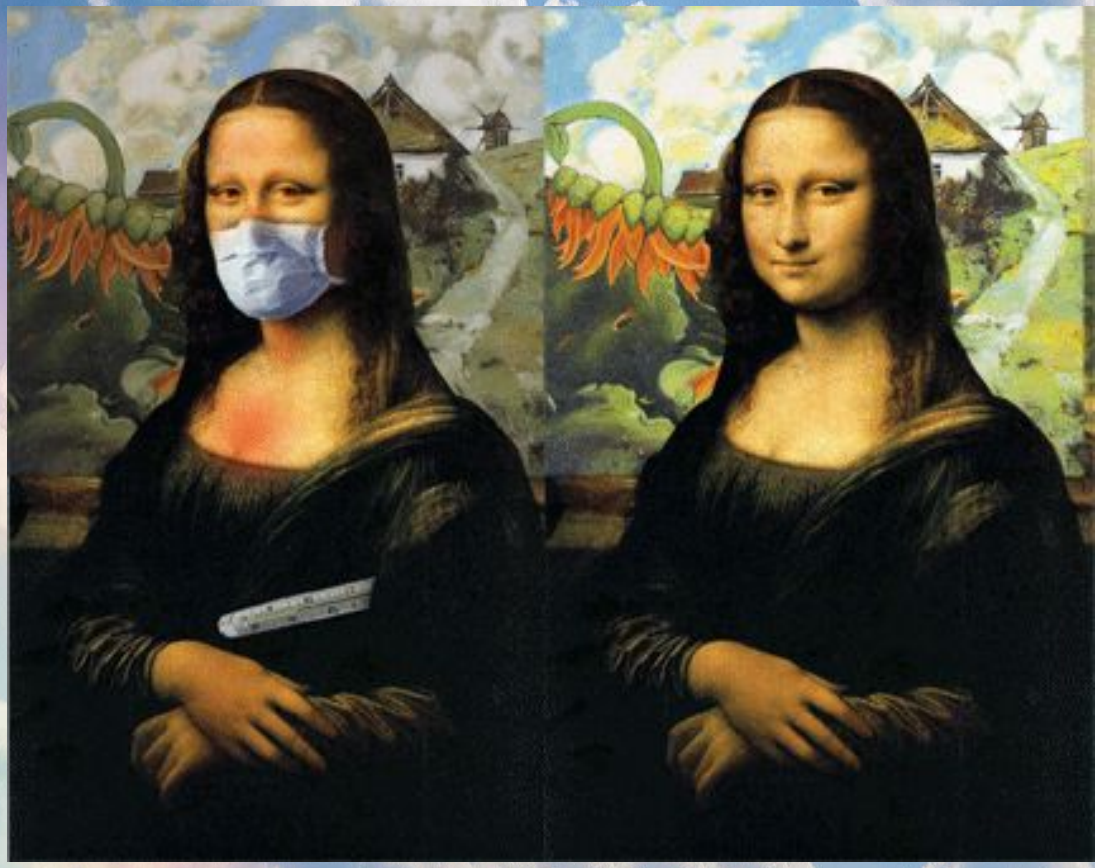
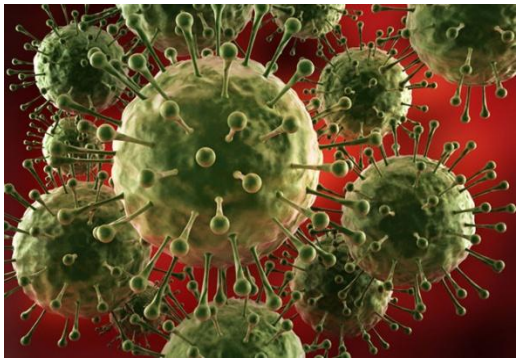
# INFLUENZA



# DEFINITION

- Acute respiratory viral infection with aerogenic transmission mechanism, antroponosis, characterized by lesions of the upper respiratory tract with the development of intoxication and catarrhal syndrome.



-Virus is pneumotropic belongs the family Orthomyxoviridae;

- contains of RNA, nucleocapsid, lipoglycoprotein envelop;
- has a rounded or oval shape;
- nucleocapsid has S - antigen, H-antigen (hemagglutinin), N-antigen (neuraminidase),

- has tropicity to the upper respiratory tract;
- resistant to low temperature;
- sensitive to heat, boiling, ultraviolet irradiation, disinfectants.

# INFLUENZA: A SERIOUS THREAT

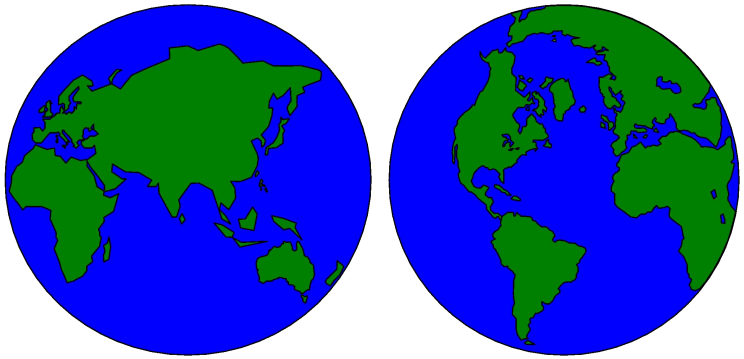
*Influenza infection is associated with high morbidity, significant economic costs and mortality!*

**According to WHO suffer from the influenza every year:**

**5-10 %** adults and **20-30 %** children

Die from complications:

**250 – 500 th.** people



Economic costs:

**1- 6 mln $ USA** on 100 000 population

# SUBTYPES OF INFLUENZA VIRUSES

- Viruses on the difference of specific antigens of the nucleoprotein and matrix protein are divided into 3 types: **A**, **B** and **C**.
- Subtypes of influenza virus are isolated by antigenic variants of the surface glycoprotein hemagglutinin (H) and neuraminidase (N)

**INFLUENZA A** → 15 types of hemagglutinin (H1 - H15)

9 types of neuraminidase (N1 - N 9)

**Every change in the antigenic structure of surface glycoproteins causes the development of new pandemics and epidemics!**

