

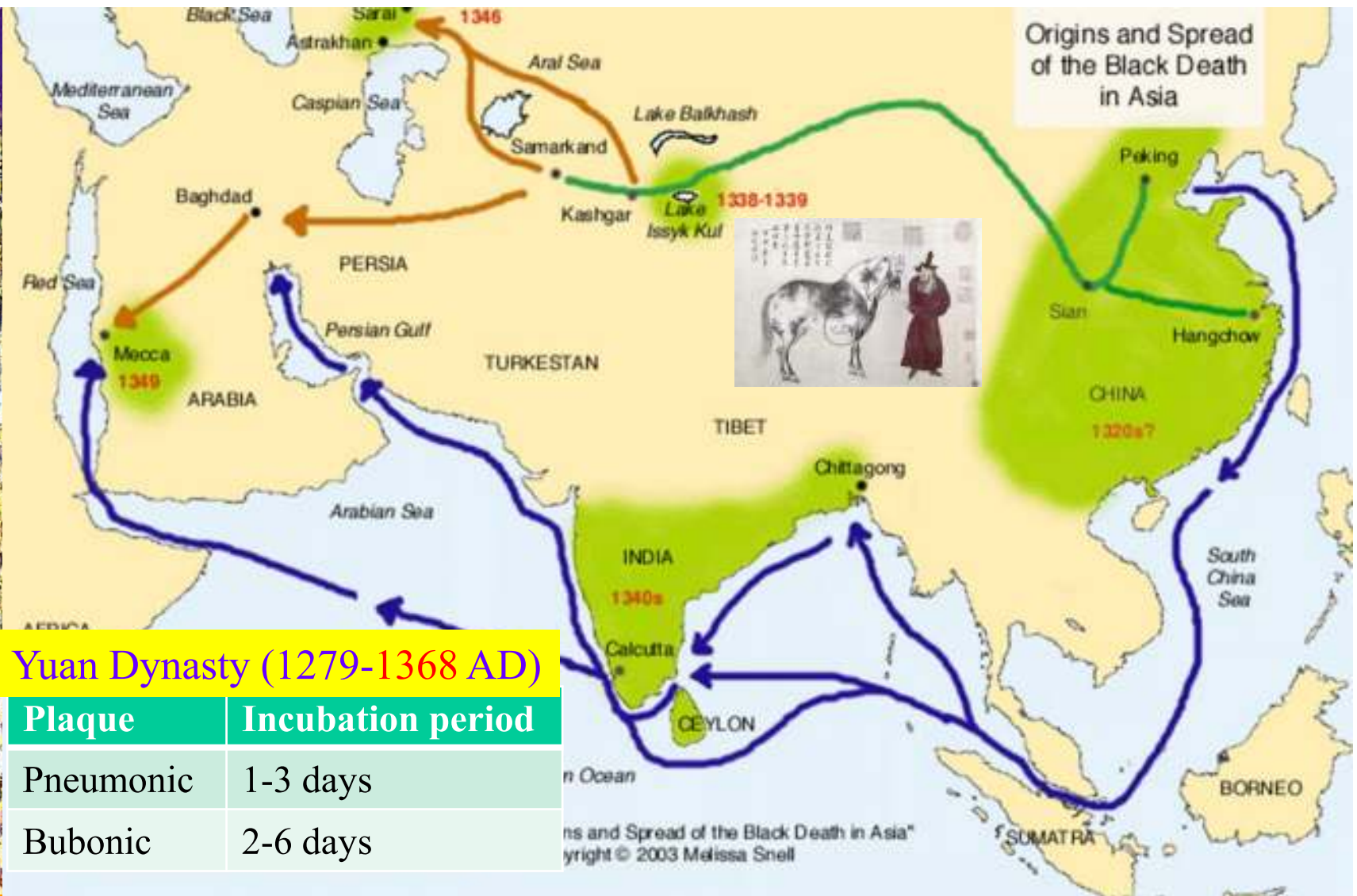
Perspective of H7N9 Avian Influenza Pandemic

Therapeutic Strategies Against Highly Conserved Viral And Bacterial Determinants

流行性感冒病毒



Dr. Lai Kang Yiu



Yuan Dynasty (1279-1368 AD)

Plaque	Incubation period
Pneumonic	1-3 days
Bubonic	2-6 days

Black Death (1333-1369) killed 1/3 of the population of Europe and 2/3 of population of China

Measures to prevent SARS is unable to prevent the spread of influenza in 2003 in H.K.

