Virusne mutacije in možnosti prenosa ptičje gripe

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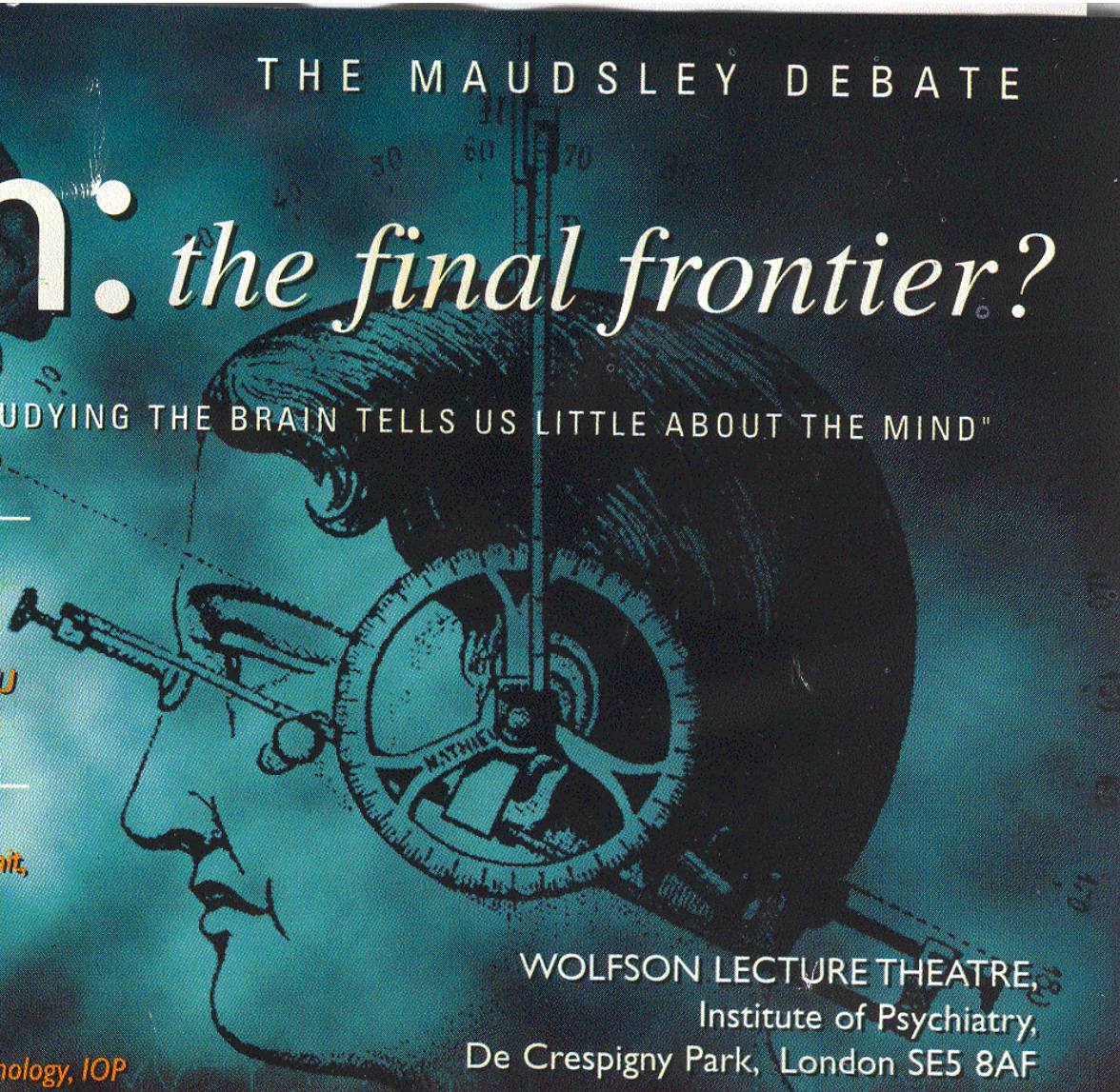
POZOR:
Prosojnice so bile osvežene 5.2.2005 in nekatere napake in pomankljivosti odpravljene. Dodana je bila zadnja prosojnica z odgovori na nekatera vprašanja na katera nisem najbolje odgovoril med predavanjem.

THE MAUDSLEY DEBATE

the brain: the final frontier?

"THIS HOUSE BELIEVES THAT STUDYING THE BRAIN TELLS US LITTLE ABOUT THE MIND"



FOR:

Peter Fonagy
Professor of Psychoanalysis, UCL

Steven Rose
Director of Brain and Behaviour Research Group, OU

AGAINST:

Tim Crow
Director, Prince of Wales Schizophrenia Research Unit, Oxford University

Ed Bullmore
Professor of Psychiatry, Cambridge University

Chair: Jeffrey Gray *Emeritus Professor of Psychology, IOP*

WOLFSON LECTURE THEATRE,
Institute of Psychiatry,
De Crespigny Park, London SE5 8AF

Wednesday 11 October 2000 @ 6.00pm

ADMISSION FREE • ALL WELCOME • REFRESHMENTS FROM 5.30PM

Further information contact 020 7848 0421 or e-mail:
maudsley.debates@iop.kcl.ac.uk
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www.iop.kcl.ac.uk/iop/news/mdebates.stm

THIS HOUSE BELIEVES
THAT A PANDEMIC FLU IS IMMINENT IN THE NEXT FEW YEARS

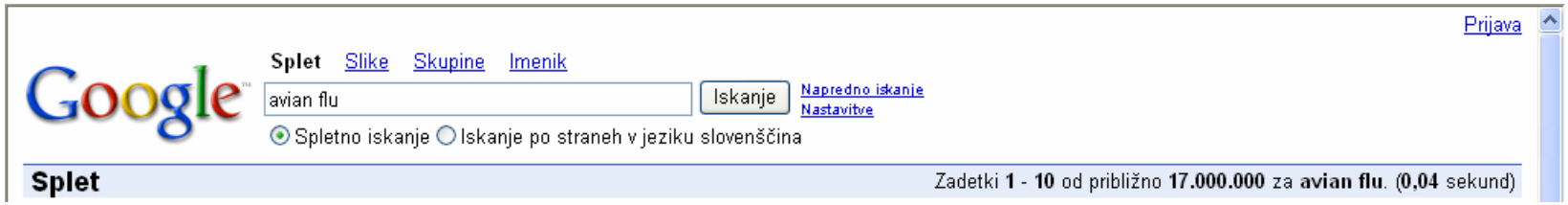
Supporting this motion

Speaking against this motion
Gregor Anderluh

Pandemic flu — communicating the risks
The Bulletin interview with Dr Margaret Chan
Representative of the Director-General for Pandemic Influenza, WHO
WHO hosted a meeting of public health experts in Geneva on 6–8 December to discuss how governments should communicate the risks posed by avian flu and the threat of a human flu pandemic to members of the public.

Q: Health ministries in many countries are concerned that they may be communicating uncertainty to the public when it comes to public information on avian influenza and human pandemic influenza? What is WHO advising them to do?
A: In accordance with WHO Outbreak Communication guidelines, WHO advises Member States to be as open and transparent as possible in their public communications regarding disease threats, including avian and pandemic influenza. **Unfortunately, there is considerable uncertainty simply because there are many unknowns about the next influenza pandemic. There is no way for anyone to accurately predict things like when the next pandemic might strike, or how many people might be killed.** While WHO recognizes that talking openly about a pandemic threat may raise concerns worldwide, we would not be fulfilling our public health mandate if we did not warn the world of this evolving threat.

Q: Do you think there is too much "hype" about avian influenza and a possible human pandemic? What happens if there is no pandemic in the next six months? Will that not detract from the credibility of WHO and the United Nations?
A: As a global public health agency, WHO has a responsibility to alert the international community when it appears that the world is moving closer to a pandemic. **It may be years before a pandemic hits the world, and it may ultimately be sparked by a virus other than [avian influenza virus] H5N1.** Investing in pandemic preparedness is essentially like investing in an insurance policy, and while we hope that we never have to make a claim, we also know that whatever investment we make now in strengthening global public health infrastructures will have benefits for our responses to all future infectious disease threats. **The preparations that we make for a pandemic are not disease specific**; they will increase our capacity to respond to all future outbreaks, including SARS (severe acute respiratory syndrome) and other new and emerging diseases.



Is **Avian Flu** another Pentagon Hoax?

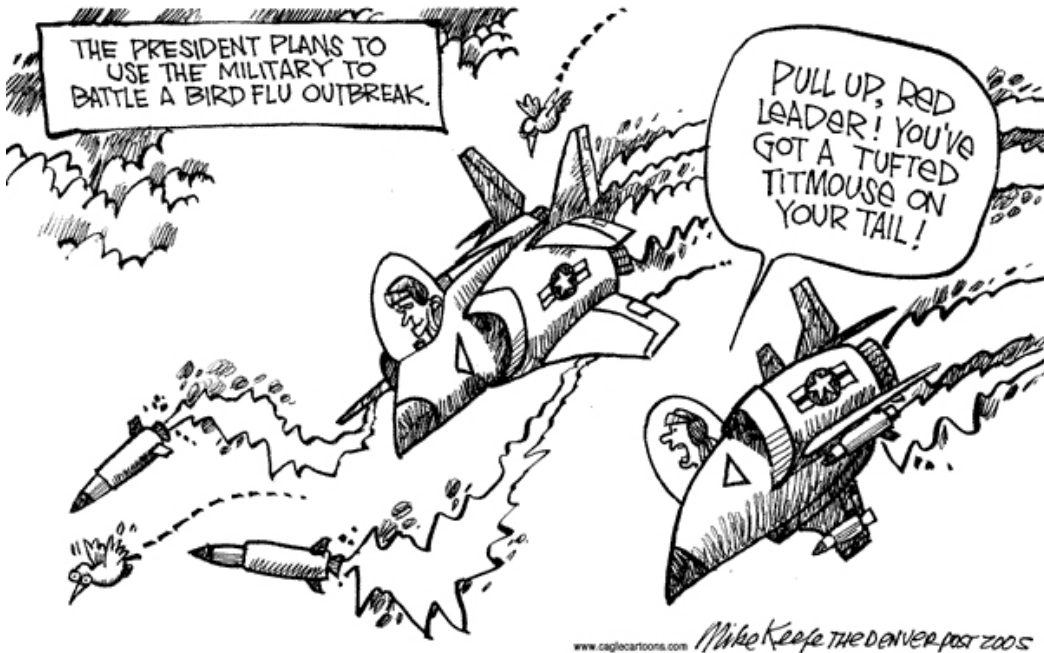
Banks and insurers prepare for **avian flu** outbreak - Yahoo! News

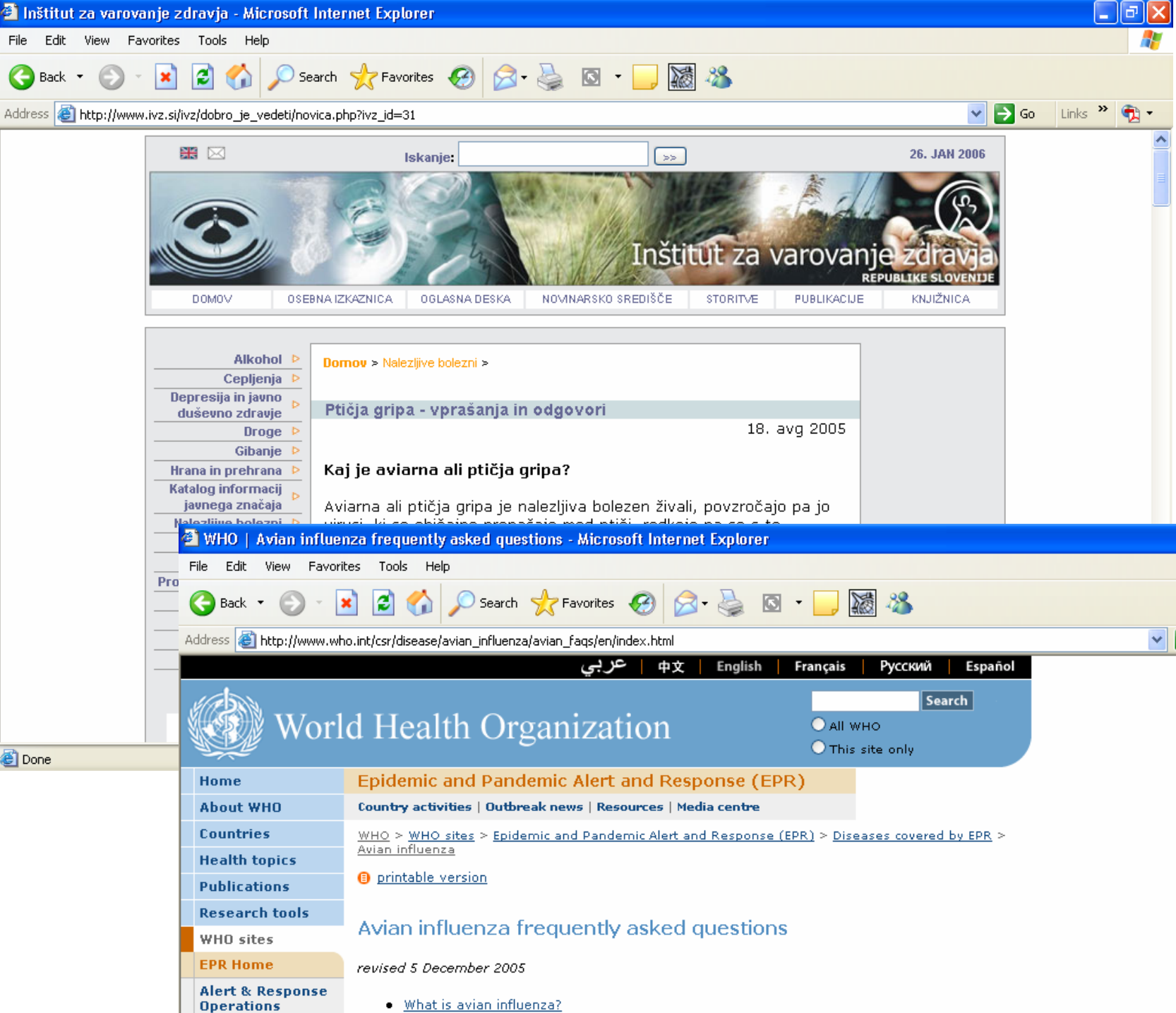
Seed: Overestimating **Avian Flu**

Avian Flu: Inoculate Your Portfolio

Chicken Implants Would Warn of **Avian Flu** Fever

Martial Law and the **Avian Flu** Pandemic

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26. JAN 2006
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NOVINARSKO SREDIŠČE
STORITVE
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KNJIŽNICA
Alkohol
Cepljenja
Depresija in javno duševno zdravje
Droge
Gibanje
Hrana in prehrana
Katalog informacij javnega značaja
Domov > Nalezljive bolezni >
Ptičja gripa - vprašanja in odgovori
18. avg 2005
Kaj je aviarna ali ptičja gripa?
Aviarna ali ptičja gripa je nalezljiva bolezen živali, povzročajo pa jo
WHO | Avian influenza frequently asked questions - Microsoft Internet Explorer
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Address http://www.who.int/csr/disease/avian_influenza/avian_faqs/en/index.html
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Epidemic and Pandemic Alert and Response (EPR)
Country activities | Outbreak news | Resources | Media centre
WHO > WHO sites > Epidemic and Pandemic Alert and Response (EPR) > Diseases covered by EPR > Avian influenza
printable version
Avian influenza frequently asked questions
revised 5 December 2005
What is avian influenza?
Done

Kako se razlikujejo ptičja gripa, sezonska gripa in pandemična gripa?

Ptičjo gripo povzročajo ptičji virusi gripe, ki se pri pticah pojavljajo v naravi.

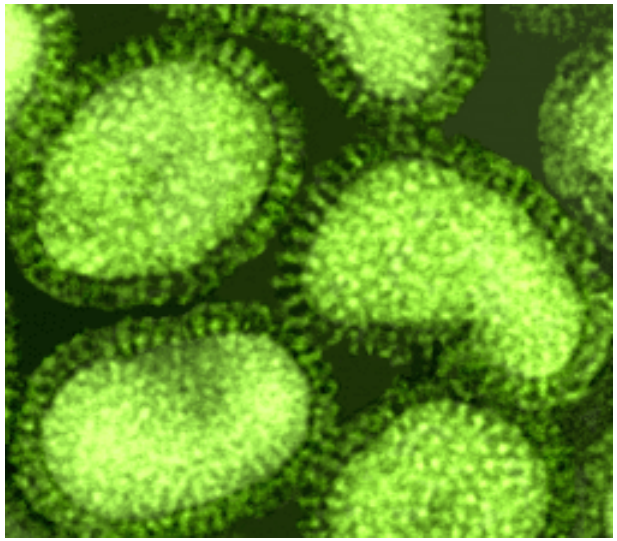
Pandemična gripa povzroča globalni izbruh bolezni (pandemijo) in se z lahkoto prenaša od osebe do osebe. Trenutno ni pandemije gripe!

Sezonska gripa je nalezljiva bolezen dihal, ki jo povzročajo virusi gripe.

Ptičja gripa ≠ Pandemična gripa ≠ Sezonska gripa

VIRUS INFLUENZE
ZGRADBA VIRUSA INFLUENZE
BIOLOGIJA VIRUSA INFLUENCE
HEMAGLUTININ
RAZLIKE MED VIRUSI
KAKO SE LAHKO OBRANIMO GRIPE
PERSPEKTIVE

Najnovejša dognanja v biologiji in molekularni biologiji
GENOM, PROTEOMIKA, HOMOLOGI, MOLEKULARNA EVOLUCIJA, MOLEKULARNA FILOGENIJA, MOLEKULARNA SISTEMATIKA, BIOINFORMATIKA, ANTIGENSKI PREMIK, ANTIGENSKI ZDRS, GENOMIKA, REVERZNA GENETIKA



Linda M. Stannard, University of Cape Town,
http://www.uct.ac.za/depts/mmi/stannard/emimages.html

Orthomyxovirus
Ortomiksovirusi (virusi gripe)

Tip A lahko povzročajo pandemije
mnogi gostitelji- ptiči, prašiči, človek, konji

Tip B povzročajo lokalne epidemije
človek

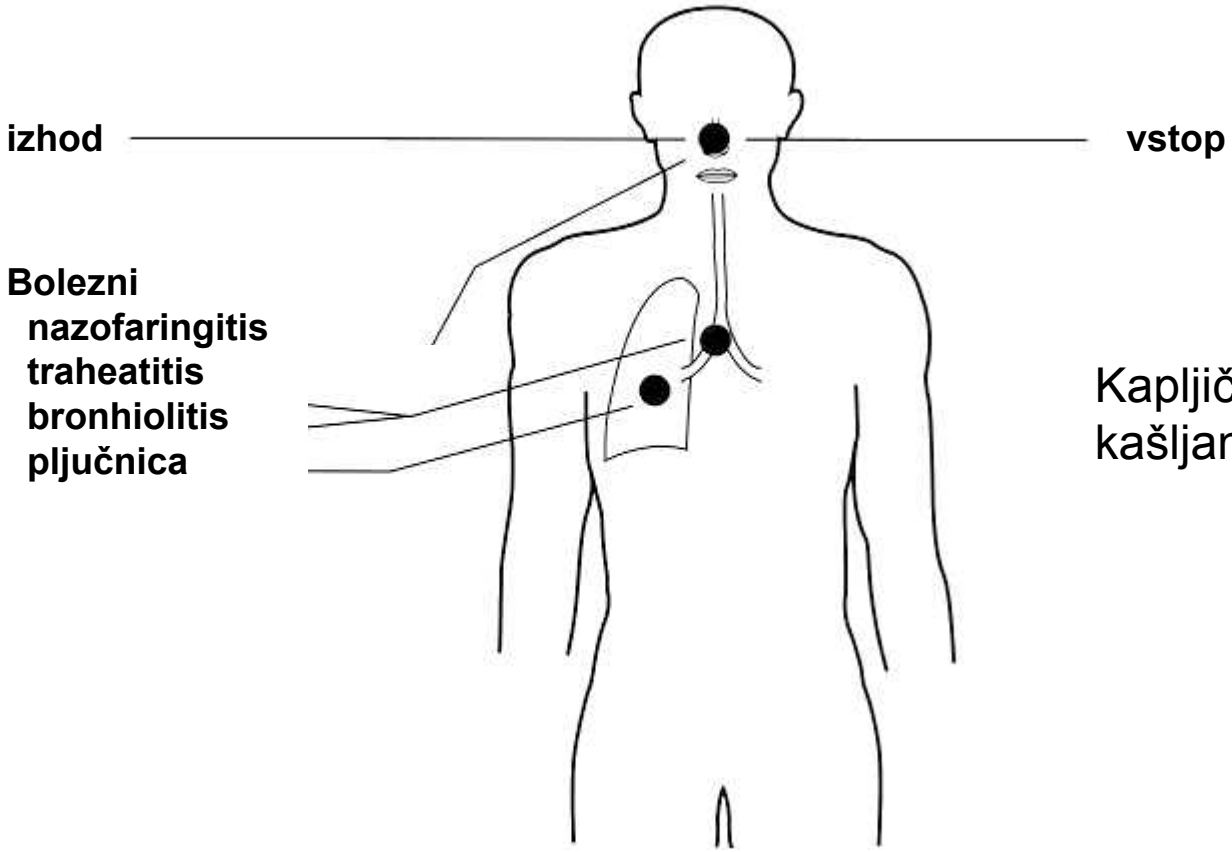
Tip C

Jih ločimo glede na nukleoprotein; ni navzkrižne serološke reakcije med njimi.