# INFLUENZA VIRUSES: A, B and C

**PANDEMIA**

**frequent EPIDEMICS associated with high morbidity and mortality**

**associated primarily with the virus** → **A**

**seldom** → **B**

**C** — **as a rule, is asymptomatic and does not affect the incidence**

# NATURAL RESERVOIRS OF INFLUENZA VIRUSES

## Influenza A

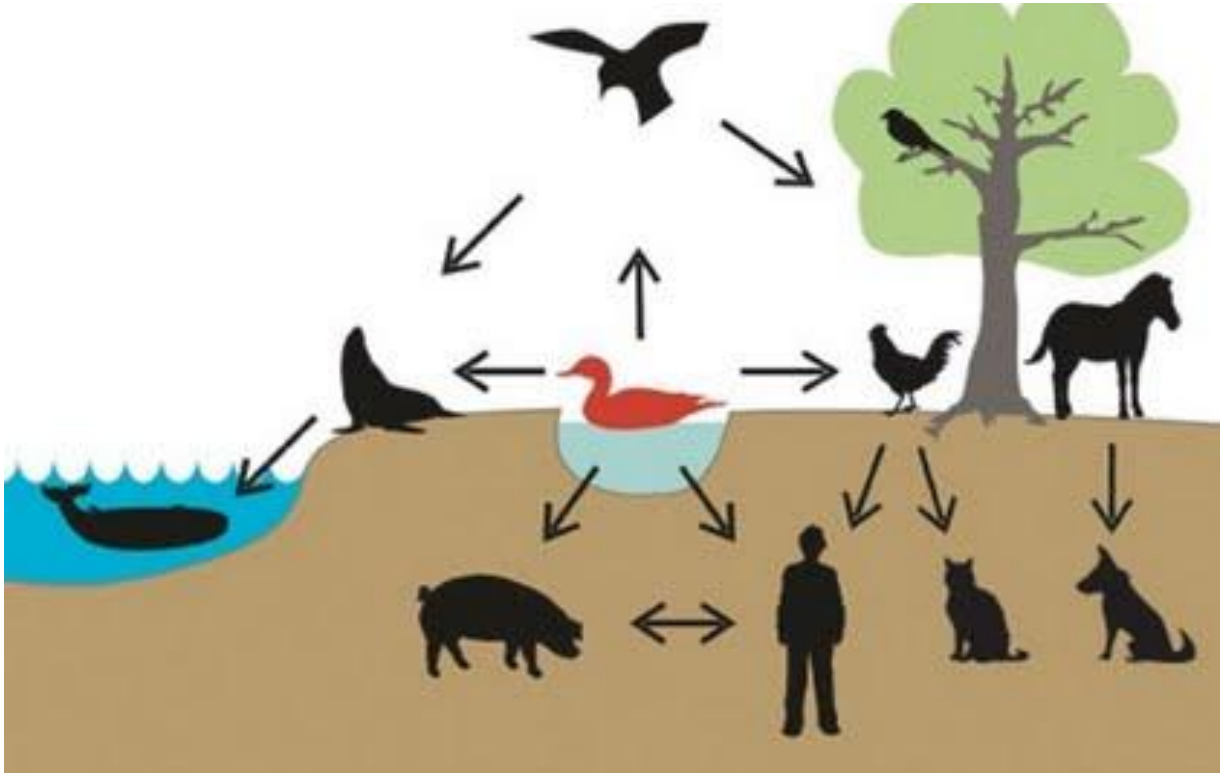
birds, rare animals

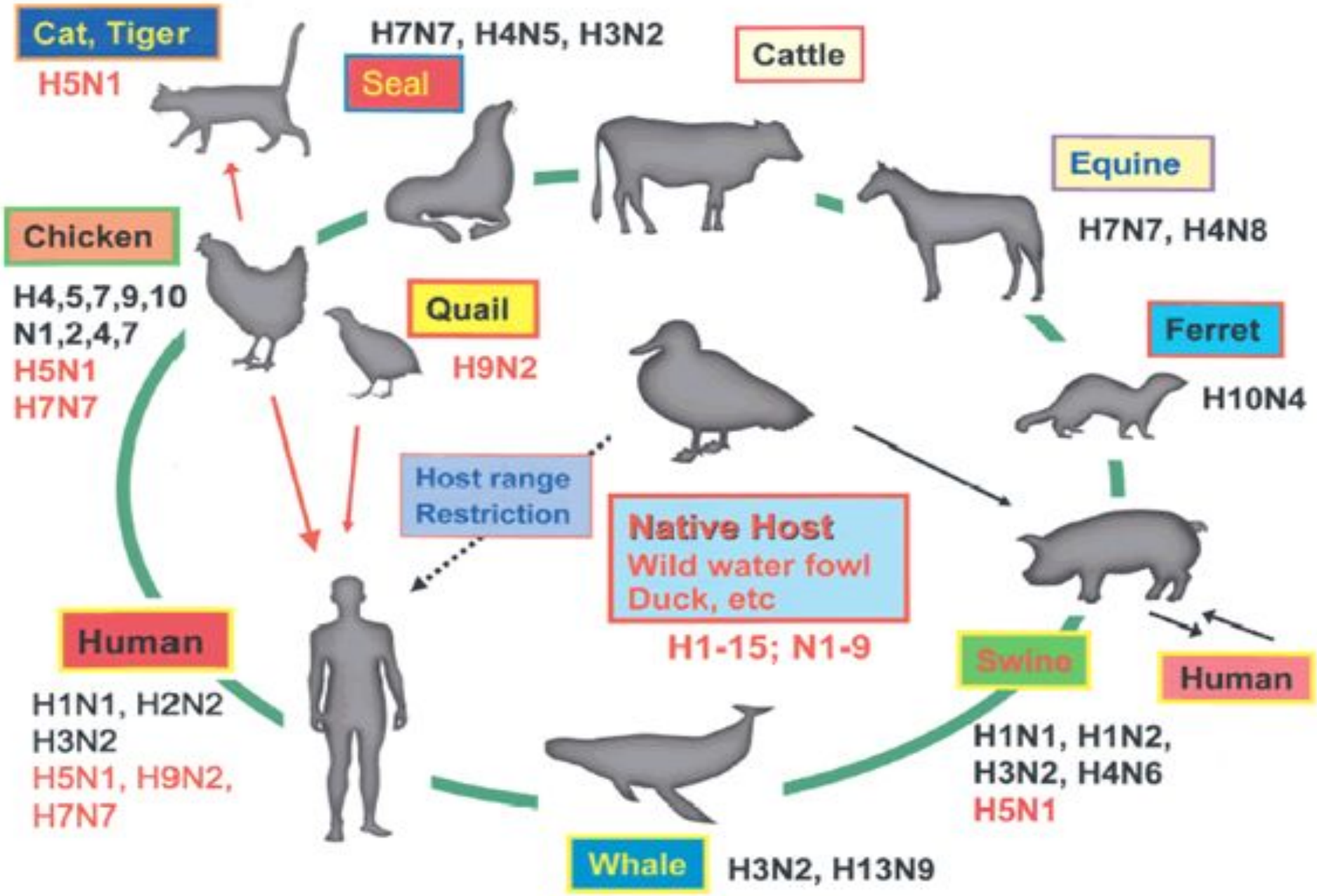
## Influenza B

only people

## Influenza C

in humans, pigs, dogs




Cat, Tiger
H5N1
H7N7, H4N5, H3N2
Seal
Cattle
Equine
H7N7, H4N8
Chicken
H4,5,7,9,10
N1,2,4,7
H5N1
H7N7
Quail
H9N2
Ferret
H10N4
Host range
Restriction
Native Host
Wild water fowl
Duck, etc
H1-15; N1-9
Human
H1N1, H2N2
H3N2
H5N1, H9N2,
H7N7
Swine
H1N1, H1N2,
H3N2, H4N6
H5N1
Human
Whale
H3N2, H13N9

# SEASONAL prevalence of INFLUENZA

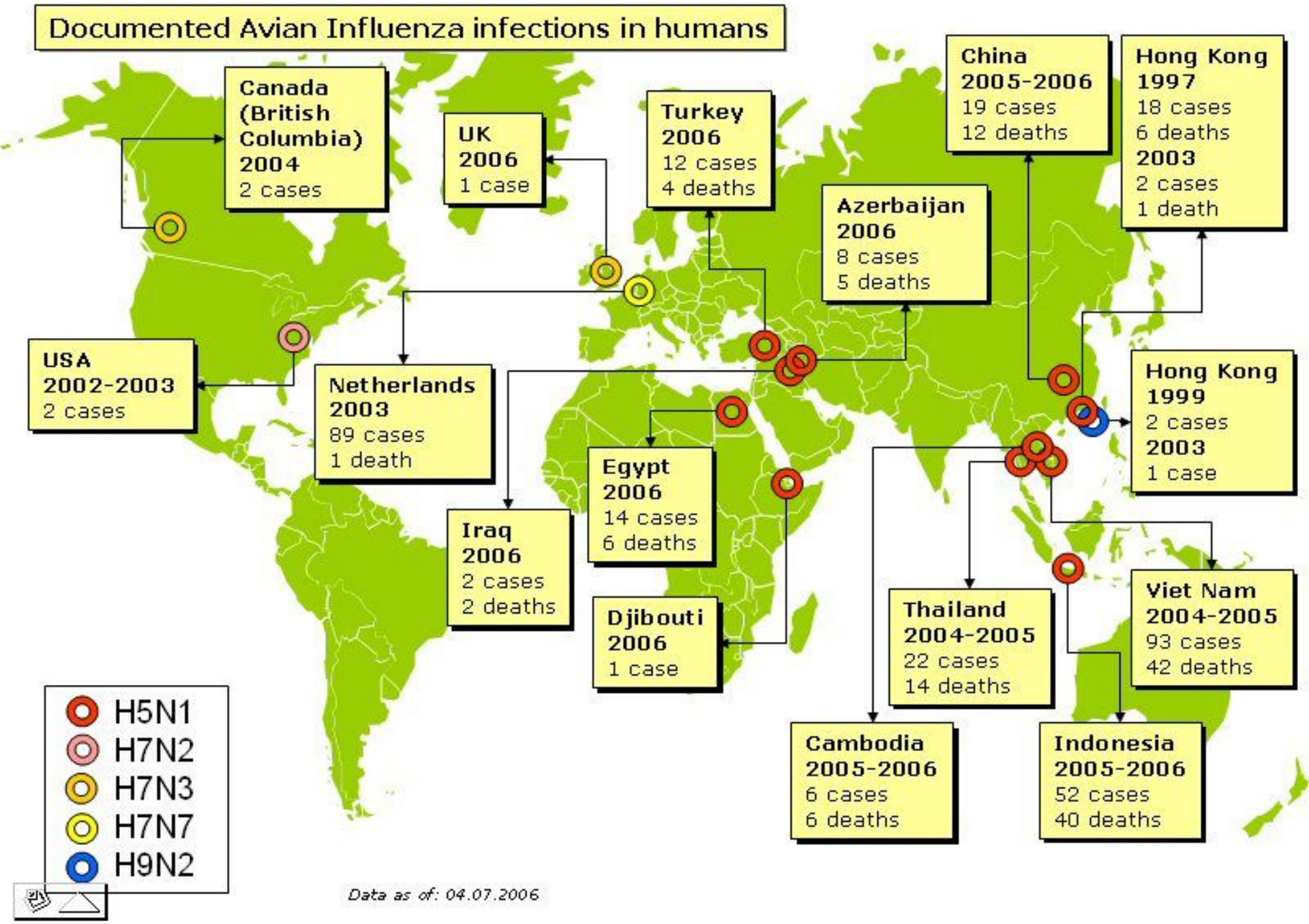
## THE PEAK OF MORBIDITY → THE AUTUMN-WINTER PERIOD

- THE BEST SURVIVAL OF VIRUS IN AEROSOLS AT LOW TEMPERATURE
- A CROWDING OF PEOPLE IN ENCLOSED ROOMS

**Outbreaks of influenza coincide with the increase in the incidence of other ARVI!**

**Revealed a clear dependence of the level of INFLUENZA morbidity of the population of the CITY:**

| > 1 MLN | FROM 500 TH TILL 1 MLN | LESS 500 TH |
|---|---|---|
| < 11,3 % | 10,9 % | 9,7 % |


Documented Avian Influenza infections in humans
Canada (British Columbia) 2004
2 cases
UK 2006
1 case
Turkey 2006
12 cases
4 deaths
China 2005-2006
19 cases
12 deaths
Hong Kong 1997
18 cases
6 deaths
2003
2 cases
1 death
Azerbaijan 2006
8 cases
5 deaths
USA 2002-2003
2 cases
Netherlands 2003
89 cases
1 death
Hong Kong 1999
2 cases
2003
1 case
Egypt 2006
14 cases
6 deaths
Iraq 2006
2 cases
2 deaths
Djibouti 2006
1 case
Thailand 2004-2005
22 cases
14 deaths
Viet Nam 2004-2005
93 cases
42 deaths
Cambodia 2005-2006
6 cases
6 deaths
Indonesia 2005-2006
52 cases
40 deaths
H5N1
H7N2
H7N3
H7N7
H9N2
Data as of: 04.07.2006

# RISK GROUPS FOR INFLUENZA

**The INFLUENZA poses a serious DANGER primarily to:**

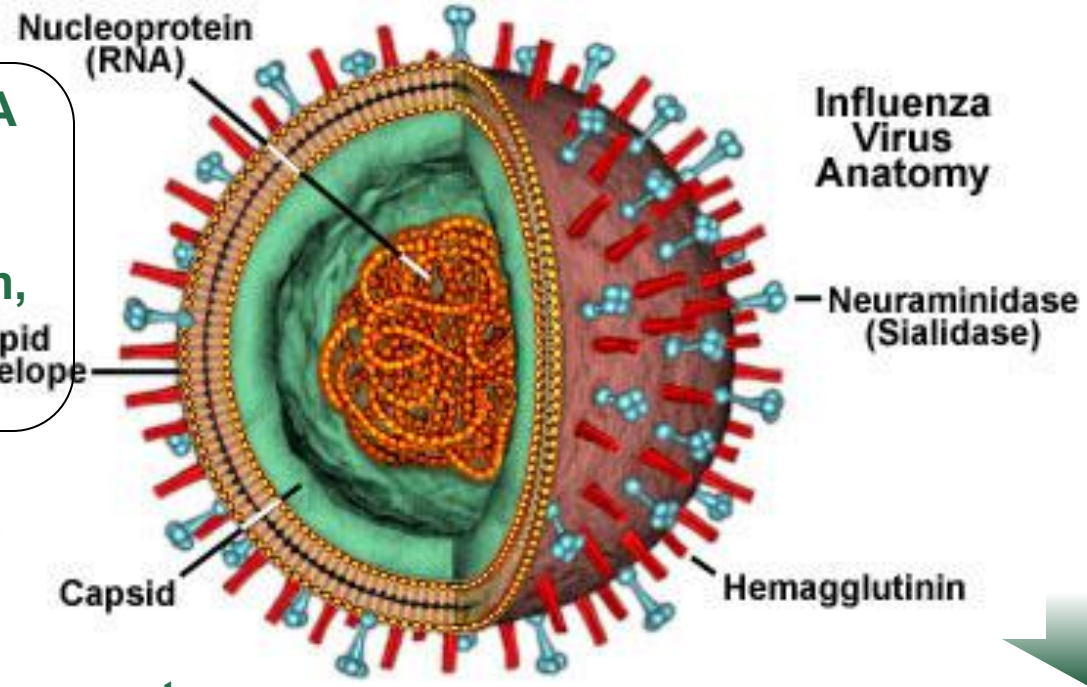
- children first year of life
- the elderly
- persons with concomitant diseases of the heart, lungs, diabetes, other chronic diseases

