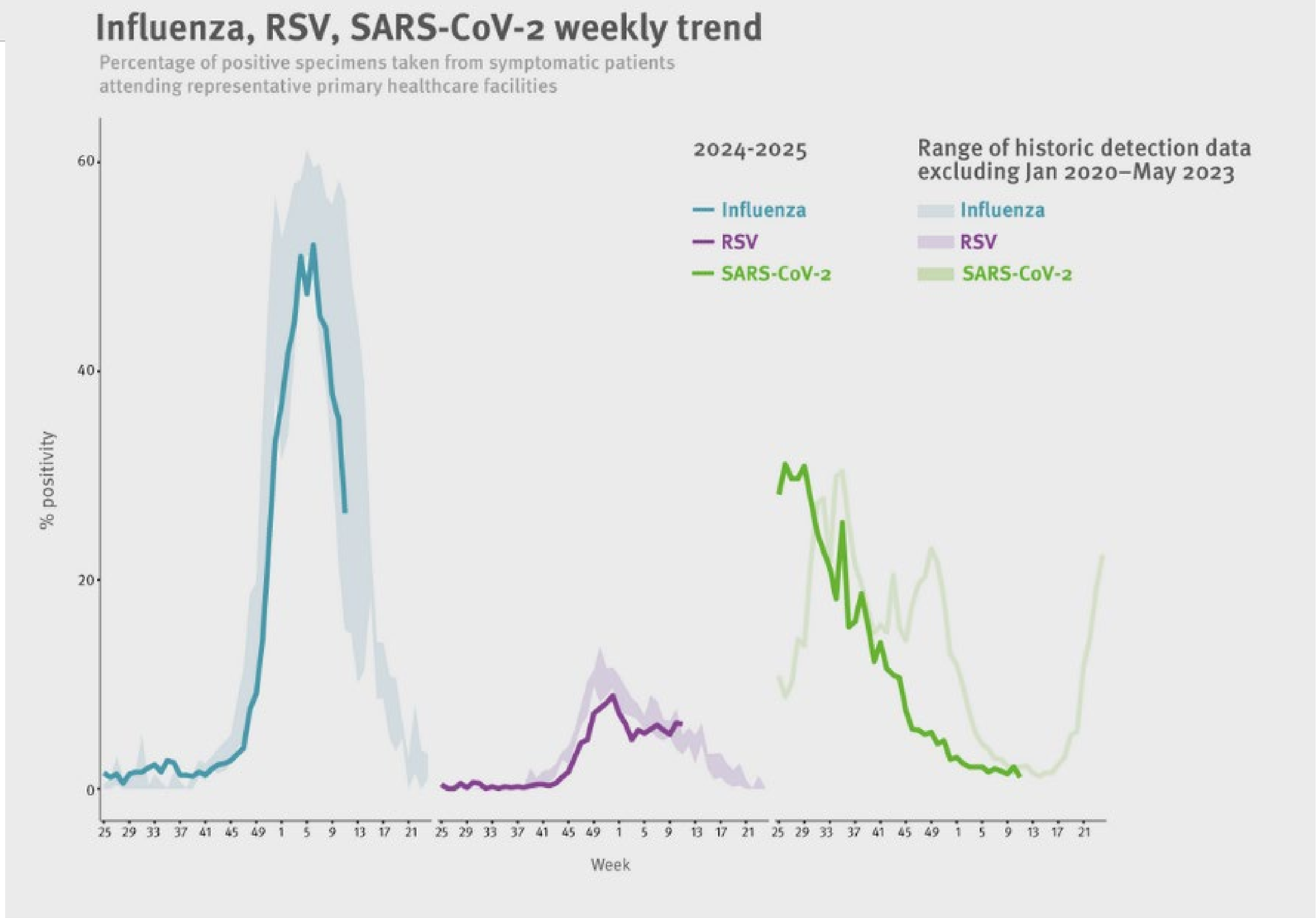
Influenza, RSV, SARS-CoV-2 in Europe

Data from EU and EEA countries

Week 11 (10 Mar–16 Mar 2025)

European Centre for Disease Prevention and Control
An agency of the European Union

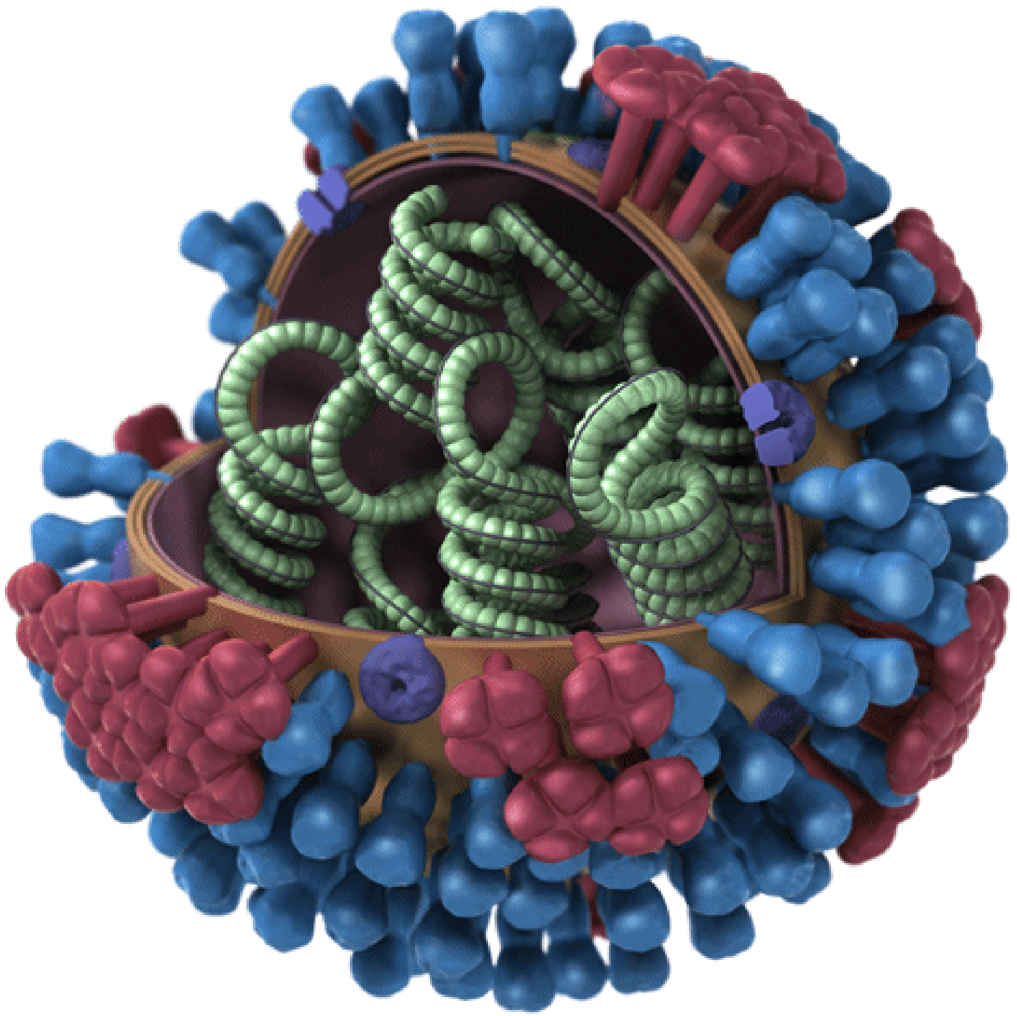
ECDC collects, analyses and shares data on **more than 50 infectious disease topics**. ECDC experts assess risks to Europe and provide guidance to help countries prevent and **respond to outbreaks** and public health threats.



Influenza virus

- *Orthomyxoviridae*
- four types of influenza viruses: A, B, C and D.
- Influenza A viruses naturally infect humans and many different animals.
- Influenza B viruses only infect humans (and seals)
- Human influenza A and B viruses cause seasonal epidemics of disease.
- Influenza type C infections generally cause mild illness and are not thought to cause human flu epidemics.
- Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people

Influenza virus structure



cdc.gov

Genome

Segmented ssRNA(-), linear

Contains 7 or 8 segments

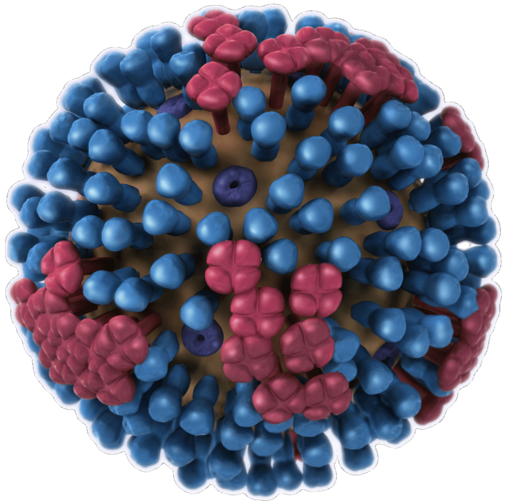
Helical capsid (RNP)