Povzročajo **akutne respiratorne infekcije** s splošnimi sistemskimi znaki. Pljučnica je lahko komplikacija pri starejših, lahko smrtna.

KLINIČNI ZNAKI
Vročinsko stanje z nenadnim začetkom. Karakteristično sta vnetje sapnika in bolečine v mišicah.
Glavobol, mrzlica, vročina, slabost, bolečine v mišicah, neješčnost in vneto grlo se lahko pojavijo nenadoma.
Pogosto je kihanje, izcedek iz nosu in zamašen nos. Lahko so prisotni tudi fotofobija, slabost, bruhanje, driska in bolečine v trebuhu.

Inkubacijska doba 1-4 dni. Respiratorni in sistemski simptomi lahko trajajo 1-5 dni.



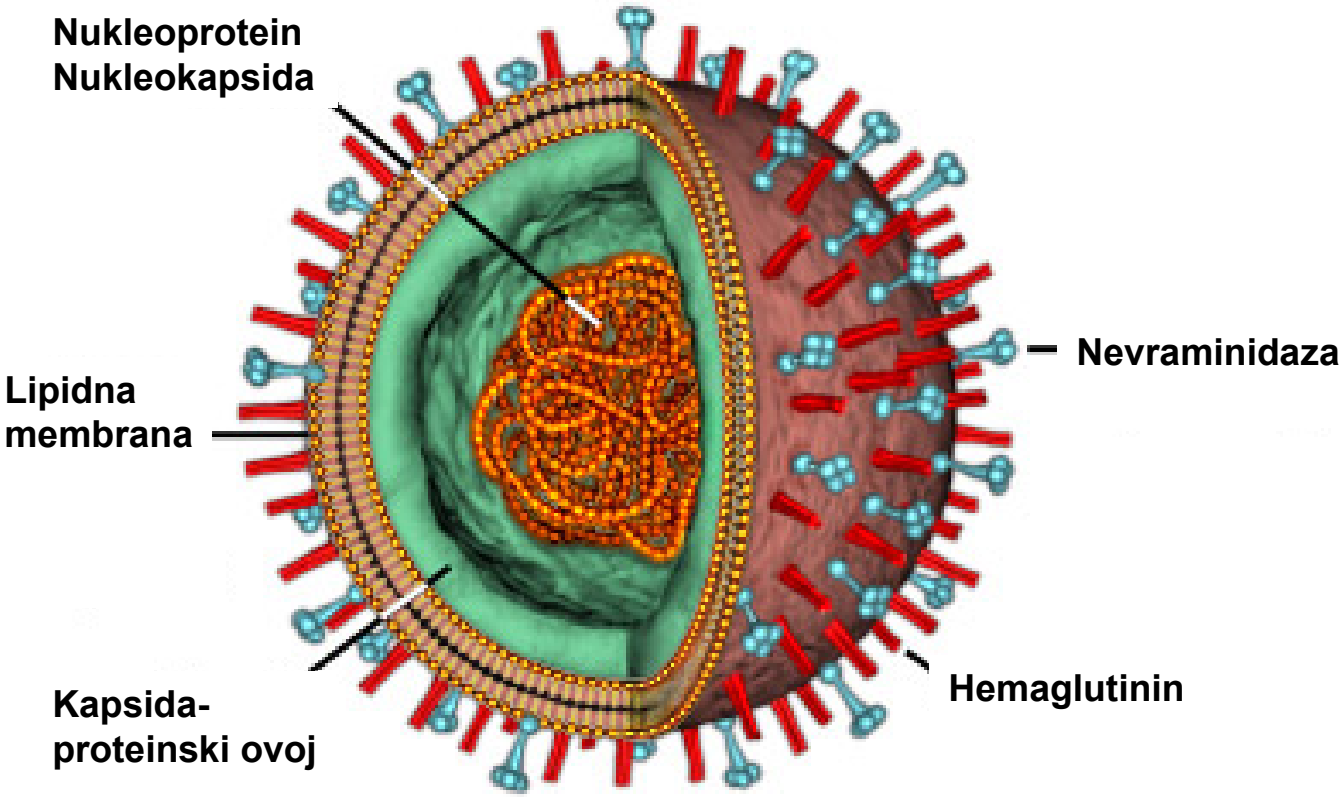
Kapljični prenos s kihanjem in kašljanjem.

Sindrom influence redko prisoten pri otrocih in odsoten pri dojenčkih. Odrasli ne izkažejo vedno vseh simptomov.

***Endemične (npr. sezonske) oblike*:** do 10-20% populacije okužene, v Ameriki **umre na leto 36.000 ljudi** (Department of Health and Human Services; Centers for Diseases Control and Prevention)

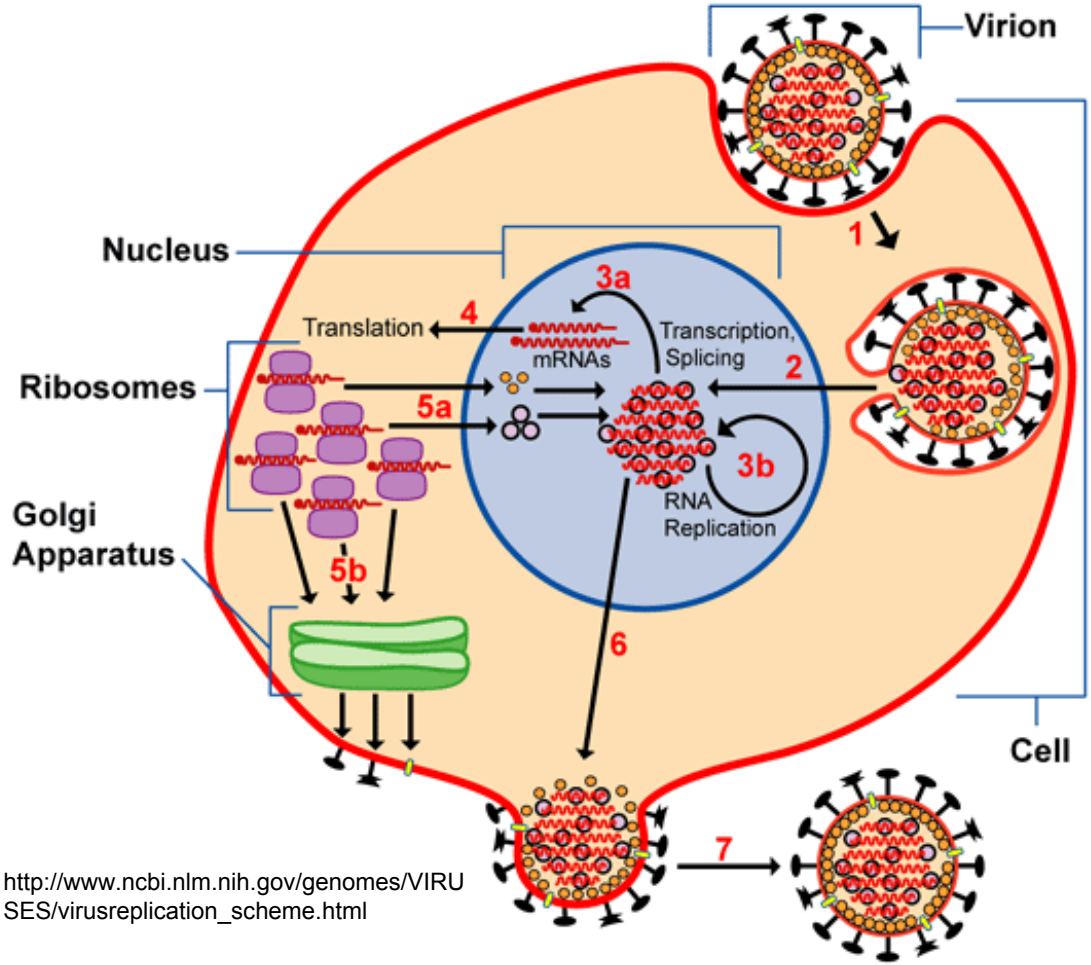
Pandemične oblike: do 40% okužene populacije

ZGRADBA VIRUSA INFLUENCE



http://micro.magnet.fsu.edu/cells/viruses/influenzavirus.html

En virusni delec tako vsebuje
okoli 500 molekul **hemaglutinina (H; HA)**
okoli 100 molekul **nevraminidaze (N; NA)**
okoli 3000 molekul **proteina matriksa**
8 molekul **RNA**
na vsako molekulo RNA je vezano večje število **nukleoproteina (NP)**
nekaj molekul **RNA polimeraze**, ki je sestavljena iz treh podenot
nestrukturni protein z neznano funkcijo



http://www.ncbi.nlm.nih.gov/genomes/VIRUSES/virusreplication_scheme.html

V glavnih vlogah

hemaglutinin	**H**
nevraminidaza	**N**
membranski protein	**M2**
protein matriksa	**M1**
nukleoprotein	**NP**
nestrukturni protein	**NS**
prot. jedrnega eksporta	**NEP**
polimeraza	**PA**
	PB1
	PB2

RNA

8 kosov (890-2341 nt)

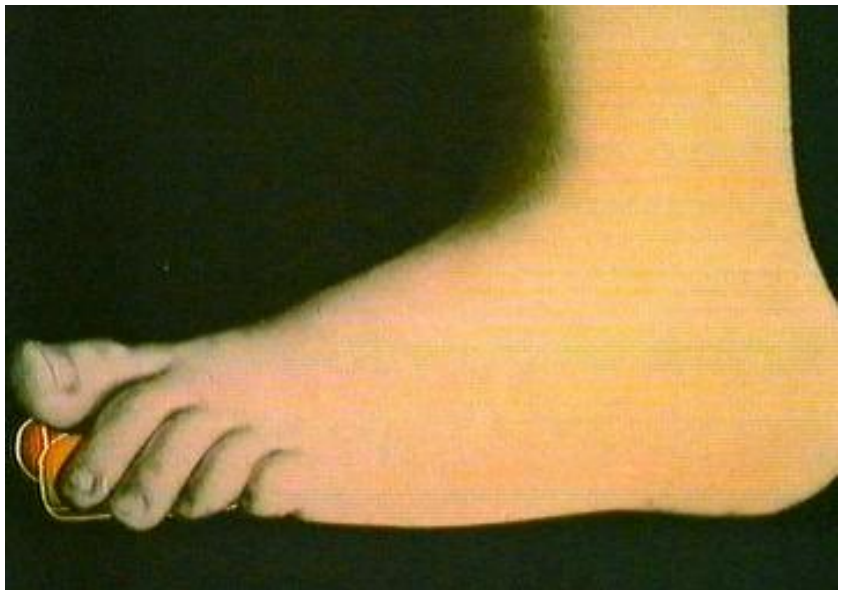
GENOM skupaj 14 kb

(=ves genetski material nekega organizma)

ribonukleoproteini

REPLIKACIJA VIRUSA

1. vezava na membrano in endocitoza.
2. sprostitev vsebine virusa (nukleokapside) v citoplazmo. Transport v jedro.
3. podvojevanje in prepisovanje virusna mRNA z virusno RNA polimerazo.
4. prehod nove mRNA v citoplazmo, kjer pride do translacije.
5. sinteza HA, NA, M2 v ER, GA, celična membrana. NP, M1, NS1 in NEP gredo v jedro, kjer se vežejo na nove kopije RNA.
6. povezava nukleokapside z membrano, ki vsebuje HA, NA, M2 preko M1 proteina.
7. zorenje novih virusov in sproščanje iz celice.



Osnovni gradniki so
NUKLEOTIDI

Adenin
Gvanin
Citozin
Timin

DNA

```
>gi|37047698|gb|CF601391.1|CF601391 tac36g08.y1 Hydra EST -IV Hydra
magnipapillata cDNA 5' similar to TR:Q9Y1U9 Q9Y1U9 EQUINATOXIN IV
PRECURSOR. ;, mRNA sequence
AACTAGCAAAGCAGACGCTGGAGGAGGCGCTGGAATAGCAATTTTAGGAGTATTAGCAAAAGTCGGCGTA
GAAGCTGCGTTACAGCAAATTGATAATATTTGGAAAGGAGATGTAGTGAGGTATTGGAAATGCGCTGTAG
AAAACAGATCCGATAAAACACTTTATGCTTACGGAACAACTACGGAATCGGGAAGTATGGGTACAGTTTT
TGCCGATATTCCCCCTGGAAGCACAGGAATTTTTGTGTGGGAAAAATCTAGAGGAGCTGCAACTGGAGCA
AGTGGTGTAGTTCATTATCGTTATGGAGACAAGATACTTAATTTAATGGCATCCATTCCATATGATTGGA
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GTTAAATGGTGCGAAACCTGCTACAAGAGGAGGAAACTGGGGCGACGTTGATGGTGCAAAATTTTTTCTT
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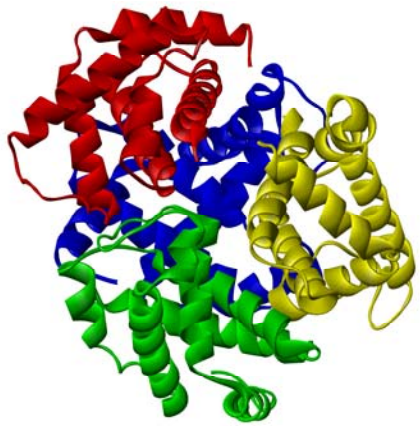
TTTTTCTGTAAA
```

Protein



Osnovni gradniki so
AMINOKISLINE

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IYETDFQRLTKLRMLQLTDNQIHTIERNSFQDLVSLERLDISNNVITTVGRRVFKGA
QSLRSLQLDNNQITCLDEHAFKGLVELEILTLNNNNLTSLPHNIFGGLGRLRALRLS
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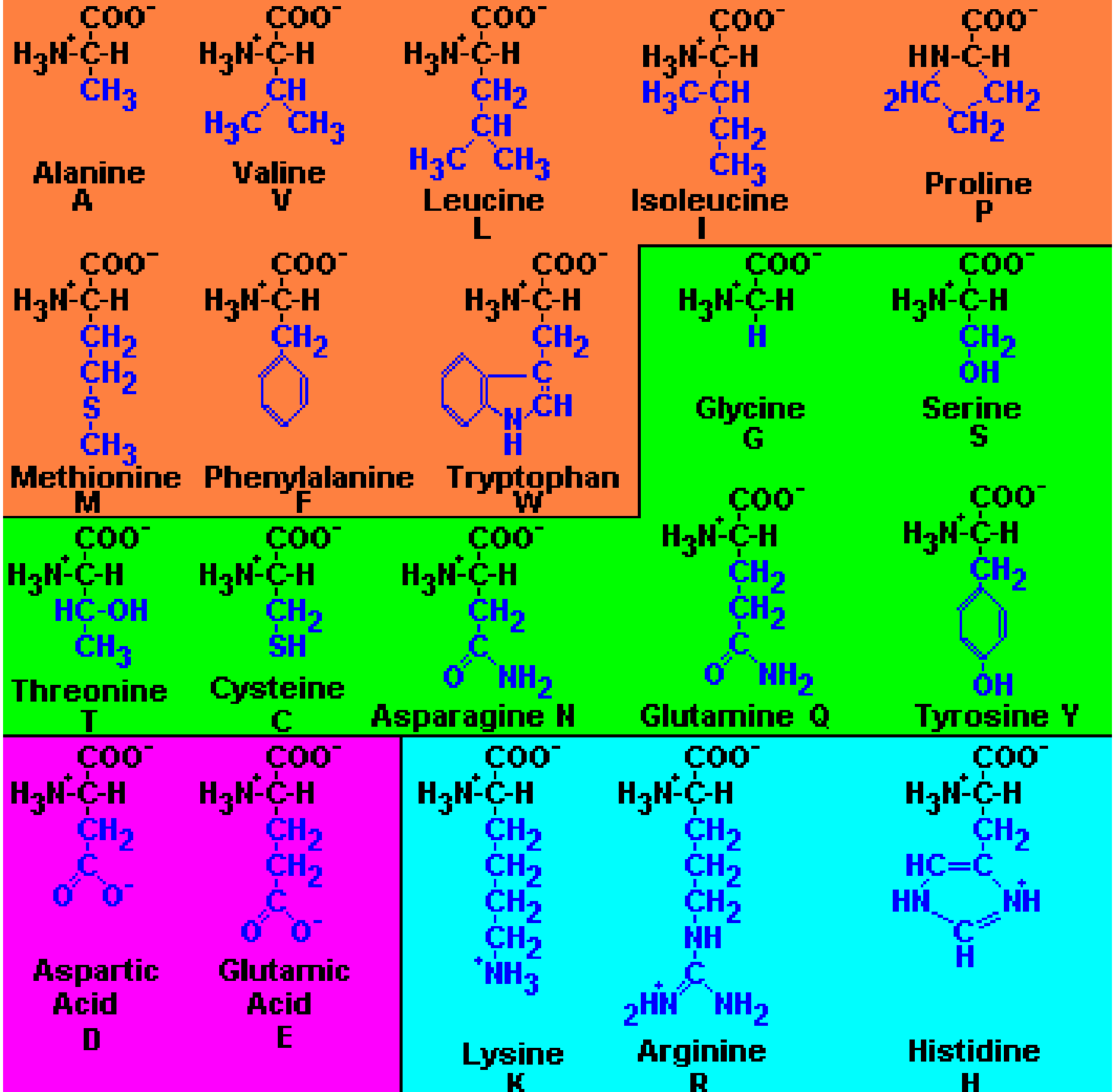
Alanine
A
Valine
V
Leucine
L
Isoleucine
I
Proline
P
Methionine
M
Phenylalanine
F
Tryptophan
W
Glycine
G
Serine
S
Threonine
T
Cysteine
C
Asparagine N
Glutamine Q
Tyrosine Y
Aspartic
Acid
D
Glutamic
Acid
E
Lysine
K
Arginine
R
Histidine
H

PRIKAZ PROTEINSKE STRUKTURE

>gi|122615|sp|P02023|HBB_HUMAN HEMOGLOBIN BETA CHAIN
MVHLTPEEKSAVTALWGKVNVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMG
NPVKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVL
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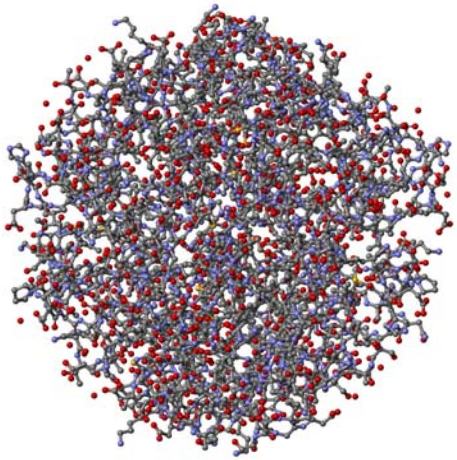
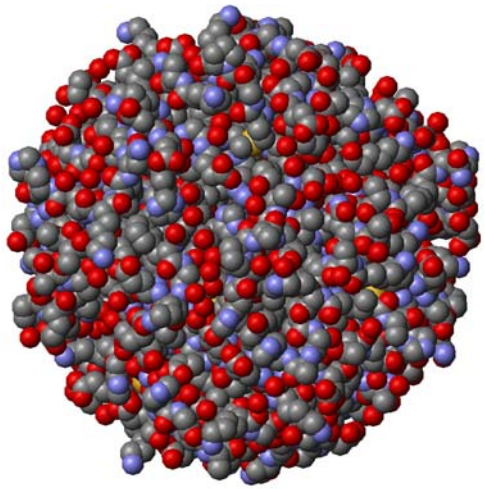
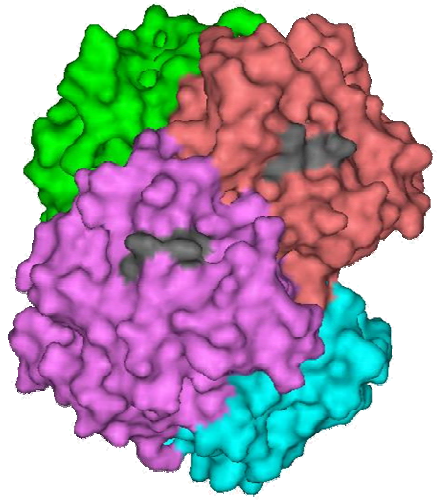


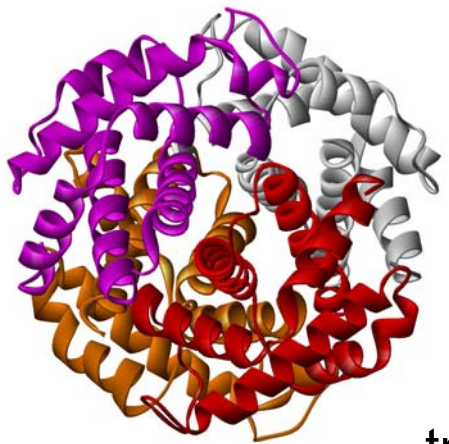
Vezi
(skeletni)