Novel H1N1 with <0.1% mortality has pushed our medical system to the limit

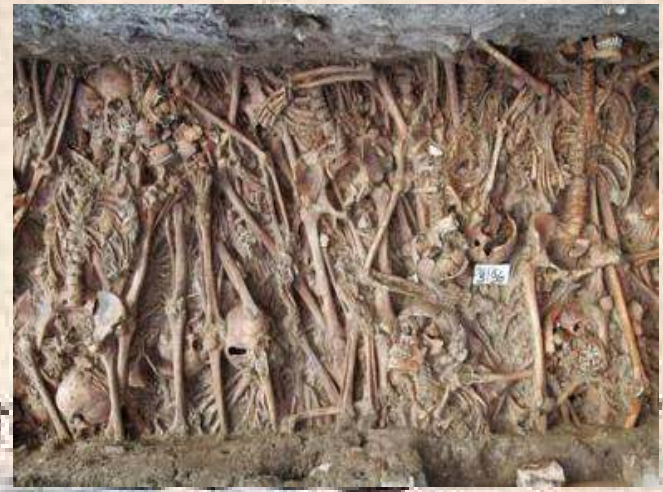
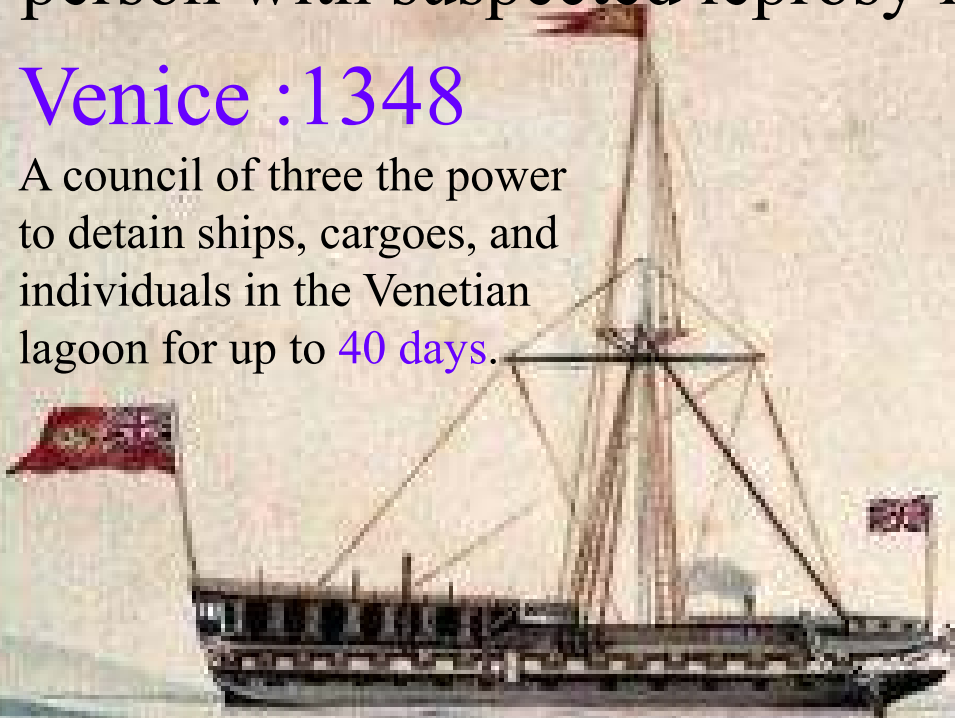
The Perspective of H5N1/H7N9 Avian Influenza Pandemic

Leviticus 13/4-5. → The priest is able to isolate person with suspected leprosy for 7 + 7 days

Venice :1348

A council of three the power to detain ships, cargoes, and individuals in the Venetian lagoon for up to 40 days.

Mass Plague Graves on Venice "Quarantine" Island Lazzaretto Nuovo



1377 Law of Ragusa “Trentina” and “Quaranta”

1423 Venice 1st “Lazaretto” (Quarantine station)



Quarantine



We are only chasing the ever-changing shadow of the moon !