Envelope

M2 ion channel

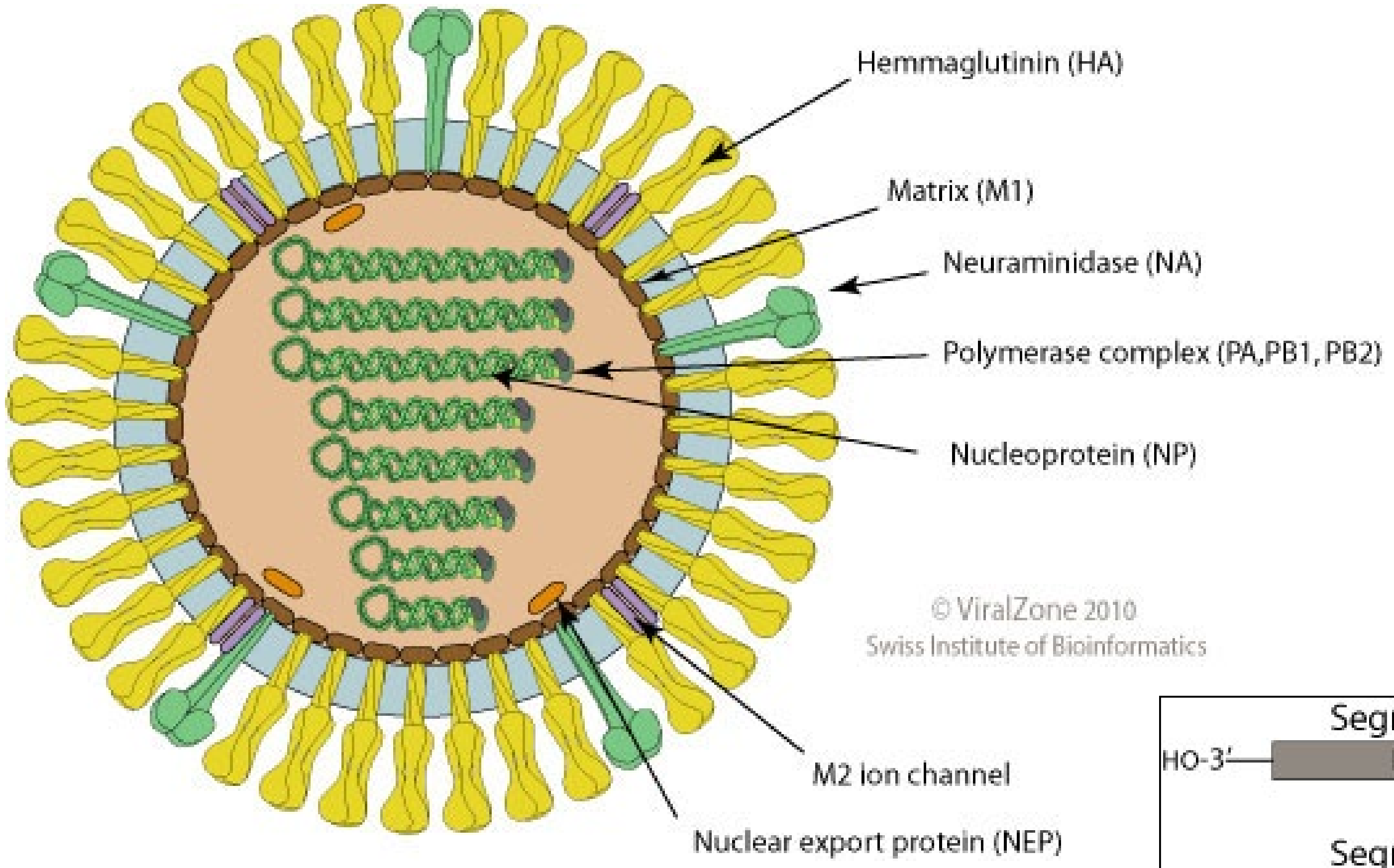
M1 matrix

Polymerase complex associated with each segment

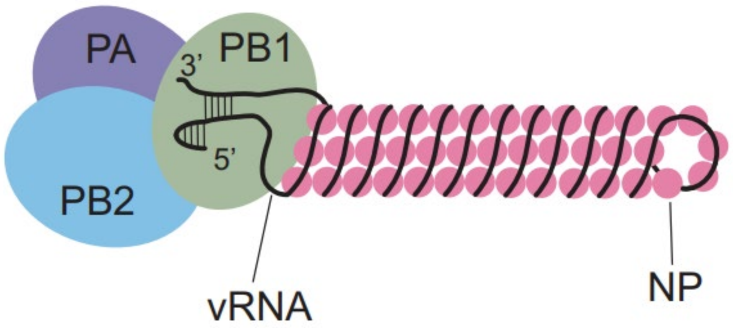


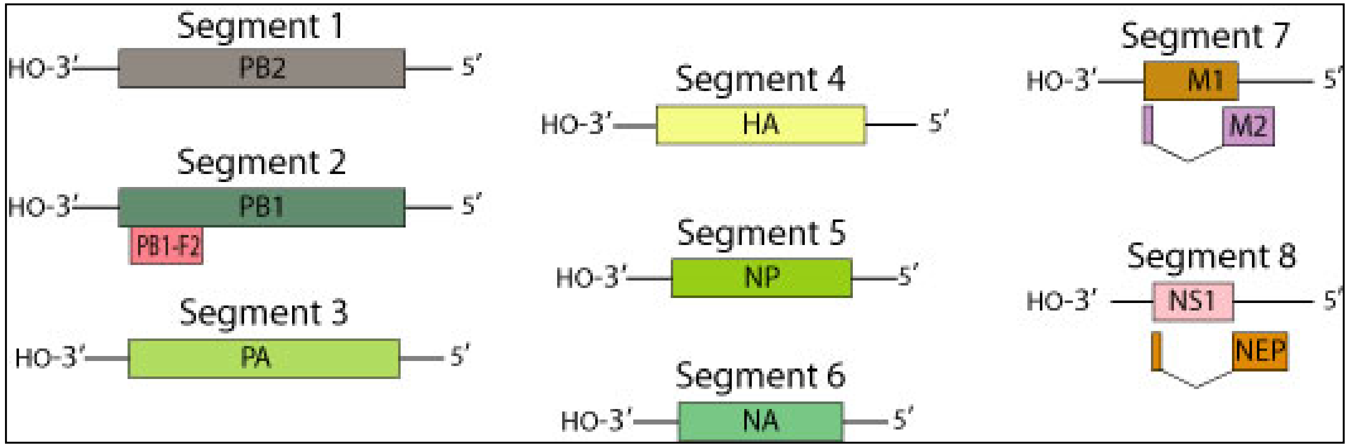
Influenza virus structure

Basic



Polymerase complex (PA, PB1, PB2) associated with each segment

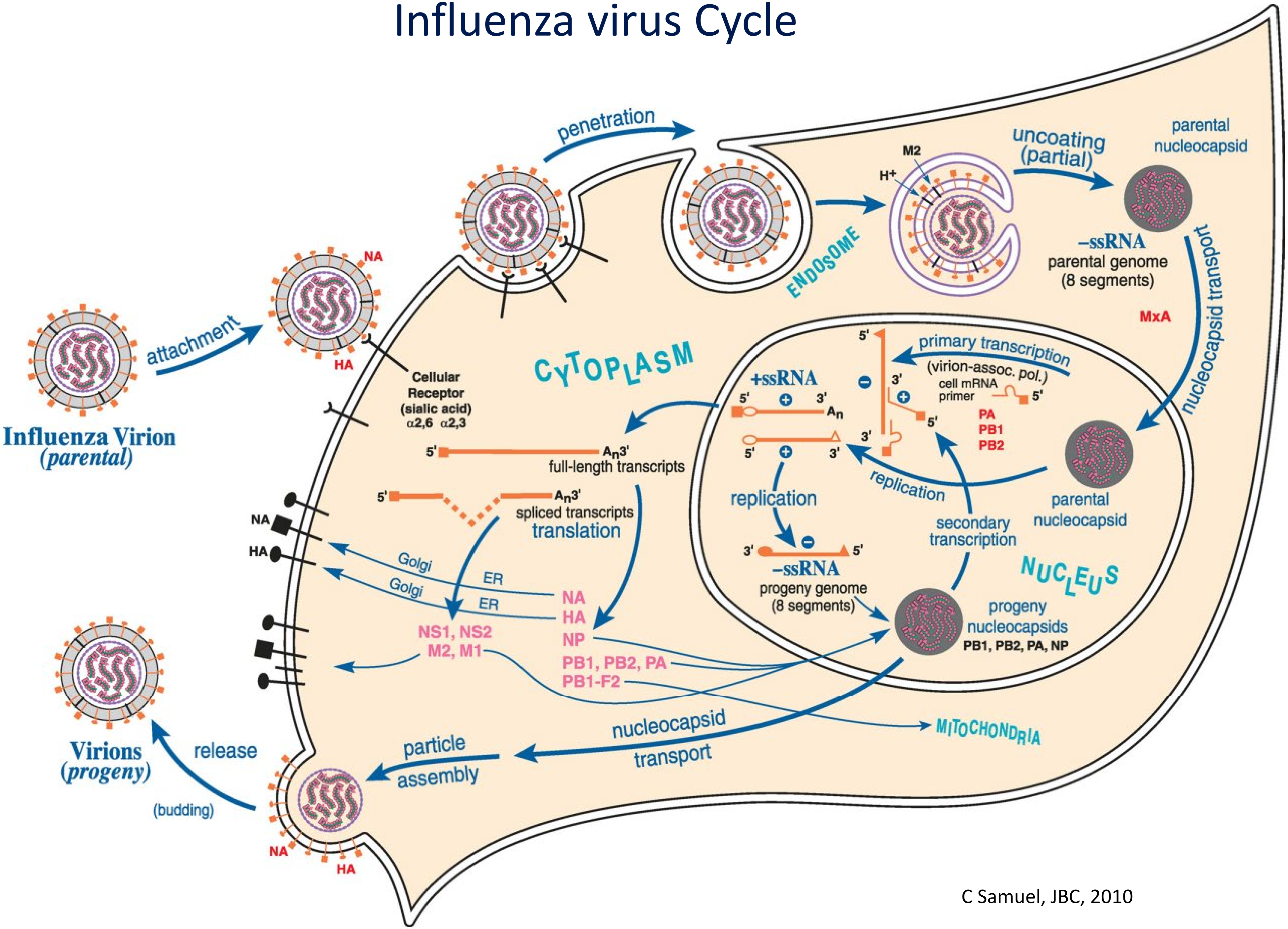




Viralzone

Influenza virus Cycle

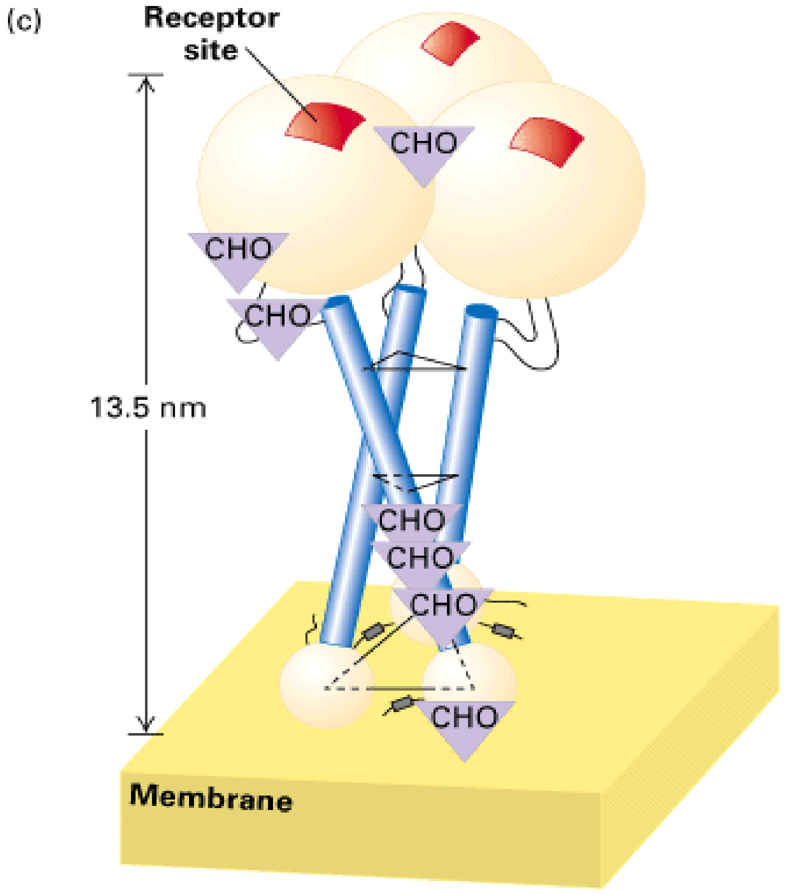
Basic



C Samuel, JBC, 2010

Influenza virus Hemagglutinin

Basic



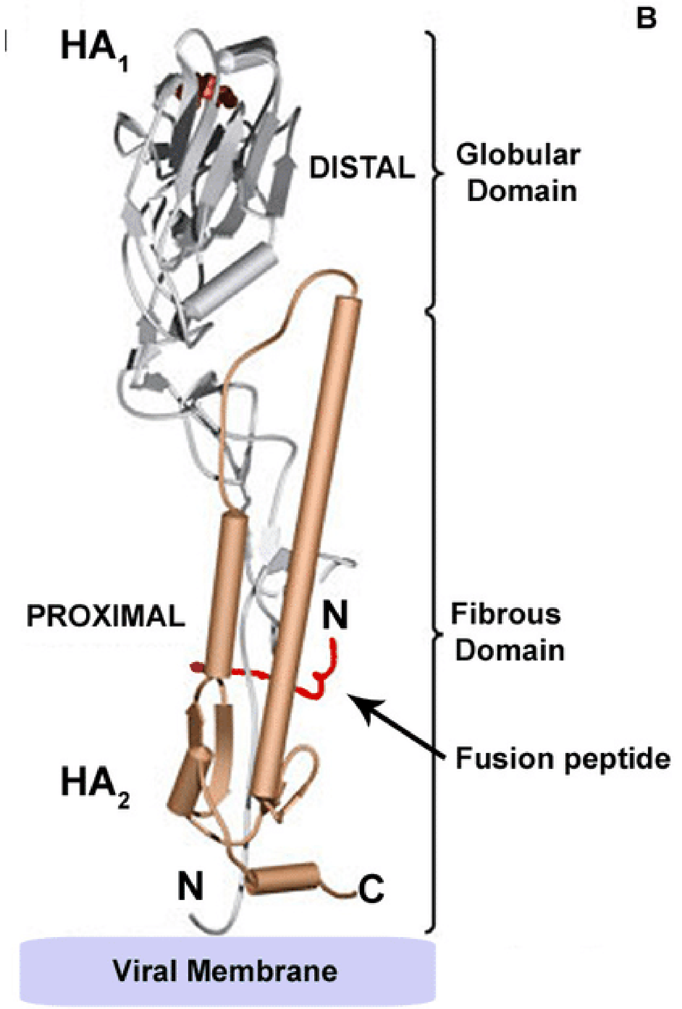
Hemagglutinin of influenza virus

- Trimer - Spicule
- Three roles

- Attachment to the cell (sialic acid)
HA1 contains the receptor site to sialic acid

- Fusion of the envelope with endosomal membrane
- fusion peptide in HA2

- Major immunogenicity
Neutralizing antibodies

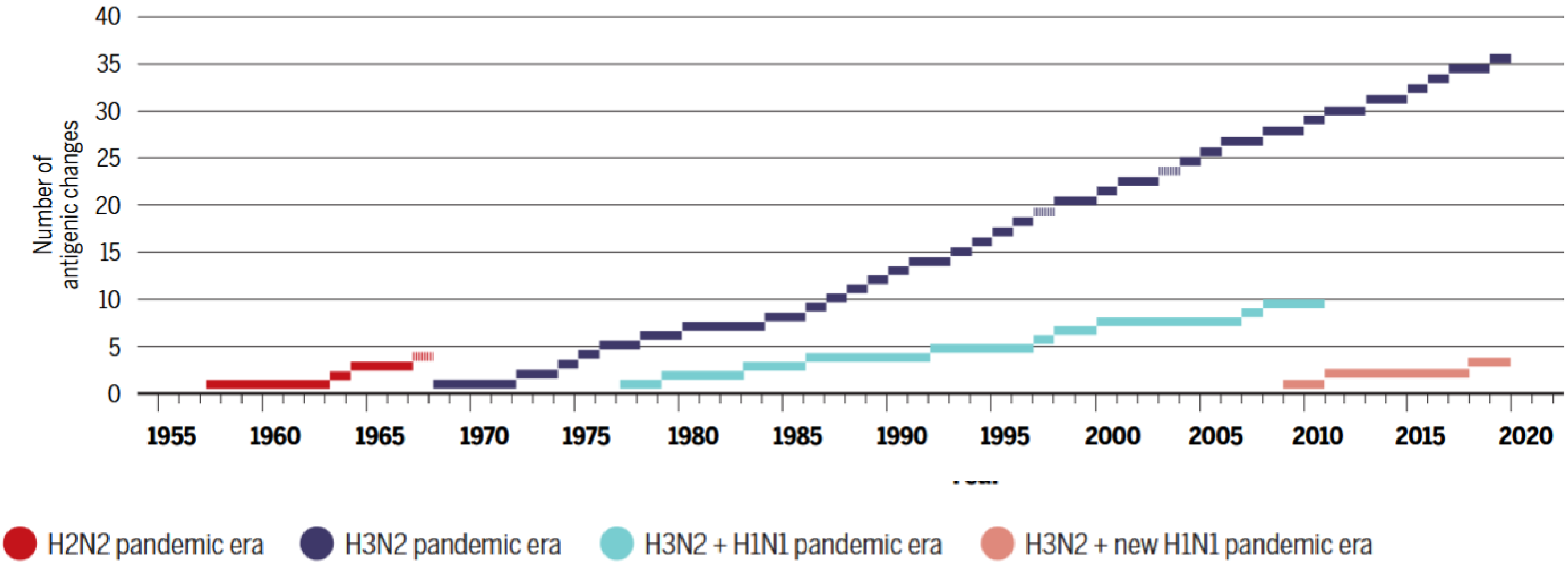


How the flu virus can change

- Antigenic drift
  - random accumulation of mutations in HA gene, and to a lesser extent neuraminidase NA gene
  - most pronounced in influenza A viruses
  - mutations occur frequently (RNA virus, no proofreading mechanism)
  - Reduce or inhibit the binding of neutralizing antibodies
  - explains the occurrence of seasonal influenza epidemics
  - Accounts for variable vaccine effectiveness
  - Annual changes in the vaccine composition

How the flu virus can change

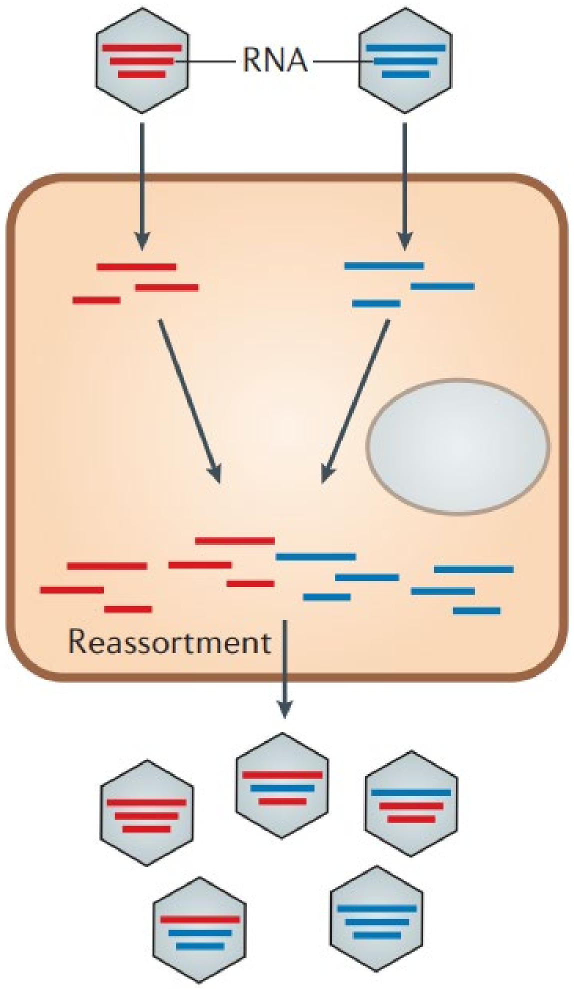
- Antigenic drift



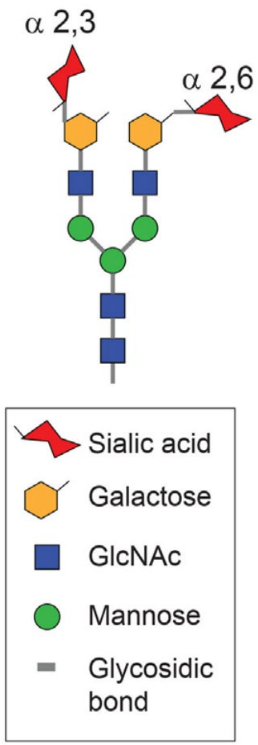
Science Translational medicine review Taubenberger et al, 2019

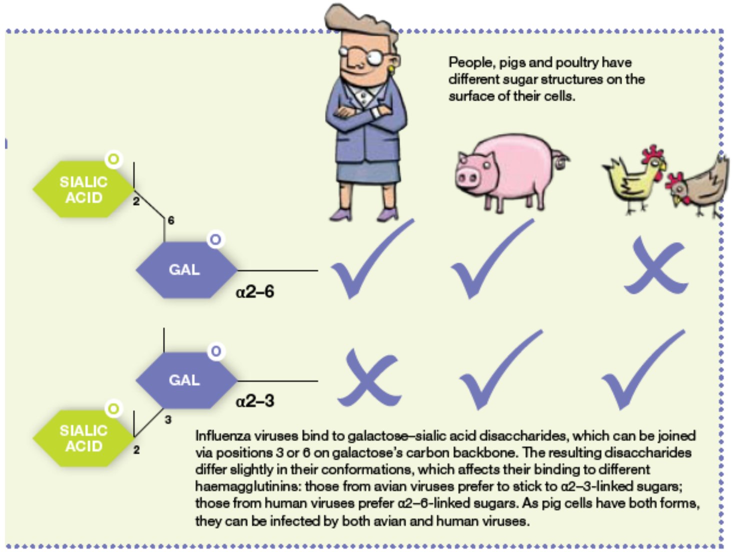
How the flu virus can change

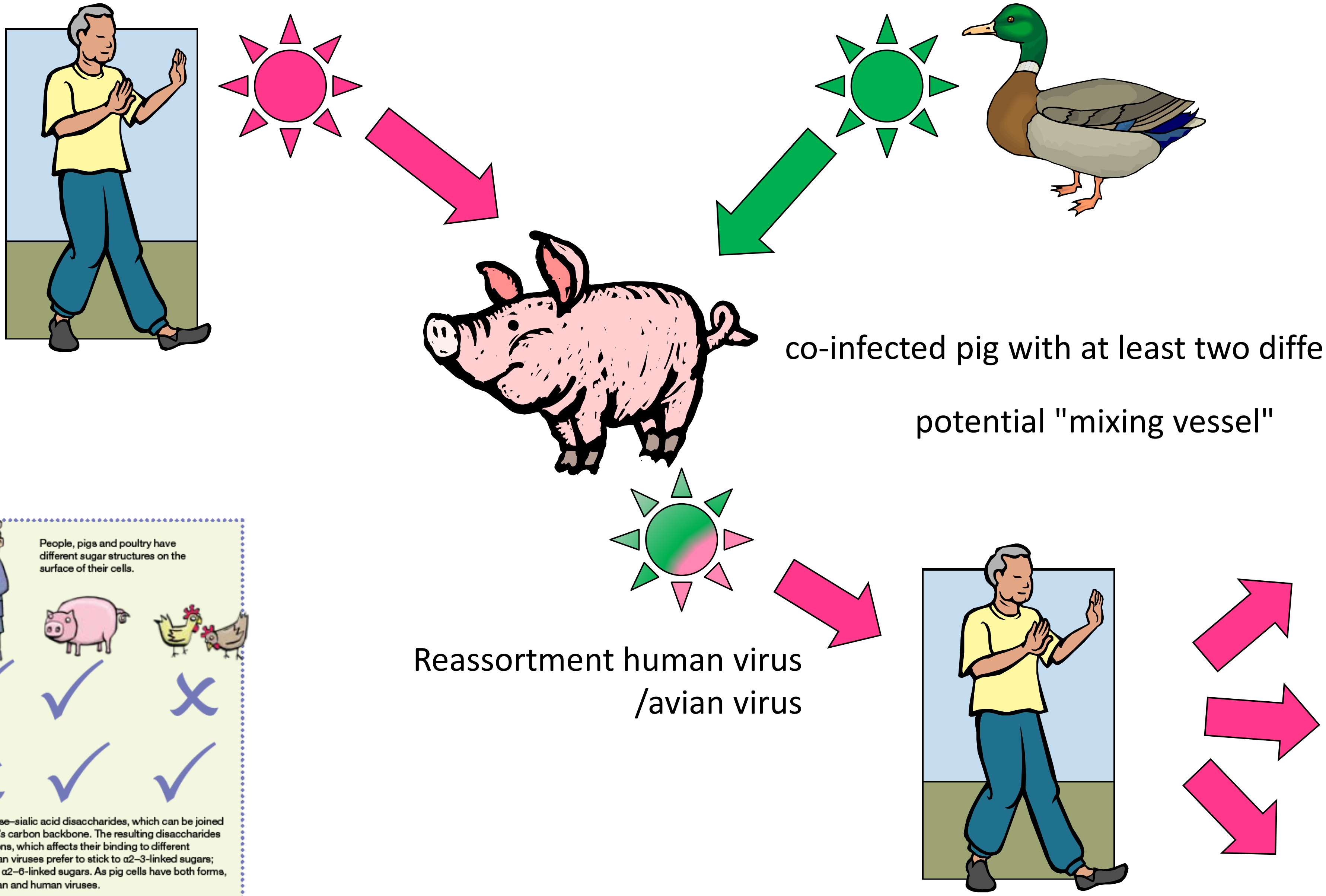
- Antigenic shift
  - Most often corresponds to reassortment
  - two different influenza viruses infect a cell and the genome segments are exchanged during replication
  - two different viruses combine, resulting in exchange of a segment and formation of a hybrid virus
  - may cause pandemics
  - appear suddenly in populations that may have no immunity
  - influenza pandemics can be expected to occur, on average, 3 to 4 times each century
  - Only for influenza A virus



Reassortment influenza virus







co-infected pig with at least two different viruses

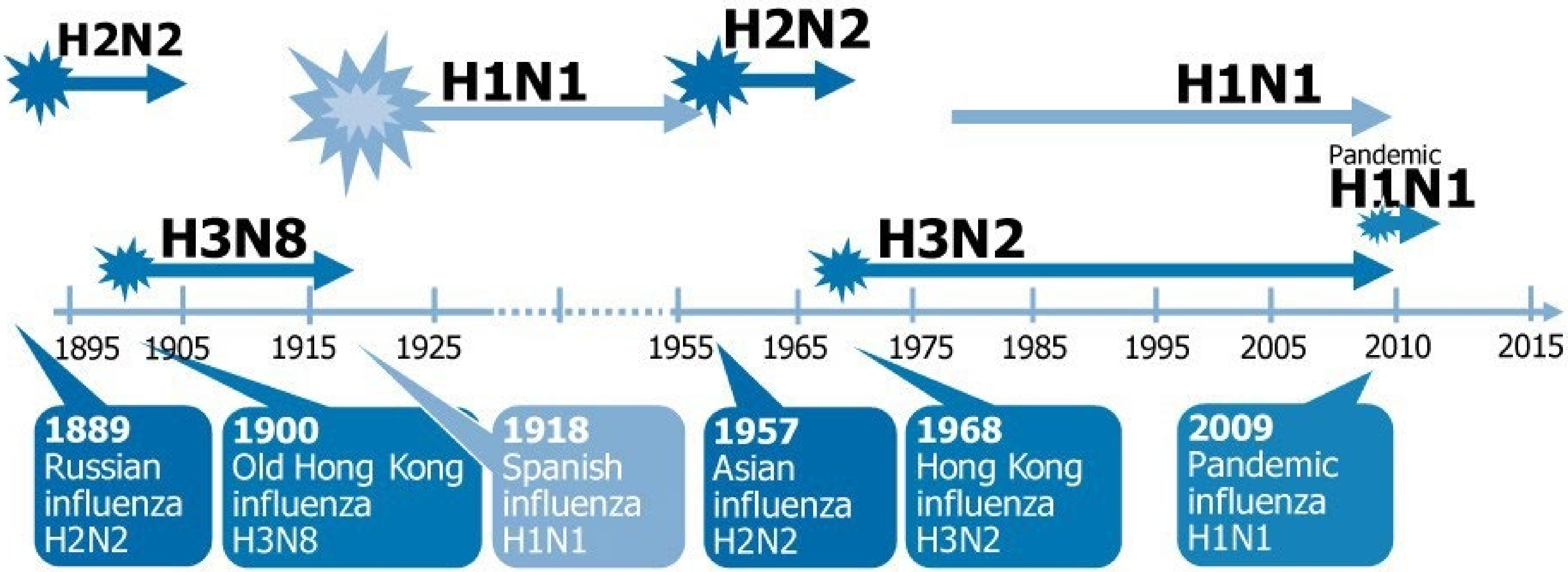
potential "mixing vessel"

Reassortment human virus
/avian virus

Pandemic influenza A history

FIGURE

Recorded human pandemic influenzas since 1885 (early sub-types inferred)



Source: European Centre for Disease Prevention and Control (ECDC) 2009

Reproduced and adapted (2009) with permission of Dr Masato Tashiro, Director, Center for Influenza Virus Research, National Institute of Infectious Diseases (NIID), Japan.