Atomi
(Van der Waalsov radii atomov: Corey-Pauling-Koltun - CPK model)



Površina



Shematsko
cilindri (α-heliks)
trakovi (β–ploskev)

PROTEOMIKA

Disciplina, ki proučuje proteinski komplement na celičnem nivoju.

```
                    10        20        30        40        50        60        70        80
ALPHA1     -MVLSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTKTYFPHFDLSH-----G-SAQVKGHGKKVADALTNAVAHVDDMPNA  80
ALPHA2     -MVLSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTKTYFPHFDLSH-----G-SAQVKGHGKKVADALTNAVAHVDDMPNA  80
THETA      -MALSAEDRALVRALWKKLGSNVGVYTTEALERTFLAFPATKTYFSHLDLSP-----G-SSQVRAHGQKVADALSLAVERLDDLPHA  80
GAMMA      MGHFTEEDKATITSLWGKVN--VEDAGGETLGRLLVVYPWTQRFFDSFGNLSSASAIMGNPKVKAHGKKVLTSLGDAIKHLDDLKGT  85
BETA       MVHLTPEEKSAVTALWGKVN--VDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPKVKAHGKKVLGAFSDGLAHLDNLKGT  85
EPSILON    MVHFTAEEKAAVTSLWSKMN--VEEAGGEALGRLLVVYPWTQRFFDSFGNLSSPSAILGNPKVKAHGKKVLTSFGDAIKNMDNLKPA  85
DELTA      MVHLTPEEKTAVNALWGKVN--VDAVGGEALGRLLVVYPWTQRFFESFGDLSSPDAVMGNPKVKAHGKKVLGAFSDGLAHLDNLKGT  85
MYOGLOBIN  -MGLSDGEWQLVLNVWGKVEADIPGHGQEVLIRLFKGHPETLEKFDKFKHLKSEDEMKASEDLKKHGATVLTALGGILKKKGHHEAE  86

                    90        100       110       120       130       140       150
ALPHA1     LSALSDLHAHKLRVDPVNFKLLSHCLLVTLAAHLPAEFTPAVHASLDKFLASVSTVLTSKYR------ 142
ALPHA2     LSALSDLHAHKLRVDPVNFKLLSHCLLVTLAAHLPAEFTPAVHASLDKFLASVSTVLTSKYR------ 142
THETA      LSALSHLHACQLRVDPASFQLLGHCLLVTLARHYPGDFSPALQASLDKFLSHVISALVSEYR------ 142
GAMMA      FAQLSELHCDKLHVDPENFKLLGNVLVTVLAIHFGKEFTPEVQASWQKMVTGVASALSSRYH------ 147
BETA       FATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH------ 147
EPSILON    FAKLSELHCDKLHVDPENFKLLGNVMVIILATHFGKEFTPEVQAAWQKLVSAVAIALAHKYH------ 147
DELTA      FSQLSELHCDKLHVDPENFRLLGNVLVCVLARNFGKEFTPQMQAAYQKVVAGVANALAHKYH------ 147
MYOGLOBIN  IKPLAQSHATKHKIPVKYLEFISECIIQVLQSKHPGDFGADAQGAMNKALELFRKDMASNYKELGFQG 154
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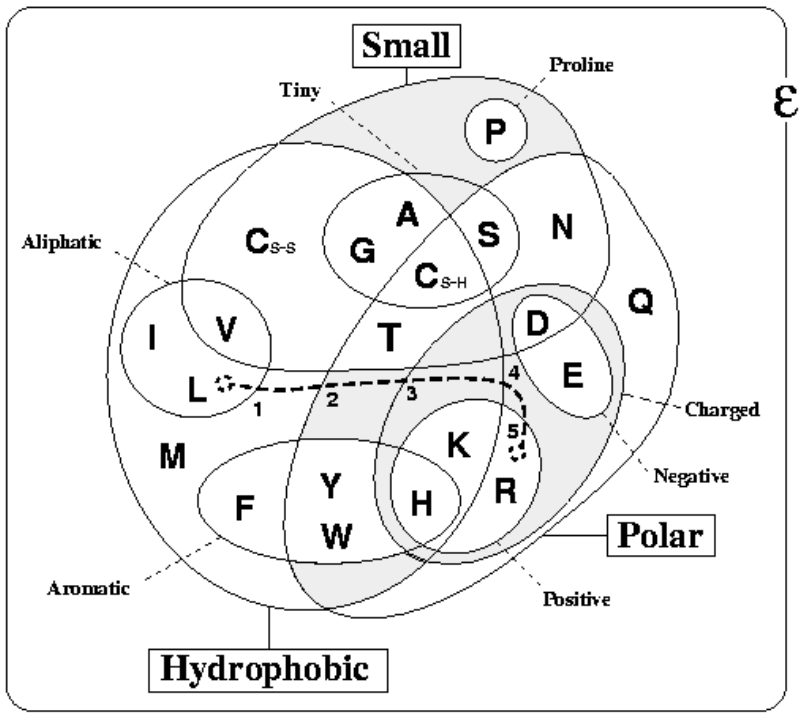
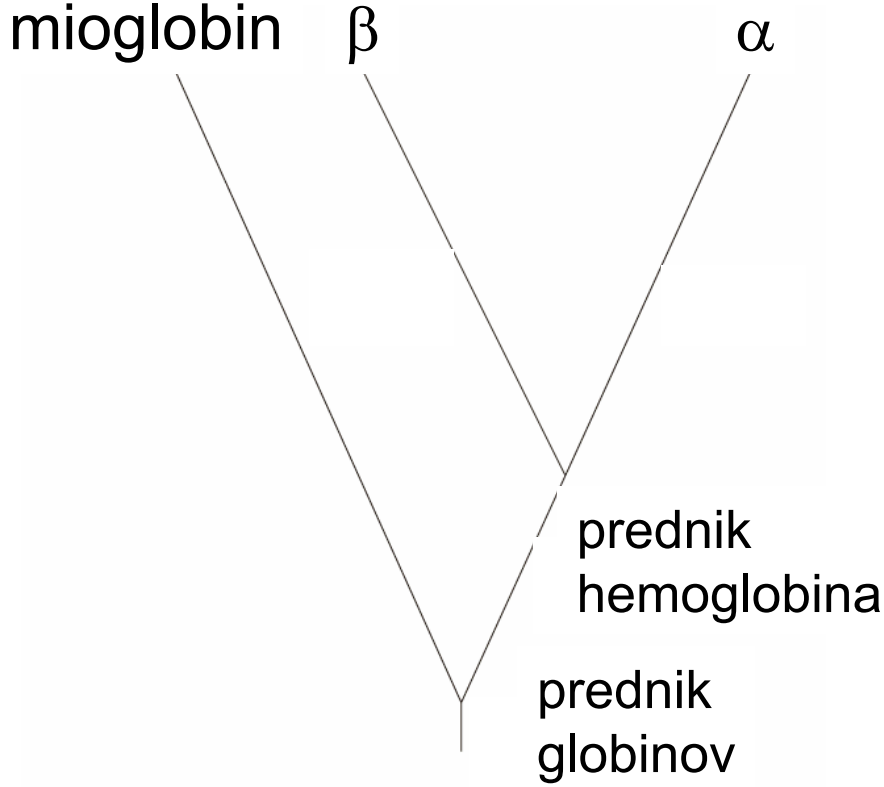
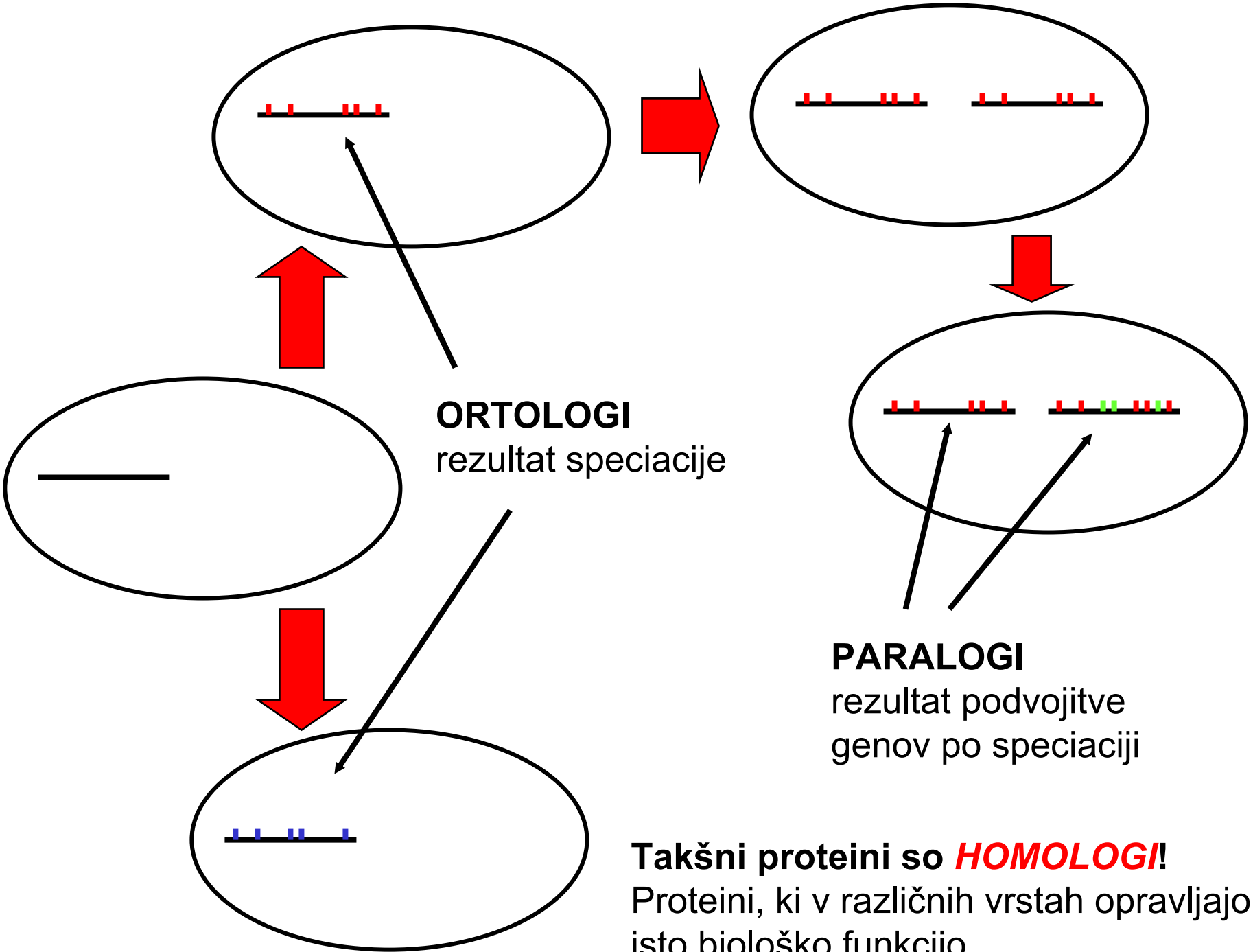


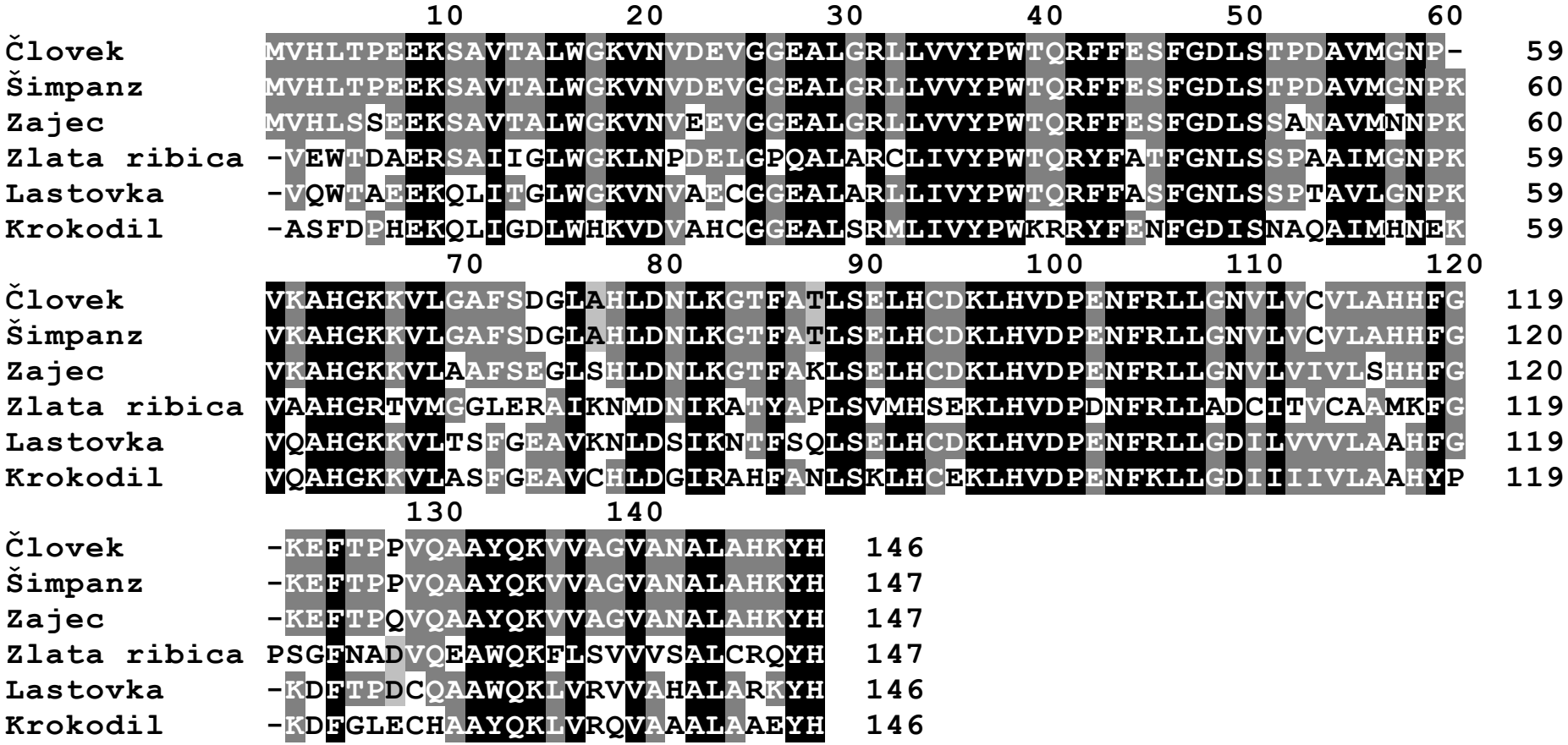




ORTOLOGI
rezultat speciacije

PARALOGI
rezultat podvojitve genov po speciaciji

Takšni proteini so *HOMOLOGI*!
Proteini, ki v različnih vrstah opravljajo isto biološko funkcijo


10 20 30 40 50 60
Človek MVHLTPEEKSAVTALWGKVNVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNP- 59
Šimpanz MVHLTPEEKSAVTALWGKVNVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPK 60
Zajec MVHLSSEEKSAVTALWGKVNVEEVGGEALGRLLVVYPWTQRFFESFGDLSSANAVMNNPK 60
Zlata ribica -VEWTDAERSAIIGLWGKLNPDELGPQALARCLIVYPWTQRYFATFGNLSSPAAIMGNPK 59
Lastovka -VQWTAEEKQLITGLWGKVNVAECGGEALARLLIVYPWTQRFFASFGNLSSPTAVLGNPK 59
Krokodil -ASFDPHEKQLIGDLWHKVDVAHCGGEALSRMLIVYPWKRRYFENFGDISNAQAIMHNEK 59
70 80 90 100 110 120
Človek VKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFG 119
Šimpanz VKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFG 120
Zajec VKAHGKKVLAAFSEGLSHLDNLKGTFAKLSELHCDKLHVDPENFRLLGNVLVIVLSHHFG 120
Zlata ribica VAAHGRTVMGGLERAIKNMDNIKATYAPLSVMHSEKLHVDPDNFRLLADCITVCAAMKFG 119
Lastovka VQAHGKKVLTSFGEAVKNLDSIKNTFSQLSELHCDKLHVDPENFRLLGDILVVVLAAHFG 119
Krokodil VQAHGKKVLASFGEAVCHLDGIRAHFANLSKLHCEKLHVDPENFKLLGDIIIIVLAAHYP 119
130 140
Človek -KEFTPPVQAAYQKVVAGVANALAHKYH 146
Šimpanz -KEFTPPVQAAYQKVVAGVANALAHKYH 147
Zajec -KEFTPQVQAAYQKVVAGVANALAHKYH 147
Zlata ribica PSGFNADVQEAWQKFLSVVVSALCRQYH 147
Lastovka -KDFTPDCQAAWQKLVRVVAHALARKYH 146
Krokodil -KDFGLECHAAYQKLVRQVAAALAAEYH 146

citokrom c- encim udeležen pri respiraciji

znano zaporedje velikega števila vrst

od okoli 100 aminokislin je

•38 invariantnih (ista aminokislina na istem mestu) pri vseh vrstah

•55 invariantnih med konjem in kvasovko

•8 mest je hipervariablinih

•zaporedje je identično pri konju, svinji, ovci, kravi

MOLEKULARNA EVOLUCIJA

Spremembe genetskega materiala v času.

MOLEKULARNA FILOGENIJA

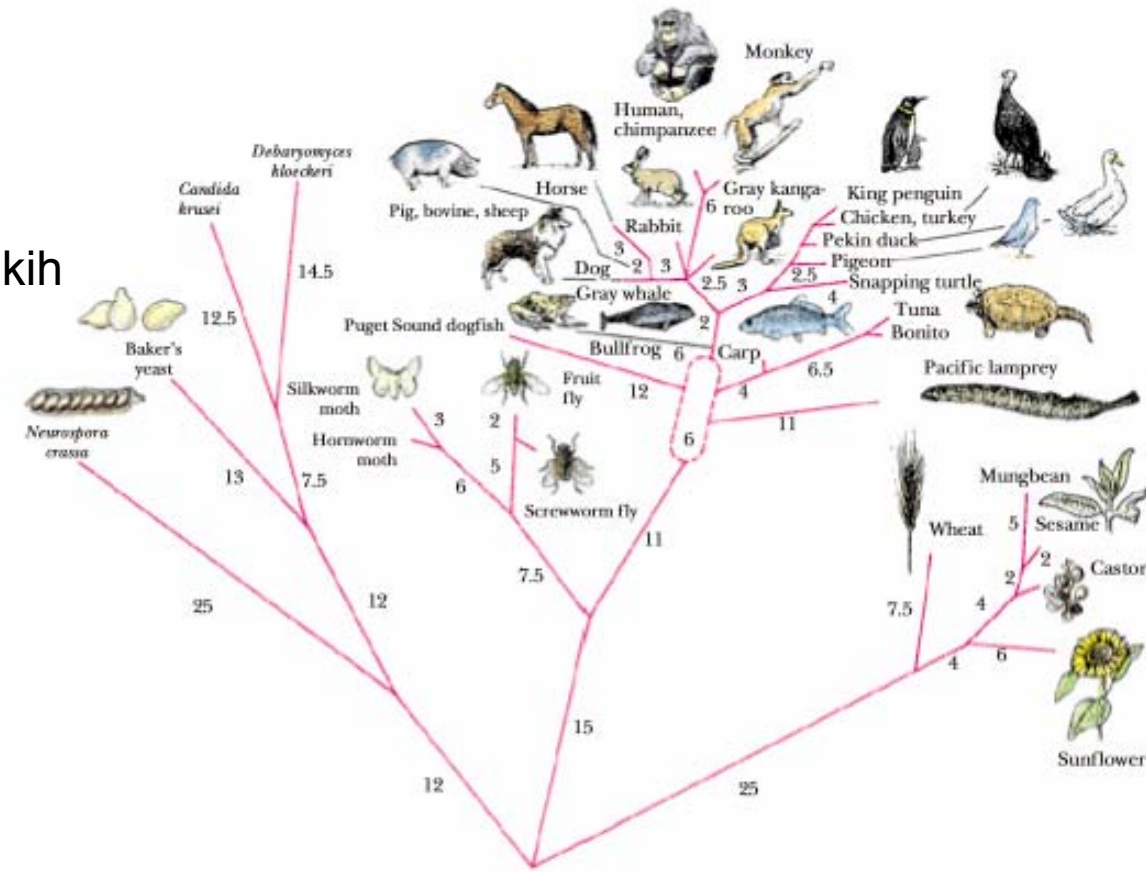
Uporaba zaporedij za opis evolucijskih odnosov med organizmi.

Metoda, ki omogoča konstrukcijo filogenetskih dreves.

FILOGENETSKA DREVESA

Omogočijo opis dogodkov, ki so privedli do današnjega stanja.

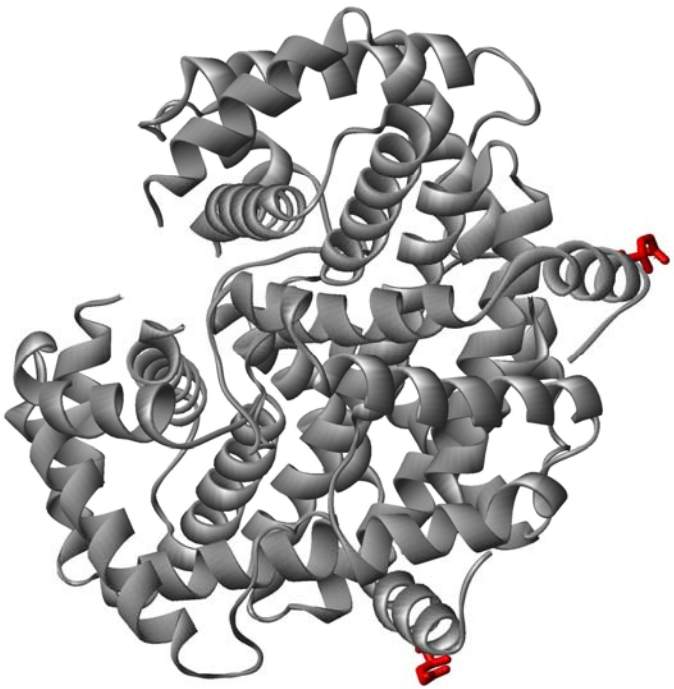
MOLEKULARNA SISTEMATIKA

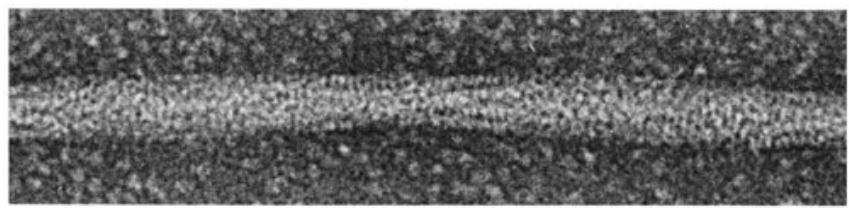


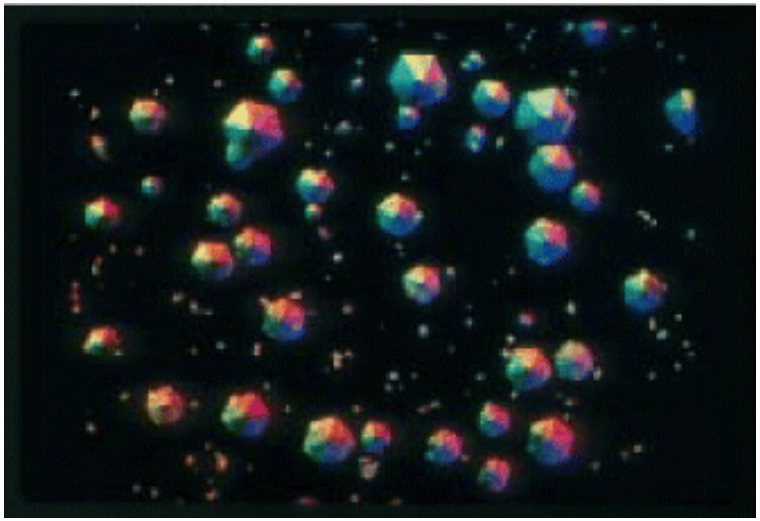
SRPASTOCELIČNA ANEMIJA

MVHLTP**E**EKSAVTALWGKVNVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPVK
AHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGKEF
TPPVQAAYQKVVAGVANALAHKYH

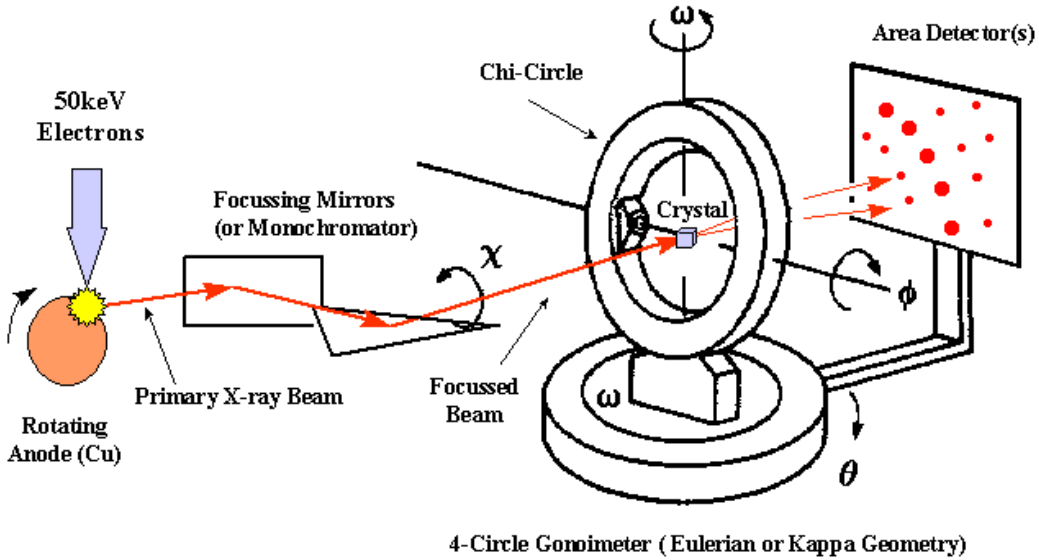
HbB	CCT	**GAG**	GAG
	P	**E**	E
HbS	CCT	**GTG**	GAG
	P	**V**	E



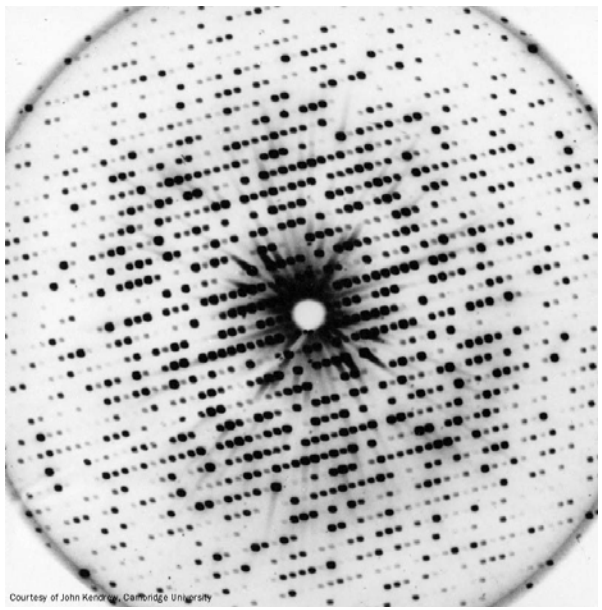


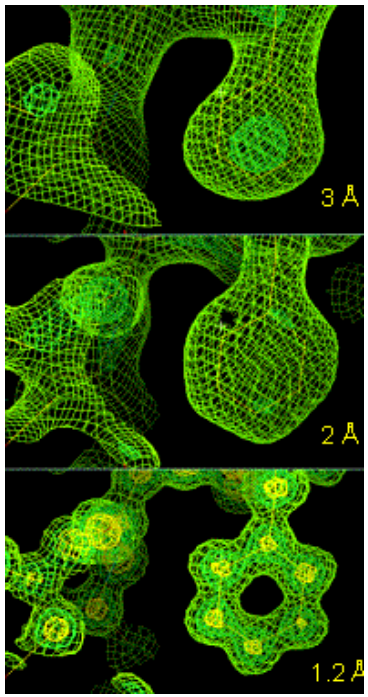


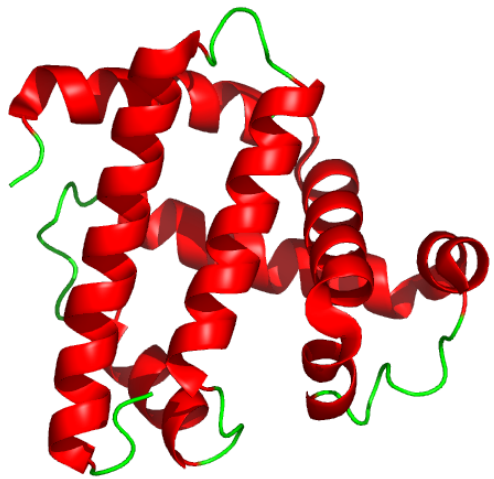
človeški inzulin



4-Circle Goniometer (Eulerian or Kappa Geometry)







Flu!

The Influenza Sequence Database

About the ISD