**The INFLUENZA can occur without fever, with scanty pulmonary symptoms, but with rapid, sometimes catastrophic, development of toxicity and complications, therefore, these portions of the population require special attention and control.**

# INFLUENZA

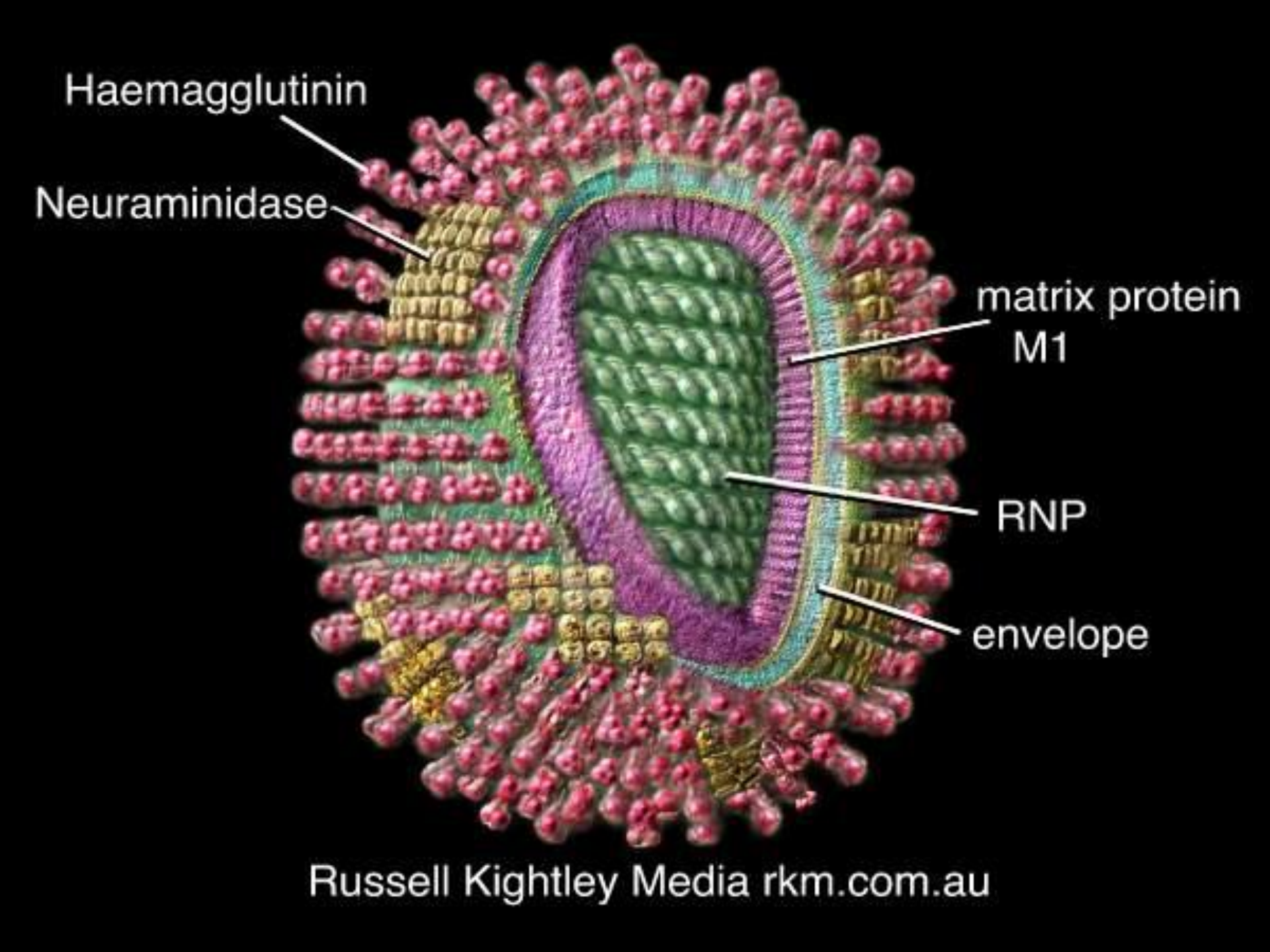
The core of the virus contains single-stranded negative chain of RNA consisting of 8 segments that encode 10 viral proteins

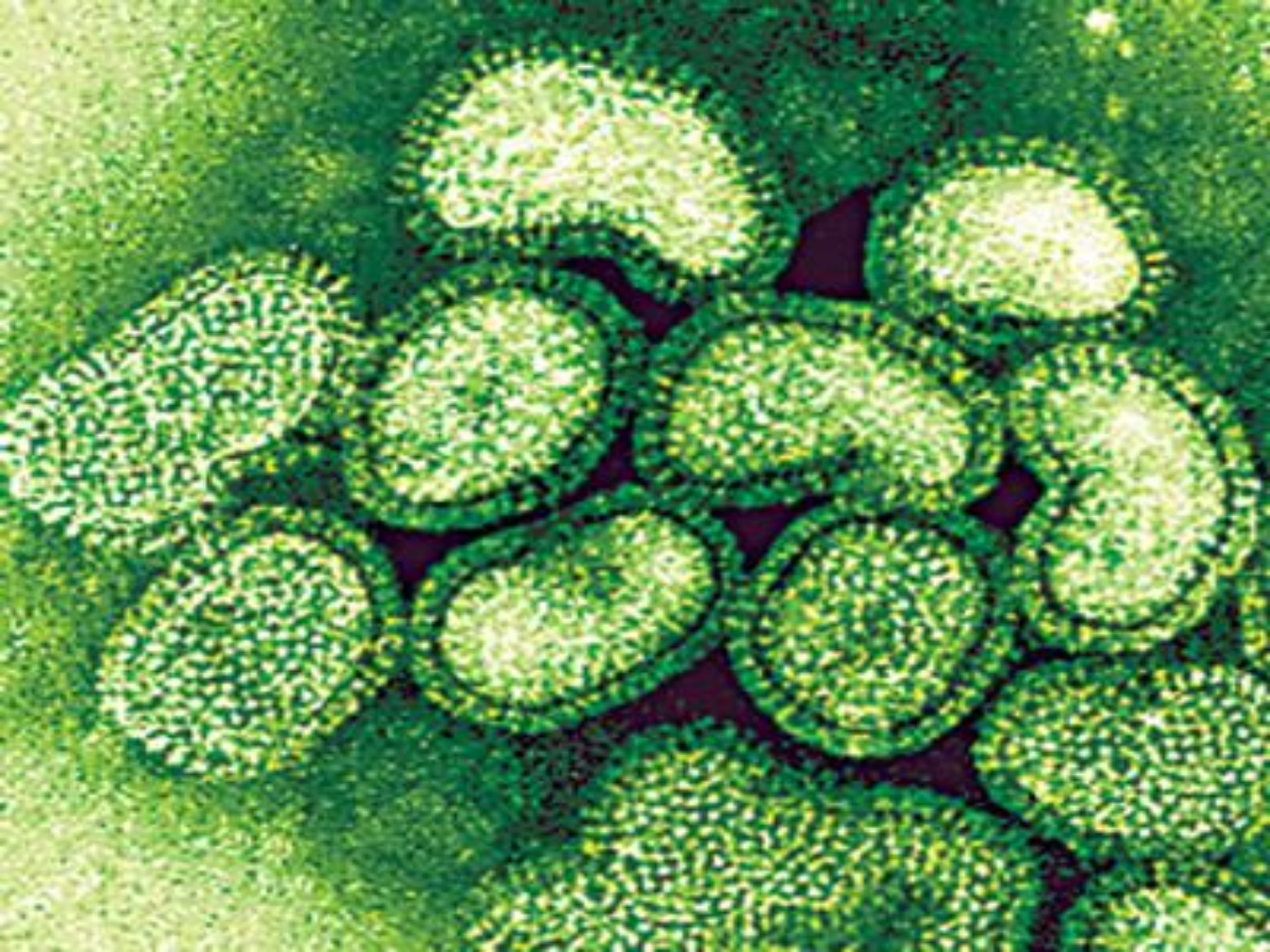
Fragments of RNA have a general protein envelope, which unites them, forming a nucleoprotein