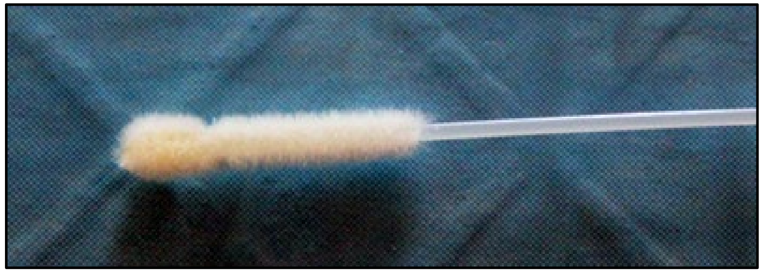
Flu : Symptoms of seasonal flu

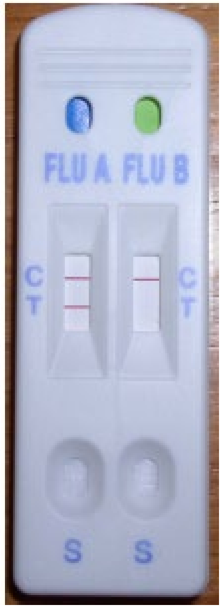
- Short incubation time, 24-72 hours
  - Abrupt onset of fever, malaise, chills, headache and myalgia
  - Begins suddenly
- Symptoms
  - Intense infectious syndrome : fever 39-40°C, chills, fatigue
  - Respiratory signs : nonproductive cough, sore throat, and rhinitis
  - Headache, myalgia (muscle aches)
  - sometimes digestive signs (nausea vomiting)
  - none of these symptoms are specific to influenza
- Evolution
  - Favorable in 4-7 days
  - Persistent asthenia
- Sometimes asymptomatic (children)

Complications

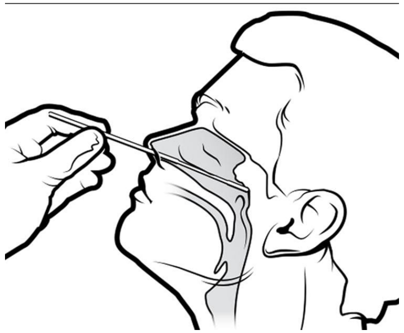
- Severe complication : viral pneumopathy with ARDS (acute respiratory Distress Syndrome)
- In elderly people: High Risk of complication, hospitalization and death
- Can lead to decompensation of a pre-existing pathology (cardiovascular, diabetes, respiratory failure)
- Infants, fever may cause hyperthermic seizures
- Bacterial infections (*Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae*)
- Guillain-Barré Syndrome : rare auto-immune disorder

Diagnosis

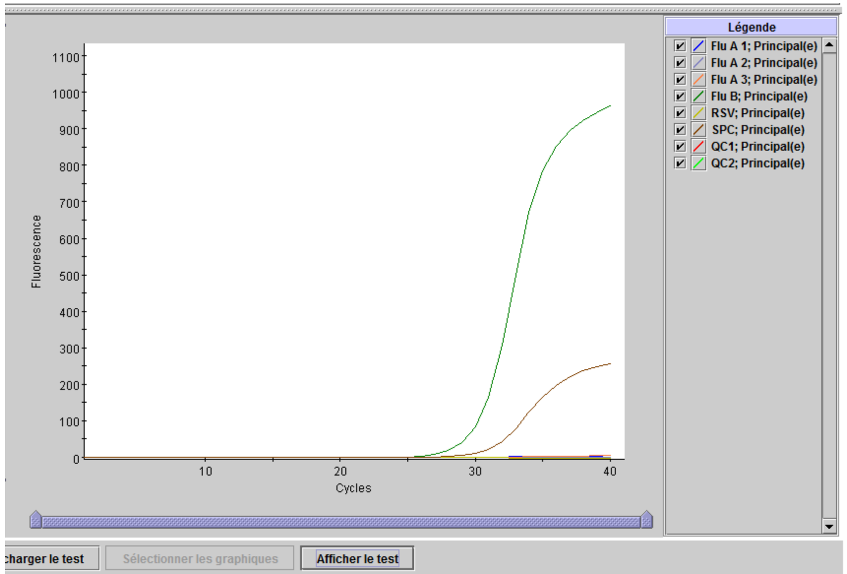




- Essentially clinical
- Biology (nasopharyngeal swab)
- Gold standard assay = Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)
- Detection of viral antigens
  - Immunofluorescence
  - Rapide immunochromatographic test



- Limited interest of serodiagnosis



WHO influenza nomenclature

Antigenic type

Geographical origin

Year of collection

Neuraminidase subtype

A / Duck / Hong-Kong / 7 / 1975 (H3N2)

Host of origin

Strain number

Hemagglutinin subtype

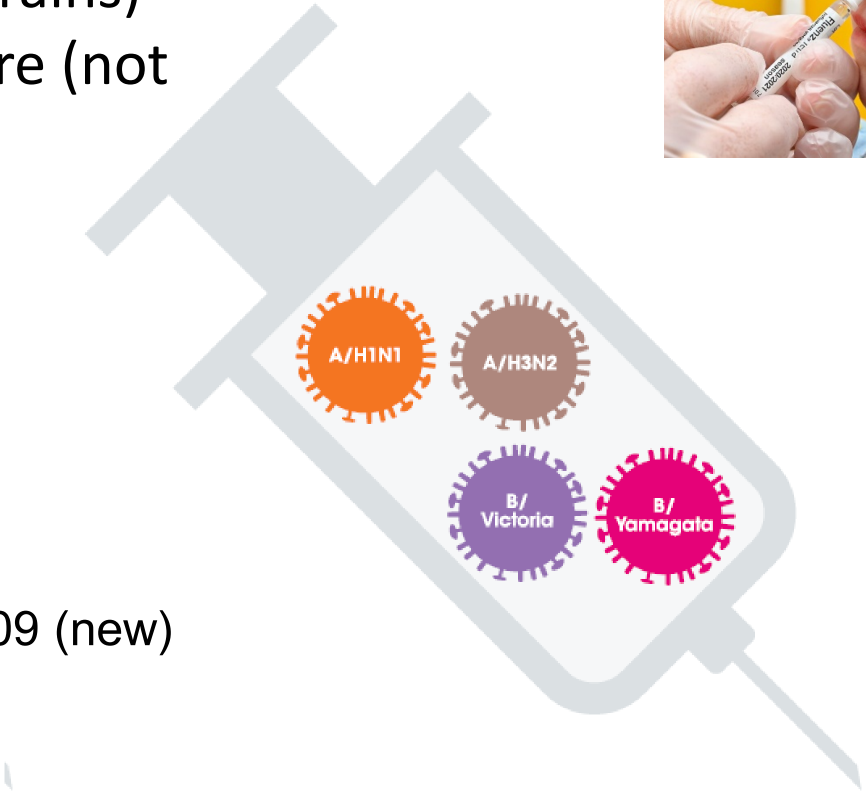
- For human-origin viruses, no host of origin designation is given
- The 2009 pandemic virus was assigned a distinct name: A(H1N1)pdm09

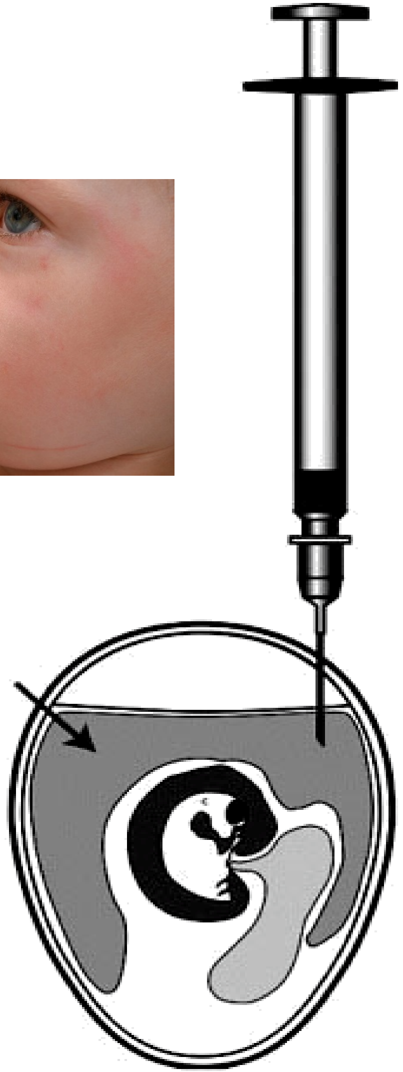
A / Puerto Rico / 8 / 1934 (H1N1)

B / Wisconsin / 1 / 2010

The seasonal influenza vaccine

Inactivated vaccine
and live attenuated vaccine (not available in France)
Quadrivalent (4 strains) or trivalent (3 strains)
Obtained in fertilized egg or in cell culture (not available in France)
One injection per year



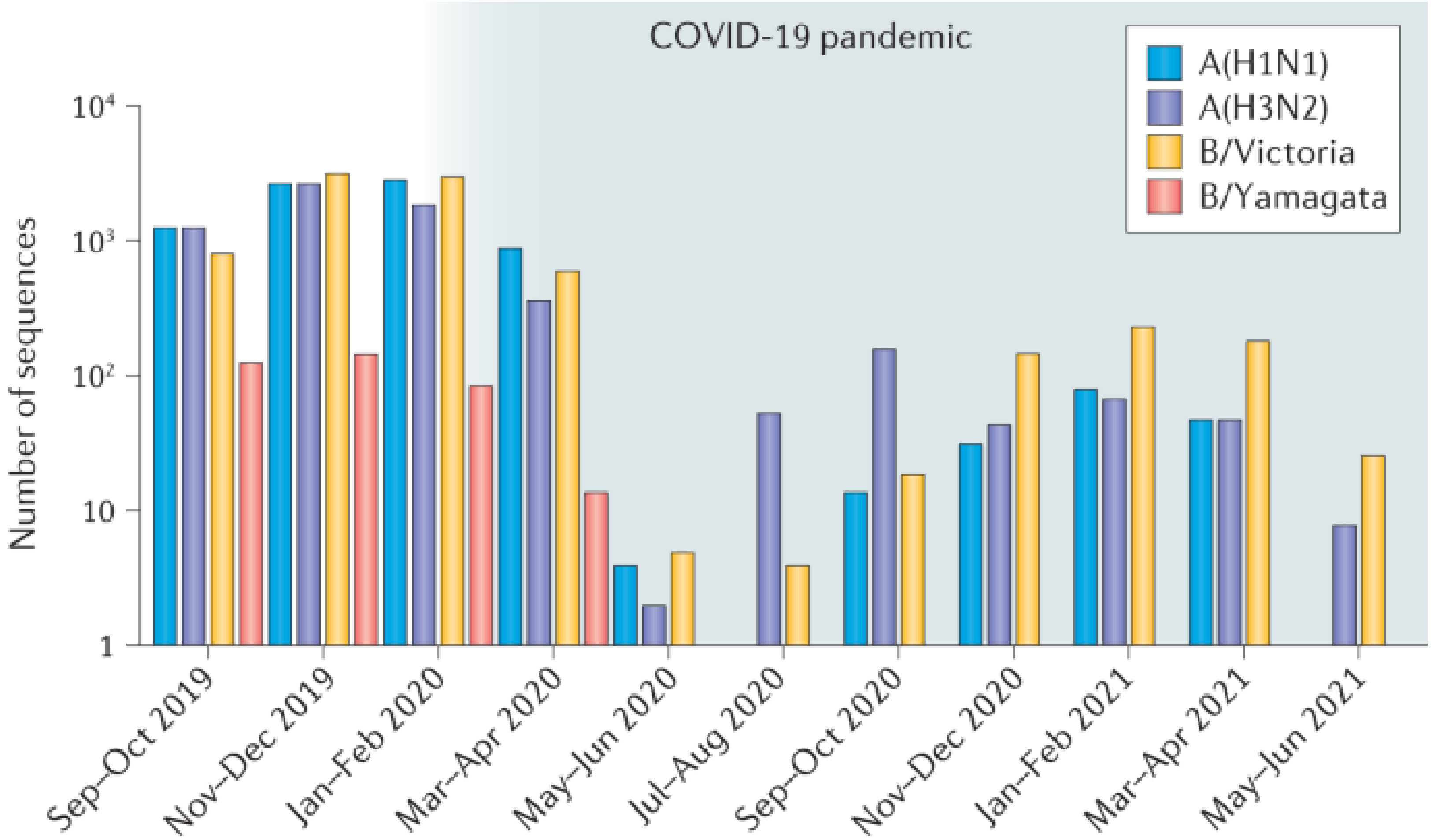


WHO recommendations for Northern hemisphere

2020/2021

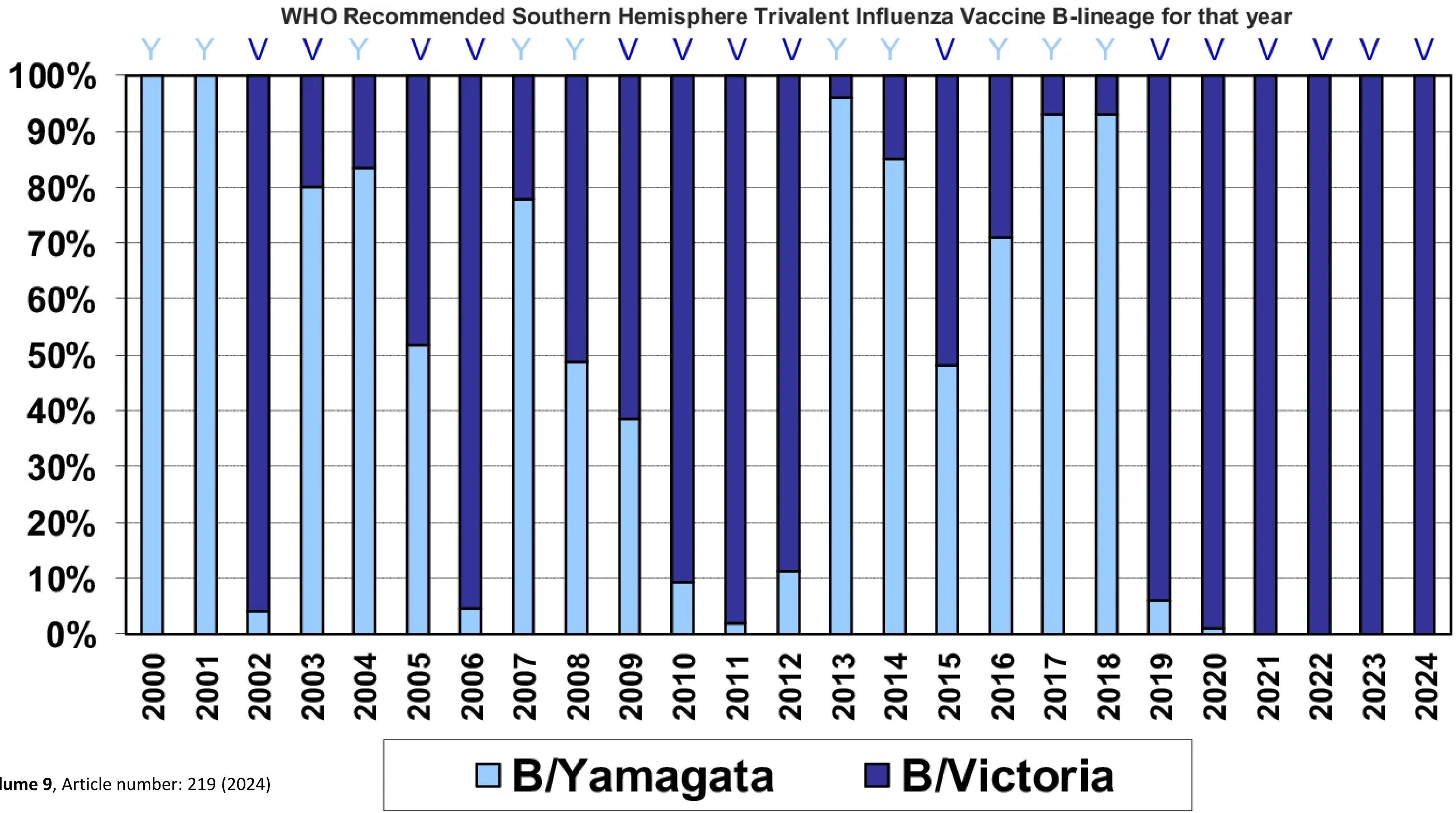
A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09 (new)
A/Hong Kong/2671/2019 (H3N2) (new)
B/Washington/02/2019 (Victoria) (new)
B/Phuket/3073/2013 (Yamagata) (inchanged)

Distribution of influenza virus subtypes and lineages



Yamagata lineage extinction during COVID19

Proportions of influenza B-lineages in Australian 2000–2024 as determined by samples submitted to the WHO influenza Centre in Melbourne



npj Vaccines **volume 9**, Article number: 219 (2024)

Epidemiology

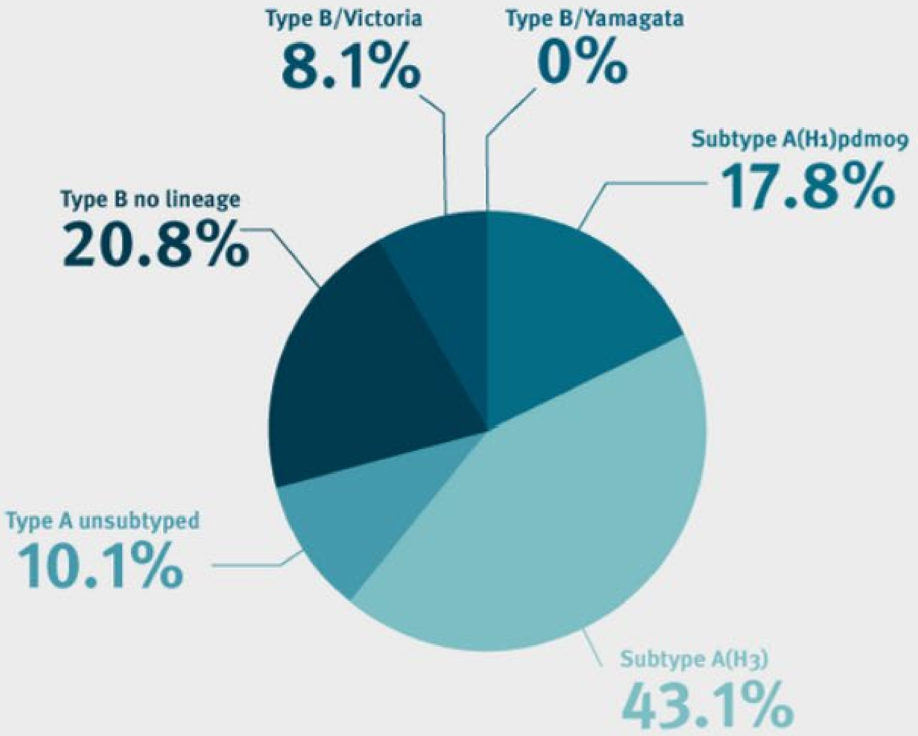
Influenza in Europe

Data from EU and EEA countries for the 2022–2023 season

Week 12 (20 Mar – 26 Mar 2023)