Influenza A viruses

H5N1
H7N9

1918PV
2009PV

H2N2
H3N2

月有陰晴圓缺
如觀諸法生滅，悟世間無常。

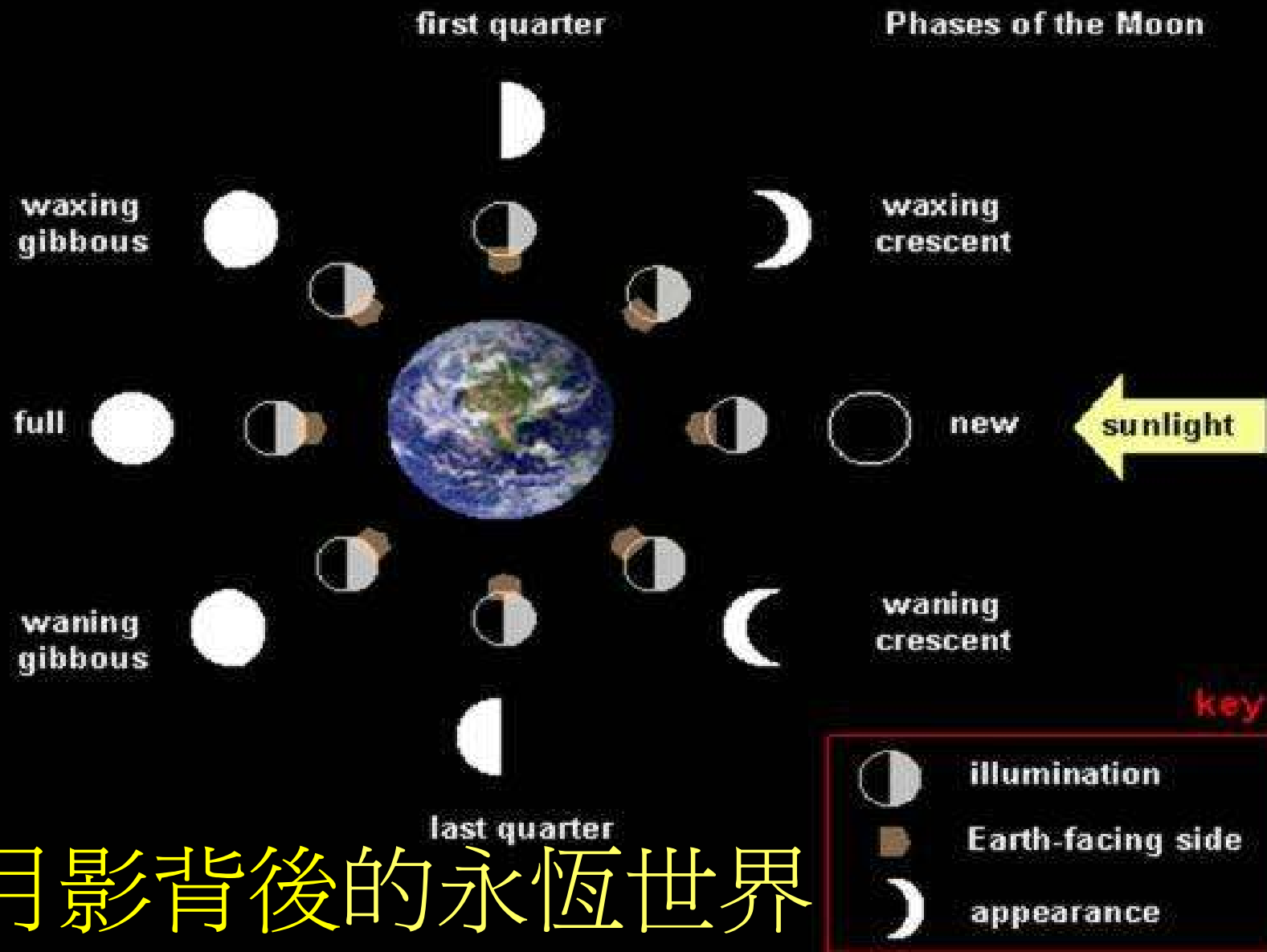


從月影的天魔萬相

窺破月影背後湛然不動的佛性

Unless we can understand the moon in a different perspective...

The eternal world behind the shadow of the moon
was formed 4.4-4.6 billions years ago



月影背後的永恆世界

一真法界，諸法平等，萬相皆殊。

NS

(非結構性蛋白)

M

(子通道蛋白)

NP

(核蛋白質)

dsRNA

雙股RNA

(雙鏈感應把關受體)

TLR3

PB2

(聚合酶鹼性蛋白質)

(神經氨酸)

NA

(聚合酶鹼性蛋白)

PB1

(聚合酶酸性蛋白)

PA

ER-overload

ROS

(活性含氧物種)

(血凝素)

HA



In the past, we are chasing after the mutable
viral determinant of influenza virus