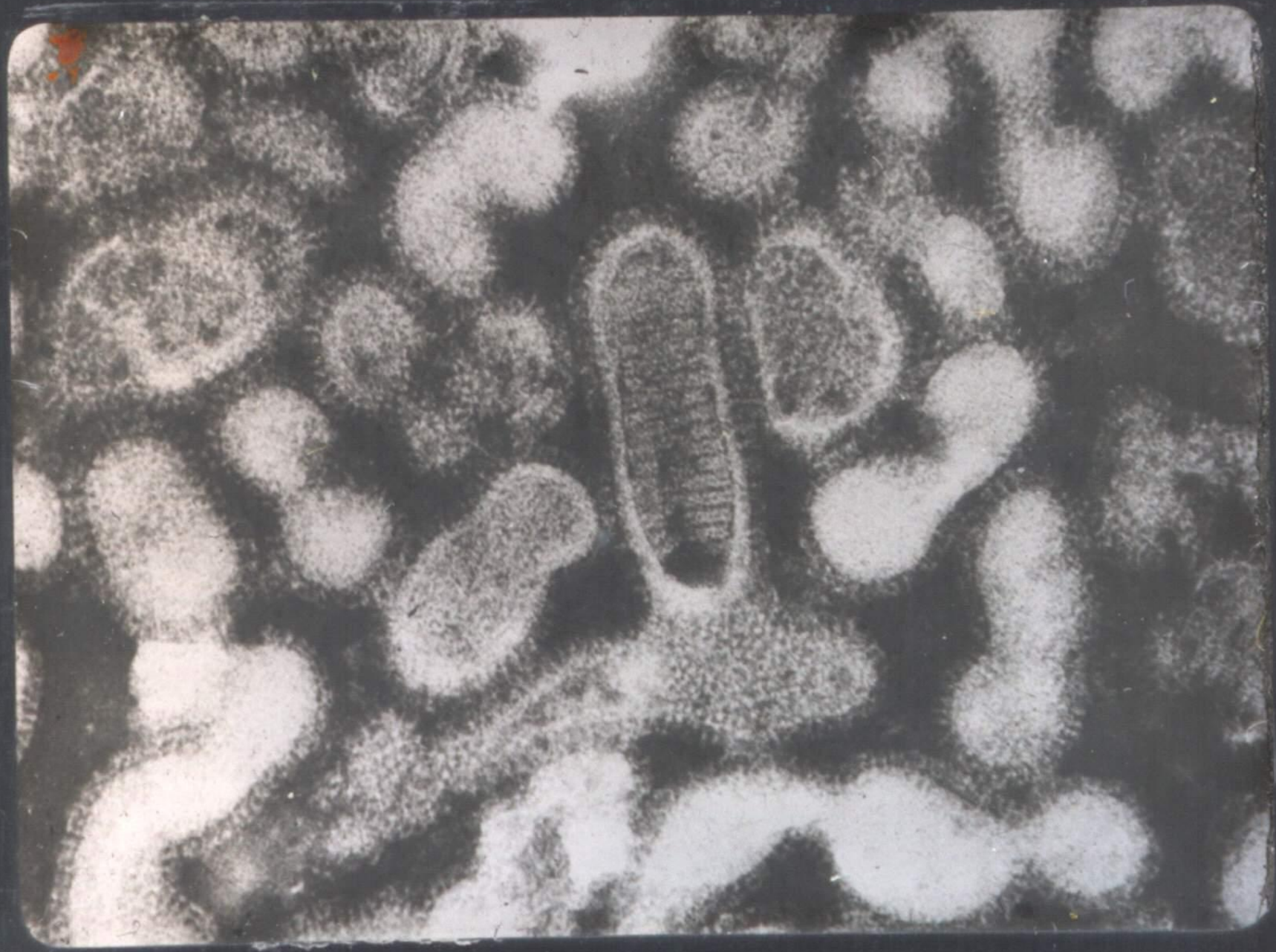



Nucleoprotein permanent in its structure and determines the virus type (A, B or C).

The surface antigens (H and N), in contrast, is variable and define different strains of the same type of virus.


Haemagglutinin
Neuraminidase
matrix protein
M1
RNP
envelope
Russell Kightley Media rkm.com.au



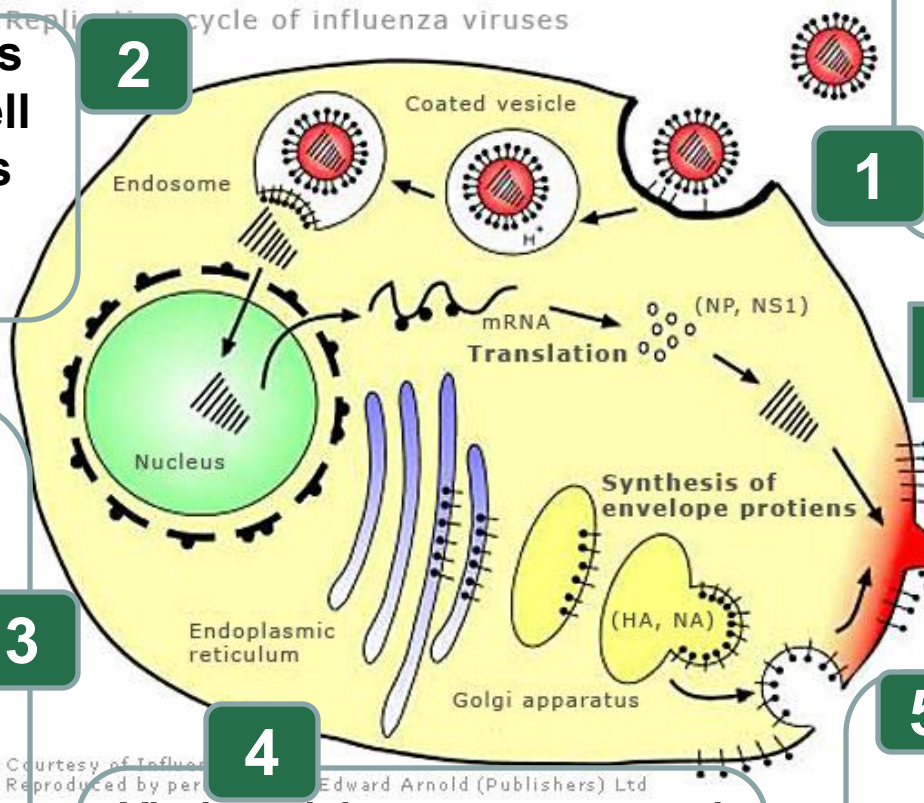


# The replication cycle of influenza virus

**The replication cycle of influenza virus in the human body lasts about 4 hours and can be described as follows:**

**1** Hemagglutinin on the surface of the virus, binds to sialic acid on epithelial cells lining the respiratory tract.

**2** The virus enters the epithelial cell by endocytosis and starts to multiply



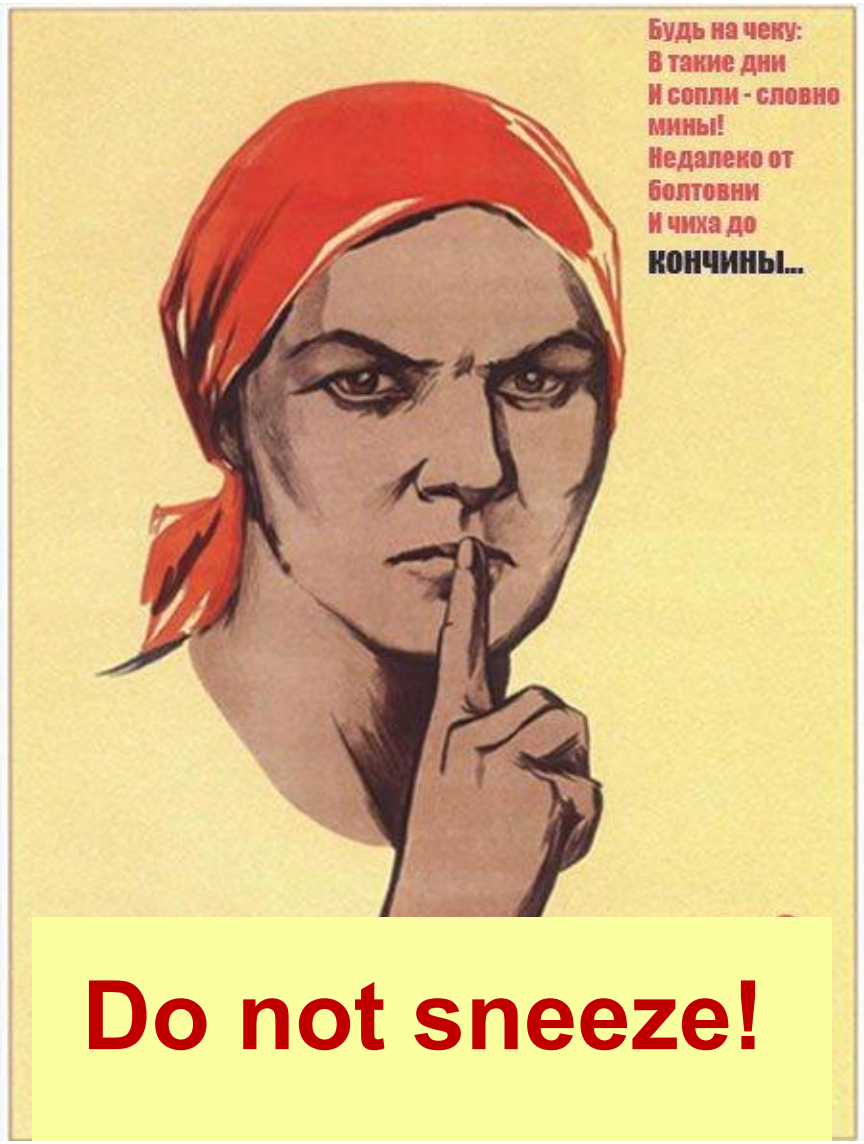

**3** The synthesis of new viral RNA and proteins, which are collected into viral particles occurs via the structures of the host cell

**4** Viral particles are transported to the surface cells in the sheath which contains the hemagglutinin, neuraminidase and M2 channels.