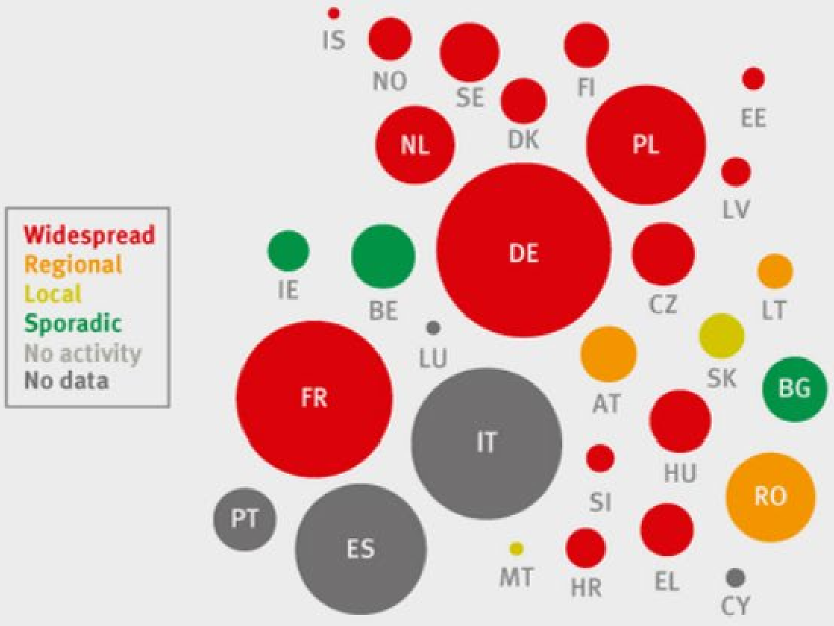
Influenza viruses circulating in 2022–2023

Only sentinel specimens are included



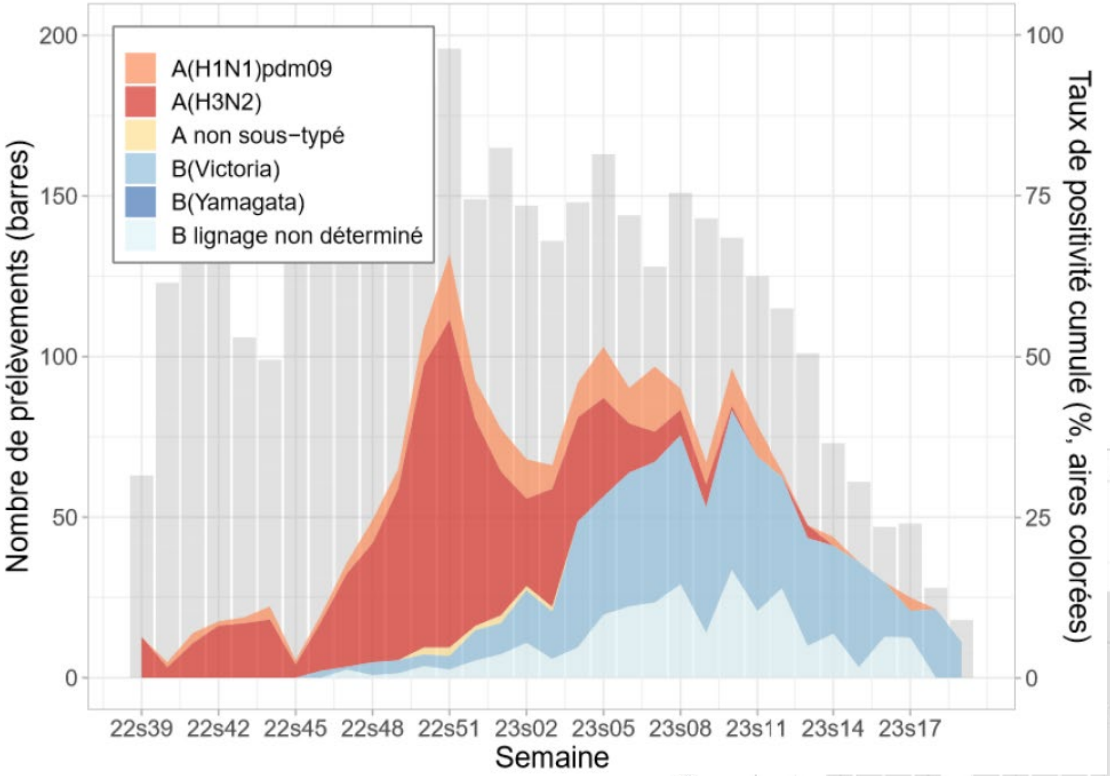
Influenza geographic spread

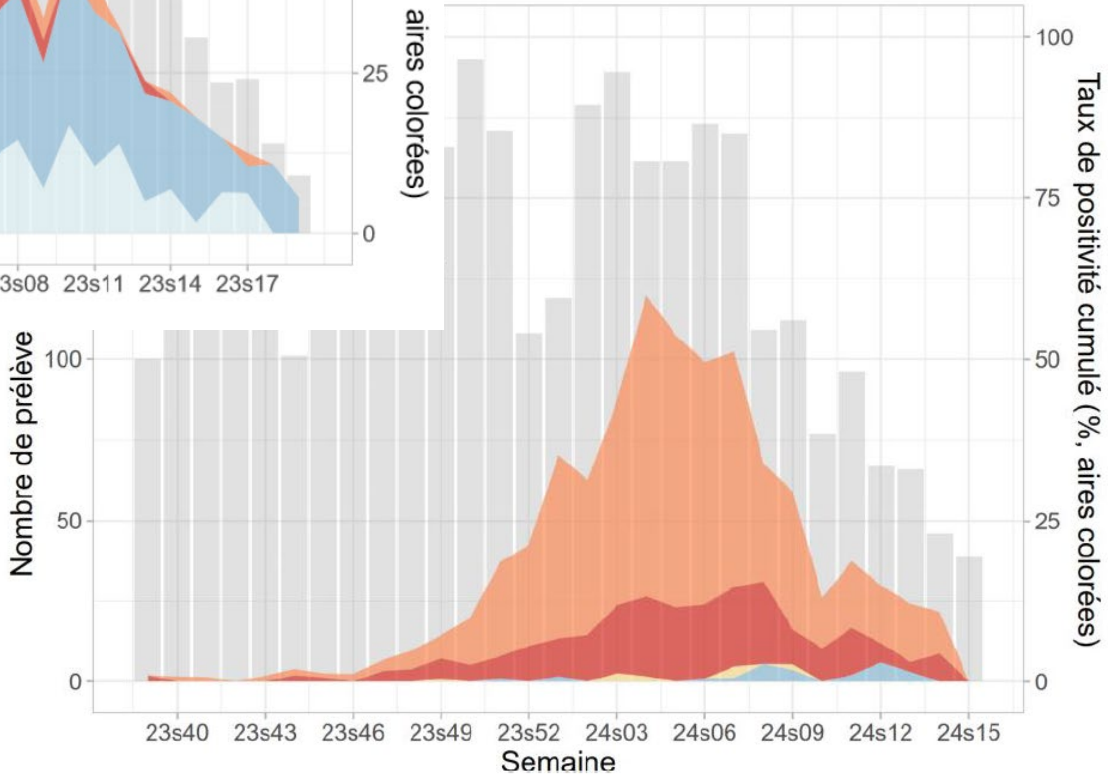
based on sentinel reports of influenza-like illness and/or acute respiratory infections

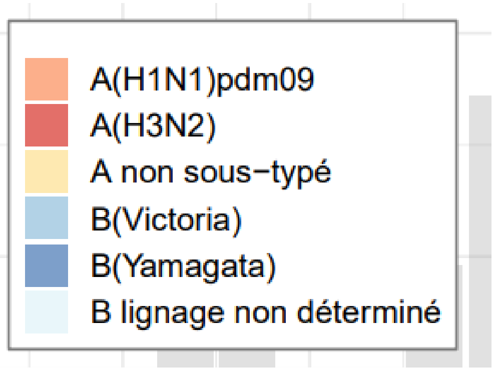


Bubble size is indicative of country population

Distribution of influenza virus subtypes







In France

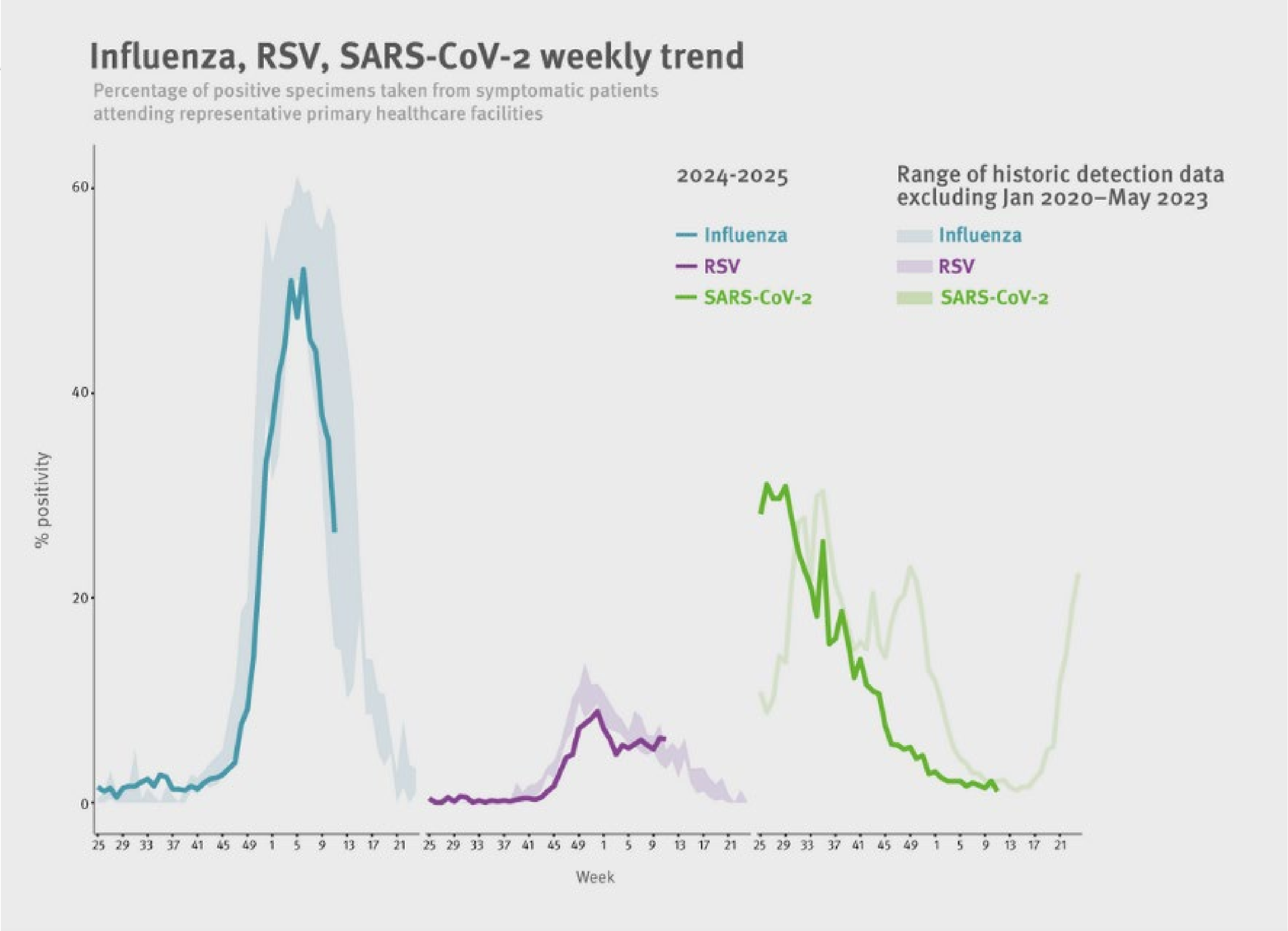
Virus de la grippe A
Sous-type H1N1
Sous-type H3N2

Virus de la grippe B
Lignage Victoria
Lignage Yamagata
(disparu depuis 2020)

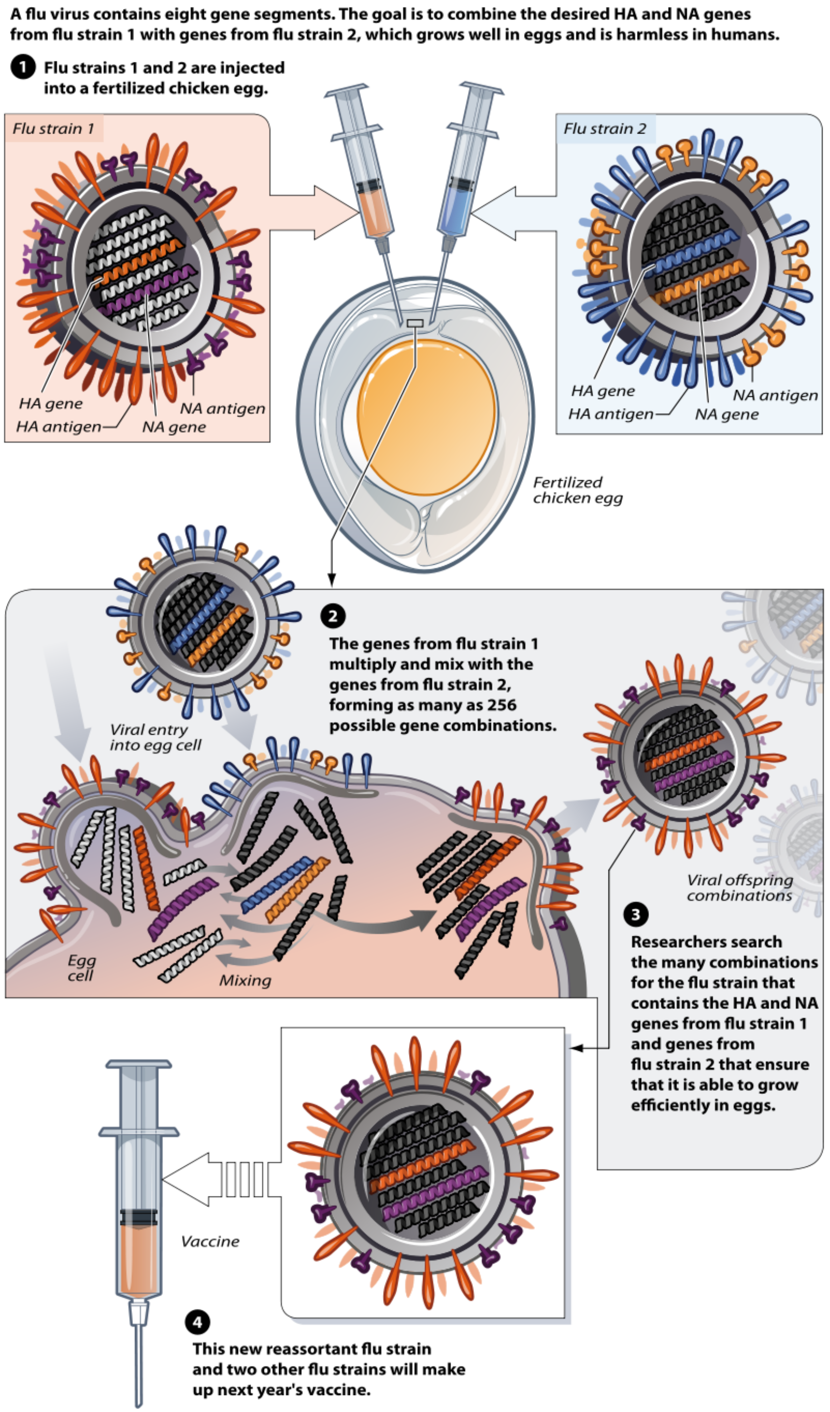
Sentinelles
Réseau Sentinelles

Influenza, RSV, SARS-CoV-2 in Europe

Data from EU and EEA countries
Week 11 (10 Mar–16 Mar 2025)



The seasonal influenza vaccine



World Health Organization

The WHO recommends that **trivalent** vaccines for use in the 2025–2026 northern hemisphere influenza season contain the following:

Egg-based vaccines

- an A/Victoria/4897/2022 (H1N1)pdm09-like virus
- an A/Croatia/10136RV/2023 (H3N2)-like virus
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

Cell culture-, recombinant protein- or nucleic acid-based vaccines

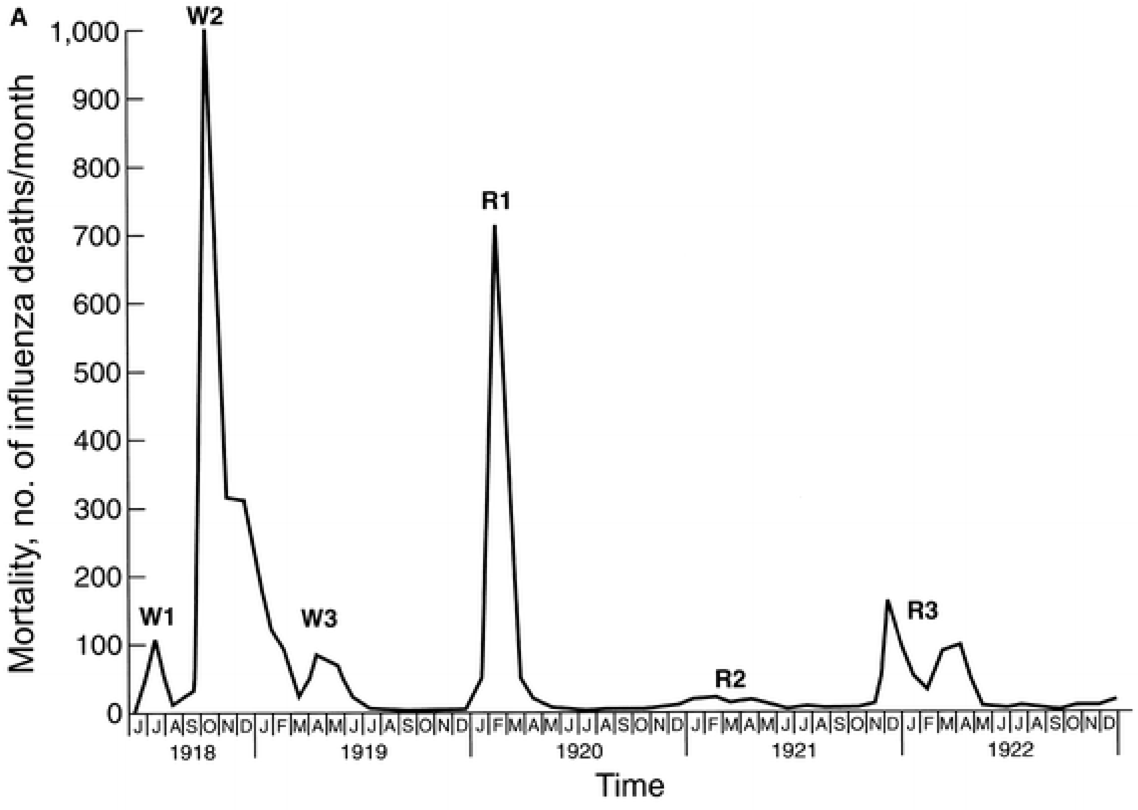
- an A/Wisconsin/67/2022 (H1N1)pdm09-like virus
- an A/District of Columbia/27/2023 (H3N2)-like virus
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

The recommendation for the B/Yamagata lineage component of quadrivalent influenza vaccines remains unchanged from previous recommendations:

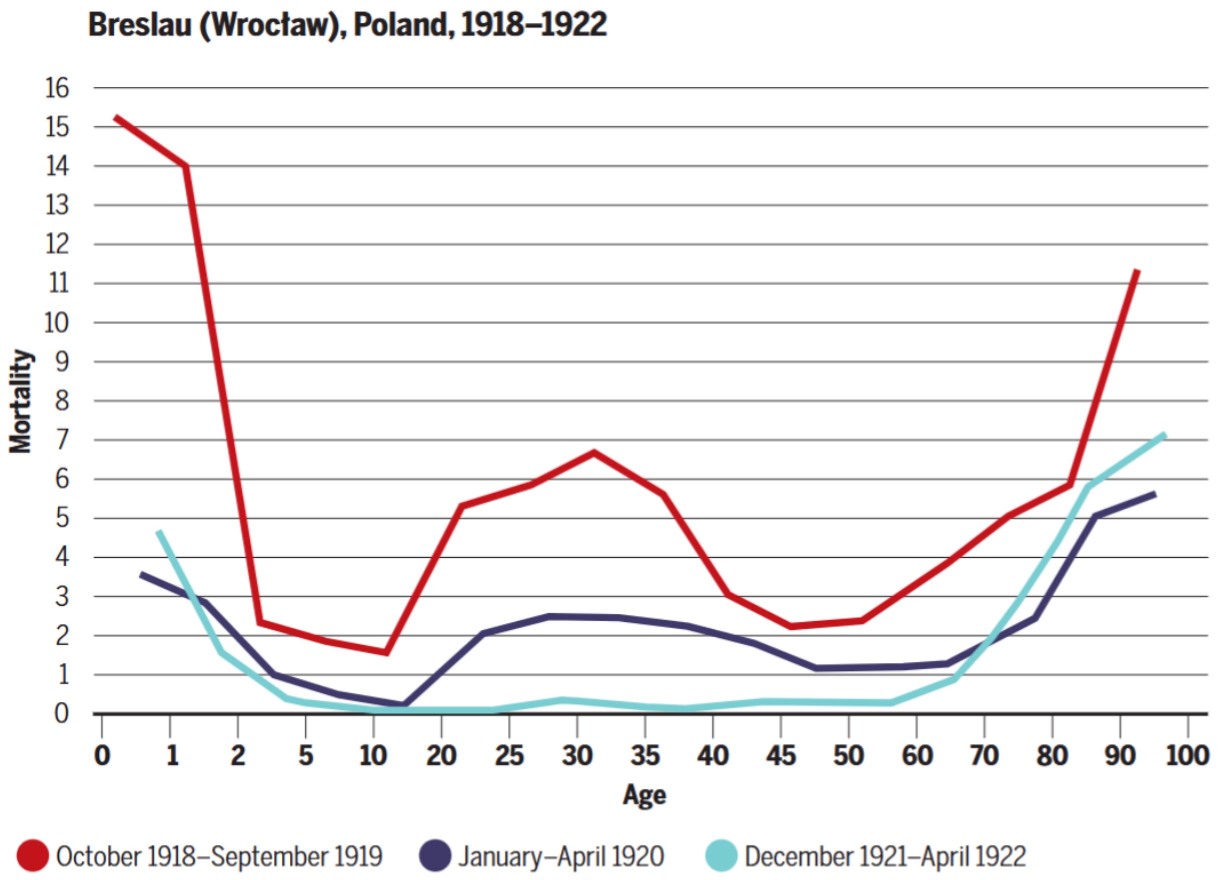
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Spanish flu in 1918

- About 40 million deaths worlwide
- Understand the reasons of the extreme pathogenicity of this H1N1 virus

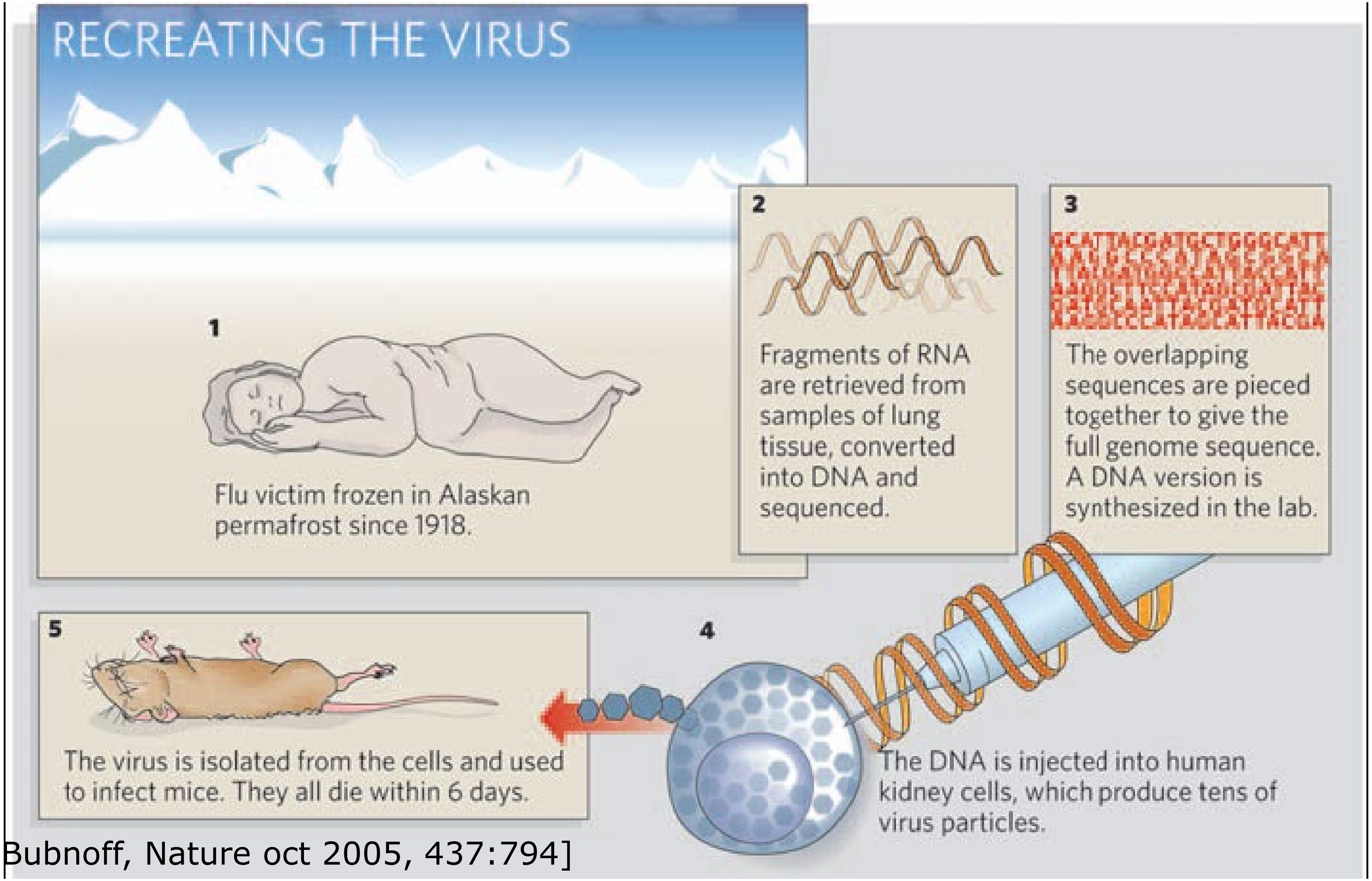


Influenza deaths/1000 persons



From Morens et Fauci, 2007

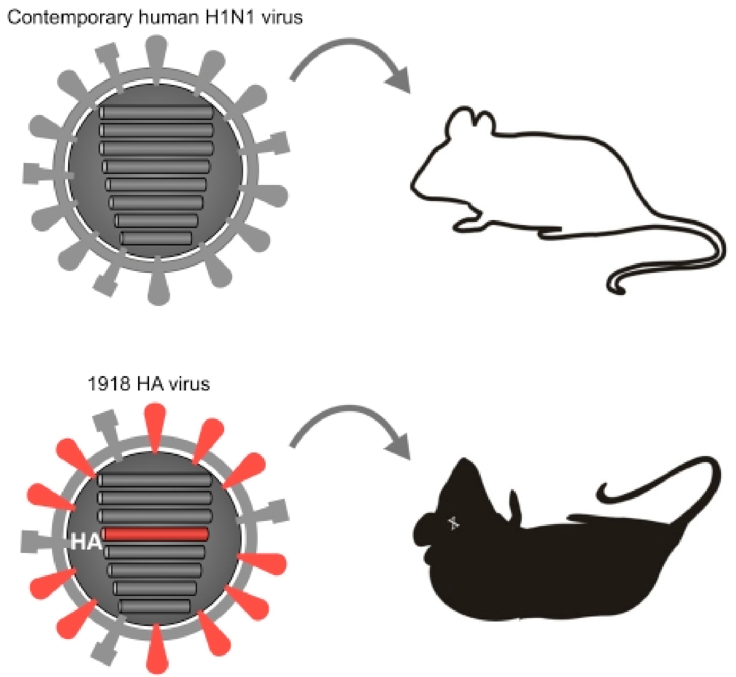
The “resurrection” of H1N1 of 1918 through reverse genetics

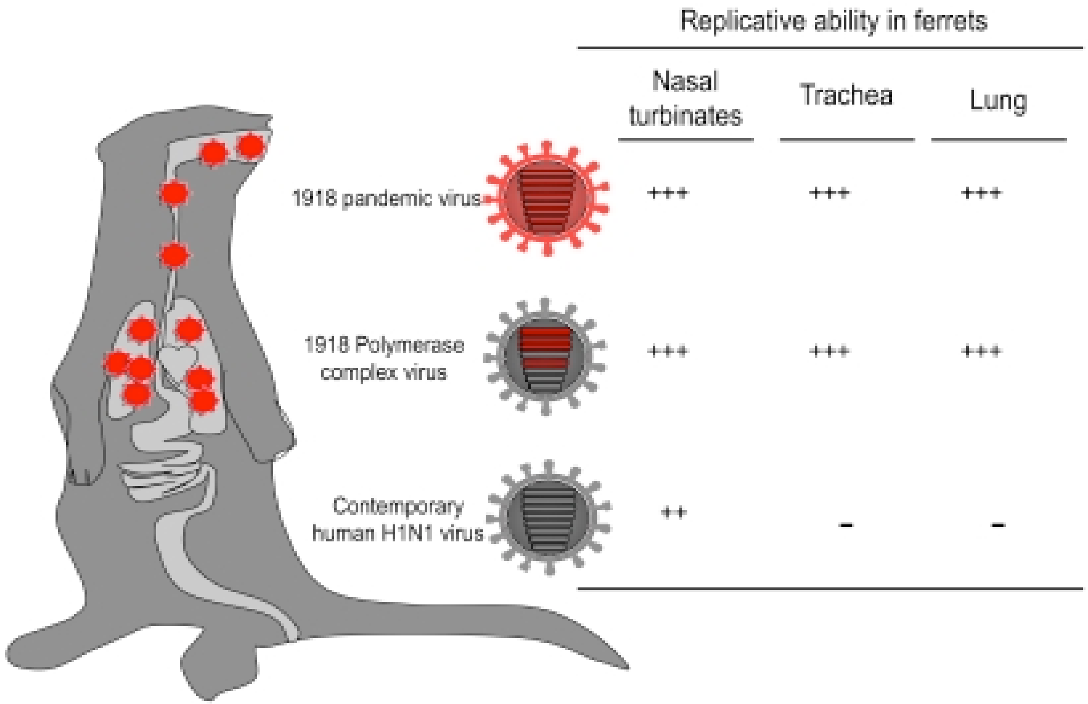


[von Bubnoff, Nature oct 2005, 437:794]

Characterization of the H1N1 virus from 1918

- 8 segments from avian origin (Taubenberger et *al.*, Nature 2005)
- Increased pathogenicity
  - aberrant Immune response (edema, exacerbation of inflammatory syndrome, massive synthesis of proinflammatory cytokines and chemokines)
  - Virulence related to HA and to RNA polymerase
  - Other factors involved PB1-F2, NA, NS1





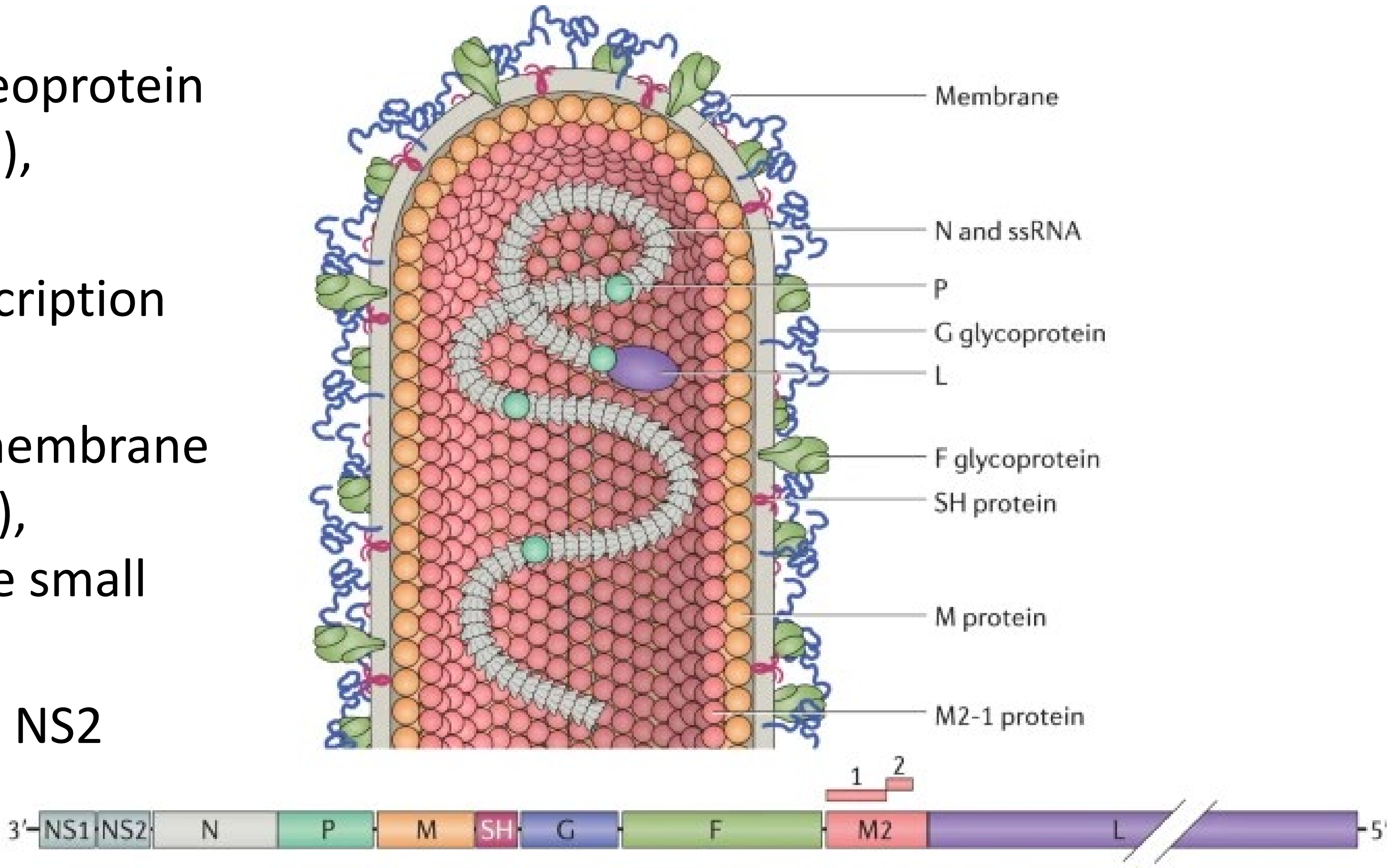
Watanabe et al, Plos pathogens, 2011

Respiratory Syncytial Virus (RSV)

- First isolated in 1955 from chimpanzees suffering from respiratory illness in the US then isolated from infants with severe lower respiratory illness
- infects nearly all children by 2 years of age
- most common cause of acute lower respiratory tract infection and hospitalization in children under 2 years of age
- belongs to the *Orthopneumovirus* genus of the *Pneumoviridae* family in the order *Mononegavirales*
- Every year, 33 million cases of acute infection, 3.6 million hospitalizations, and over 100,000 deaths
- Most hospitalizations occur in infants less than 6 months old
- Older adults are also at risk for severe RSV disease, in particular with co-morbidity

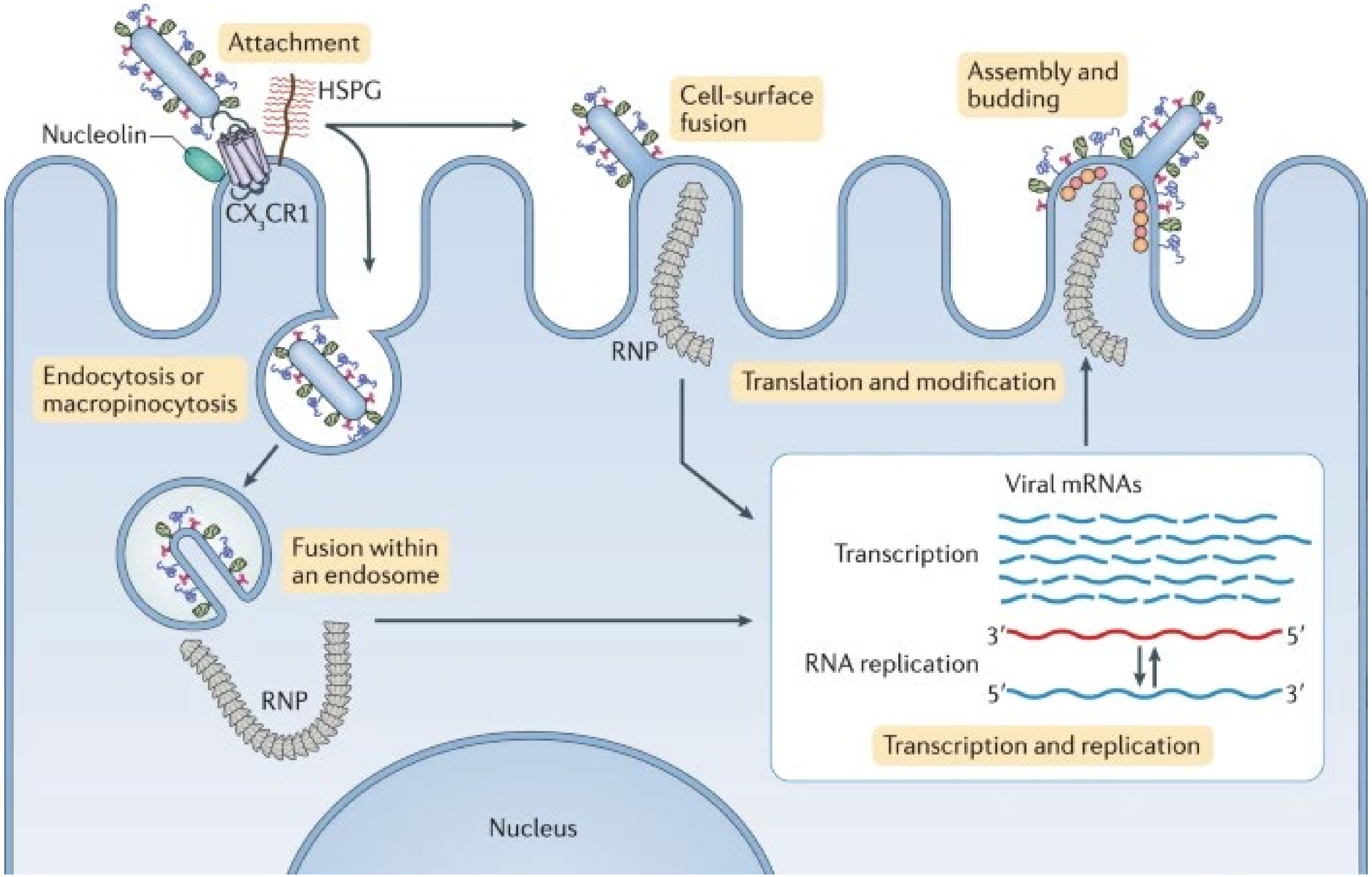
Respiratory Syncytial Virus (RSV)

- negative-sense ssRNA genome encoding 11 proteins
- Nucleocapsid = genome + nucleoprotein (N), + RdRp (phosphoprotein (P), polymerase (L))
- Matrix protein and M2–1 transcription processivity factor
- Envelope studded with three membrane proteins = the fusion protein (F), attachment protein (G), and the small hydrophobic protein (SH)
- nonstructural proteins NS1 and NS2