HA

NA

變幻原是永恆

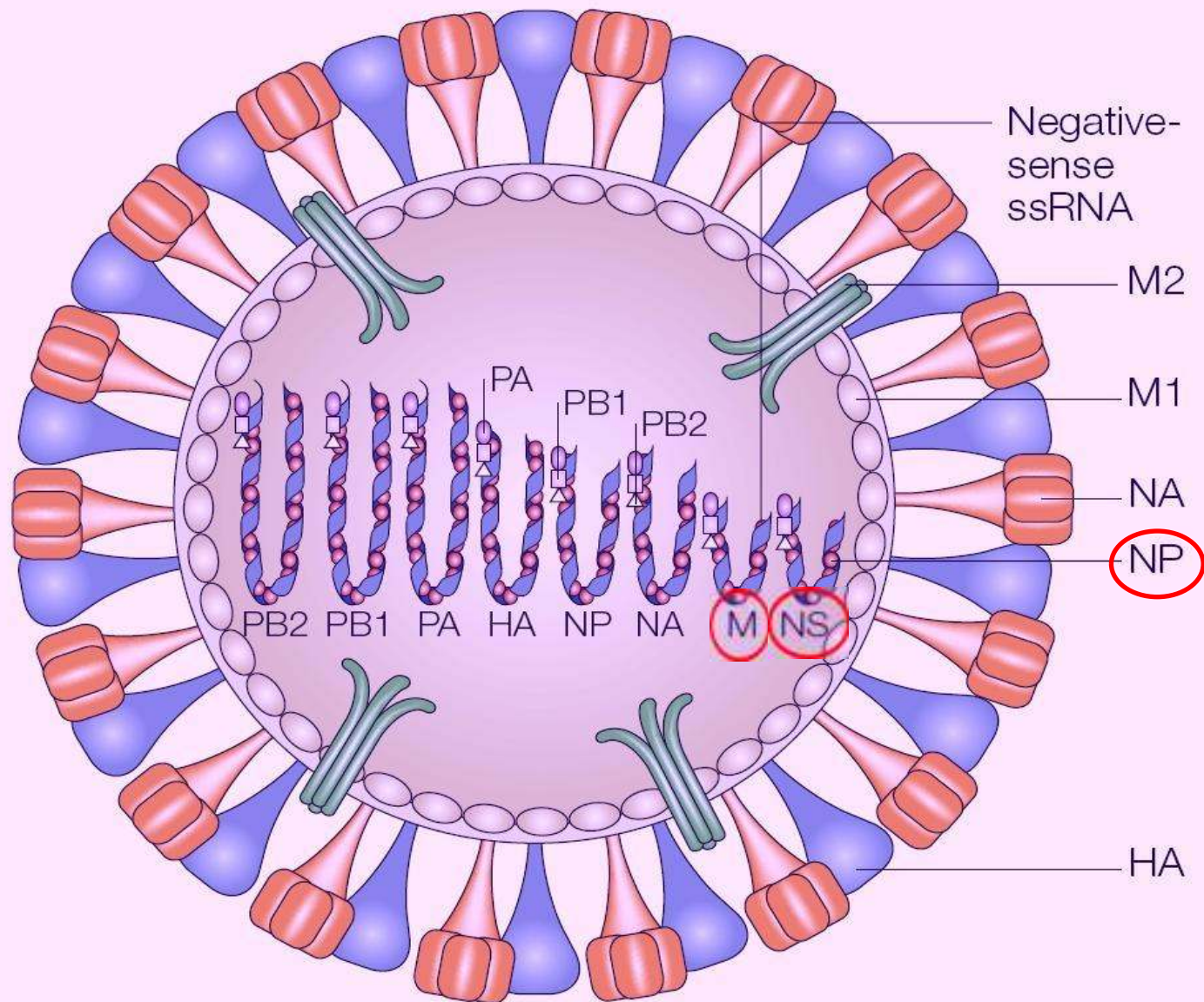
Mutation and Reassortment

Antigenic drift and shift

Epidemic and Pandemic

Vaccination

Being an RNA virus, the RNA polymerase of influenza has no proofreading mechanism. ~1 error per replicated genome → each cell can produce 10,000 new viral mutants to infect neighbouring cells. (300x than DNA virus)



Although there is prominent avian and swine influenza virus contribution to polymerases and surface antigens, the NP, NS and M genes are persistently mammalian in the last four pandemics.

象摸人盲

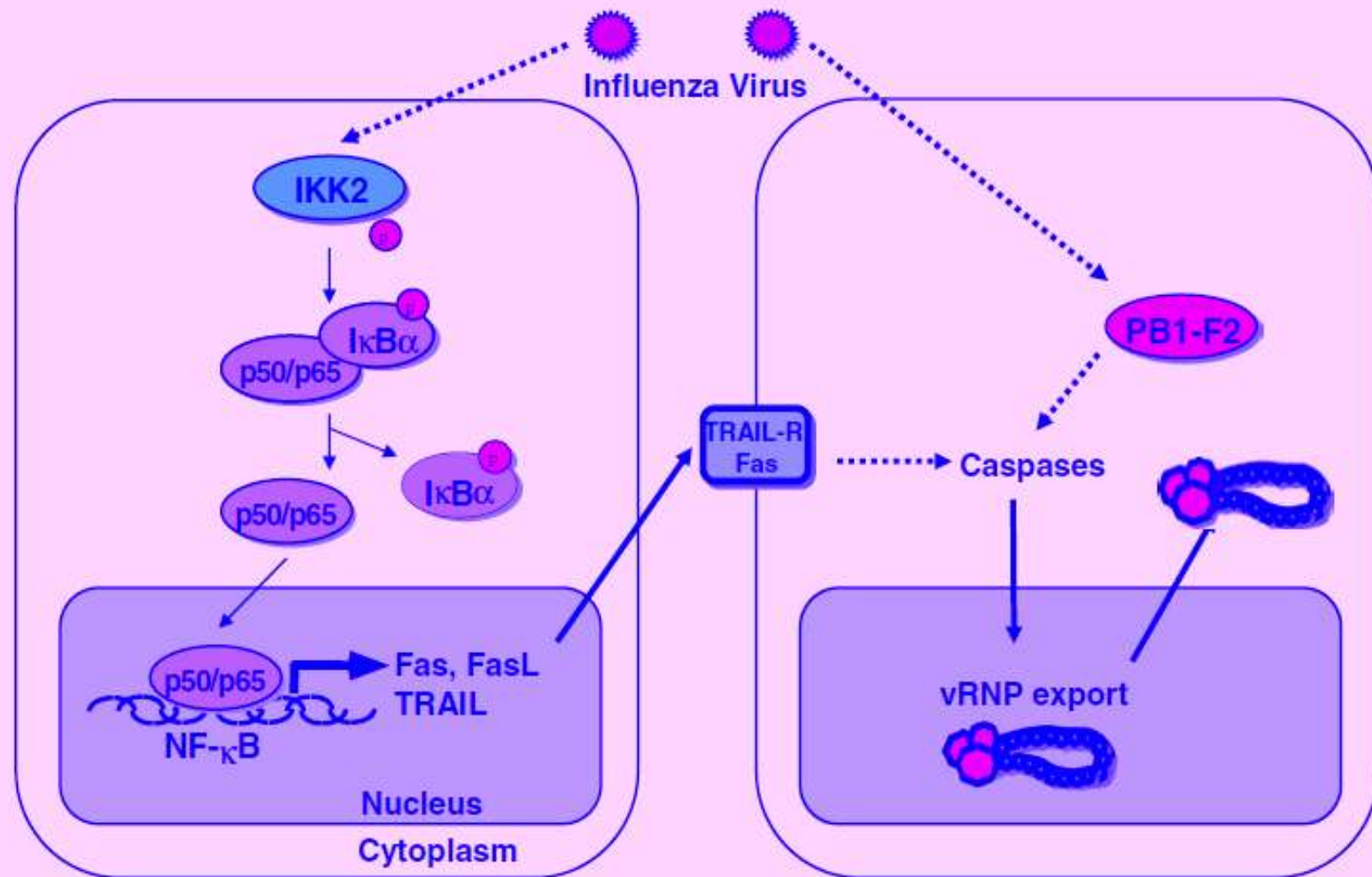
Inhibit apoptosis
(replication)
(複製繁殖)