**5** Collecting of virions is completed, but they remain bound to cell surface via hemagglutinin and sialic acid.

**6** The neuraminidase releases new viruses which infect other cells

# INFLUENZA : THE DEVELOPMENT OF THE PATHOLOGICAL PROCESS




«ENTRANCE GATE»

epithelium of the respiratory tract

↓

involvement of intact cells

↓

replication of the virus in the cells

↓

structural changes, degradation, rejection of cells

# INFECTION WITH INFLUENZA VIRUSES

From a sick person, who is the source of the infection, the virus through coughing and sneezing transmitted to healthy people by aerogenic mechanism through airborne, air–dust way

and by contact–household route

the replication cycle of 4-6 hours

isolation of virus from the respiratory tract

STARTS 1-2 days before onset of symptoms

ENDS after 5 –7days after the disappearance of clinical manifestations

# CLINICAL PICTURE OF INFLUENZA INFECTION

**2 days**
**Incubation period**

**3-5 days**
**CLIMAX (febrile) period**

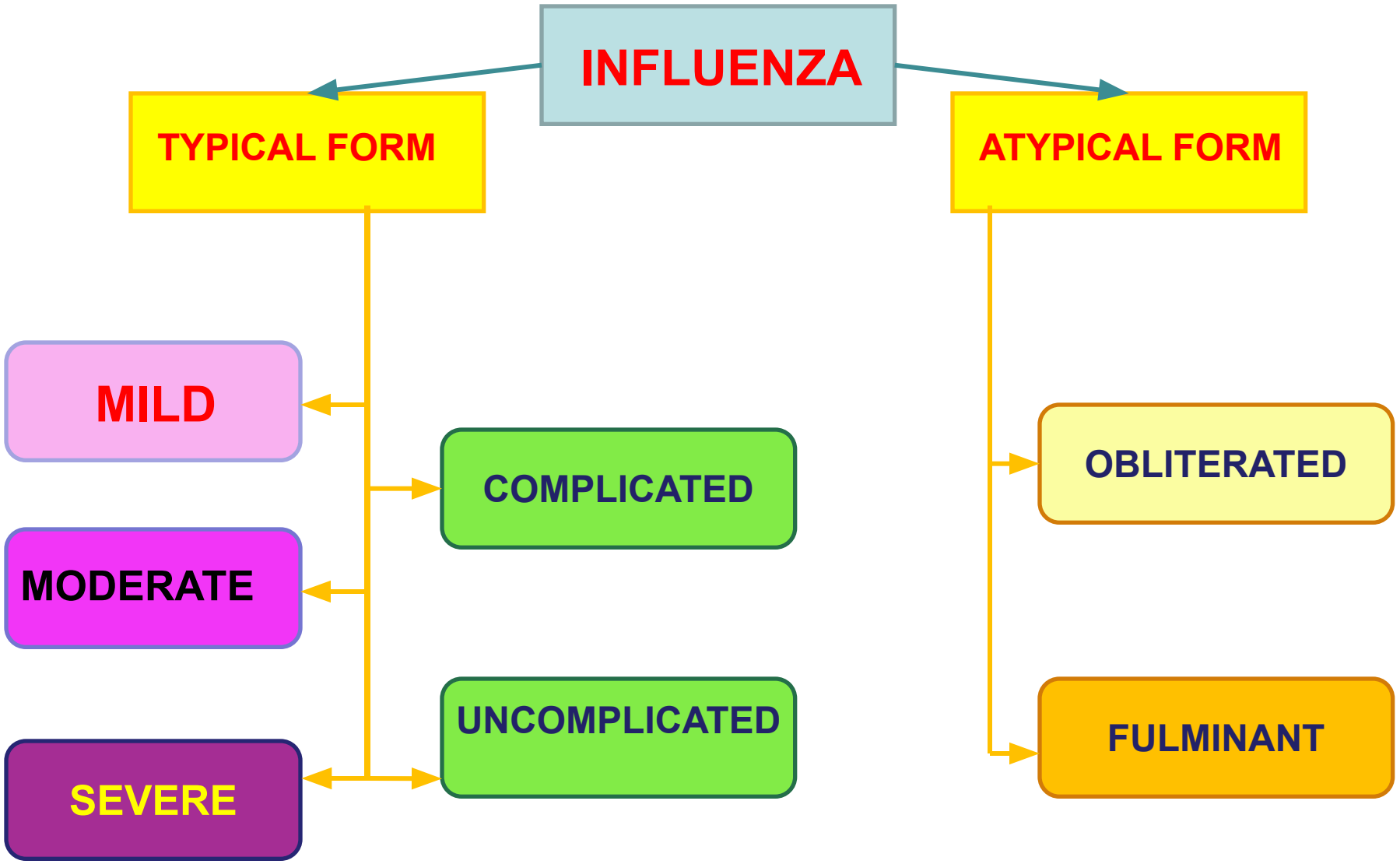
- The sudden rise of body **temperature** (38-40°C);
- **Chills**, dizziness, muscle pain, **headache**, weakness;
- Rhinorrhea usually not observed, patients often complain of a feeling of **dryness** in the nose and throat;
- In some cases there is a **dry, hard cough** accompanied by **pain behind the breastbone**;

**The total duration of disease is 7-10 days**

# CLINICAL PERIODS OF INFLUENZA

| | | |
|---|---|---|
| 1 | PENETRATION | INCUBATION: ASIMPTOMATICAL |
| 2 | VIREMIA | INITIAL: NONSPESIFIC SD – GENERAL INTOXICATION |
| 3 | LOCAL DEMIGE | CLIMAX: SPESIFIC SDs – CATARRHAL AND INTOXICATION |
| 4 | BACTERIOLOGIC COMPLICATION | CLIMAX: DEVELOPMENT OF COMPLICATIONS |
| 5 | IMMUNIC | CONVALESCENCE: DISAPPEARANCE OF LIDING SDs; ASTENOVEGETATIVE SD |

# CLINICAL CLASSIFICATION OF INFLUENZA



# SEVERITY OF INFLUENZA

**MILD**

body temperature can to remain normal or not rise above 38°C, the symptoms of intoxication less expressed or absent

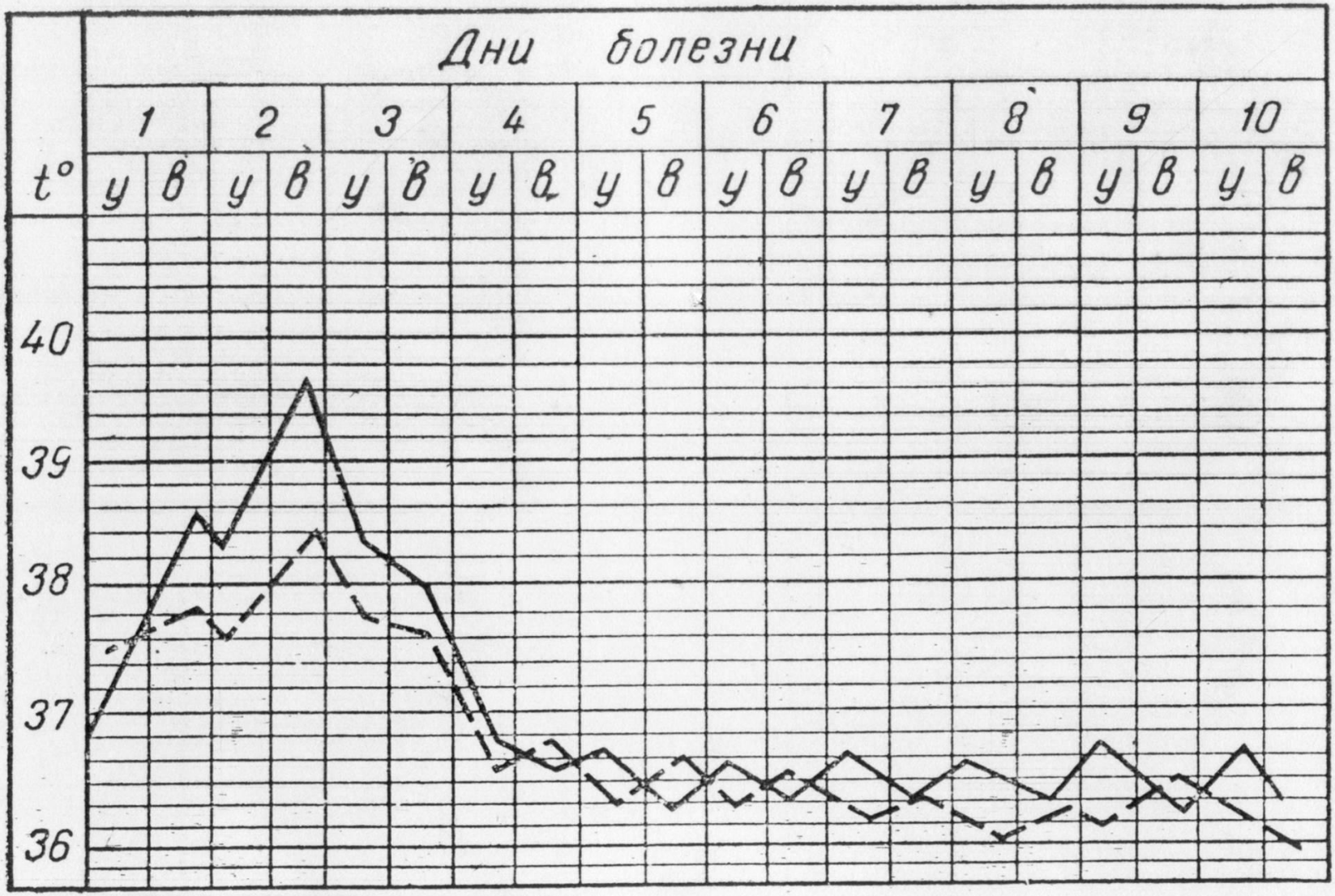
**MODERATE**

increase of body temperature in the range of 38.5–39°C, moderate intoxication, weakness, headache

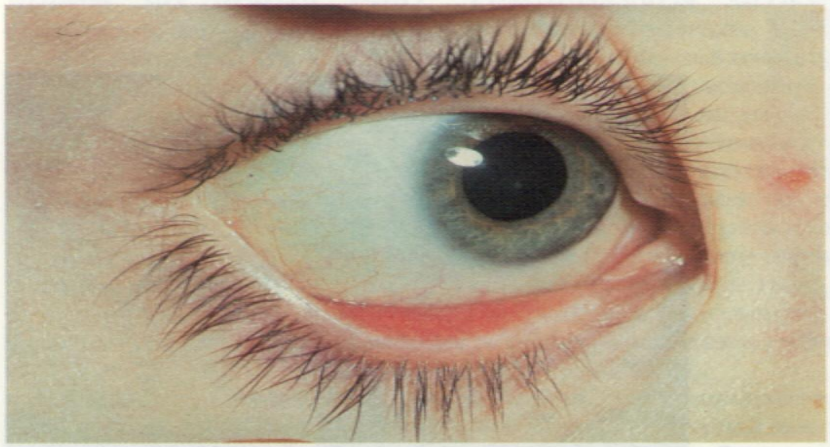
**SEVERE**

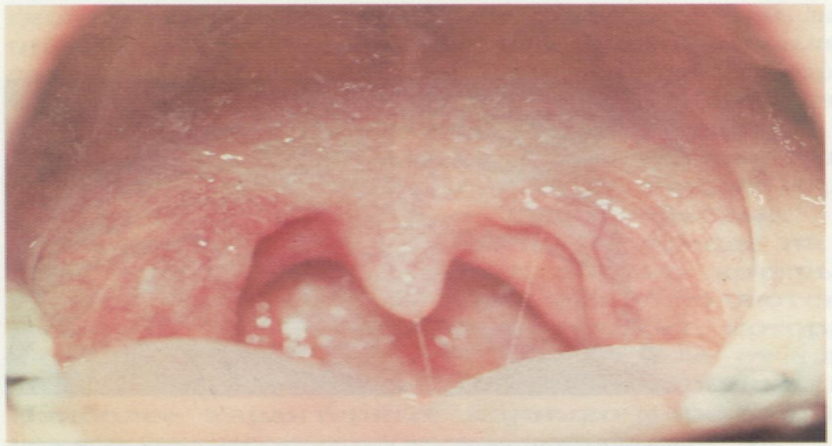
Increase of body temperature up to 40-40,5°C, dizziness, delirium, seizures, hallucinations, vomiting