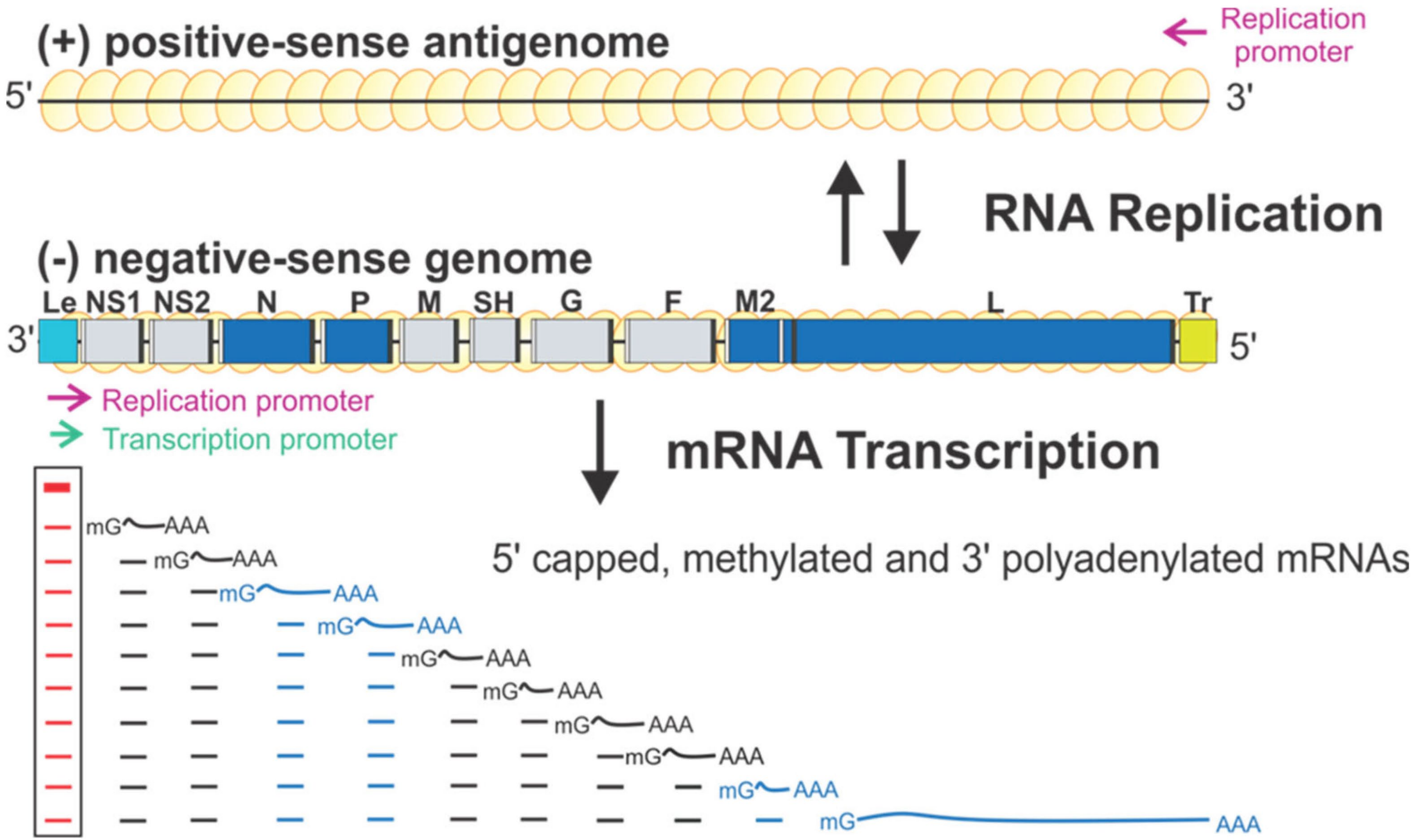
Nature Reviews Microbiology **volume 17**, pages 233–245 (2019)

Life cycle of RSV



Nature Reviews Microbiology **volume 17**, pages 233–245 (2019)

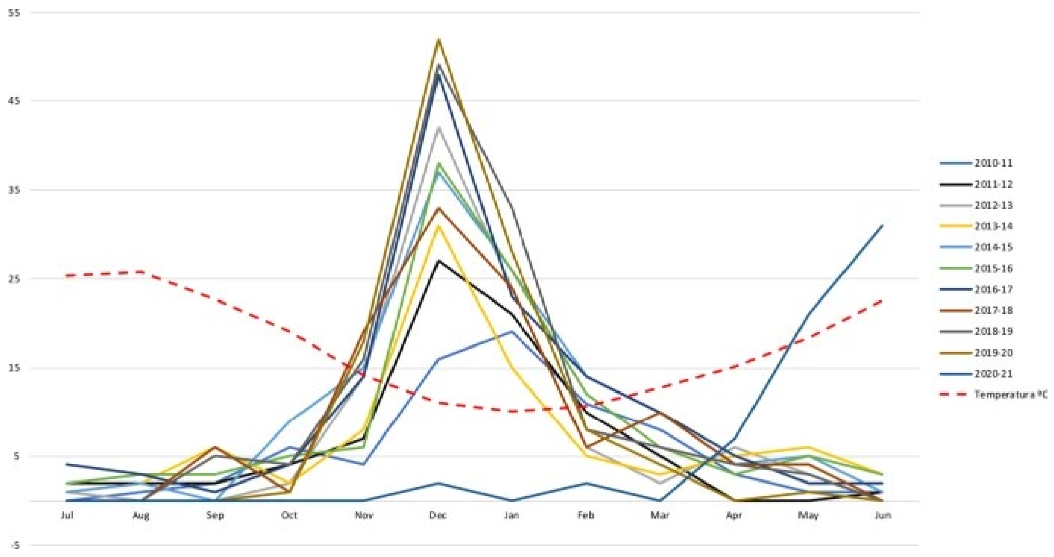
Genome organization and RNA synthesis of RSV



- leader (Le, cyan) and trailer (Tr, gold) are at 3′ and 5′ ends

Bronchiolitis in infants

- Involvement of the bronchioles (small bronchi)
- Affects newborns and infants up to 2 years of age. Peak frequency between 2 and 8 months of age
- Epidemic from mid-October to the end of winter, peaking in December
- Highly contagious
- Nearly 300,000 cases by 2022
- Most often benign, treated in the community
- but 2-3% of children hospitalized under 1 year old
- Complications
  - Bacterial superinfections
  - Dehydration
  - Respiratory distress



BMC Infectious Diseases **volume 22**, Article number: 84 (2022)

Bronchiolitis

- **Early Symptoms**
  - Runny or congested nose
  - Sneezing, Mild cough
  - Slight fever
- **Progressive Symptoms (**infection moves to the lower respiratory tract)
  - Severe cough
  - Wheezing (high-pitched noise during exhalation)
  - Rapid or labored breathing
  - Difficulty feeding or eating

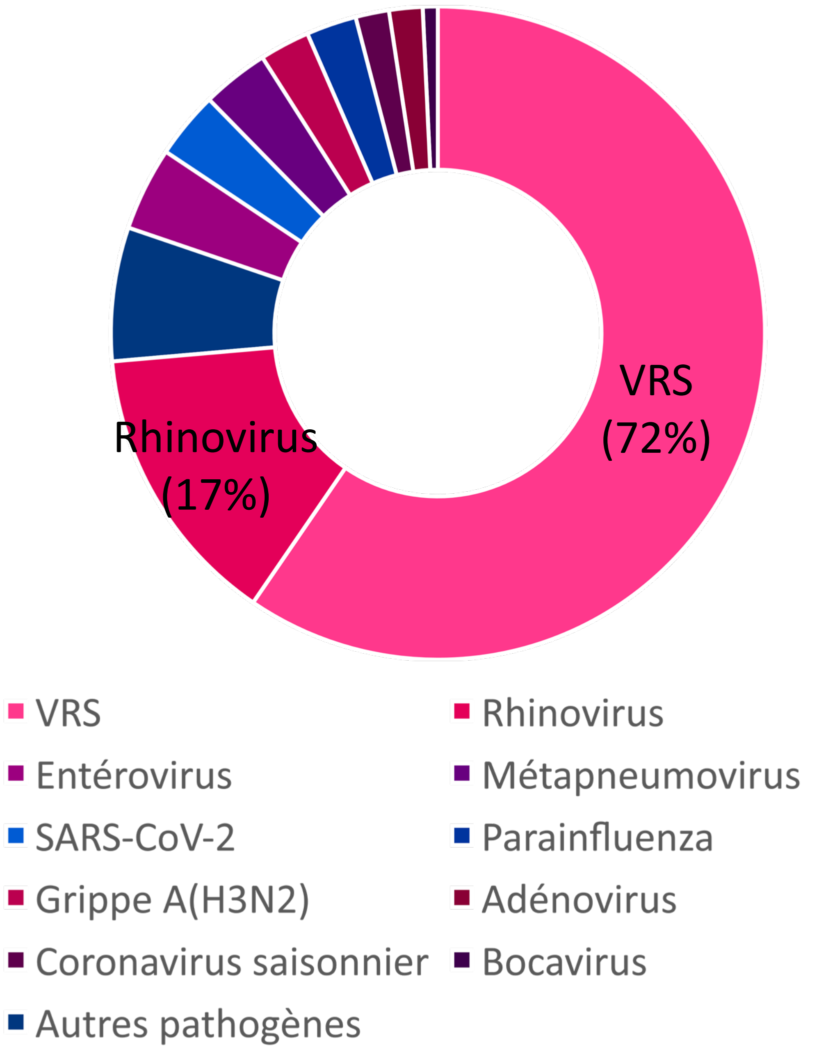
Bronchiolitis

- **Severe cases, especially in infants:**
  - Rapid breathing
  - Struggling to breathe (chest muscles pulling inward)
  - Cyanosis (bluish skin due to lack of oxygen)
  - Poor feeding and dehydration
  - Unusual tiredness or lethargy
- Most cases resolve at home, but hospitalization may be required for severe infections
- Infants, premature babies, and immunocompromised individuals are at higher risk for complications

Etiologic agents of bronchiolitis

- ❑ Respiratory syncytial virus (RSV) +++
- ❑ Rhinovirus
- ❑ Metapneumovirus
- ❑ Adenovirus
- ❑ para influenza Virus…

Agents pathogènes responsables de la bronchiolite
(nourrissons admis en service de réanimation pour une bronchiolite en France au cours de la saison 2023-2024)



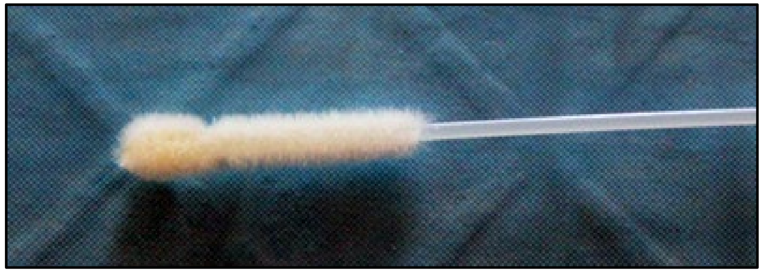
Bulletin

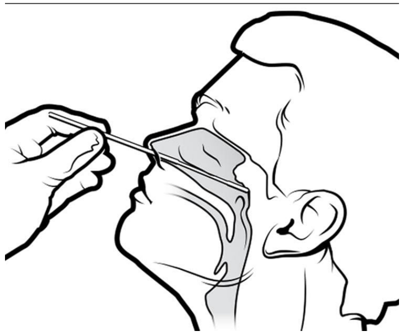
Santé publique France

Infections respiratoires aiguës

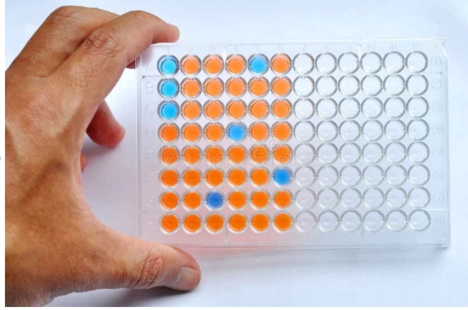
The majority of cases were less than 6 months old (79%) and 28% of cases had at least one identified co-morbidity or were premature.

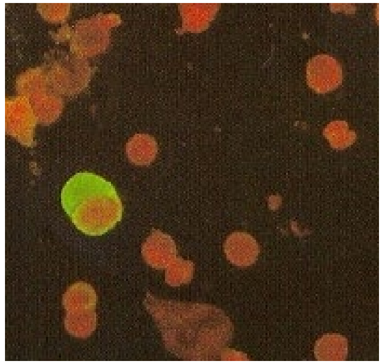
Diagnosis

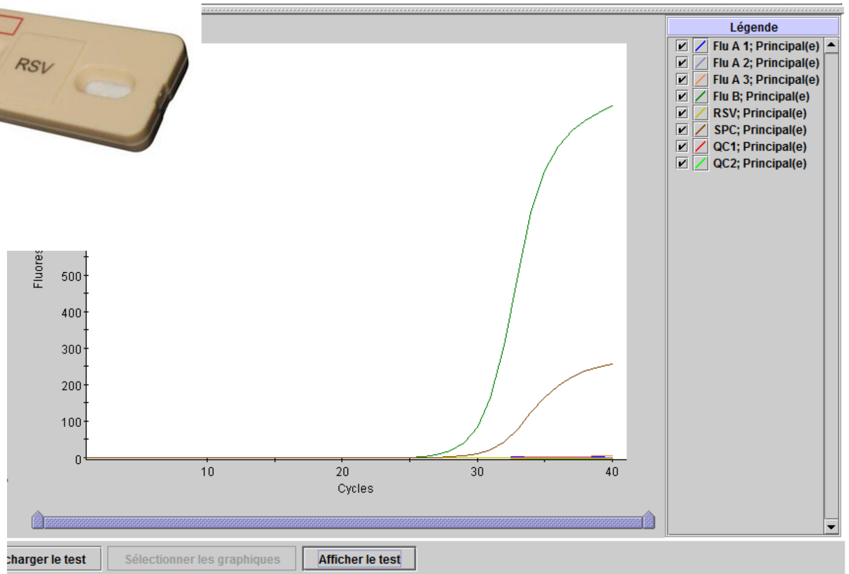




- Essentially clinical for bronchiolitis
- Important for severe infections
- Biology (nasopharyngeal swab)
- Gold standard assay = Reverse Transcriptase Polyme Chain Reaction (RT-PCR)
  - Multiplex PCR
- Detection of viral antigens
  - Immunofluorescence
  - Rapide immunochromatographic test







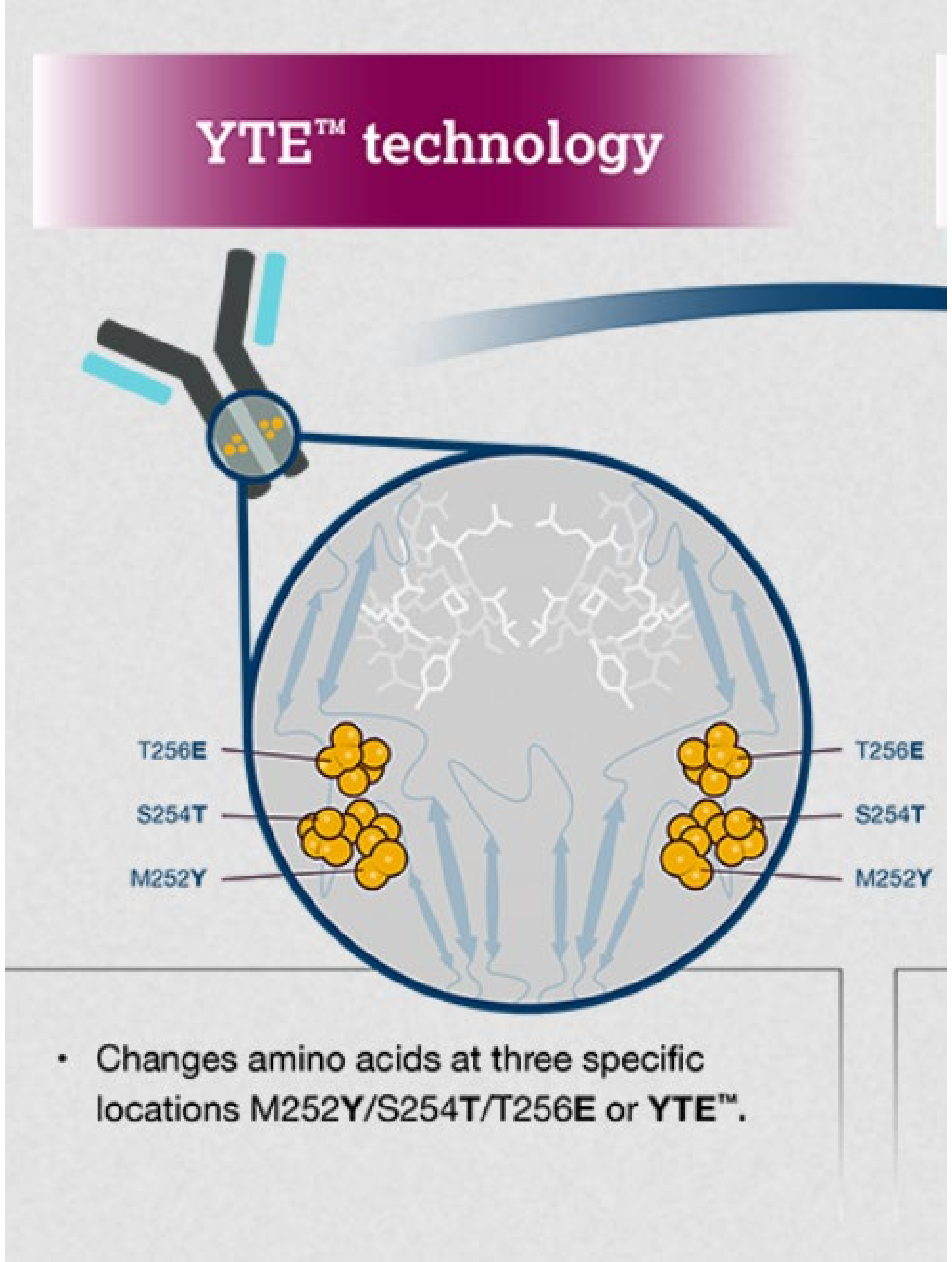
- Limited interest of serodiagnosis

Prevention

- 2 objectives :
  - Limiting transmission
  - postponing the age of primo-infection
  - Importance of hygiene rules +++
- Two alternative strategies to prevent the infection:
- **Monoclonal antibodies** (NIRSEVIMAB, BEYFORTUS®)
  - Passive immunisation using monoclonal Ab against F of RSV
  - For newborns
- **vaccine** ABRYSVO® for pregnant woman
  - Administration during the 3rd trimester of pregnancy (between 32 and 36 weeks of amenorrhoea)
  - Passive protection of the baby by transfer of Ab during pregnancy