Enhance apoptosis
(propagation)
(傳播)

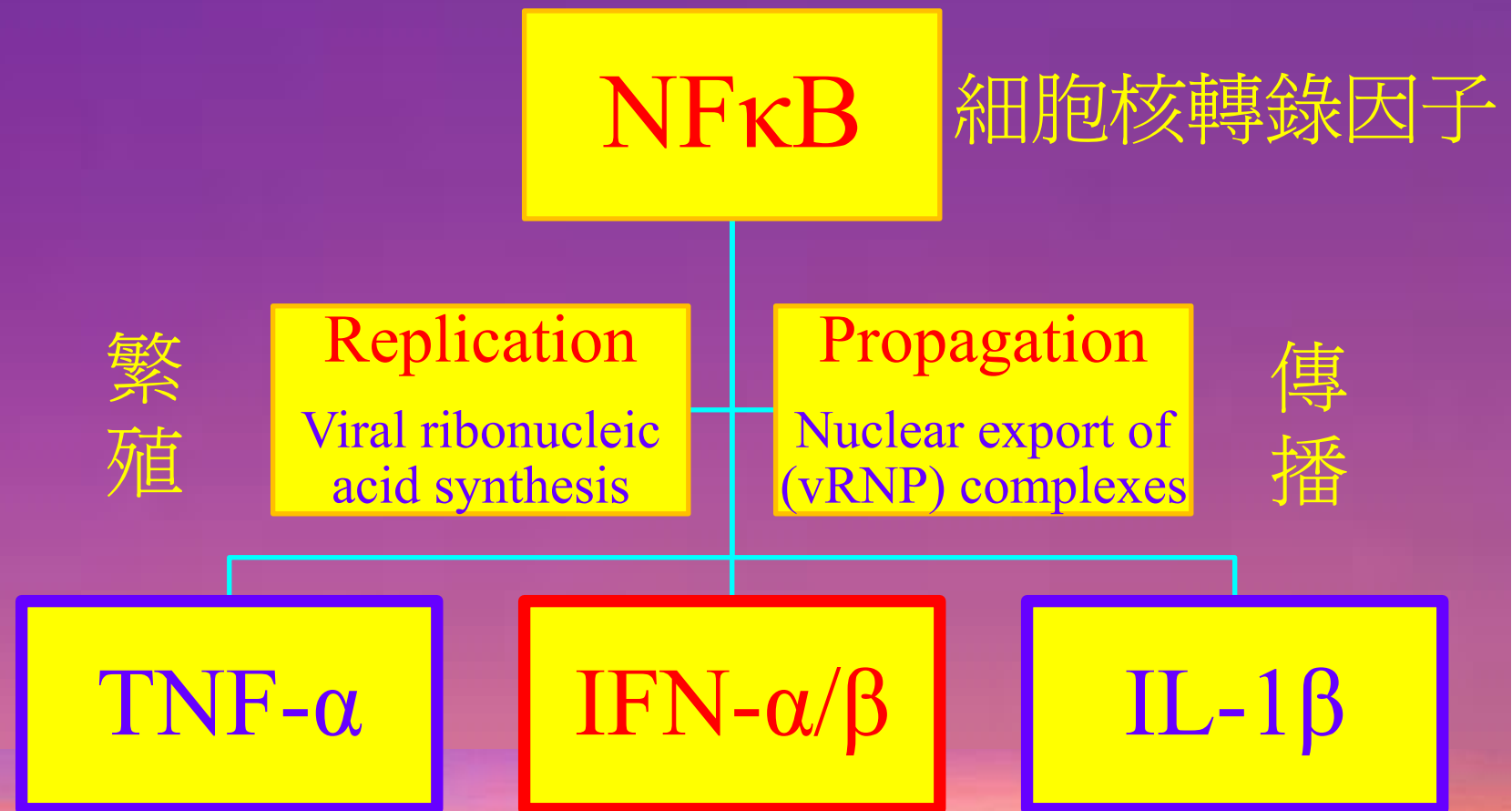
Geographic profile	18 pandemic	1510 - 2013
Antigenic profile	10 pandemic	1847 -2013
Genomic profile	5 pandemic	1918 - 2013