The Influenza Sequence Database (ISD) contains all published influenza viral sequences, which have been curated by domain experts to ensure high standards of accuracy and completeness. ISD tools for management of influenza viral sequences and study of the molecular evolution of the influenza virus are designed to expedite the typical tasks of molecular epidemiology. Subscriptions to the ISD are required for full access to tools; information on the purchase of subscriptions can be obtained by emailing flu@lanl.gov.

New & Noteworthy

- March 1, 2005:
  Third Letter to ISD Users
- Nov 22, 2004:
  Second Letter to ISD Users
- Nov 15, 2004:
  First Letter to ISD Users
- Previous Noteworthy items

October 18, 2005

Dear Influenza Sequence Database user:

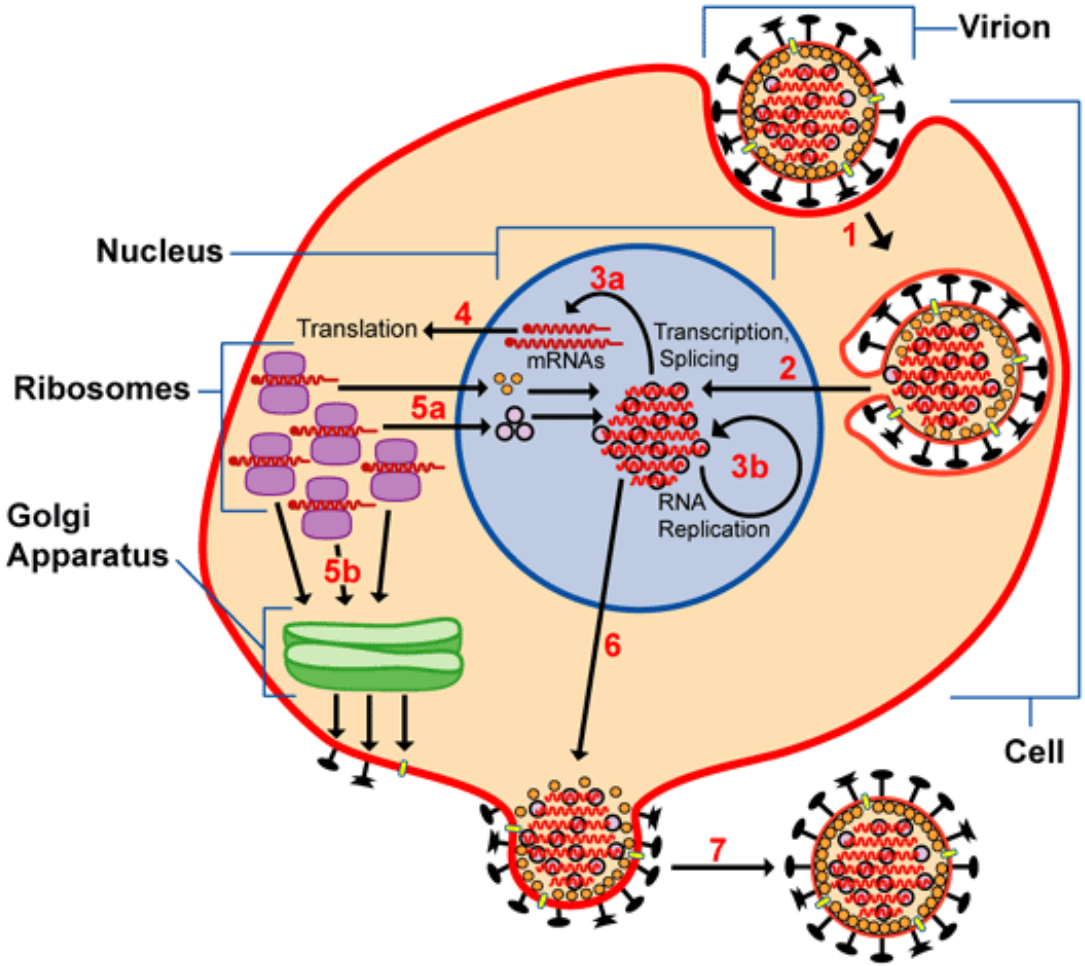
As I have described in my previous letters [1, 2, 3], we are closing to free public usage, and transitioning to a subscription basis, in order to cover the basic costs of maintaining and curating the database. In this way, we will be able to continue to offer access for those who wish it.

We will continue to offer a simple search function to enable free access to data on the ISD. However, from today, you will need a login for additional capabilities.

You will need to decide which of the three following levels of access you wish in the future:

1. Free -- limited search function, to enable access to sequences;
2. Subscriptions -- the same tool and data availability as the previously free access;
3. Work-for-others -- allows users to store their own data on our server, as well as provides additional tools for data management and analysis.

For details of comparisons of these levels of access, please see our explanation of access



V glavnih vlogah

hemaglutinin	**H**
nevraminidaza	**N**
membranski protein	**M2**
protein matriksa	**M1**
nukleoprotein	**NP**
nestrukturni protein	**NS**
prot. jedrnega eksporta	**NEP**
polimeraza	**PA**
	PB1
	PB2

RNA

8 kosov (890-2341 nt)

GENOM skupaj 14 kb

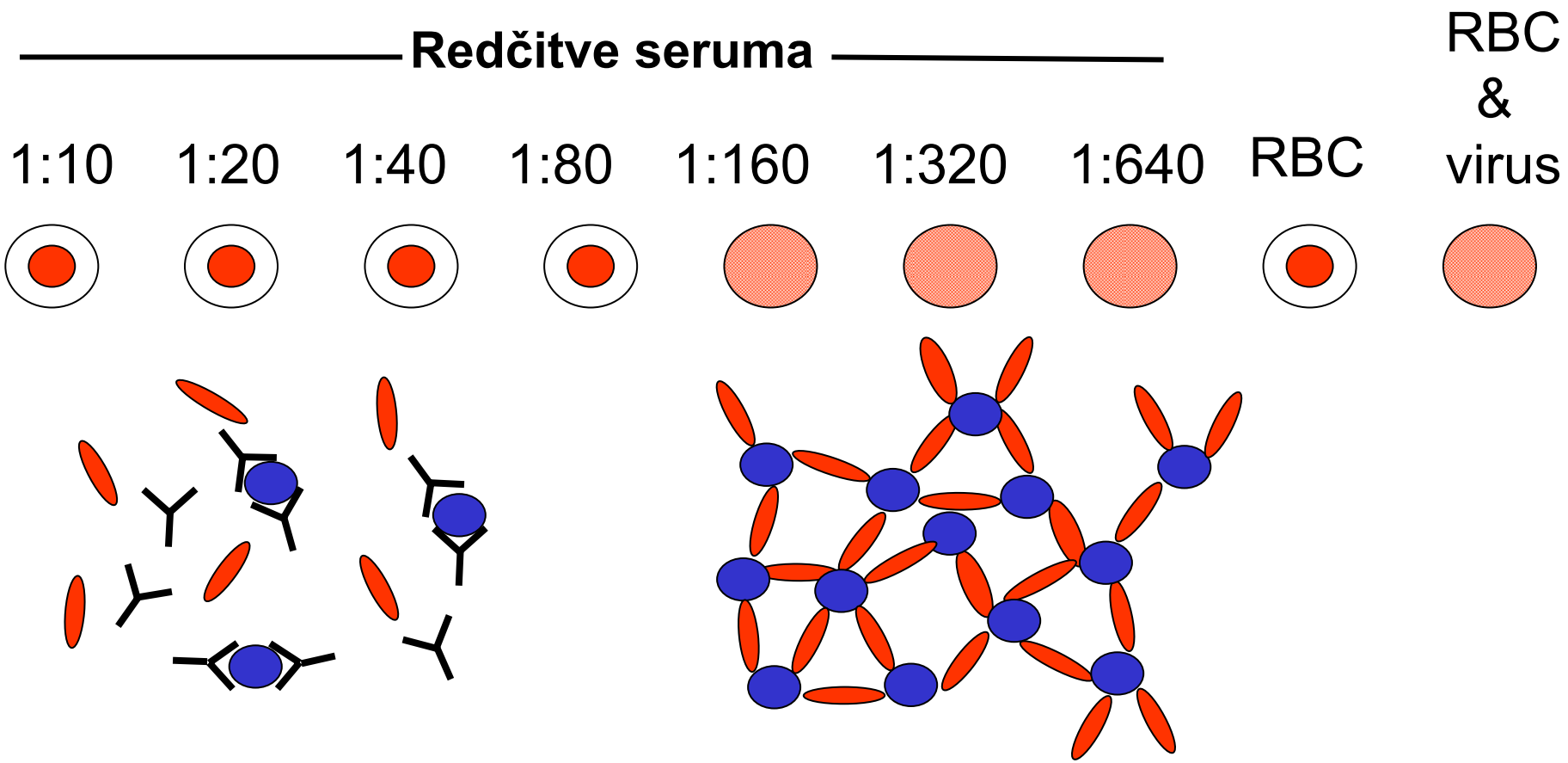
(=ves genetski material nekega organizma)

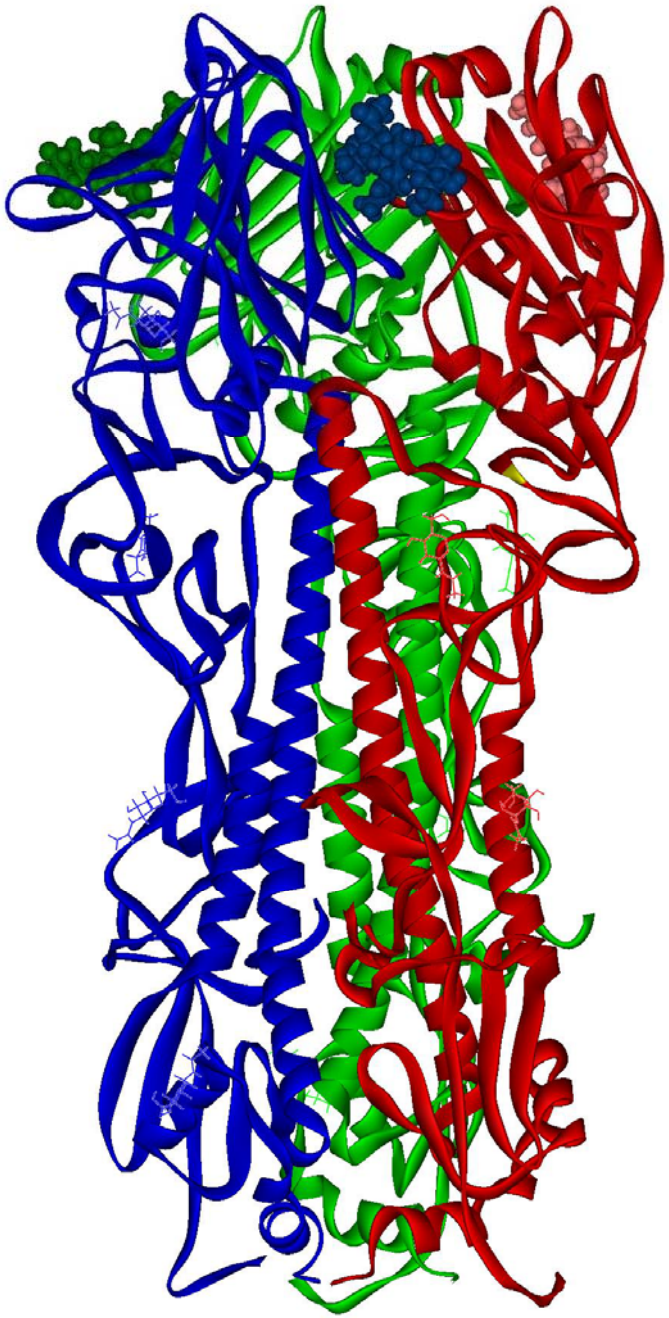
ribonukleoproteini

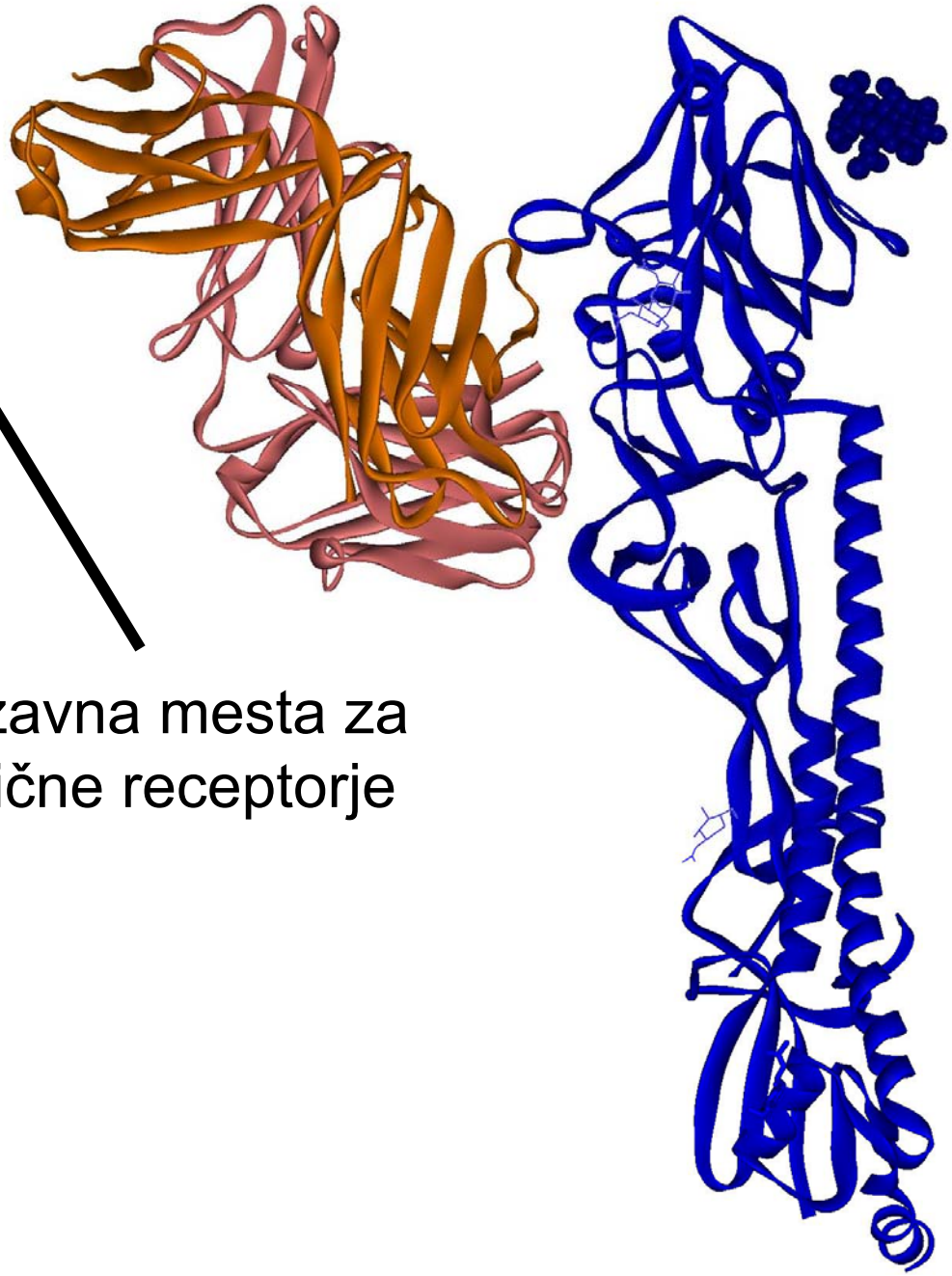
HEMAGLUTININ IN NEVRAMINIDAZA STA GLAVNA VIRULENČNA DEJAVNIKA!

Po njih ločujemo tipe influence A!

Serološka diagnoza
inhibicija hemaglutinacije





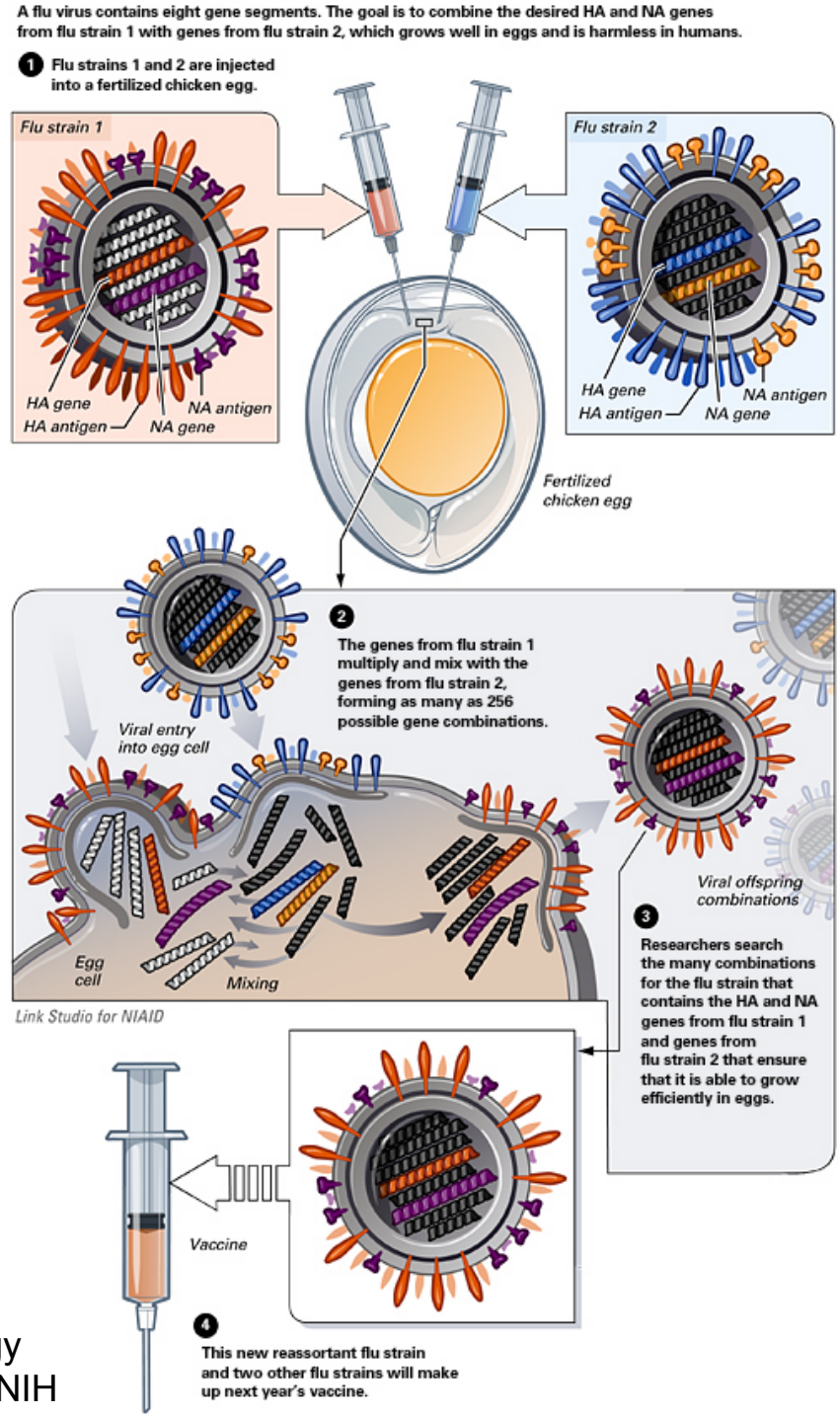


vezavna mesta za
celične receptorje

Priprava cepiv

Uporabijo sev, ki je najbolj pogost v prejšnji sezoni.

Zaradi mutacij bo lahko cepivo proti spremenjenim sevom **slabše učinkovito** ali celo **neuporabno**.



National Institute of Allergy and Infectious Diseases, NIH

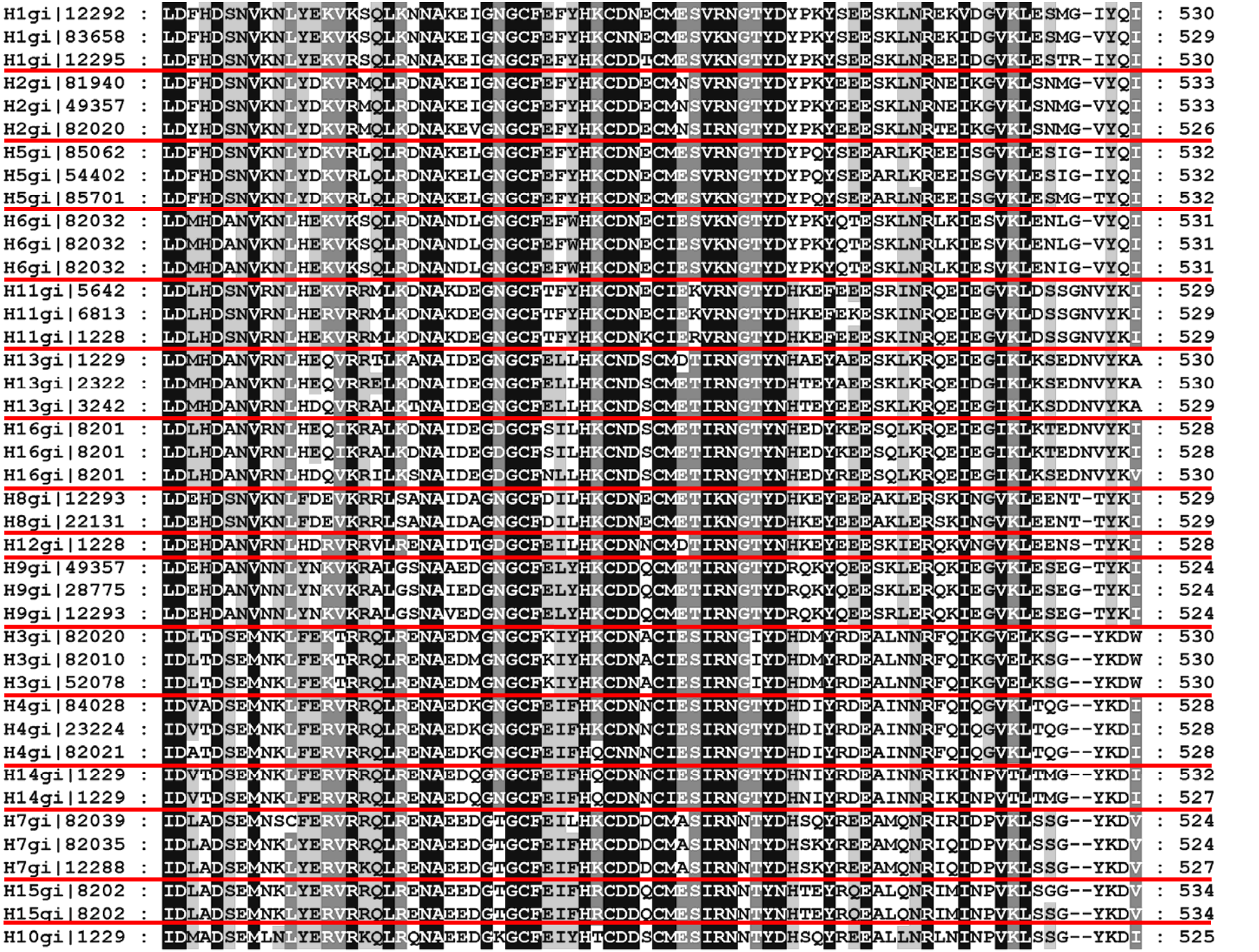
Tip A
16 tipov glede na hemaglutinin H1-H16
9 tipov glede na nevraminidazo N1-N9

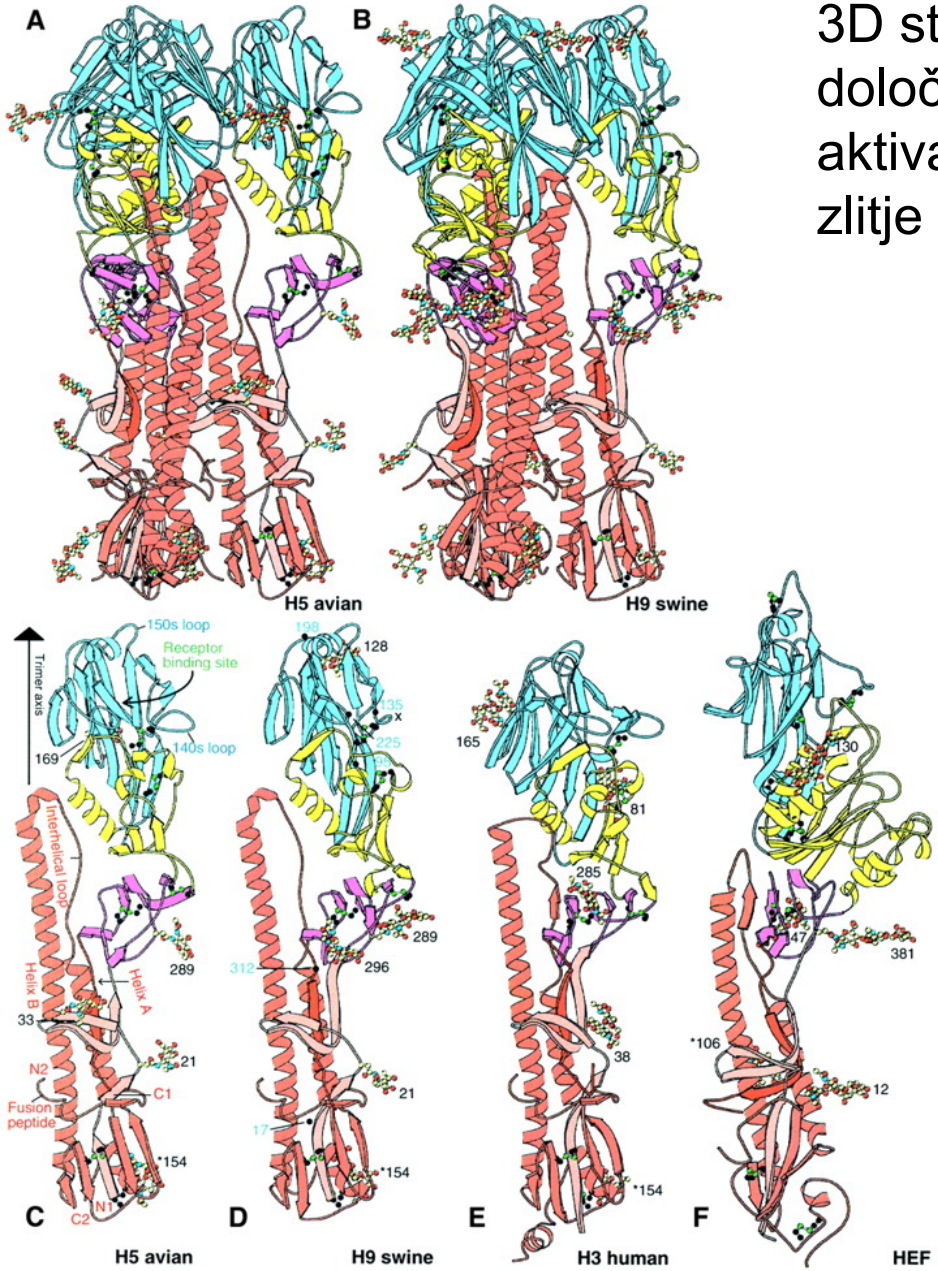
Divje ptice rezervoar za vse tipe tipa A (izvorne);
nekateri visoko patogeni, npr. H5 in H7

Prašiči so lahko okuženi s človeškimi in ptičjimi virusi. Lahko pride do sočasne infekcije z obemi

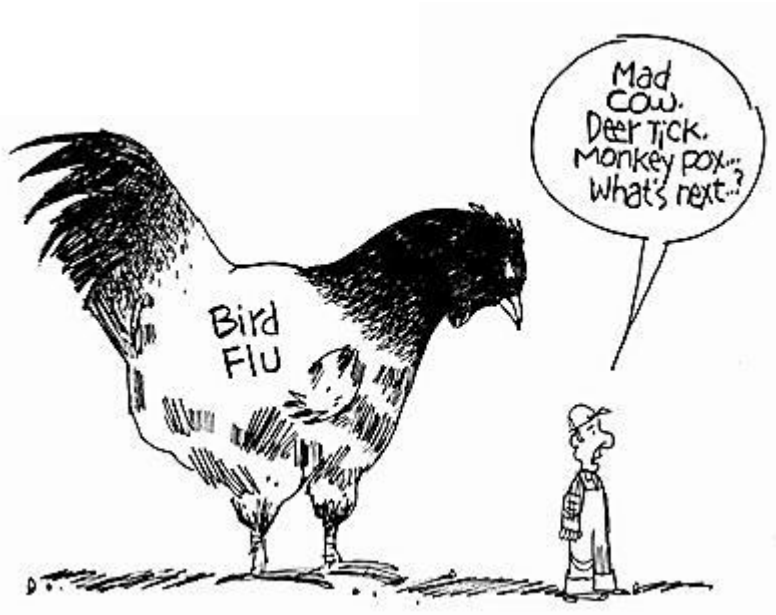
Človeški tipi so H1, H2, H3

1918	H1N1	????	Španska gripa	20-40 milijonov mrtvih
1957	H2N2	Ptiči	Azijska gripa	70.000 mrtvih v ZDA
1968	H3N2	Ptiči	Hong Kong	34.000 mrtvih v ZDA
1977	H1N1	Ptiči	Ruska gripa	
1997	H5N1	Ptiči	Hong Kong; Ptičja gripa	
2003	H7N7	Ptiči	Nizozemska; Ptičja gripa	1 mrtev


H1gi|12292 : LDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCDNECMESVRNGTYDYPKYSEESKLNREKVDGVKLESMG-IYQI : 530
H1gi|83658 : LDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCNNECMESVKNGTYDYPKYSEESKLNREKIDGVKLESMG-VYQI : 529
H1gi|12295 : LDFHDSNVKNLYEKVRSQLRNNAKEIGNGCFEFYHKCDDTCMESVKNGTYDYPKYSEESKLNREEIDGVKLESTR-IYQI : 530
H2gi|81940 : LDFHDSNVKNLYDKVRMQLRDNAKEIGNGCFEFYHKCDDECMNSVRNGTYDYPKYEEESKLNRNEIKGVKLSNMG-VYQI : 533
H2gi|49357 : LDFHDSNVKNLYDKVRMQLRDNAKEIGNGCFEFYHKCDDECMNSVRNGTYDYPKYEEESKLNRNEIKGVKLSNMG-VYQI : 533
H2gi|82020 : LDYHDSNVKNLYDKVRMQLKDNAKEVGNGCFEFYHKCDDECMNSIRNGTYDYPKYEEESKLNRTEIKGVKLSNMG-VYQI : 526
H5gi|85062 : LDFHDSNVKNLYDKVRLQLRDNAKELGNGCFEFYHKCDNECMESVRNGTYDYPQYSEEARLKREEISGVKLESIG-IYQI : 532
H5gi|54402 : LDFHDSNVKNLYDKVRLQLRDNAKELGNGCFEFYHKCDNECMESVRNGTYDYPQYSEEARLKREEISGVKLESIG-IYQI : 532
H5gi|85701 : LDFHDSNVKNLYDKVRLQLRDNAKELGNGCFEFYHKCDNECMESVKNGTYDYPQYSEEARLNREEISGVKLESMG-TYQI : 532
H6gi|82032 : LDMHDANVKNLHEKVKSQLRDNANDLGNGCFEFWHKCDNECIESVKNGTYDYPKYQTESKLNRLKIESVKLENLG-VYQI : 531
H6gi|82032 : LDMHDANVKNLHEKVKSQLRDNANDLGNGCFEFWHKCDNECIESVKNGTYDYPKYQTESKLNRLKIESVKLENLG-VYQI : 531
H6gi|82032 : LDMHDANVKNLHEKVKSQLRDNANDLGNGCFEFWHKCDNECIESVKNGTYDYPKYQTESKLNRLKIESVKLENIG-VYQI : 531
H11gi|5642 : LDLHDSNVRNLHEKVRRMLKDNAKDEGNGCFTFYHKCDNECIEKVRNGTYDHKEFEEESRINRQEIEGVRLDSSGNVYKI : 529
H11gi|6813 : LDLHDSNVRNLHERVRRMLKDNAKDEGNGCFTFYHKCDNECIEKVRNGTYDHKEFEKESKINRQEIEGVKLDSSGNVYKI : 529
H11gi|1228 : LDLHDSNVRNLHEKVRRMLKDNAKDEGNGCFTFYHKCDNKCIERVRNGTYDHKEFEEESKINRQEIEGVKLDSSGNVYKI : 529
H13gi|1229 : LDMHDANVRNLHEQVRRTLKANAIDEGNGCFELLHKCNDSCMDTIRNGTYNHAEYAEESKLKRQEIEGIKLKSEDNVYKA : 530
H13gi|2322 : LDMHDANVKNLHEQVRRELKDNAIDEGNGCFELLHKCNDSCMETIRNGTYDHTEYAEESKLKRQEIDGIKLKSEDNVYKA : 530
H13gi|3242 : LDMHDANVRNLHDQVRRALKTNAIDEGNGCFELLHKCNDSCMETIRNGTYNHTEYEEESKLKRQEIEGIKLKSDDNVYKA : 529