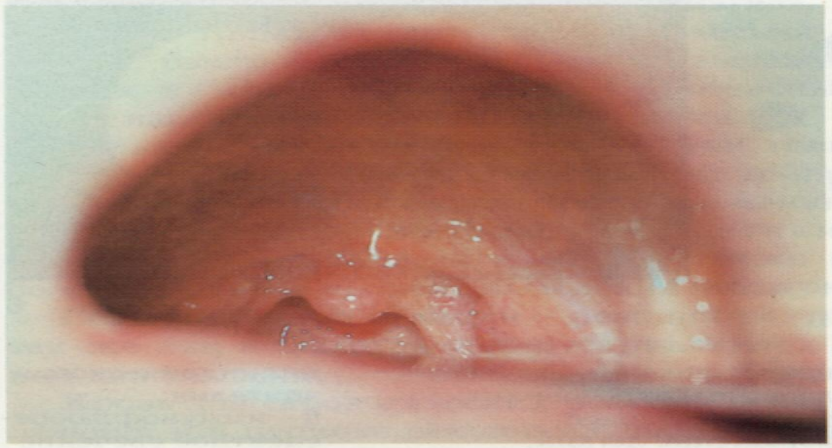
**Hypertoxic form occurs only in influenza, accompanied by expressed hyperthermic, meningo - encephalitic and hemorrhagic syndrome !**

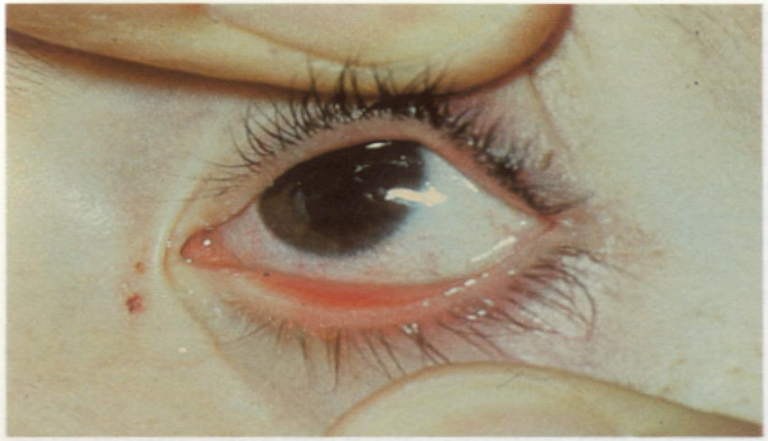


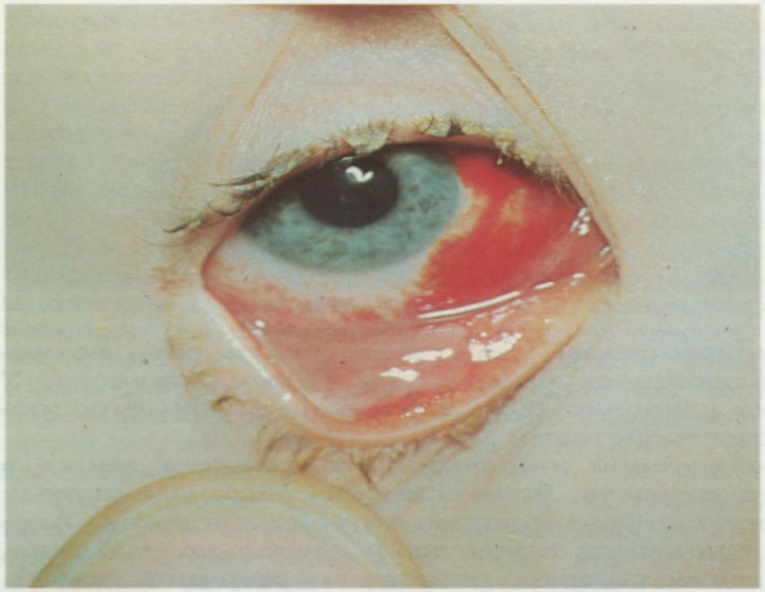

Температурная кривая у больного неосложненным гриппом.











# INFLUENZA : OUTCOMES OF VIRUS INTRODUCTION

## INFLUENZA VIRUS

LESIONS OF EPITHELIUM OF RESPIRATORY TRACT

SUPPRESSION OF FUNCTION
of mucociliary clearance
macrophages
T - lymphocytes

NEURAMINIDASE OF INFLUENZA VIRUS

modifies cell surface glycoproteins

promotes the formation of new places for bacteria adhesion and the development of secondary purulent infection !

# INTOXICATION at the INFLUENZA

From a place of primary localization of the influenza virus gets into the blood, causing viremia that resulted in severe intoxication.

## Intoxication at the influenza

Is characterized by:

increased permeability and fragility of blood vessels of different severity

SEVERE CASES:

- HEMORRHAGIC SYNDROME
- BLEEDING
-HEMORRHAGES OF DIFFERENT LOCALIZATION
-Disturbance of MICROCIRCULATION (until the development of DIC – syndrome, infectious-toxic shock!)

In the development of the neurotoxic syndrome in influenza plays an important role disorder of cerebral hemodynamics and cerebral edema!

# Complications of the INFLUENZA

**THE MOST COMMON:**

- ❑ PNEUMONIA
- ❑ ACUTE BRONCHITIS
- ❑ BRONCHIOLITIS

## PNEUMONIA DEVELOPS:

**5-38% with influenza A**

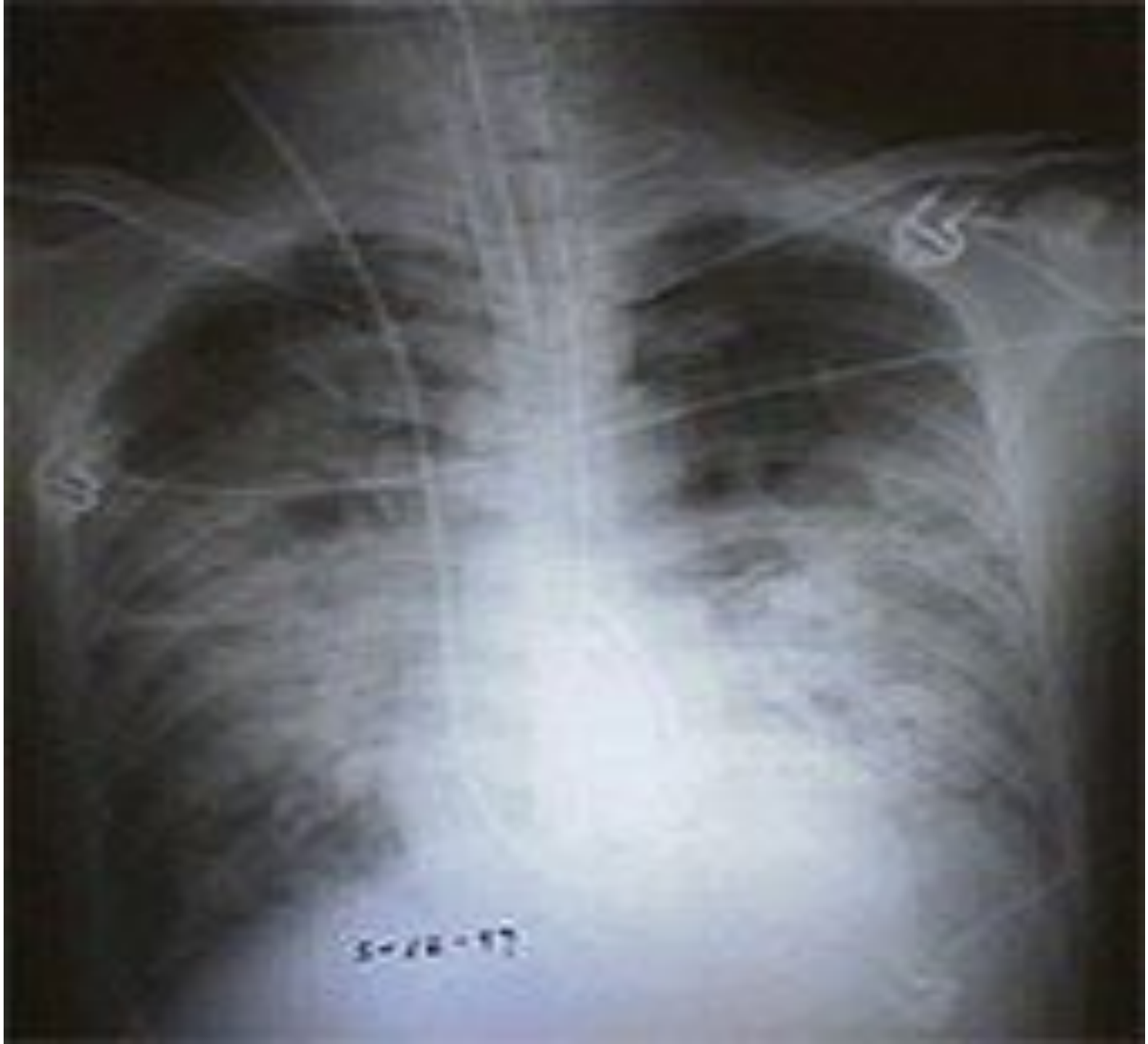
**10 % with influenza B**


### Distinguish

- primary viral pneumonia (developed as a result of direct viral infection of the lungs) and
- secondary bacterial pneumonia (bacterial superinfection can complicate the course of primary viral pneumonia, and or to be independent late complication of the flu).