管中窺豹，瞎子摸象。



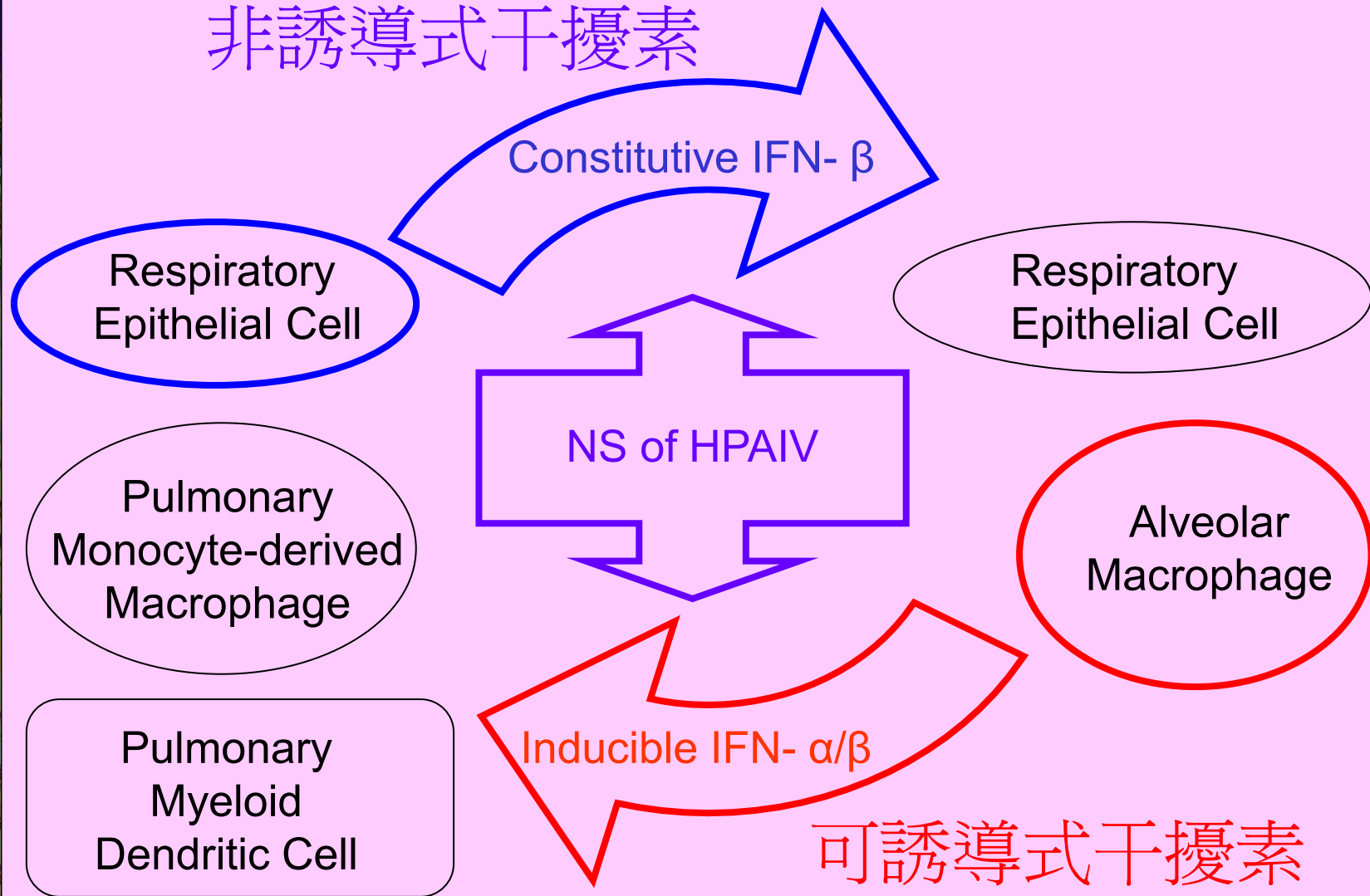
Being a small RNA virus with relatively small coding capacity, influenza A viruses have taken advantage of the host cell functions for viral replication and intracellular trafficking of viral components and during the process has led to apoptosis of the host cells and both cytokine and interferon dysregulation

NF κ B activation (活化) is a prerequisite for influenza infection and cytokine dysregulation



干擾素是動物細胞在受到某些病毒感染後分泌的具有抗病毒功能的宿主特異性糖蛋白。細胞感染病毒後分泌的干擾素能夠與周圍未感染的細胞上的相關受體作用，促使這些細胞合成抗病毒蛋白防止進一步的感染，從而起到抗病毒的作用，但干擾素對已被感染的細胞沒有幫助。