Passive immunisation

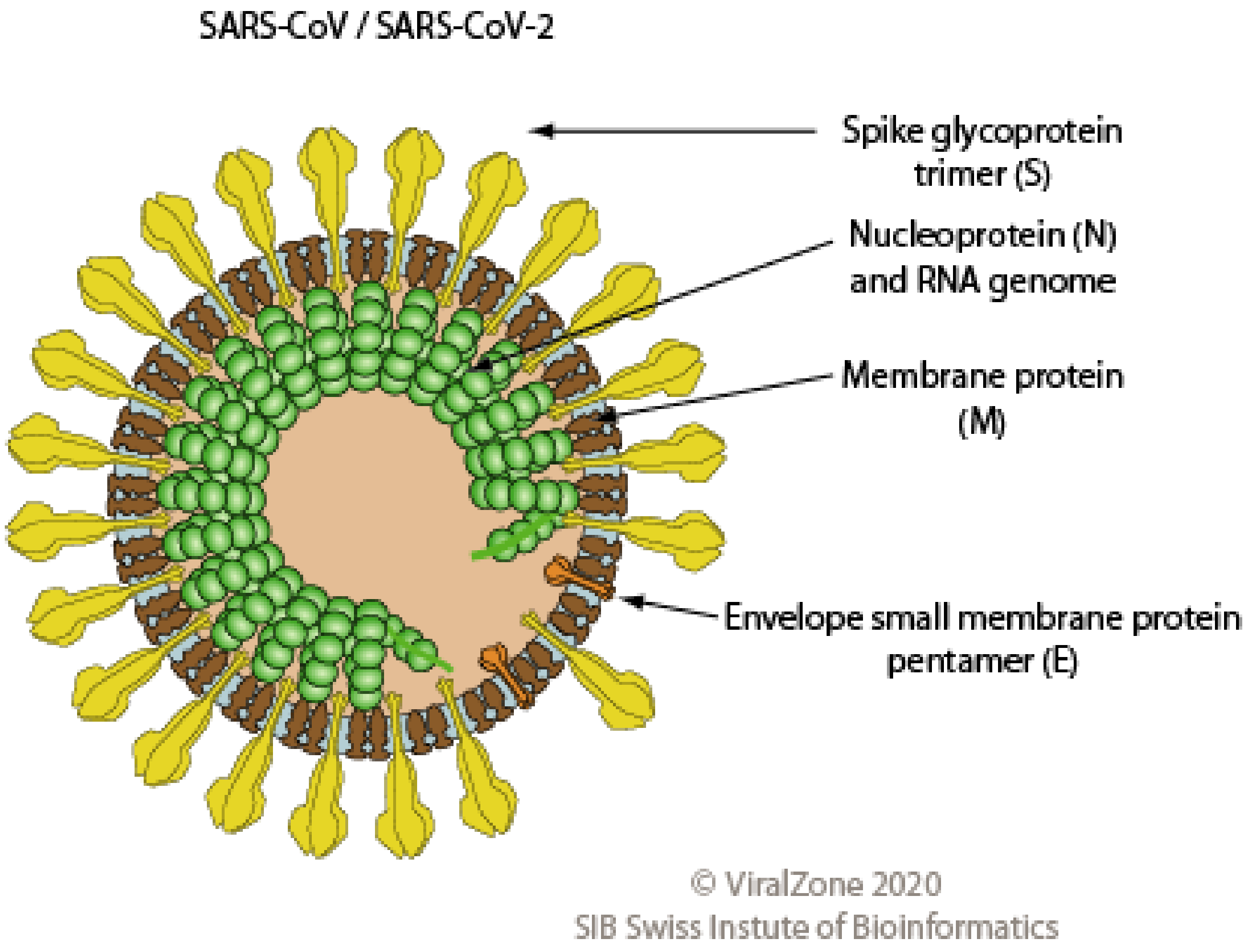
- NIRSEVIMAB, BEYFORTUS®
  - For all the newborns
  - **Only one IM injection per year** because it has a long duration of action
  - Directed against an antigenic site of the F fusion protein, inhibits cell fusion
  - modified by a triple amino acid substitution (YTE) in the Fc region to prolong serum half-life
  - Protect during at least 5 months



SARS-CoV-2

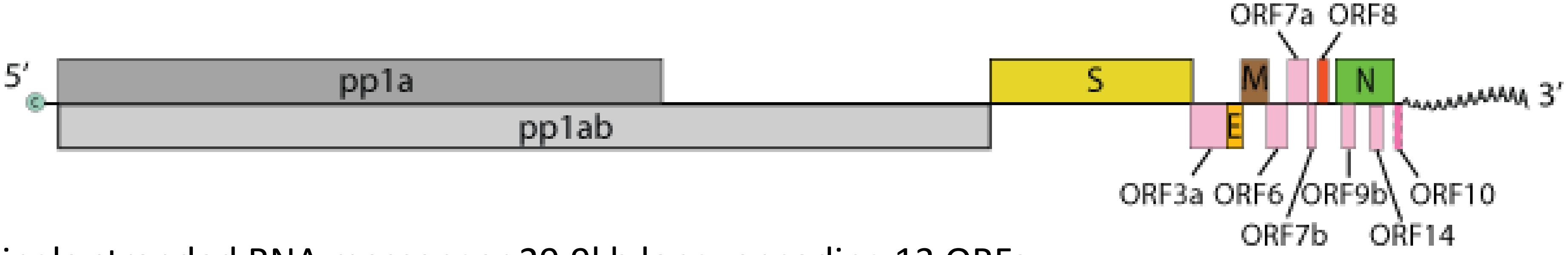
Basic

Coronavirus SARS-CoV-2



- Single-stranded positive-sense linear RNA
- ~30 kbp
- Helical capsid (N)
- Envelope
- Spike S (trimer)
- Pentamer E
- M link between capsid and envelope

Genome and Proteome of SARS-CoV-2

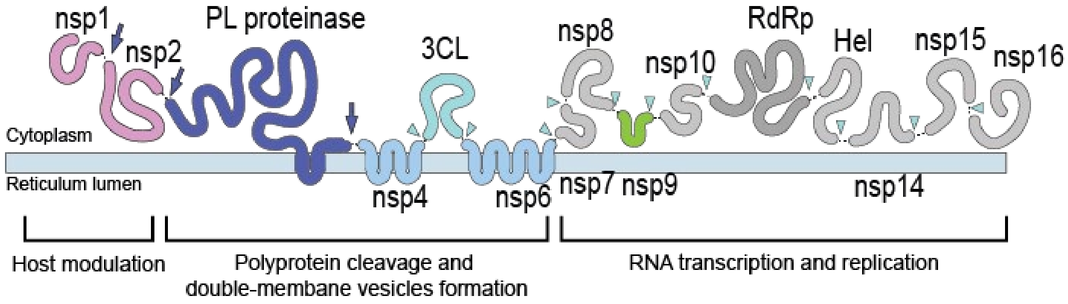


Genome: single stranded RNA messenger 29.9kb long, encoding 13 ORFs

The proteins are expressed by two ways: primary translation of polyprotein that initiates the infection, and after some replication, subgenomic mRNA expression which produces all structural proteins

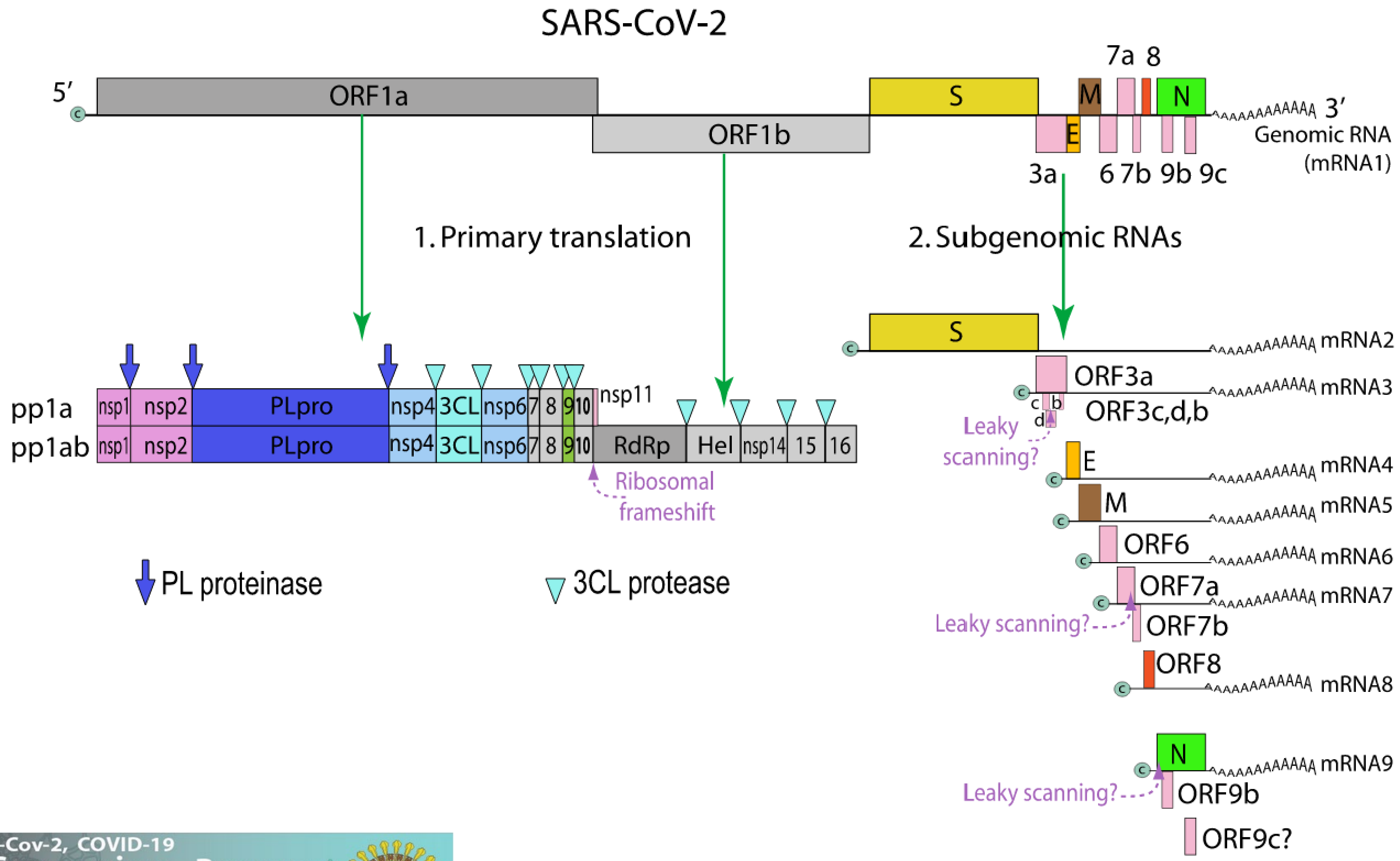
proteome contains
- 2 polyproteins pp1a et pp1ab cleaved by viral proteases to give replicase (RNA dependent RNA polymerase) and other non structural proteins involved in viral replication
- Structural proteins S, E M et N and 8 non structural proteins

pp1ab topology



RdRp is the viral polymerase, PL and 3CL are responsible of the polyprotein cleavages

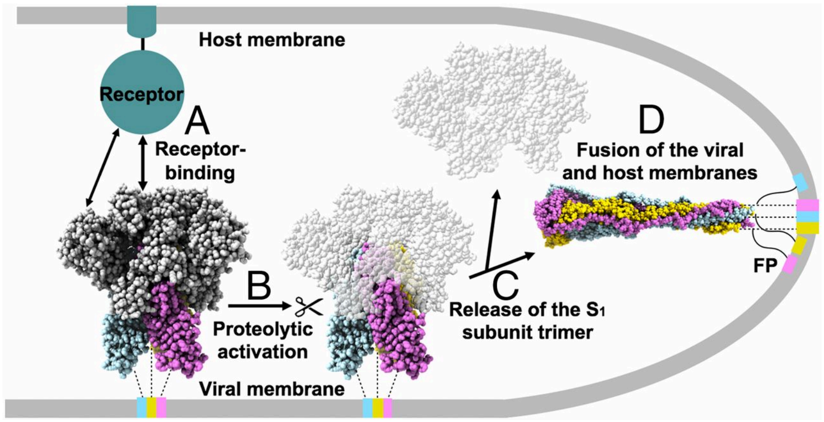
Genome and Proteome of SARS-CoV-2

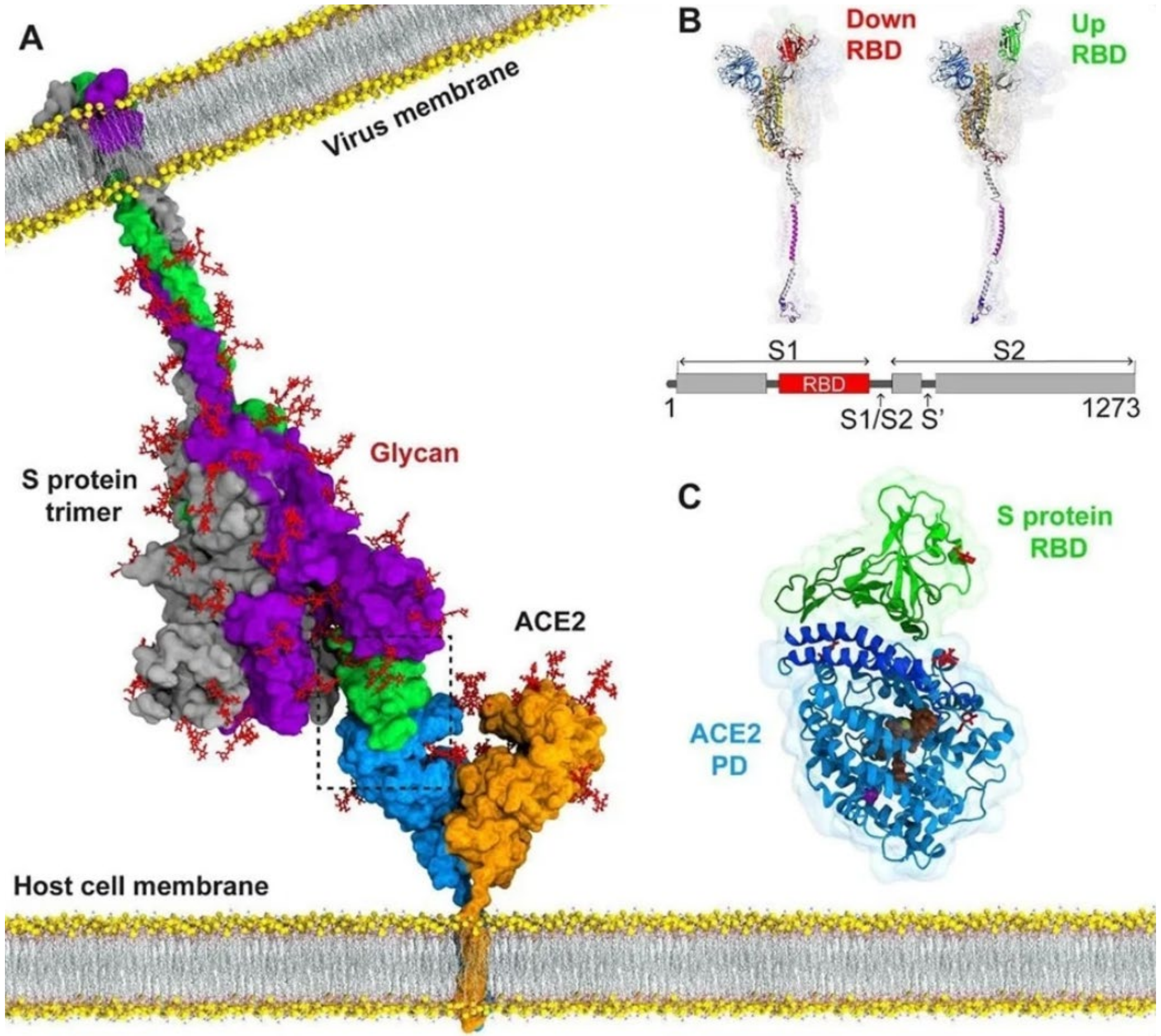


Basic

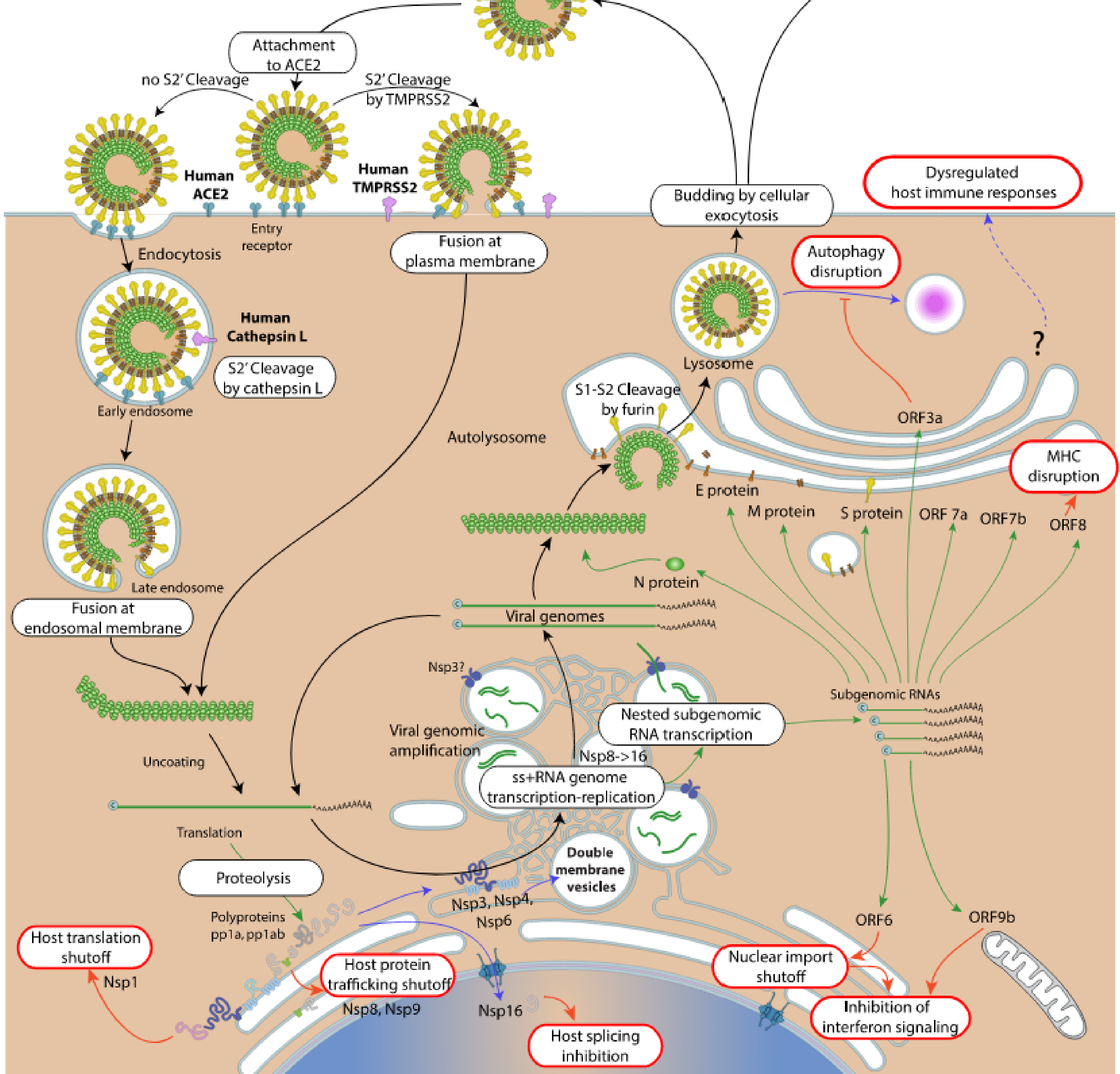
The Spike S

- Trimer
- S divided in 2 domains S1 et S2, involved in fixation and fusion
- S1 binds ACE2 (angiotensin I-converting enzyme-2)
- S1 contains the RBD (receptor binding domain)
- Several conformations
- S2 contains fusion peptide (FP)