**Influenza infection leads to EXACERBATION:**

- ❑ chronic bronchitis/ chronic obstructive pulmonary disease;
- ❑ bronchial asthma;
- ❑ mucoviscidosis;



# INFLUENZA : THE RISK OF COMPLICATIONS

**Mortality from influenza and its complications takes the first place among all infectious diseases!**

**80 - 90 %** of patients older than 65 years in the structure of mortality from the flu

**6 %** of deaths due to influenza in adults, young patients without apparent risk factors!

**1/3** complications associated with influenza occur among people, healthy in all other indicators

**Most cases of influenza in hospitalized patients are younger <u>than 65 years</u>**

# ETIOLOGICAL DIAGNOSIS OF INFLUENZA

**METHODS:**

- the method of direct immunofluorescence
- polymerase chain reaction – PCR
- reaction of complement binding
- enzyme-linked immunosorbent assay
- virological method

**Etiologic diagnosis for most patients in clinical practice is not possible (!), due to technical difficulties, the complexity and relative high cost of virological and immunological methods.**

**During epidemics of influenza the performance of clinical diagnosis is high and reaches 70%!**

# DIFFERENTIAL DIAGNOSIS of colds and influenza

**Non-specific diagnosis of influenza:**

-GBC: leukopenia, shift to the left formula, increased ESR;

- urinalysis: leukocyturia, proteinuria, microhematuria, cylindruria;
- biochemical blood: the increase of urea, creatinine;
- coagulogramm changes in severe forms;


# DIFFERENTIAL DIAGNOSIS of colds and influenza

| SIGN | ARVI | INFLUENZA |
|---|---|---|
| ONSET | GRADUAL | ACUTE<br>SOMETIMES SUDDEN |
| FEVER | MILD INCREASE OF TEMPERATURE TO 38.5º | THE MAXIMUM LEVEL (HECTIC) IS ACHIEVED IN A FEW HOURS. PERSISTS FOR 3-4 DAYS |
| INTOXICATION | MODERATE OR ABSENT | EXPRESSED, INCREASES RAPIDLY: CHILLS, SWEATING |
| HEADACHE | MILD, MODERATE | SEVERE, LOCALIZED IN THE FRONTO-TEMPORAL REGION |
| MYALGIA<br>ARTHRALGIA | MILD OR ABSENT | SEVERE |
| FATIGUE WEAKNESS | MILD OR ABSENT | EXPRESSED, PAIN IN THE SMALL AND MEDIUM JOINTS |

# DIFFERENTIAL DIAGNOSIS of colds and influenza

| SIGN | ARVI | INFLUENZA |
|---|---|---|
| RUNNY NOSE | TYPICAL | ABSENT |
| NASAL CONGESTION | SELDOM | OFTEN |
| SNEEZING | OFTEN | NONTYPICAL |
| CATARRHAL SYNDROME OF THE OROPHARYNX | GRAININESS, MODERATE REDNESS AND SWELLING | ON THE 2-3-d DAY BRIGHT HYPEREMIA OF OROPHARYNX AND SOFT PALATE |
| SORE THROAT | MODERATE | SEVERE |
| EYE SYMPTOMS | LACRIMATION | PAIN WHEN MOVING THE EYEBALLS, PHOTOPHOBIA, BURNING, SCLERITIS, CONJUNCTIVITIS |

# DIFFERENTIAL DIAGNOSIS of colds and influenza

| SIGN | ARVI | INFLUENZA |
|---|---|---|
| COUGH | DRY, LATER MOIST | APPEARS ON 2ND DAY DRY PAINFUL, ACCOMPANIED BY PAIN BEHIND THE BREASTBONE |
| ASTHENOVEGETATIVE SYNDROME | INSIGNIFICANT | FATIGUE, WEAKNESS, HEADACHE, INSOMNIA FOR 2-3 WEEKS |
| DURATION | 5-7 DAYS | 7-10 DAYS |
| COMPLICATION | RARELY: ACUTE SINUSITIS OTITIS | OFTEN ACUTE BRONCHITIS PNEUMONIA |

# SPECIFIC TREATMENT

**ways of influence the infectious process**

**IMMUNOCORRECTIVE THERAPY**

**PATHOGENETIC THERAPY**

**SYMPTOMATIC THERAPY**

**LEADING ROLE**

**ETIOTROPIC DRUGS**

**have a direct effect on the reproduction of the virus and some virus-specific target in its cycle**

**1st generation – amantadine and rimantadine**

**2 generation – zanamivir and oseltamivir**

# SPECIFIC TREATMENT

## RIMANTADINE

**MECHANISM of ACTION: inhibition of the synthesis of M-protein of influenza virus, disrupts the process of reproduction and formation of complete virions.**

**Limitation:**

1) **rapid development of resistance in viruses (resistance);**
2) **narrow spectrum of activity (only influenza A);**
3) **common side effects;**

# SPECIFIC TREATMENT

## THE ATTACK ON NEURAMINIDASE

one of the main enzymes involved in replication of influenza viruses A and B.

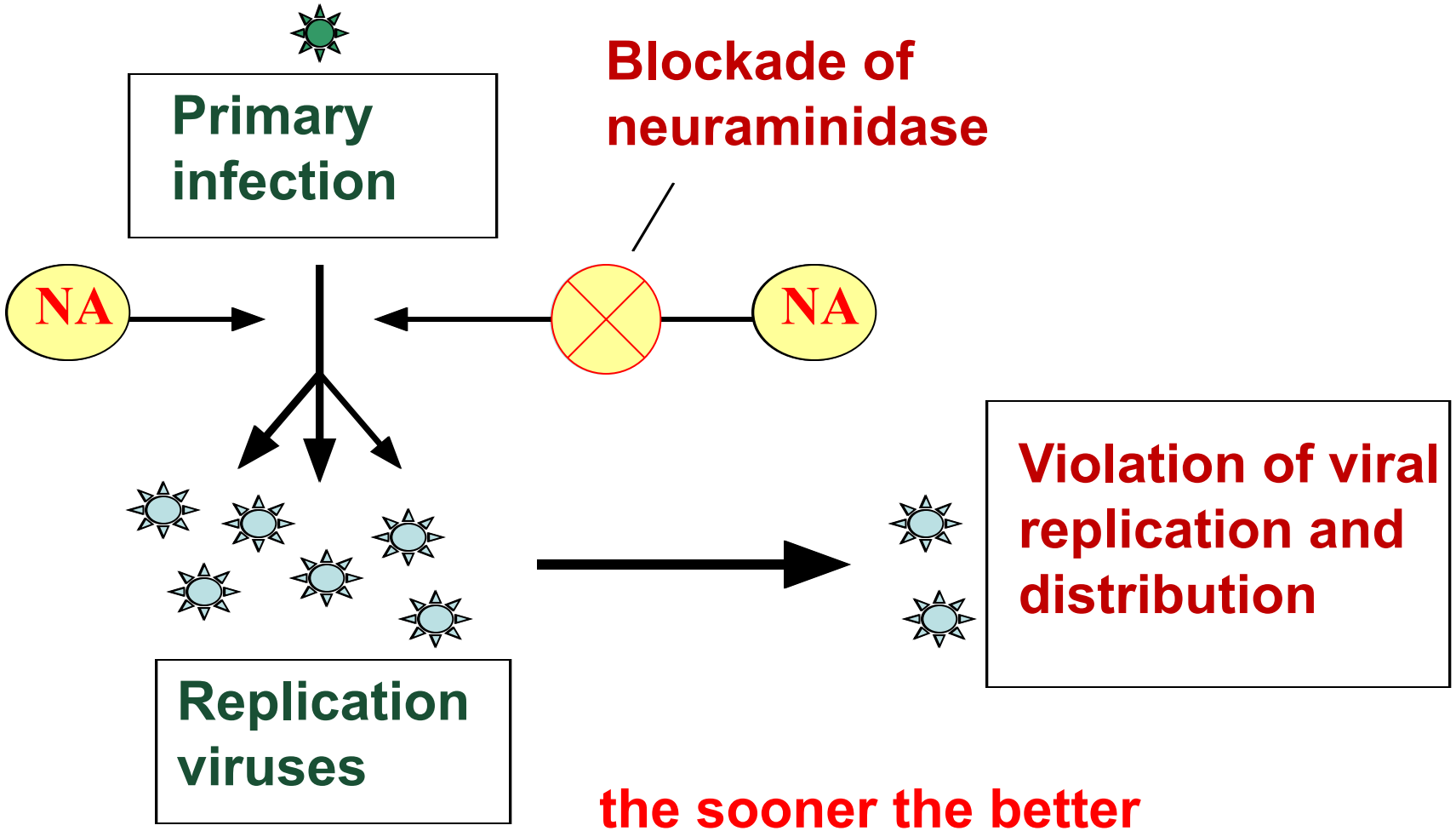
**INHIBITION**

Violates penetration of the virus into healthy cells

inhibites further spread of the virus in the body

- Reduces production of proinflammatory cytokines;
- Prevents development of local inflammatory reaction;
- Attenuates systemic symptoms of influenza (fever, myalgia);

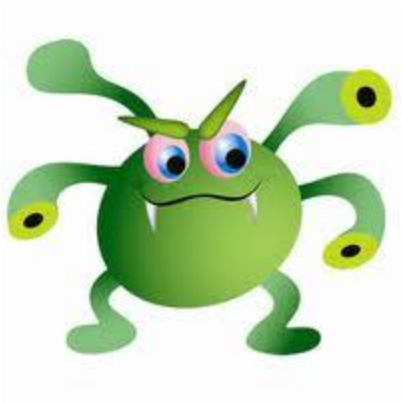
# mechanism of action of neuraminidase inhibitors



# SPECIFIC TREATMENT

## OSELTAMIVIR

- Selective inhibitor of neuraminidase;
- Inhibits the release of formed virus;
- It is used to treat influenza A and B;
- It is used to prevent influenza A or B in people who had contact with patients



NEUROAMINIDASE

OSELTAMIVIR

# TREATMENT

(Patients with mild forms can be treated ambulatory, with severe forms- should be hospitalized)