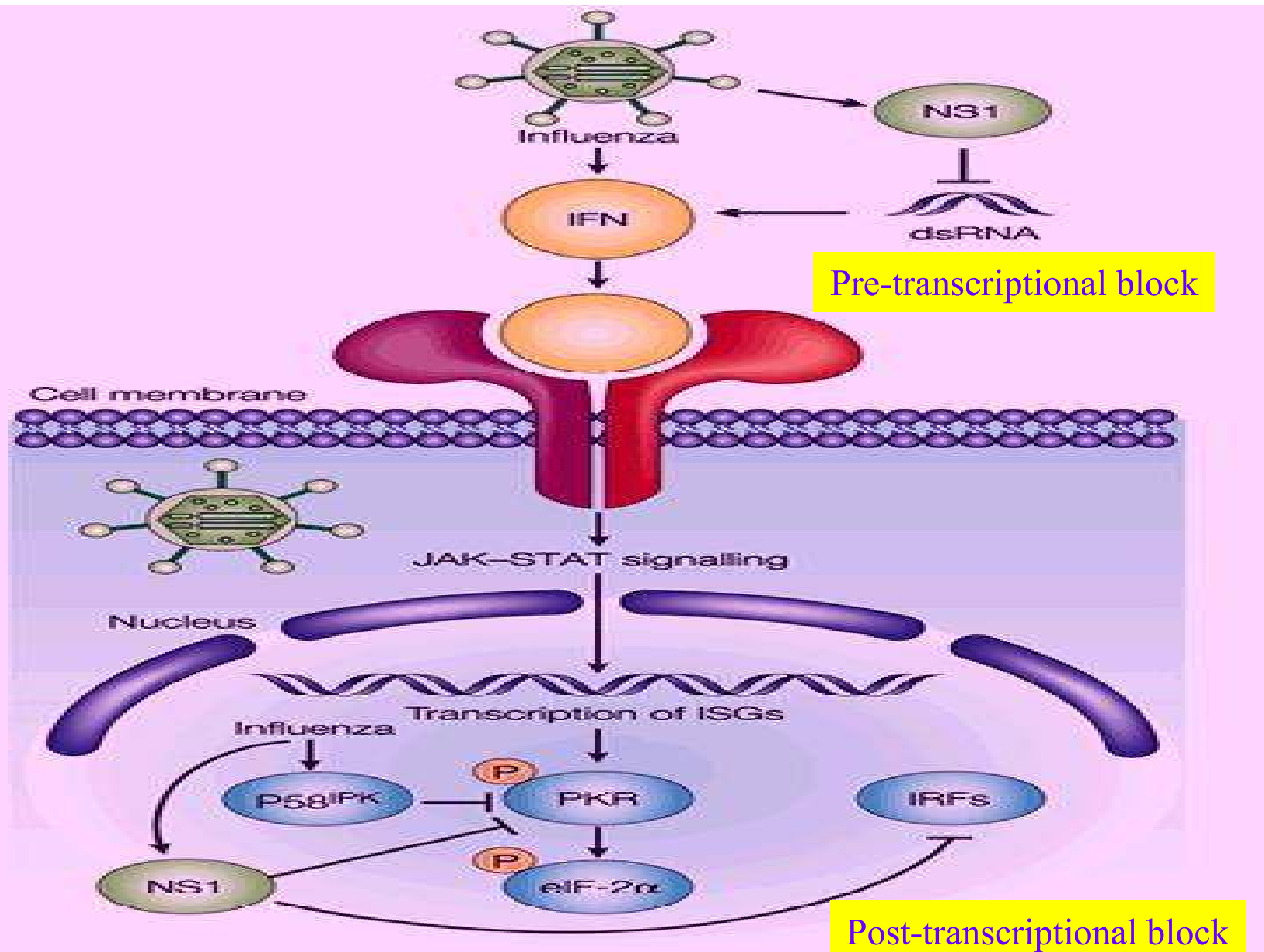
非誘導式干擾素



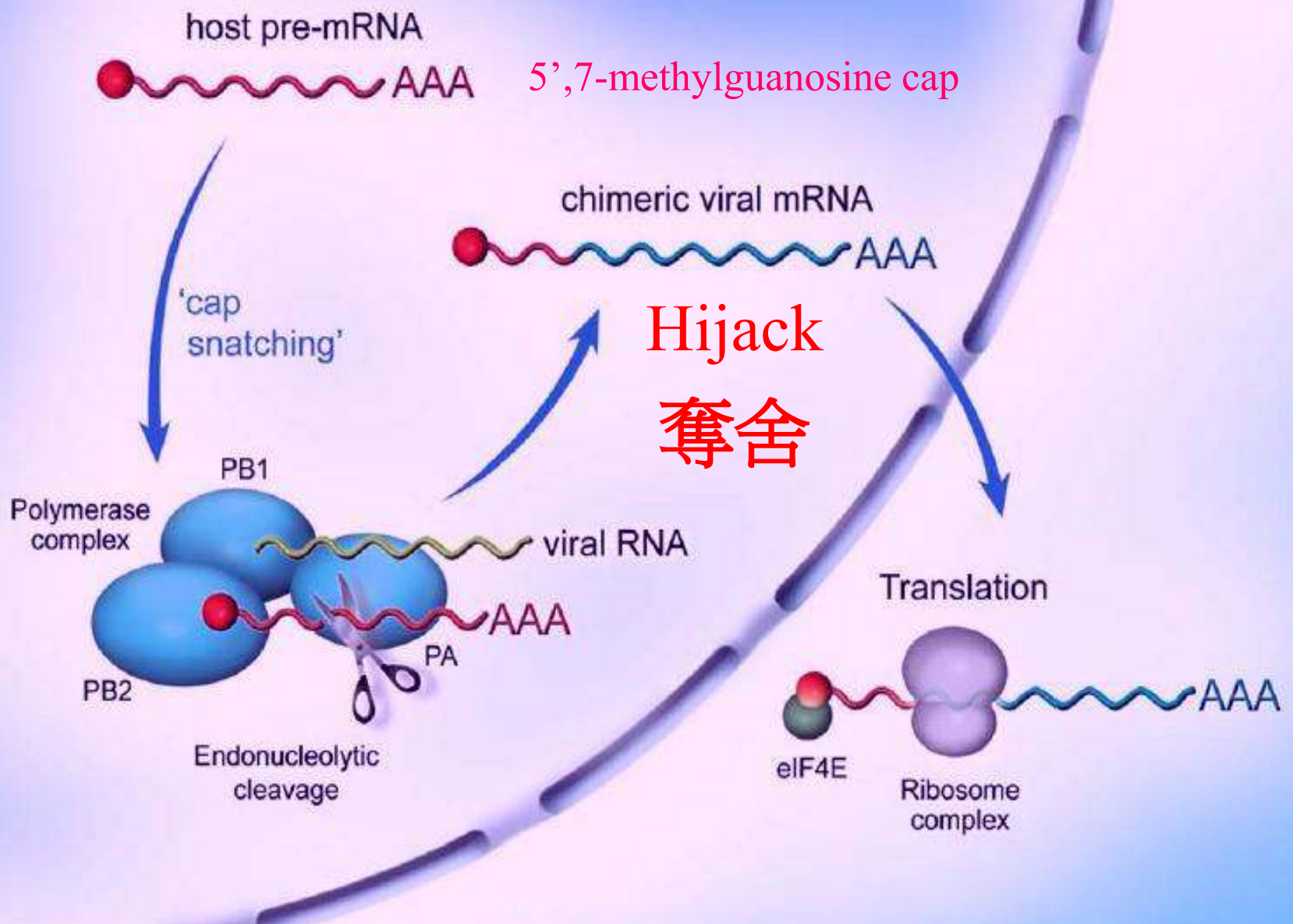
可誘導式干擾素

IFN- β plays an important role in the defense against influenza A virus that cannot be compensated for by IFN- α .

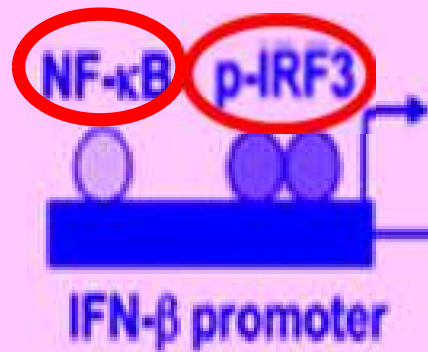
Constitutive and Inducible IFN- β



The inducible Type I interferon can be blocked at the pre-transcriptional and post-transcriptional level.



Host cell enzymes (cellular kinases) convert T-705(favipiravir) into T-705 ribofuranosyl phosphate (T-705RTP), a form that inhibits virus polymerase without affecting host cellular RNA or DNA synthesis.



Upon activation by **dsRNA**, **TLR3** binds to adaptor protein TIR-domain-containing adapter-inducing IFN- β (**TRIF**) to induce **MyD88-independent NF κ B activation** and **IFN- β production** through **IRF-3**. Co-ordinated activation of IRF-3 and NF κ B is essential for maximal induction of type I IFNs.