H16gi|8201 : LDLHDANVRNLHEQIKRALKDNAIDEGDGCFSILHKCNDSCMETIRNGTYNHEDYKEESQLKRQEIEGIKLKTEDNVYKI : 528
H16gi|8201 : LDLHDANVRNLHEQIKRALKDNAIDEGDGCFSILHKCNDSCMETIRNGTYNHEDYKEESQLKRQEIEGIKLKTEDNVYKI : 528
H16gi|8201 : LDLHDANVRNLHDQVKRILKSNAIDEGDGCFNLLHKCNDSCMETIRNGTYNHEDYREESQLKRQEIEGIKLKSEDNVYKV : 530
H8gi|12293 : LDEHDSNVKNLFDEVKRRLSANAIDAGNGCFDILHKCDNECMETIKNGTYDHKEYEEEAKLERSKINGVKLEENT-TYKI : 529
H8gi|22131 : LDEHDSNVKNLFDEVKRRLSANAIDAGNGCFDILHKCDNECMETIKNGTYDHKEYEEEAKLERSKINGVKLEENT-TYKI : 529
H12gi|1228 : LDEHDANVRNLHDRVRRVLRENAIDTGDGCFEILHKCDNNCMDTIRNGTYNHKEYEEESKIERQKVNGVKLEENS-TYKI : 528
H9gi|49357 : LDEHDANVNNLYNKVKRALGSNAAEDGNGCFELYHKCDDQCMETIRNGTYDRQKYQEESKLERQKIEGVKLESEG-TYKI : 524
H9gi|28775 : LDEHDANVNNLYNKVKRALGSNAIEDGNGCFELYHKCDDQCMETIRNGTYDRQKYQEESKLERQKIEGVKLESEG-TYKI : 524
H9gi|12293 : LDEHDANVNNLYNKVKRALGSNAVEDGNGCFELYHKCDDQCMETIRNGTYDRQKYQEESRLERQKIEGVKLESEG-TYKI : 524
H3gi|82020 : IDLTDSEMNKLFEKTRRQLRENAEDMGNGCFKIYHKCDNACIESIRNGIYDHDMYRDEALNNRFQIKGVELKSG--YKDW : 530
H3gi|82010 : IDLTDSEMNKLFEKTRRQLRENAEDMGNGCFKIYHKCDNACIESIRNGIYDHDMYRDEALNNRFQIKGVELKSG--YKDW : 530
H3gi|52078 : IDLTDSEMNKLFEKTRRQLRENAEDMGNGCFKIYHKCDNACIESIRNGIYDHDMYRDEALNNRFQIKGVELKSG--YKDW : 530
H4gi|84028 : IDVADSEMNKLFERVRRQLRENAEDKGNGCFEIFHKCDNNCIESIRNGTYDHDIYRDEAINNRFQIQGVKLTQG--YKDI : 528
H4gi|23224 : IDVTDSEMNKLFERVRRQLRENAEDKGNGCFEIFHKCDNNCIESIRNGTYDHDIYRDEAINNRFQIQGVKLTQG--YKDI : 528
H4gi|82021 : IDATDSEMNKLFERVRRQLRENAEDKGNGCFEIFHQCNNNCIESIRNGTYDHDIYRDEAINNRFQIQGVKLTQG--YKDI : 528
H14gi|1229 : IDVTDSEMNKLFERVRRQLRENAEDQGNGCFEIFHQCDNNCIESIRNGTYDHNIYRDEAINNRIKINPVTLTMG--YKDI : 532
H14gi|1229 : IDVTDSEMNKLFERVRRQLRENAEDQGNGCFEIFHQCDNNCIESIRNGTYDHNIYRDEAINNRIKINPVTLTMG--YKDI : 527
H7gi|82039 : IDLADSEMNSCFERVRRQLRENAEEDGTGCFEILHKCDDDCMASIRNNTYDHSQYREEAMQNRIRIDPVKLSSG--YKDV : 524
H7gi|82035 : IDLADSEMNKLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKYREEAMQNRIQIDPVKLSSG--YKDV : 524
H7gi|12288 : IDLADSEMNKLYERVRKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKYREEAMQNRIQIDPVKLSSG--YKDV : 527
H15gi|8202 : IDLADSEMNKLYERVRRQLRENAEEDGTGCFEIFHRCDDQCMESIRNNTYNHTEYRQEALQNRIMINPVKLSGG--YKDV : 534
H15gi|8202 : IDLADSEMNKLYERVRRQLRENAEEDGTGCFEIFHRCDDQCMESIRNNTYNHTEYRQEALQNRIMINPVKLSSG--YKDV : 534
H10gi|1229 : IDMADSEMLNLYERVRKQLRQNAEEDGKGCFEIYHTCDDSCMESIRNNTYDHSQYREEALLNRLNINPVKLSSG--YKDI : 525

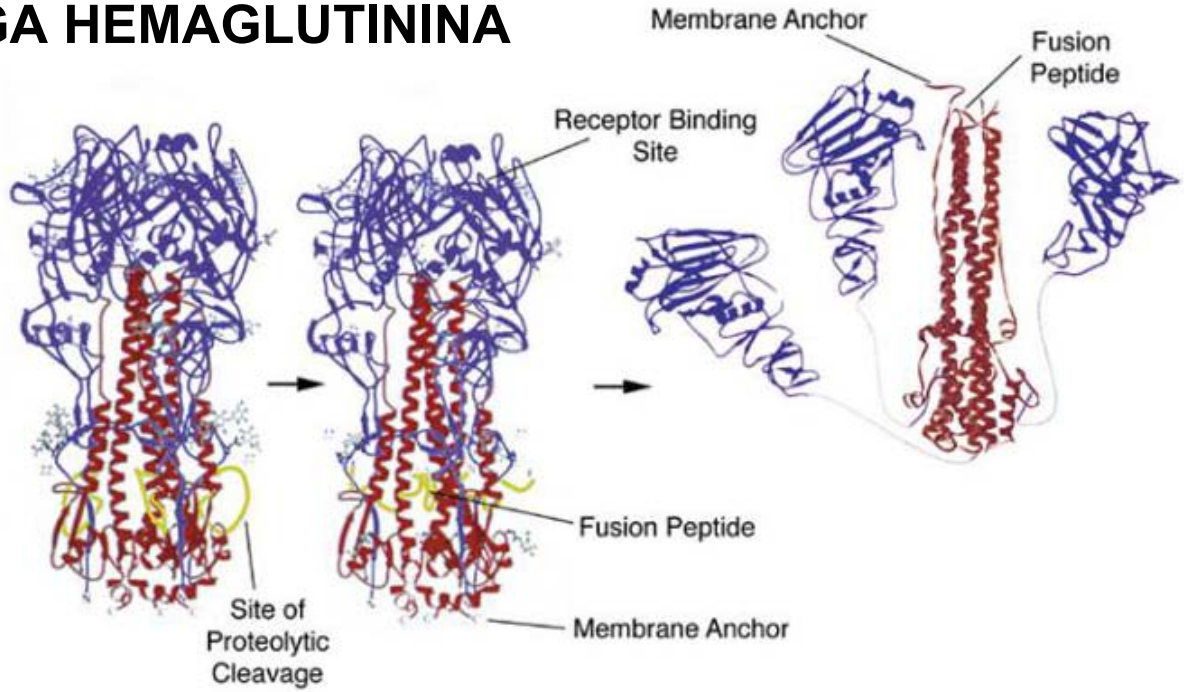


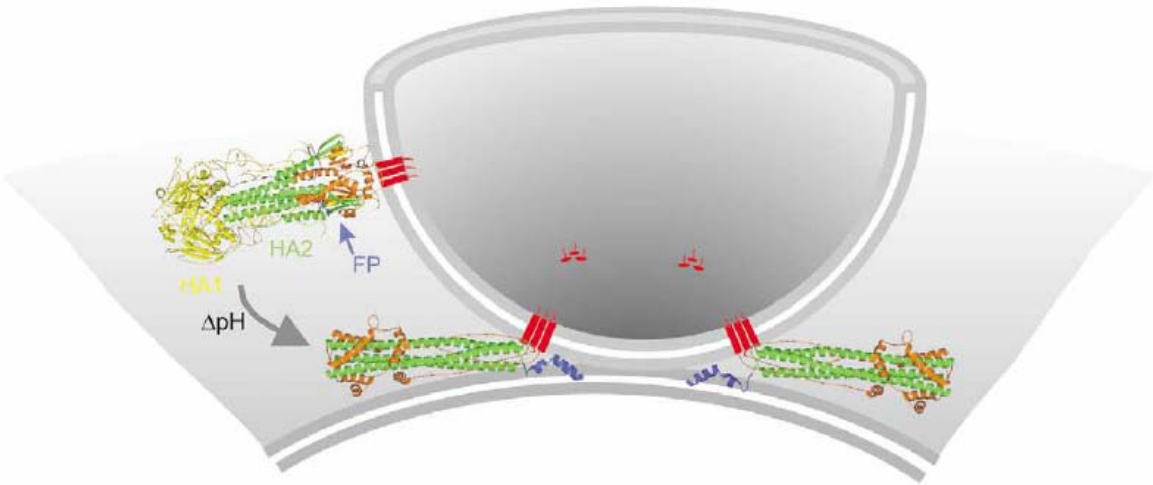
3D struktura je ohranjena, spremenjene so določeni deli- ki so npr. pomembni za aktivacijo HA, vezavo na celični receptor in zlitje membran.

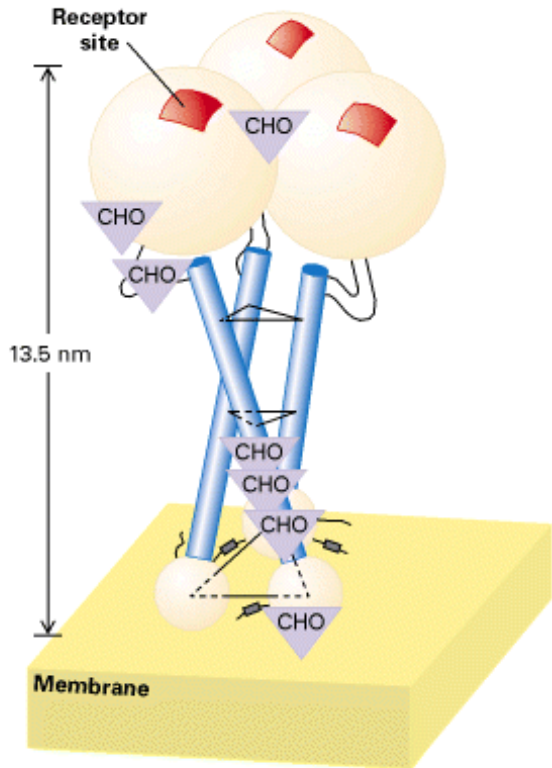


Ha Y. et al. (2002) H5 avian and H9 swine influenza virus haemagglutinin structures: possible origin of influenza subtypes. EMBO Journal 21, 865-875.

VLOGA HEMAGLUTININA

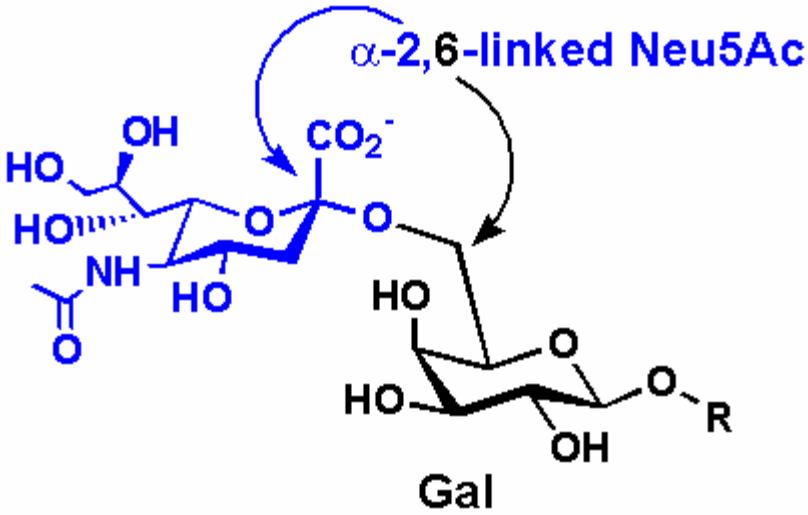


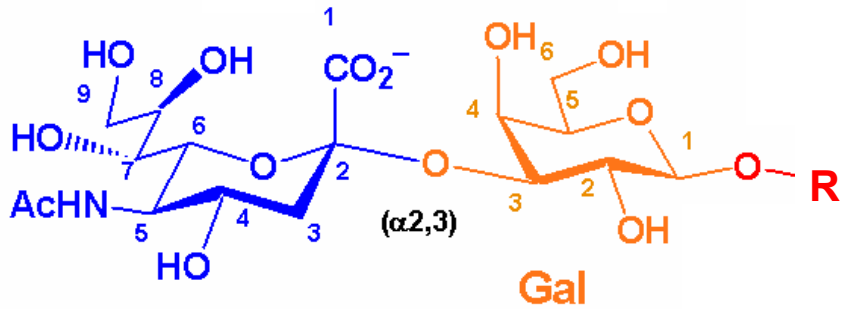




Tamm K. L. et al. (2003) Membrane fusion: a structural perspective on the interplay of lipids and proteins. Current Opinion in Structural Biology 13, 453-466.

ZAKAJ PTIČJI VIRUS NE INFICIRA ČLOVEŠKIH CELIC?

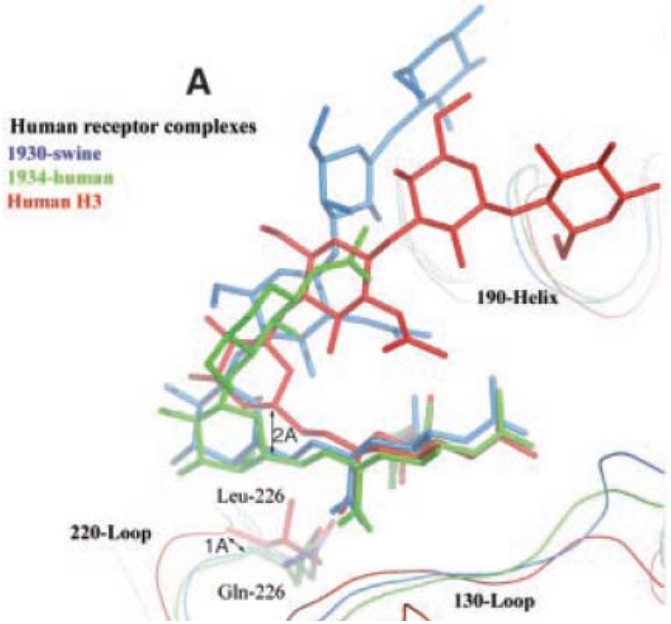


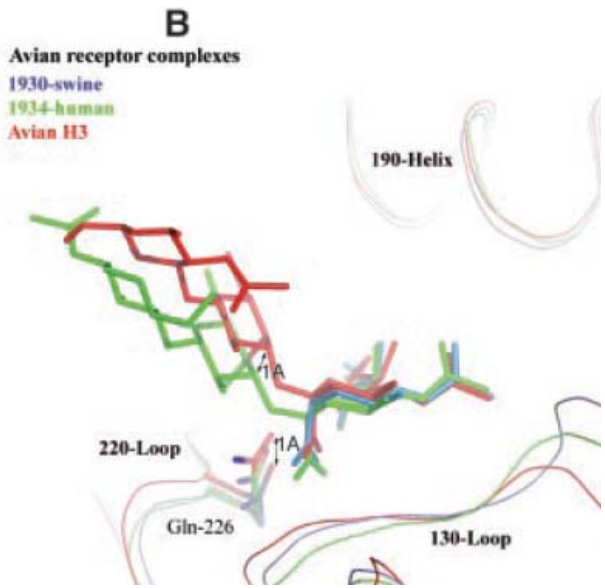


Hemaglutinin prepozna N-acetilneuraminsko kislino (sialna kislina) vezano na glikolipide in glikoproteine na celični površini.

Vsi HA **ptičjih virusov** prepoznajo sialno kislino vezano z α**2-3** vezjo na galaktozo. Vsi HA **človeških virusov** prepoznajo sialno kislino vezano z α**2-6** vezjo.

Okužba človeških celic s ptičjimi virusi zato zahteva **spremembe v vezavni specifičnosti.**

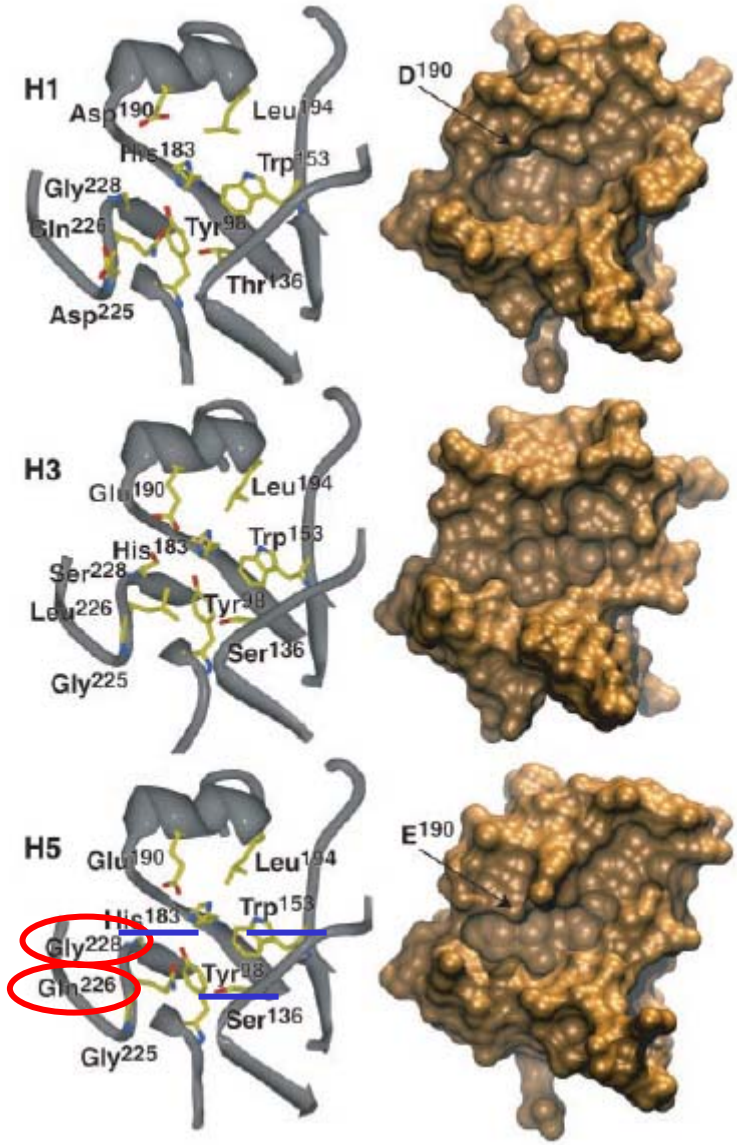




Človeški 1918

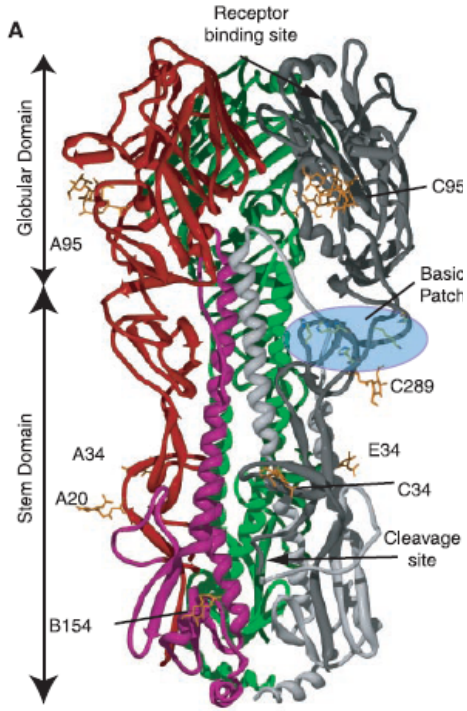
Človeški

Ptičji



Gamblin S.J. et al. (2004) The Structure and Receptor Binding Properties of the 1918 Influenza Hemagglutinin. Science 303, 1838-1842.

Stevens J. et al. (2004) Structure of the Uncleaved Human H1 Hemagglutinin from the Extinct 1918 Influenza virus. Science 303, 1866-1870.



ZAKAJ SO TIPI H5 IN H7 TAKO INFEKTIVNI?

Gruča pozitivno nabitih aminokislin, ki tvorijo mesto cepitve, kar vodi do lažje aktivacije virusa.

Stevens J. et al. (2004) Structure of the Uncleaved Human H1 Hemagglutinin from the Extinct 1918 Influenza virus. Science 303, 1866-1870.

KAKŠEN JE VISOKO INFEKTIVEN VIRUS?

Mnogo (slabo poznanih) faktorjev omogoča virulenčnost virusov:

-HA za vezavo na celični receptor

-Interakcije virusnih proteinov med seboj in s komponentami celic

-Efektivnost replikacije

-Prilagojenost gostitelju

-Transmisibilnost

PB2	PB1	PA	NP	NA	M1	M2	NS1	NS2
T9N[a]	I179M	N27D	S27A	A18S	T218A	N23S	G71E	R87K
R340K	I469T	R262K	R77K	L23F	V219I	I51V	A82V	G26D
K389R	K586R	T332S	K98R	V30I		R56K	N143T	
G590S	D619N	V348I	R103K	H40Y				
V667I	V709I	V421I	M136I	C42F				
			I197V	G143V				
			I406T	R172K				
			I425V	K199E				
			E480D	G216V				
				I265T				
				V307I				
				K385N				
				E399D				
				W437L				

Holmes E.C. et al. (2004) Whole-Genome Analysis of Human Influenza A Virus Reveals Multiple Persistent Lineages and Reassortment Among Recent H3N2 Viruses. Plos Biology 3, 1579-1589.