1. Bed rest;
2. Diet № 15, drink plenty of liquids;

3. Etiotropic treatment:
   - anti-influenza gamma-globulin (3ml) - i/m in the first 3 days,
   - interferon 2-3 drops every 1-2 h for 3 days,
   - rimantadine – 1-st day: 0,1 g × 3 t/d,
     2-nd day and 3-rd day: 0,1 g × 2 t/d;
   - oseltamivir – 0,75 g × 2 t/d (5 days);
   - zanamivir - 1 inhalation × 2 t/d

4. Pathogenic therapy: - desintoxication; - desensitization;
   - angioprotectors; - metabolites;

5. Symptomatic treatment: antipyretics, vitamins, local antiseptics;
6. Antitussive drugs, mucolytics, vasoconstrictor nasal drops;
7. Antibiotics - in complications, exacerbation of chronic diseases

# DIFFERENTIAL DIAGNOSIS of ARVI

| SIGN | INFLUENZA | PARAINFLUENZA | ADENOVIRUS INFECTION | RESPIRATORY SYNCYTIAL INFECTION | RHINOVIRUS INFECTION |
|---|---|---|---|---|---|
| LEADING SYNDROME OF DAMAGE | TRACHEITIS | LARYNGITIS | RHINOPHARYNGITIS CONJUNCTIVITIS TONSILLITIS | BRONCHIOLITIS | RHINITIS |
| INCUBATION | A FEW HOURS TO 1-2 DAYS | 2-7 DAYS OFTEN 3-4 DAYS | 4-14 DAYS | 3-6 DAYS | 2-3 DAYS |
| ONSET | ACUTE | GRADUAL | GRADUAL | GRADUAL | ACUTE |
| CURRENT | ACUTE | SUBACUTE | LINGERING, WAVY | SUBACUTE SOMETIMESLINGERING | ACUTE |
| INTOXICATION | SEVERE | MILD MODERATE | MODERATE | MODERATE | MILD OR ABSENT |

# DIFFERENTIAL DIAGNOSIS of ARVI

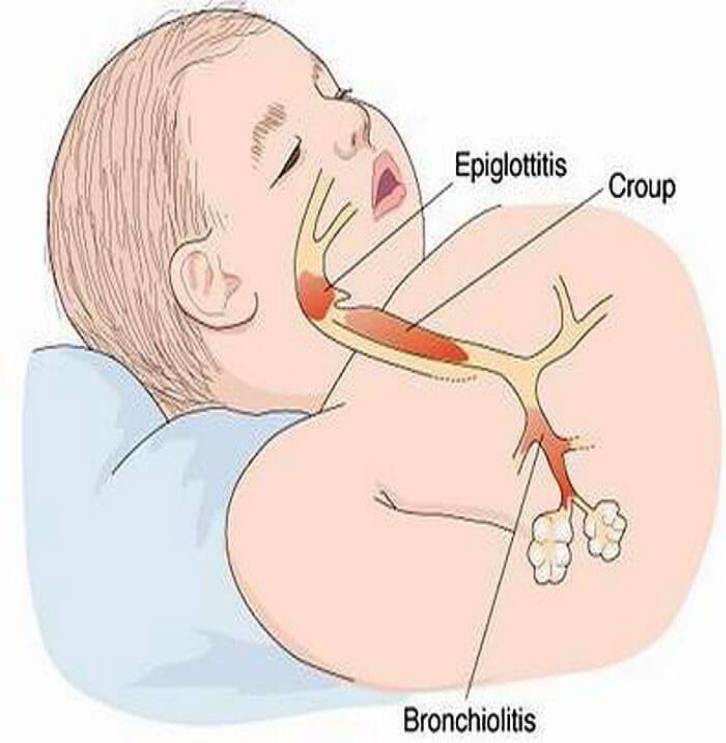
| SIGN | INFLUENZA | PARAINFLUENZA | ADENOVIRUS INFECTION | RESPIRATORY SYNCYTIAL INFECTION | RHINOVIRUS INFECTION |
|---|---|---|---|---|---|
| DURATION OF INTOXICATIO N | 2-5 DAYS | 1-3 DAYS | 8-10 DAYS | 2-7 DAYS | 1-2 DAYS |
| BODY TºC | HECTIC | 37-38C MAY LONG REMAIN | FEBRILE | SUBFEBRILE | NORMAL OR SUBFEBRILE |
| CATARRHAL SYNDROME | MODERATE EXPRESSED | EXPRESSED FROM THE 1-st DAY, HOARSENESS | EXPRESSED FROM THE 1-st DAY | EXPRESSED INCREASE GRADUALLY | EXPRESSED FROM THE 1-st DAY |
| RINITIS | NASAL CONGESTION | NASAL CONGESTION | ABUNDANT SEROUS DISCHARGE DIFFICULTY IN NASAL BREATHING | SCUNTY SEROUS DISCHARGE STUFFY NOSE | ABUNDANT SEROUS DISCHARGE DIFFICULTY IN NASAL BREATHING |

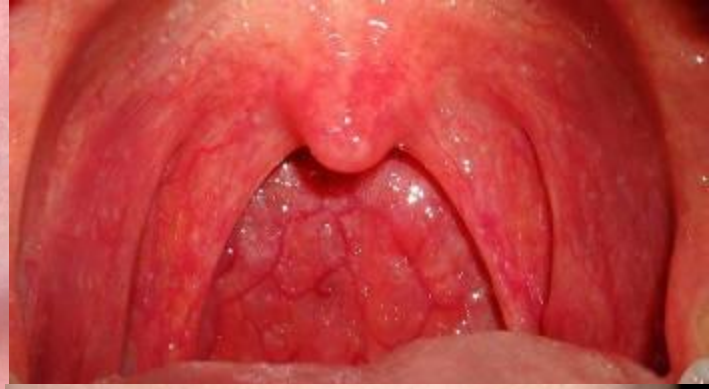
# DIFFERENTIAL DIAGNOSIS of ARVI

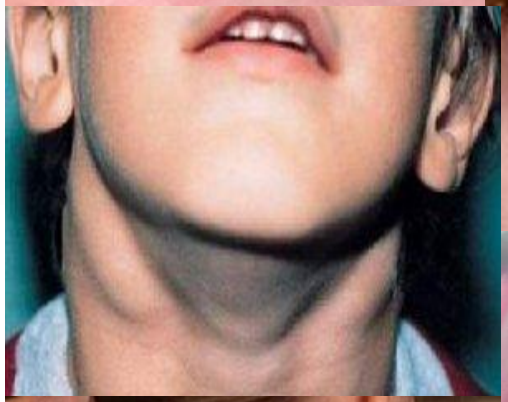
| SIGN | INFLUENZA | PARAINFLUENZA | ADENOVIRUS INFECTION | RESPIRATORY SYNCYTIAL INFECTION | RHINOVIRUS INFECTION |
|---|---|---|---|---|---|
| COUGH | DRY WITH PAIN BEHIND THE BREASTBONE UP TO 7-10 DAYS, ON 3-d DAY MOIST | DRY BARKING COUGH UP TO 12-21 DAY | MOIST | DRY PAROXYSMAL COUGH UNTIL 3 WEEKS | ABSENT OR TICKLE |
| THE CHANGE IN THE OROPHARYN GEAL CAVITY | NJECTION OF VESSELS OF MODERATE HYPEREMIA | MILD OR MODERATE HYPEREMIA | MODERATE HYPEREMIA EDEMA HYPERPLASIA OF THE FOLLICLES OF THE TONSILS, POSTERIOR PHARYNGEAL WALL | MILD HYPEREMIA | MILD HYPEREMIA |

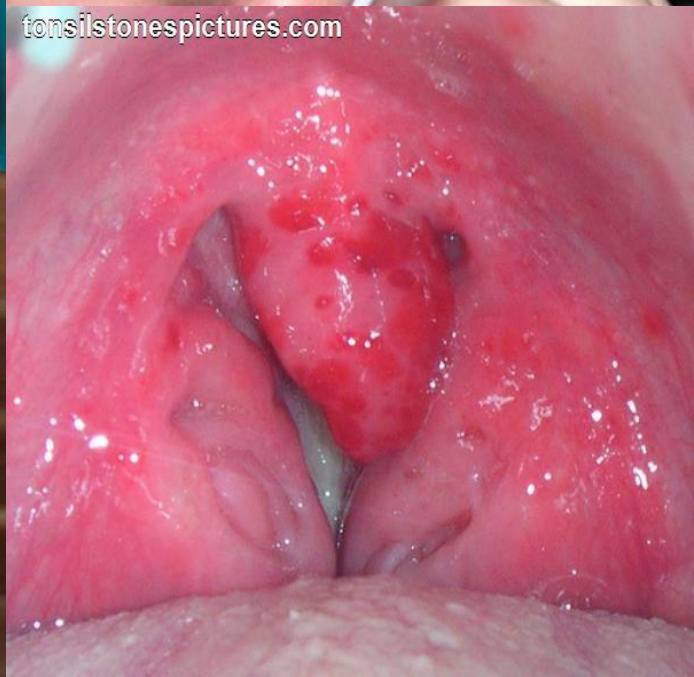
# DIFFERENTIAL DIAGNOSIS of ARVI

| SIGN | INFLUENZA | PARAINFLUENZA | ADENOVIRUS INFECTION | RESPIRATORY SYNCYTIAL INFECTION | RHINO-VIRUS INFECTION |
|---|---|---|---|---|---|
| LYMPHADENOPATHY | ABSENT | NONTYPICAL | GENERALIZED | INCREASE PARATRACHEAL AND PARABRONCHIAL LYMPH NODES | ABSENT |
| HEPATOSPLENOMEGALY | ABSENT | ABSENT | PRESENT | ABSENT | ABSENT |
| EYE DAMAGE | NJECTION OF VESSELS , SCLERITIS, BILATERAL CONJUNCTIVITIS | ABSENT | ONE-SIDED CONJUNCTIVITIS | ABSENT | ABSENT |


Epiglottitis
Croup
Bronchiolitis



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# PROFILAXIS OF INFLUENZA

1. Strict adherence to sanitary-hygienic regime in the epidemic and pre-epidemic period, regular general wet cleaning, bactericidal air disinfection.

2. The use of personal protective equipment (disposable masks).

3. Specific prevention (vaccination). Routine immunization can be carried out throughout the year, but the greatest its effectiveness in the autumn before the influenza season.

4. Nonspecific prevention of influenza and ARVI aimed at increasing the general resistance of the human body:
   - improvement of immune status with immunomodulators;
   - promotion of healthy lifestyle, tempering;
   - creation of favourable temperature in the room;