Viral multiplication cycle

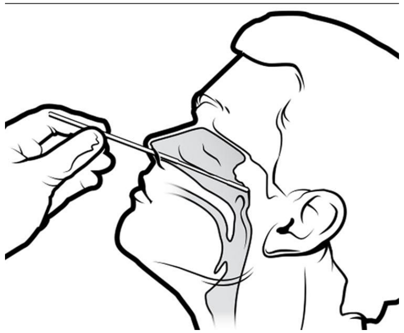


Symptoms of COVID19

- incubation time, 4-5 days (from 2 to 14 days)
  - fever, malaise, chills, headache and myalgia
  - Begins progressively in several days (different from flu)
- Symptoms
  - Intense infectious syndrome : fever 39-40°C, chills, fatigue
  - Respiratory signs : nonproductive cough, sore throat, conjunctivitis and rhinitis
  - Headache, myalgia (muscle aches)
  - sometimes digestive signs (abdominal pain, nausea, vomiting)
  - Abrupt onset anosmia (lost of smell) or hyposmia without associated rhinitis; ageusia (lost of taste) or dysgeusia
- Evolution
  - Favorable in 7 days
  - ARDS (acute respiratory Distress Syndrome) even without do-morbidity
- Often asymptomatic in children or PIMS Pediatric inflammatory multisystem syndrome (specific for young children)

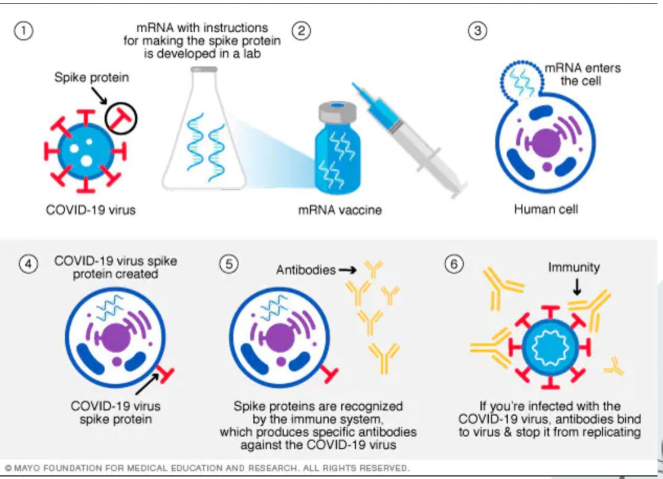
Diagnosis

- not clinical
- Biological diagnosis (nasopharyngeal swab)
- Gold standard assay = Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)
- Detection of viral antigens
  - Rapid immunochromatographic test

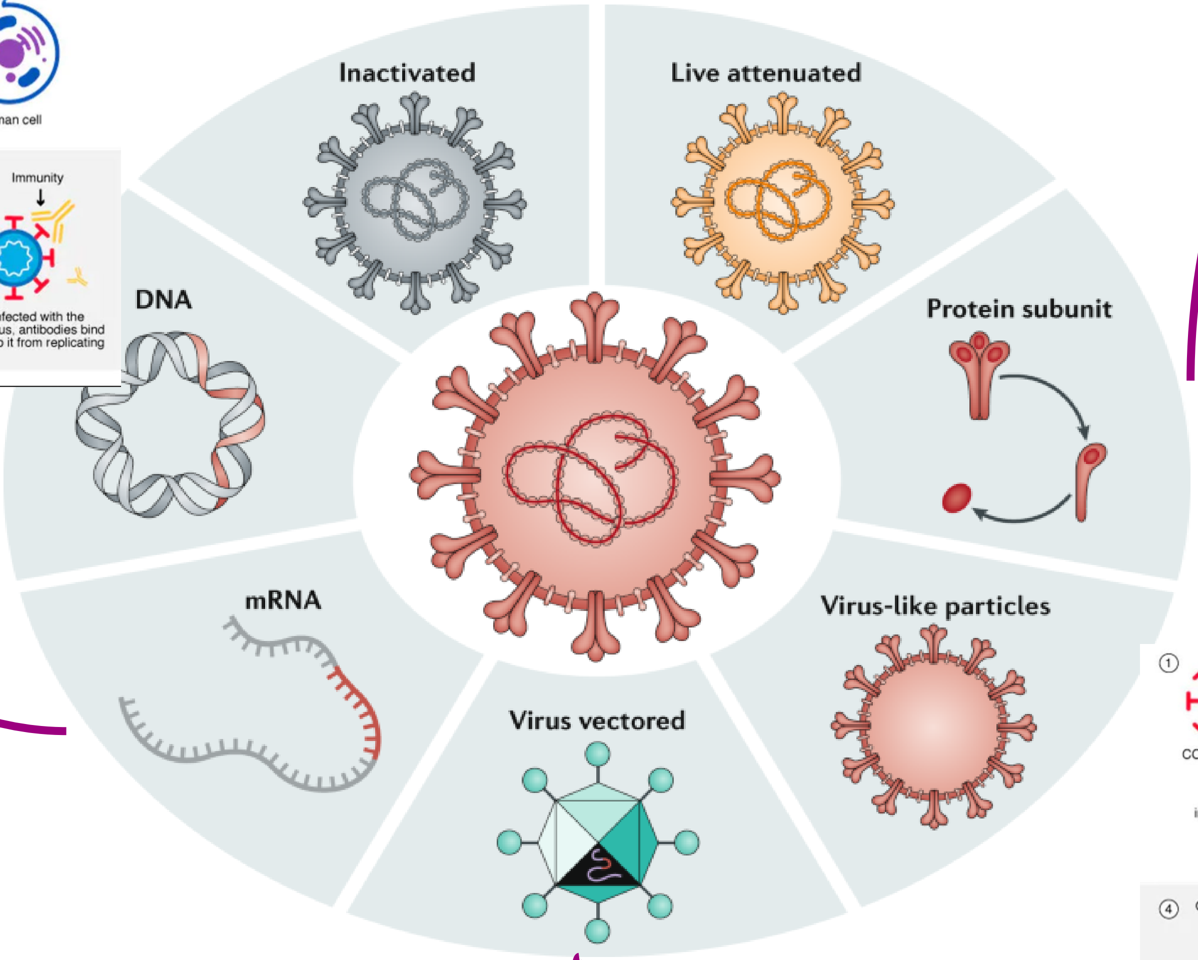


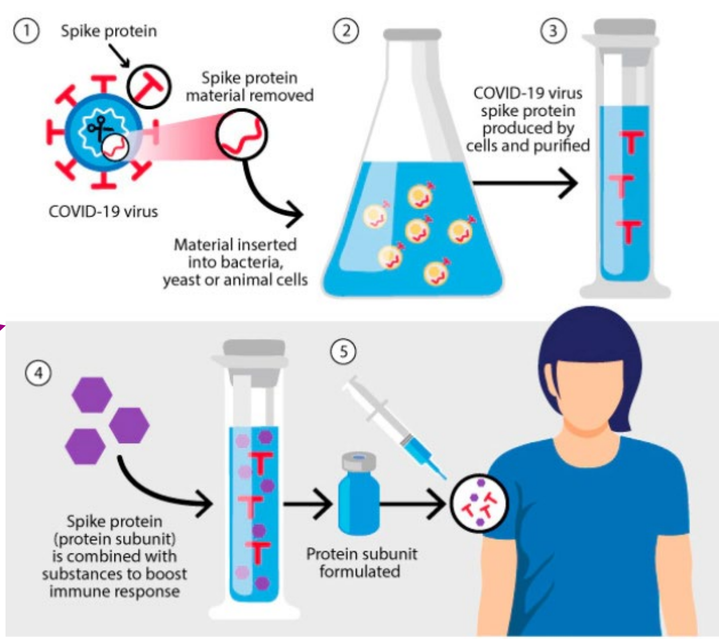
- Indirect diagnosis (serodiagnosis)
  - ELISA
  - Transient antibody response

SARS-CoV-2 Vaccines

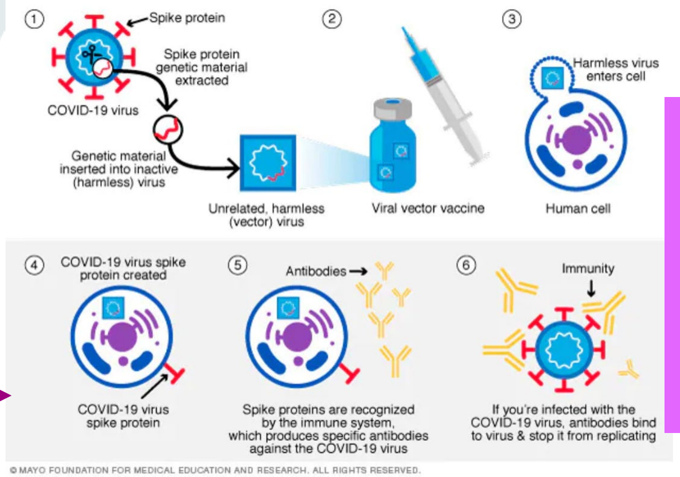


Moderna
Pfizer BioNTech
Lipidic nanoparticles with mRNA corresponding to S in prefusion config
(2 mut S>P)





Novavax
Lipidic nanoparticle with S in prefusion config
+Adjuvant Matrix M

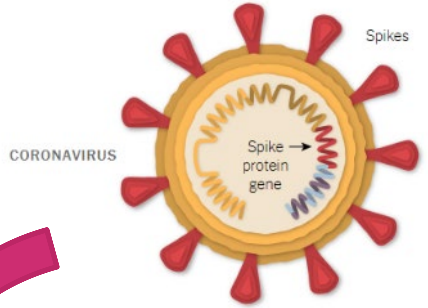


Astra Zeneca
Chimpanzee ADV
Sputnik V
Janssen
different human ADV

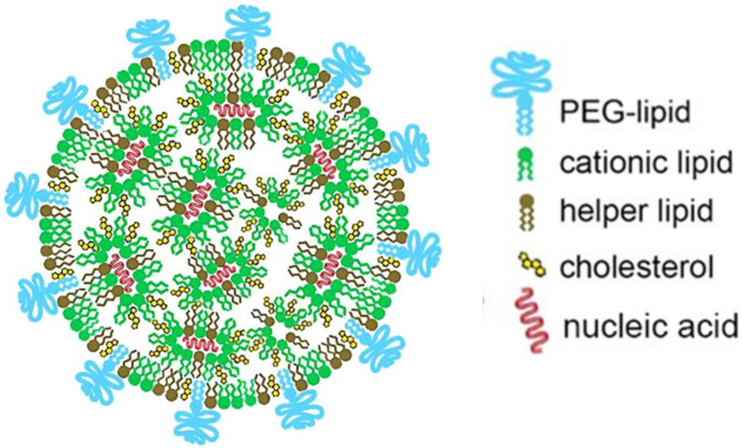
Coronavirus SARS-CoV-2

How works the mRNA vaccine?

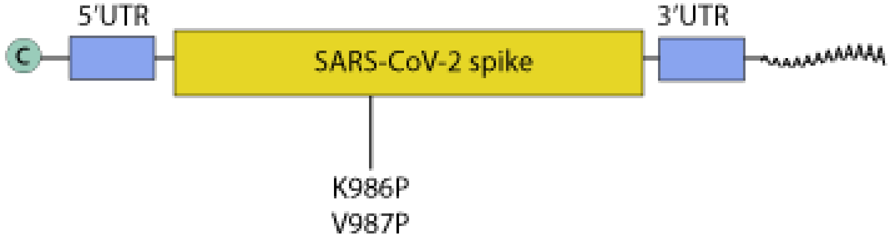
SARS-CoV-2



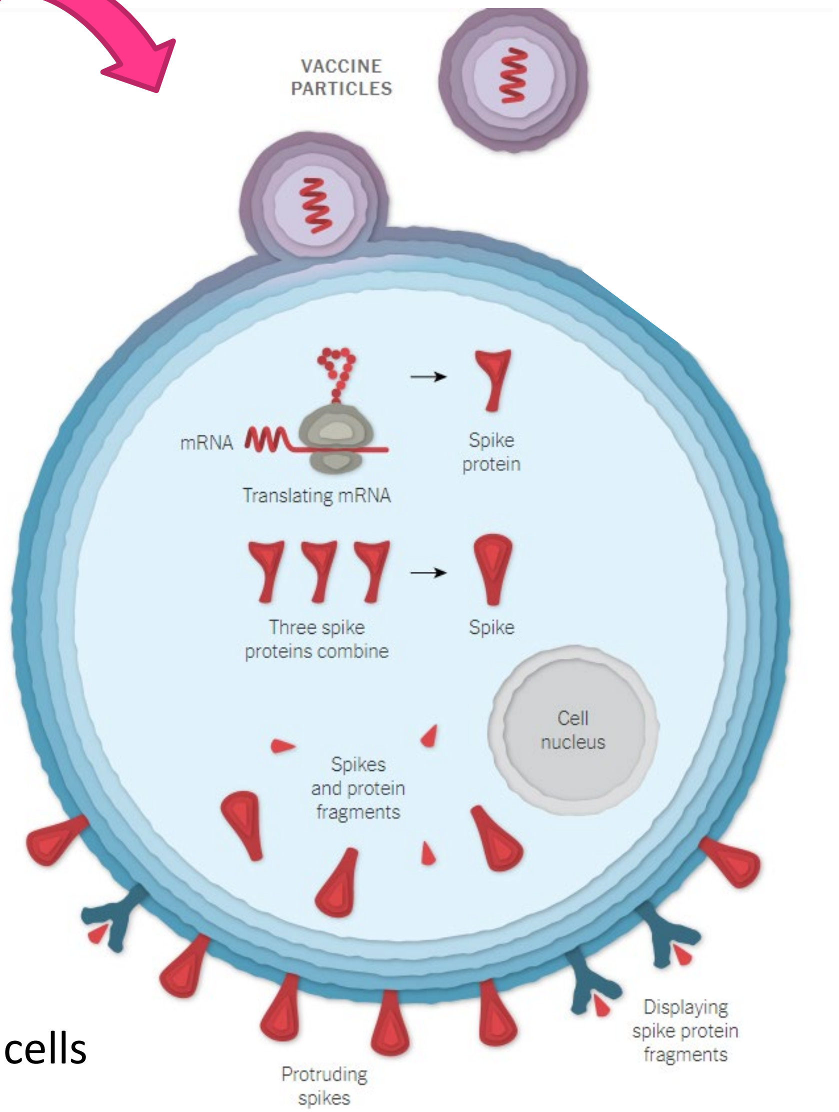
Lipidic particles containing the mRNA



in vitro synthesis of mRNA corresponding to Spike protein

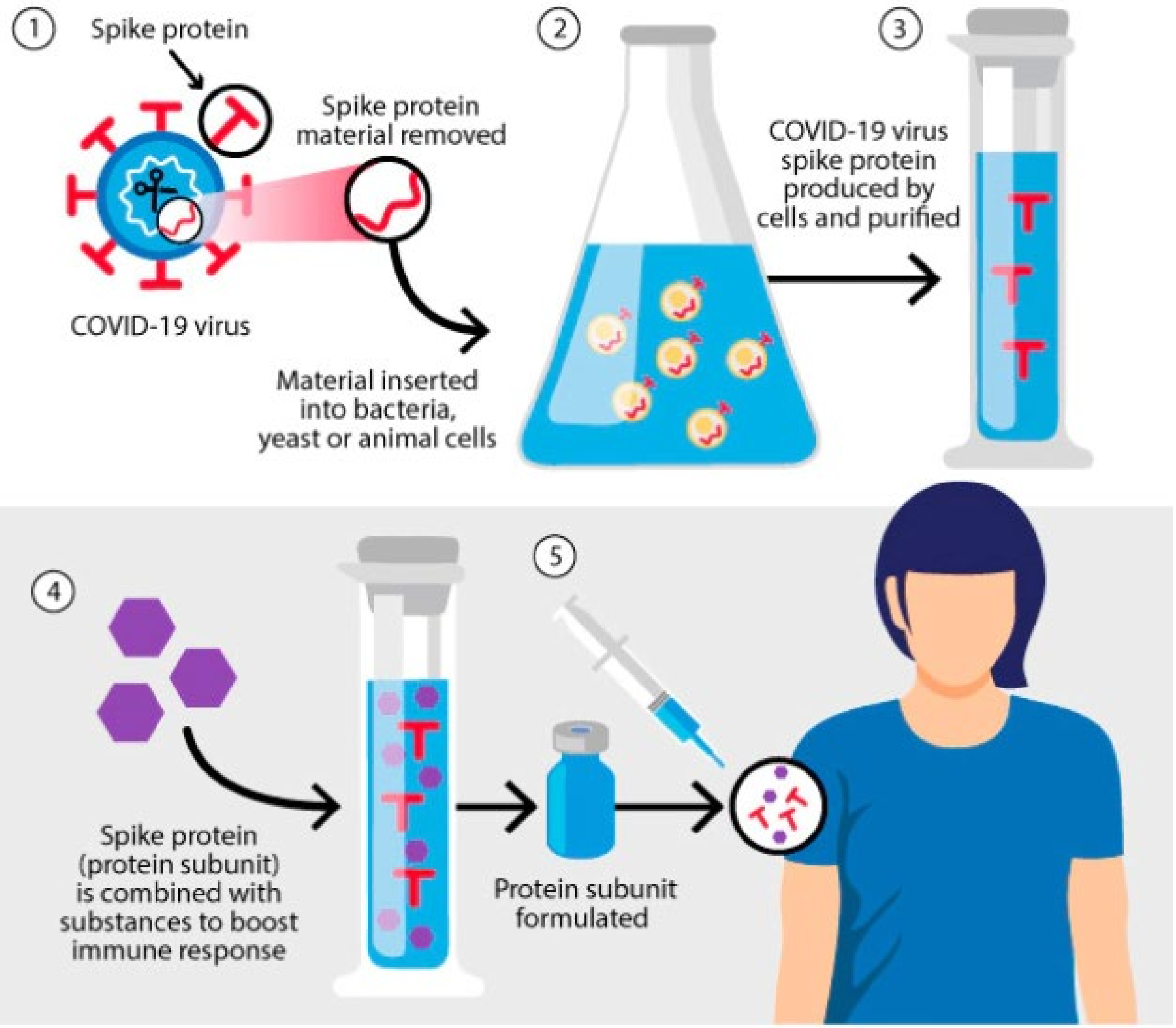


Spike protein is synthesized by our cells and express at their surface

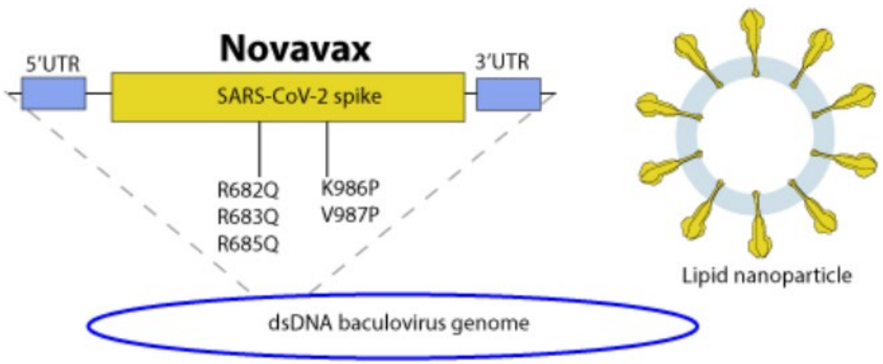


Coronavirus SARS-CoV-2

How works the recombinant vaccine?



Subunit vaccines



Novavax
Lipidic nanoparticle
with S in prefusion config
+Adjuvant Matrix M

Coronavirus SARS-CoV-2

How works the virus vector vaccine?