KAKO TOREJ PRIDE DO VIRUSOV, KJER CEPIVA NISO UČINKOVITA ALI NI ODPORNOSTI V POPULACIJI?

1918	H1N1	????	Španska gripa	????	
1957	H2N2	Ptiči	Azijska gripa	**antigenski premik** ("antigenic shift")	
1968	H3N2	Ptiči	Hong Kong	**antigenski premik**	
1977	H1N1	Ptiči	Ruska gripa		
1997	H5N1	Ptiči	Hong Kong; Ptičja gripa		*mrtvi v tesnem stiku z okuženimi živalmi*
2003	H7N7	Ptiči	Nizozemska	1 mrtev	

ANTIGENSKI ZDRS ("antigenic drift")

Točkovne mutacije, ki spremenijo vezavna mesta za celične receptorje, epitope kamor se vežejo protitelesa, etc. Virusna polimeraza nima kontrolnega branja, kar omogoča visoko mutagenost.

ANTIGENSKI PREMIK

Pride do **prerazporejanja ("reassortment") virusne dednine** v gostitelju, ki je naenkrat okužen z dvema virusoma (npr. prašič okužen s človeškim in ptičjim virusom).

Do pandemije lahko pride, ko se pojavi virus s HA, za katerega ima malo ljudi razvito odpornost.

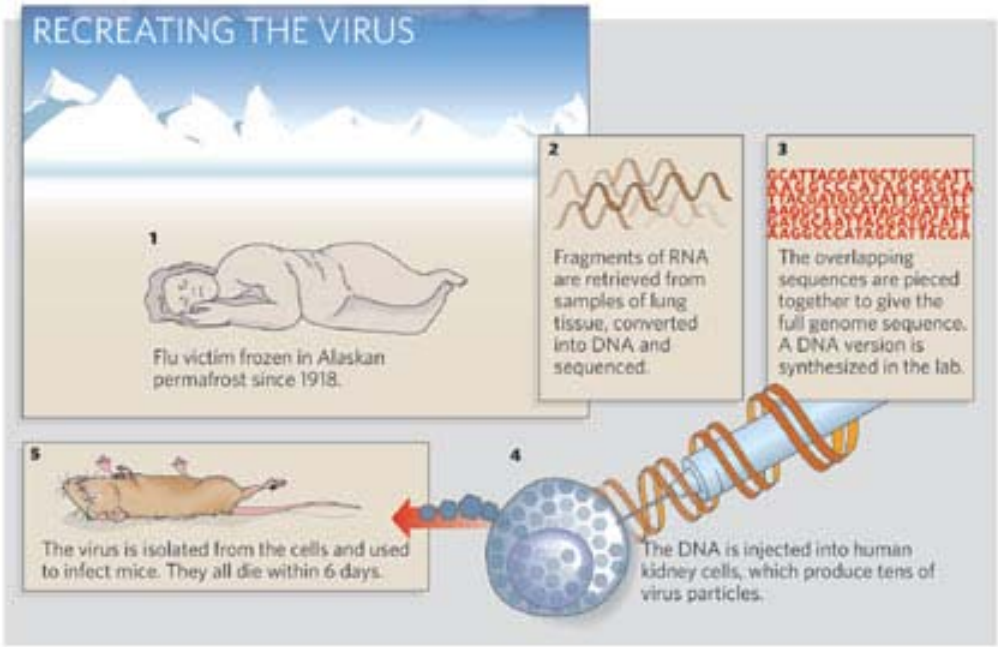
Do zdaj še niso odkrili reasortant s ptičjimi HA in N in ostalimi človeškimi proteini, ostale kombinacije so odkrili (npr. človeške reasortante)

In the fall of 1918 the Great War in Europe was winding down and peace was on the horizon. The Americans had joined in the fight, bringing the Allies closer to victory against the Germans. Deep within the trenches these men lived through some of the most brutal conditions of life, which it seemed could not be any worse. Then, in pockets across the globe, something erupted that seemed as benign as the common cold. The influenza of that season, however, was far more than a cold. In the two years that this scourge ravaged the earth, **a fifth of the world's population was infected**. The flu was most deadly for people ages 20 to 40. This pattern of morbidity was unusual for influenza which is usually a killer of the elderly and young children. It infected 28% of all Americans (Tice). **An estimated 675,000 Americans died of influenza during the pandemic, ten times as many as in the world war**. Of the U.S. soldiers who died in Europe, half of them fell to the influenza virus and not to the enemy (Deseret News). An estimated 43,000 servicemen mobilized for WWI died of influenza (Crosby). 1918 would go down as unforgettable year of suffering and death and yet of peace. As noted in the Journal of the American Medical Association final edition of 1918:

> *"The 1918 has gone: a year momentous as the termination of the most cruel war in the annals of the human race; a year which marked, the end at least for a time, of man's destruction of man; unfortunately a year in which developed a most fatal infectious disease causing the death of hundreds of thousands of human beings.* ***Medical science for four and one-half years devoted itself to putting men on the firing line and keeping them there. Now it must turn with its whole might to combating the greatest enemy of all--infectious disease****," (12/28/1918).*

In 1918 children would skip rope to the rhyme (Crawford):

I had a little bird,
Its name was Enza.
I opened the window,
And in-flu-enza.



Skrivnostni virus 1918!
Genetsko težko določiti izvor. Bolj podoben ptičjim H1N1 kot človeškim H1N1.

Izjemno infektiven, najbolj od vseh znanih!

Posebnost: aktivacija HA z nevraminidazo in ne proteazo na površju celic- lahko inficira katerokoli človeško celico in ne samo človeških, ki imajo veliko tripsina na površini. Tudi polimeraza bolj prilagojena na človeške celice.
Dobro orodje pri načrtovanju novih zdravil ali eroristično orožje?

Kobasa D. et al. (2004) Enhanced virulence of Influenza A viruses with the hemagglutinin of the 1918 pandemic virus. Nature 431, 703-707.
Tumpey T.T. Et al. (2005) Characterization of the reconstructed 1918 Spanish Influenza Pandemic Virus. Science 310, 77-80.

WHO | Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO - Microsoft Internet Explorer

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Address http://www.who.int/csr/disease/avian_influenza/country/cases_table_2006_01_23/en/index.html

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Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO

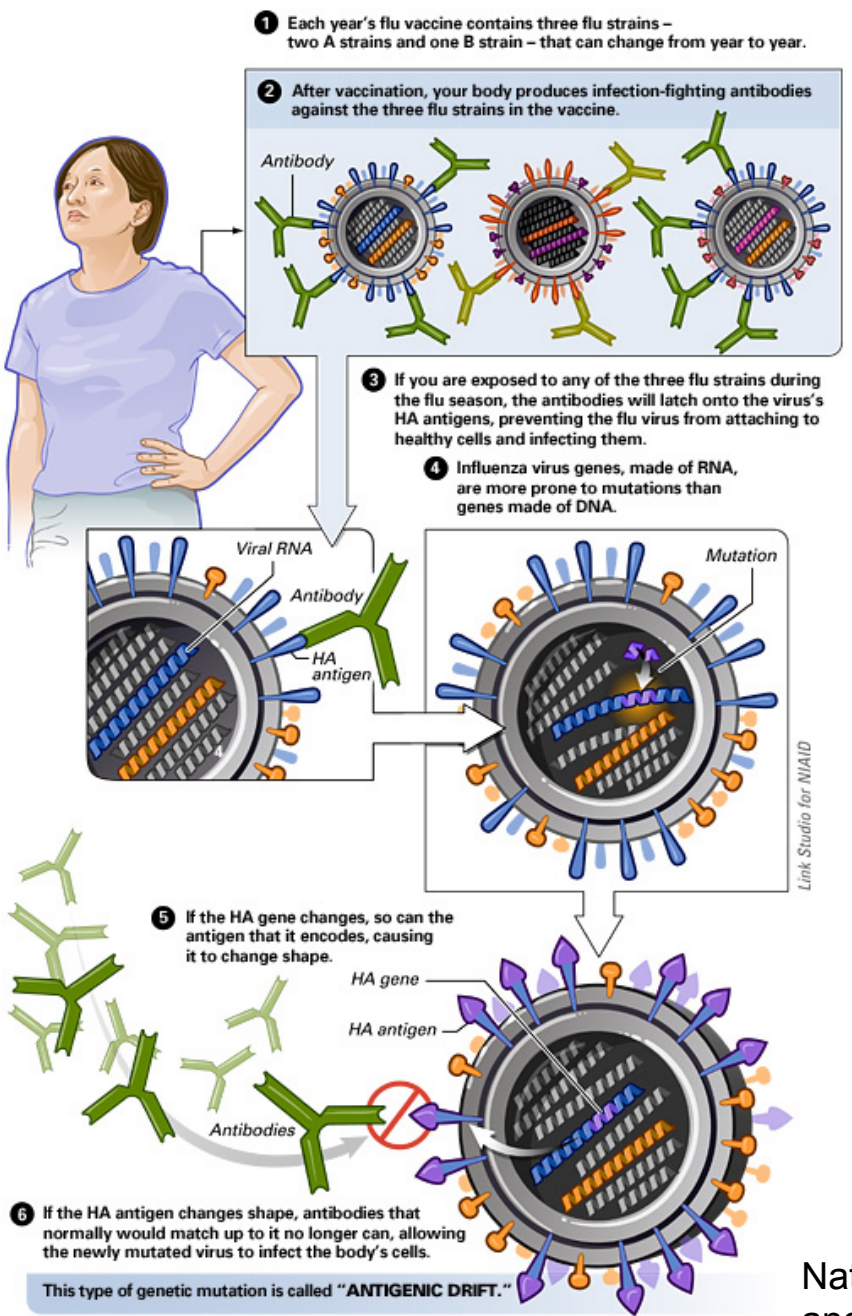
23 January 2006

Date of onset	Cambodia		China		Indonesia		Thailand		Turkey		Viet Nam		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
2003	0	0	0	0	0	0	0	0	0	0	3	3	3	3
2004	0	0	0	0	0	0	17	12	0	0	29	20	46	32
2005	4	4	8	5	16	11	5	2	0	0	61	19	94	41
2006	0	0	1	1	3	3	0	0	4	2	0	0	[illegible]	[illegible]
Total	4	4	9	6	19	14	22	14	4	2	93	42	151	82

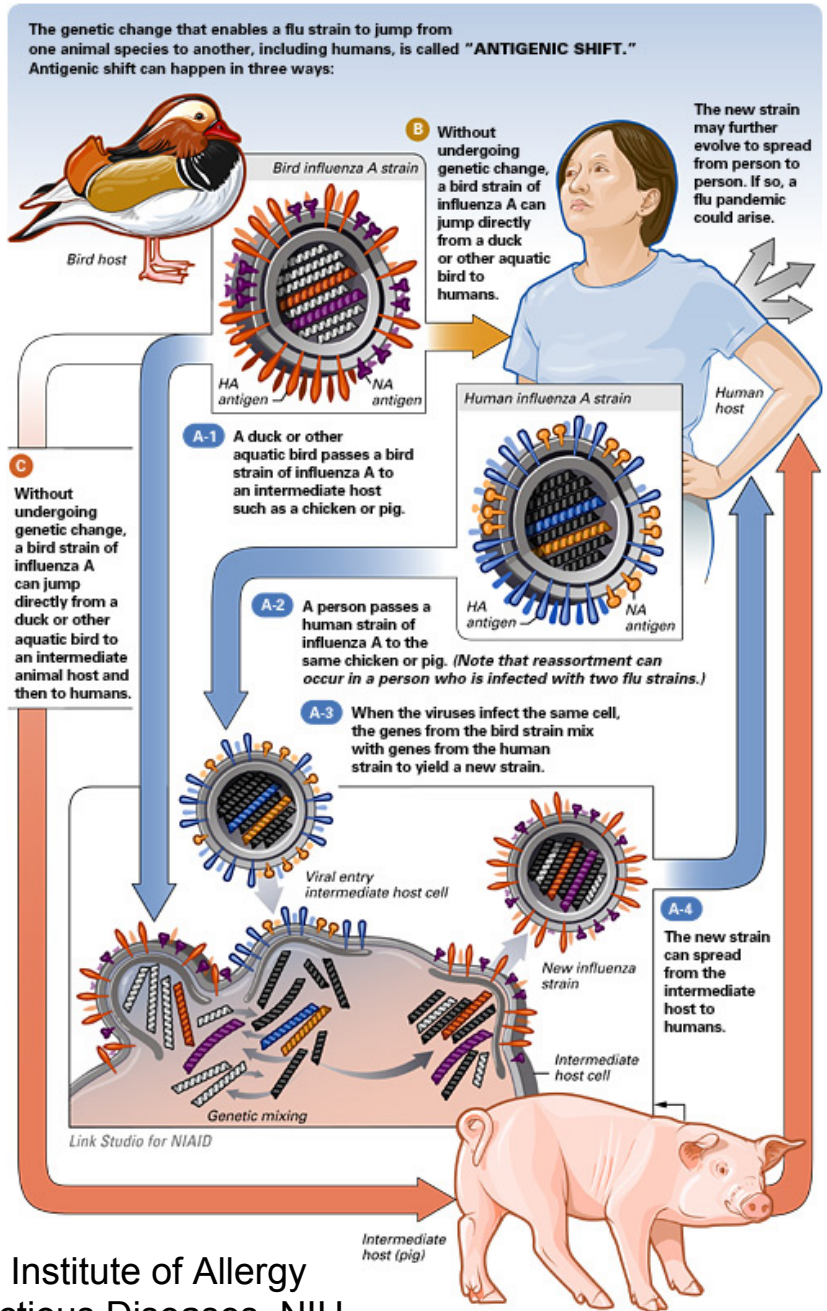
Total number of cases includes number of deaths.
WHO reports only laboratory-confirmed cases.

Ni nujno, da je prašič vmesni gostitelj!

antigenski zdrs



antigenski premik



National Institute of Allergy and Infectious Diseases, NIH

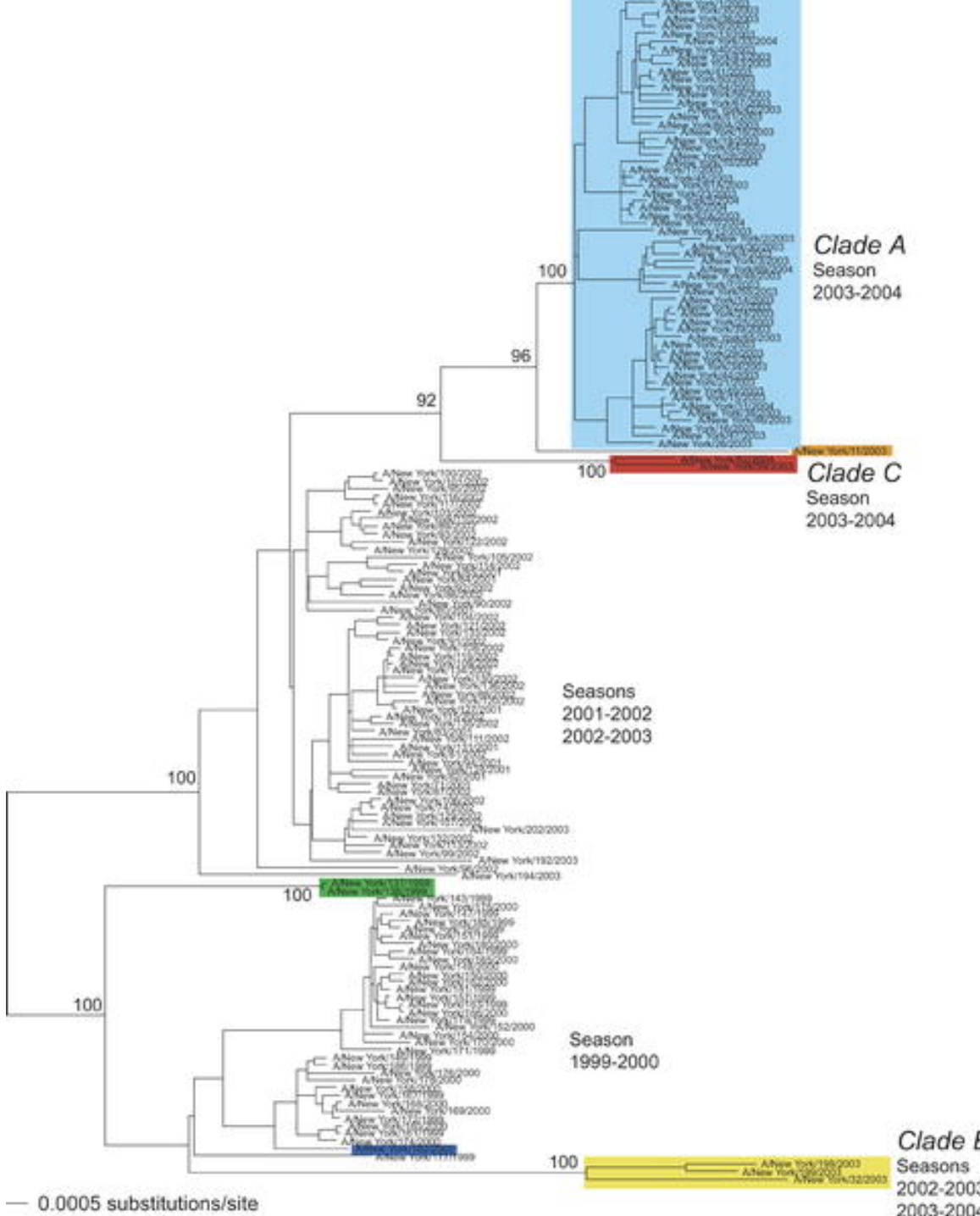
KAKO OPAZIMO TAKŠNE DOGODKE?

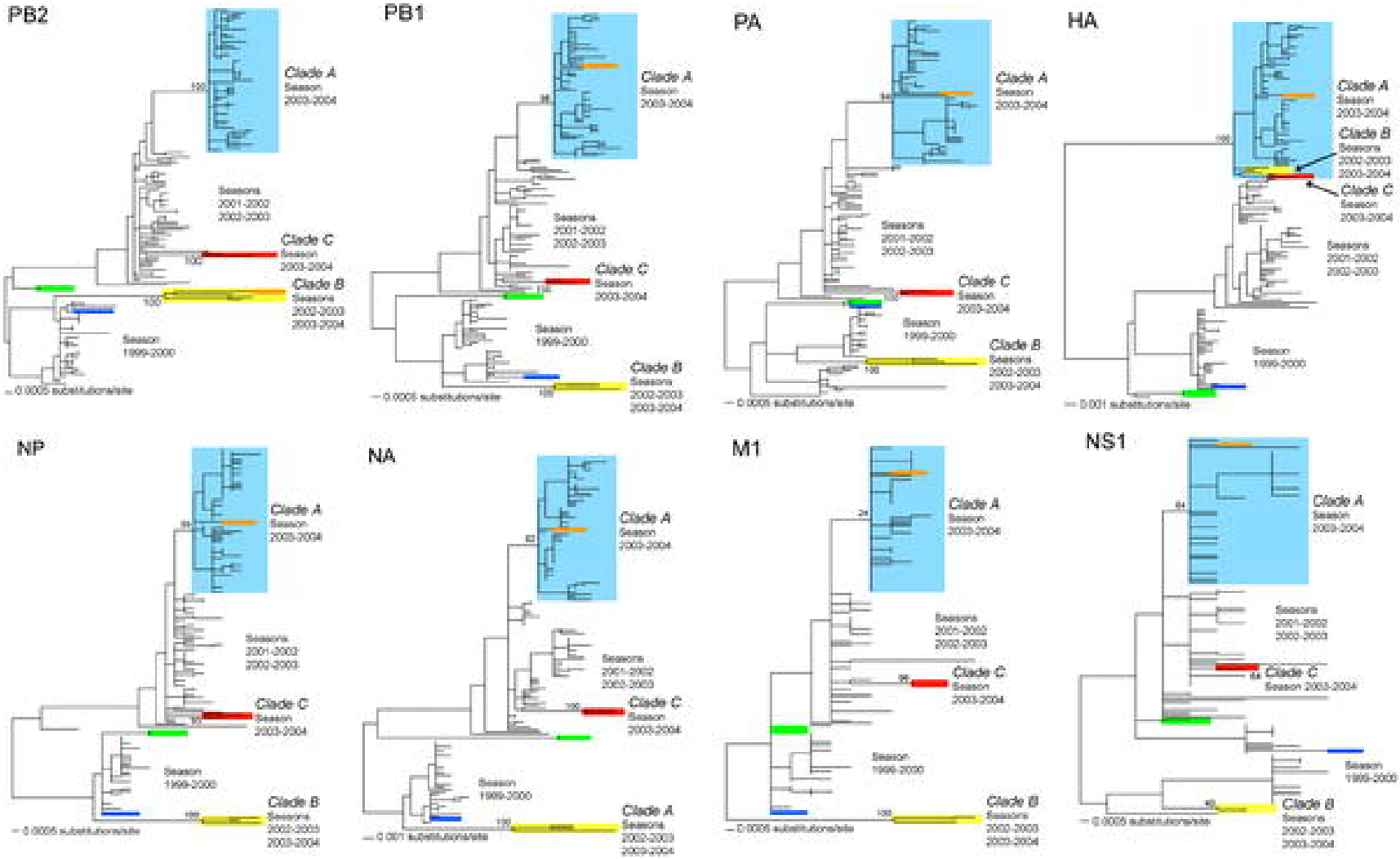
Primerjave zaporedij virusnih genomov in/ali proteinov

GENOMIKA

veda, ki se ukvarja z analizo in primerjavami genomov

Holmes E.C. et al. (2004)
Whole-Genome Analysis of Human Influenza A Virus Reveals Multiple Persistent Lineages and Reassortment Among Recent **H3N2** Viruses.
Plos Biology 3, 1579-1589.

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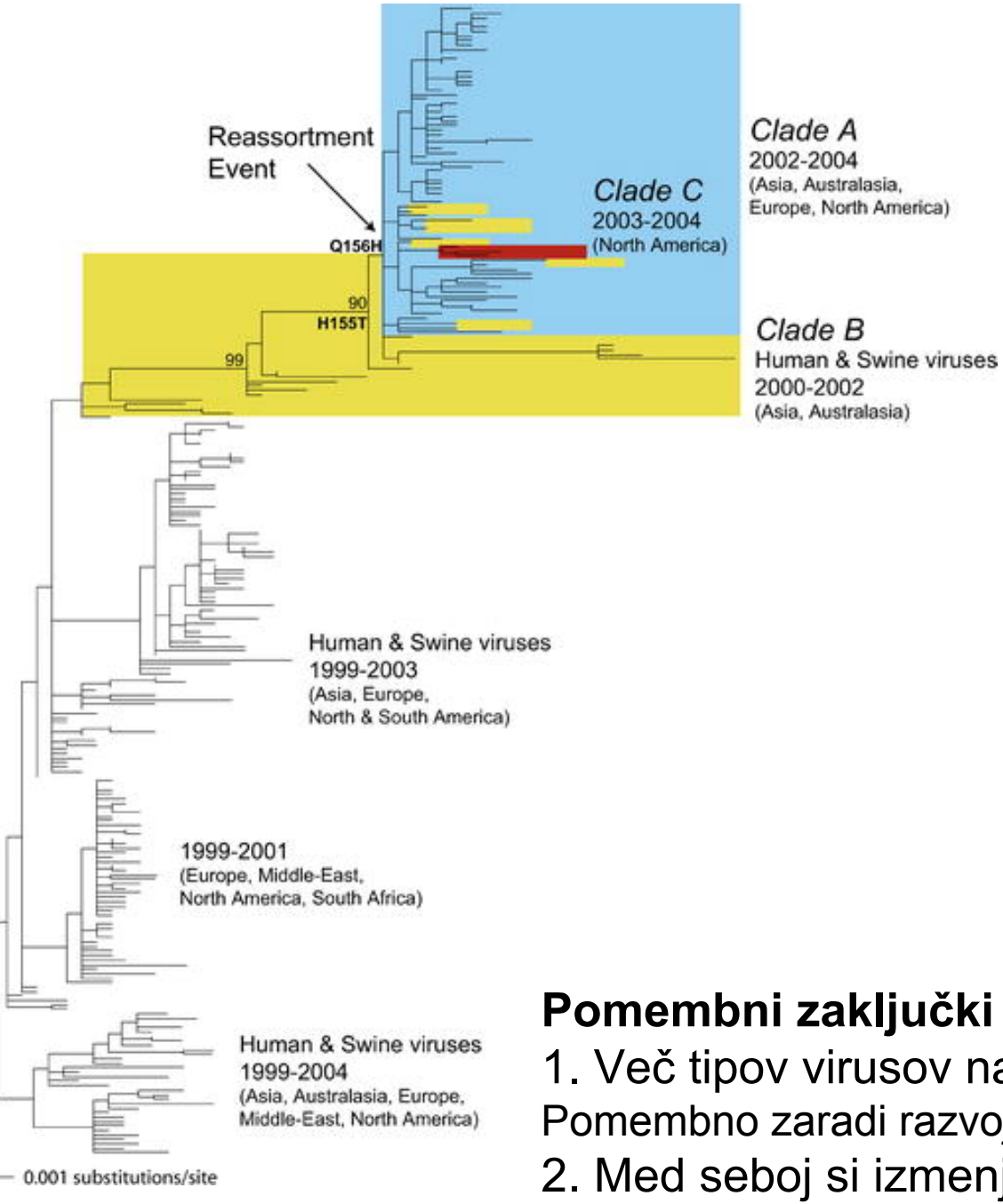
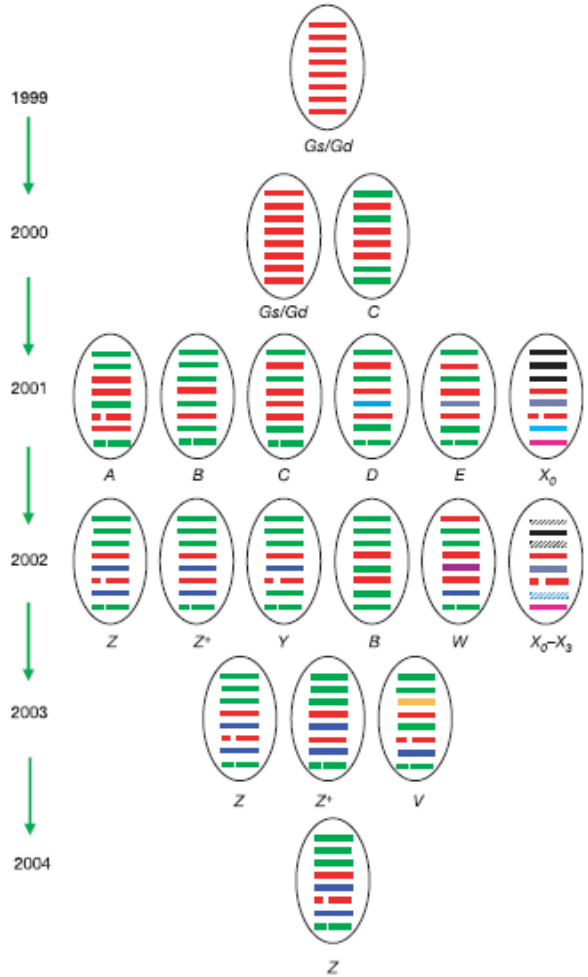




Li K.S. (2004) Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. Nature 430, 209-213.

Pomembni zaključki

1. Več tipov virusov naenkrat kroži v populaciji

Pomembno zaradi razvoja cepiv- več antigenskih variant!

2. Med seboj si izmenjujejo material z preurejanjem

KAKO SE TOREJ LAHKO BRANIMO?

Protivirusna zdravila

•Inhibitorji H^+ kanalčka (M2): *amantadin, rimantidin*

•Inhibitorji nevraminidaze: *oseltamivir (Tamiflu), zanimivir*

pozor: virus H5N1 izoliran iz vietnamske deklice je bil odporen na oseltamivir (v N je bila prisotna mutacija H274Y.

Mai Le Q. et al. (2005) Isolation of drug-resistant H5N1 virus. Nature 437, 1108.

Cepiva

Razvoj cepiv

Reverzna genetika

Izogibanje stikov z živalmi

perjad — tesni stiki

mačke — najnovejše študije kažejo, da so imele mačke, okužene z virusom H5N1, poškodbe po celem telesu (možganh, jetrah, ledvicah, srcu itn). Pomembno! (pot okužbe je lahko drugačna- oralni vnos s kontaminirano vodo ali hrano).

Rimmelzwaan G.F. et al. (2006) American Journal of Pathology 168, 176-183.

Table 2. Serologic and Clinical Characteristics of Avian Influenza A (H5N1) Infection among Contacts of Patients or Infected Animals.*

Group	Location	Year	Assay Method†	No. Tested	No. (%) Positive	Comment	Reference
Household contacts Tour group contacts Workplace contacts	Hong Kong	1997	MN, ELISA, WB	51 26 47	6 (12) 1 (4) 0	Concurrent exposure to poultry in 5 of 6 positive household contacts; 0 of 9 non-household contacts positive	Katz et al.[8]
Poultry cullers	Hong Kong	1997	MN, WB	293	9 (3)	Seroconversion in 1 with mild acute respiratory illness	Bridges et al.[7]
Poultry-market workers	Hong Kong	1997	MN, WB	1525	— (estimated 10%)	Most asymptomatic	Bridges et al.[7]
Health care workers with contact	Hong Kong	1997	MN, WB	217	8 (4)‡	Seroconversion in 2; most asymptomatic	Buxton Bridges et al.[9]
Household contacts§	Vietnam	2004	MN	51	0	0 of 83 controls positive	
Contacts of sick poultry§	Vietnam	2004	MN	25	0	—	
Health care workers with contact	Vietnam	2004	MN	83	0	2 with suspected illness (not confirmed)	Liem et al.[10]
Health care workers with contact	Vietnam	2004	MN, RT-PCR	60	0	No recognized illness	Schultsz et al.[11]
Health care workers with contact§	Thailand	2004	Clinical only	54	0	No recognized illness	
Health care workers with contact	Thailand	2004	Clinical only	35	0	No fever or influenza-like illness	Apisarnthanarak et al.[12]
Poultry cullers§	Indonesia	2005	MN	79	1 (1)	Asymptomatic	

* Some serologic surveys of apparent human-to-human transmission may have been confounded by concurrent exposure to ill poultry.
† MN denotes identification of serum antibody against influenza A (H5N1) by microneutralization, ELISA enzyme-linked immunosorbent assay, WB detection of influenza A (H5)–specific bands by Western blotting, and RT-PCR reverse-transcriptase–polymerase-chain-reaction assay for viral RNA.
‡ P=0.01 for the comparison with 2 of 309 health care workers without contact (0.6 percent).
§ Data are from the WHO Meeting on Case Management and Research on Human Influenza A (H5) held in Hanoi, May 10 through 12, 2005.

The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. (2005) The New England Journal of Medicine 353, 1374-1385.

Turčija in ptičja gripa

Smrt na pragu Evrope

Na vzhodu Turčije umrl še tretji otrok, domnevno okužen s smrtonosnim sevom virusa ptičje gripe – Vzorce bodo zdaj pregledali še v Britaniji

ANKARA, BRUSELJ – Potem ko je v petek bolezni s simptomi, ki spominjajo na ptičjo gripo, podlegla še tretja žrtev v tednu dni, se je na vzhodu Turčije razširil strah pred izbruhom epidemije. Preminula enajstletna deklica iz vasi Dogubayezit blizu turške meje z Iranom in Armenijo je sestra 15-letne deklice, ki je za ptičjo gripo umrla v četrtek, in 14-letnega dečka, ki je umrl v nedeljo. Turški kmetijski minister je potrdil vsaj štiri nova žarišča ptičje gripe v provincah Igdir, Erzurum in Sanliurfa na vzhodu države.

Prvi testi, opravljeni v Turčiji, so pokazali, da sta prvi žrtvi umrli za smrtonosnim sevom ptičje gripe H5N1. Vzorce zdaj pregledujejo še v Britaniji. Če bodo potrdili ugotovljeni vzrok smrti, bosta turška najstnika postala prvi človeški žrtvi ptičje gripe zunaj jugovzhodne Azije in Kitajske, kjer je od leta 2003 umrlo 74 ljudi; samo lani skoraj 40. Na veliko verjetnost takšnega scenarija je v četrtek, sklicujoč se na rezultate prvih testov, opozoril tudi predstavnik Svetovne zdravstvene organizacije (WHO) v Ženevi.

Zdravniki v bolnišnici v mestu Van, kjer so zdravili otroke, pravijo, da so ti najverjetneje prišli v stik z virusom med igro z odsekanimi glavami okuženih piščancev. »Z glavami so se igrali več dni. Bili so v zelo tesnem stiku z mrtvimi piščanci,« je izjavil lečeči zdravnik Huseyin Avni Sahin. V bolnišnici so zaradi domnevnih simptomov ptičje gripe v petek zdravili še 26 ljudi – trije so na intenzivni negi, stanje enega so opisali kot kritično. Med obolelimi je tudi šestletni brat umrlih otrok, njegovo stanje se menda izboljšuje.

Novice o smrti otrok so močno prestrašile prebivalce kraja, kjer so živeli. Hodniki tamkajšnje bolnišnice so prepolni ljudi, ki bi se radi testirali. Preplah je poskušal pomiriti zdravstveni minister Recep Akdag. »Ne pričakujemo okužbe večjega števila ljudi. Ne verjamemo, da bo v Turčiji izbruhnila pandemija, obstaja pa resno tveganje za ljudi, ki so v tesnih stikih s perutnino.« Vlada se zdaj poskuša otresti kritik, ki jo zaradi domnevno prepočasnega odziva nanjo naslavljajo javnost in mediji. Na petih območjih na vzhodu države je že razglasila karanteno in odredila zakol približno 7000 živali.

WHO je na zahtevo Ankare v petek na ogroženo območje že poslala skupino strokovnjakov, ki naj bi proučila ozadje smrti otrok, veterinarskega strokovnjaka je tja napotila tudi evropska komisija. Iz Bruslja so sporočili, da so v tesnem stiku s turškimi oblastmi in WHO, s katerimi poskušajo ugotoviti, kakšna je dejanska narava in obseg zadnjega izbruha bolezni. V veljavi ostaja tudi oktobra lani – ko je Turčija na zahodu države odkrila prvo žarišče ptičje gripe – sprejeta prepoved uvoza živih ptic in perutninskih izdelkov iz te države.

A. M.

Delo, 7.1.2006

Table 4. Exposures That May Put a Person at Risk for Infection with Influenza A (H5N1).*

Countries and territories where influenza A (H5) viruses have been identified as a cause of illness in human or animal populations since October 1, 2003

During the 7 to 14 days before the onset of symptoms, one or more of the following:

- Contact (within 1 m) with live or dead domestic fowl or wild birds or domestic ducks
- Exposure to settings in which domestic fowl were confined or had been confined in the previous 6 weeks
- Unprotected contact (within touching or speaking distance) with a person for whom the diagnosis of influenza A (H5N1) is confirmed or being considered
- Unprotected contact (within touching or speaking distance, 1 m) with a person with an unexplained acute respiratory illness that later resulted in severe pneumonia or death
- Occupational exposure†

Countries and territories where influenza A (H5) viruses have not been identified as a cause of illness in human or animal populations since October 1, 2003

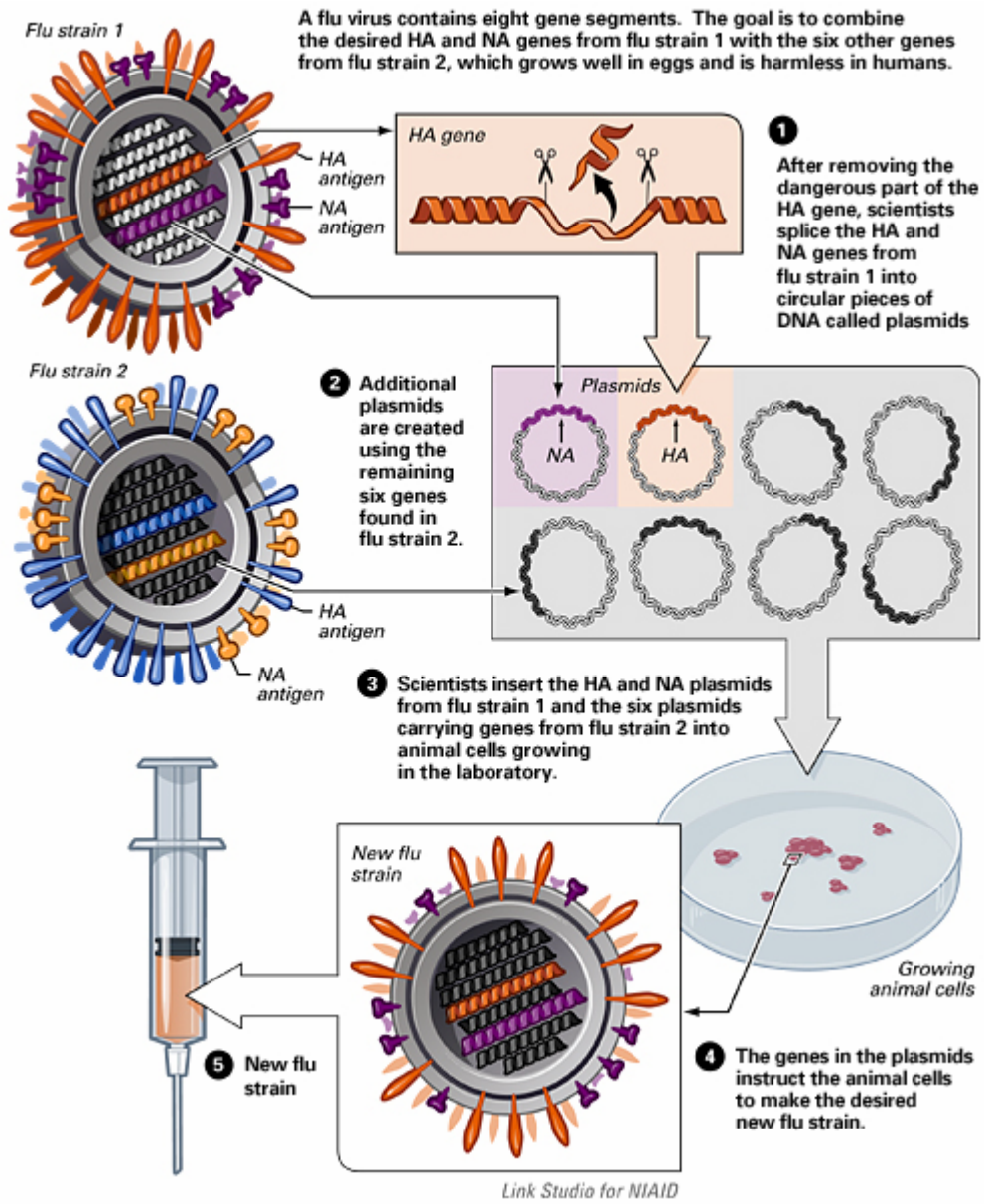
- During the 7 to 14 days before the onset of symptoms, close contact with an ill traveler from one of the areas with known influenza A (H5) activity, history of travel to a country or territory with reported avian influenza activity due to influenza A (H5N1) in the animal populations, or living in an area in which there are rumors of the death of domestic fowl, and one or more of the following:
- Contact (within 1 m) with live or dead domestic fowl or wild birds in any setting or with domestic ducks
- Exposure to settings in which domestic fowl were confined or had been confined in the previous 6 weeks
- Contact (within touching or speaking distance) with a patient with a confirmed case of influenza A (H5)
- Contact (within touching or speaking distance) with a person with an unexplained acute respiratory illness that later resulted in severe pneumonia or death
- Occupational exposure†

The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. (2005) The New England Journal of Medicine 353, 1374-1385.

REVERZNA GENETIKA

Študij vloge genov z načrtnim spreminjanjem genetskega materiala.

Lahko pomembna vloga pri razvoju zdravil.



National Institute of Allergy and Infectious Diseases, NIH

ALI SE LAHKO PONOVI ŠPANSKA GRIPA?

- Pojav novih oblik virusov.
- Sredstva obveščanja (TV, radio, internet, dnevno časopisje)
- Stil življenja (več potovanja, večja odpornost)
- Napredek v farmaciji in medicini

THIS HOUSE BELIEVES

THAT A PANDEMIC FLU IS IMMINENT IN THE NEXT FEW YEARS

Supporting this motion

Speaking against this motion
Gregor Anderluh

Vprašanja med predavanjem o virusu gripe

Ali gostiteljska celica umre med pomnoževanjem in sproščanjem virusa?
Replikacijski cikel (vstop v celico, pomnoževanje in pakiranje novih virusnih delcev) traja okoli 6 ur. Virusni delci se v roku nekaj ur postopoma sproščajo s površine gostiteljske celice. Gostiteljska celica sčasoma umre, verjetno zaradi motenj v sintezi makromolekul.

Koliko virusnih delcev se sprosti iz gostiteljske celice?
Nekaj ur po infekciji se lahko na slikah z elektronsko mikroskopijo vidi v citoplazmi preko 100 nekompletnih virusnih delcev, ki se potem obdajo z lipidno membrano in počasi brstijo iz celice.

Kako stabilen je virus gripe?
Virus gripe zaradi lipidnega ovoja **ni** stabilen. Uničijo ga vročina, sušenje, detergenti in organska topila. V okolju lahko v hladnih in vlažnih razmerah lahko vseeno preživi dlje časa, npr. nekaj tednov.