Transcription of
IFN- β gene

Haemagglutinin $\rightarrow$ IFN- α $\rightarrow$ IFN- α , IFN- β and IFN- λ 1

Interferon Dysregulation

The last attempt of the body to control influenza infection with disastrous consequences.

The **heavy viral load** produced by the infected respiratory epithelial cells, vascular endothelial cells and macrophages might have contributed to the profound TLR3, NF κ B and IRF-3 activation and interferon dysregulation of H5N1 infection.

The observed interferon dysregulation in the presence of a heavy viral load was previously erroneously attributed to interferon resistant by H5N1.

Pandemic Severity Index

Case
Fatality
Ratio

Projected
Number of Deaths*

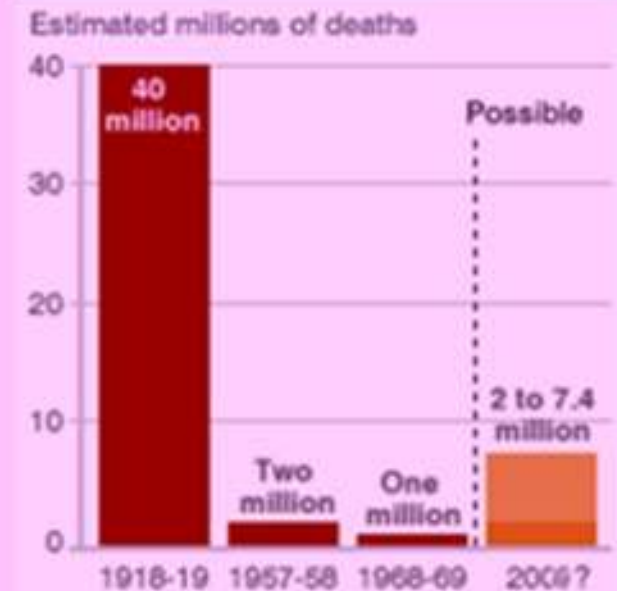
Population of HKSAR 7 million

30% population = 2.1 million



*Assumes 30% Illness Rate and Unmitigated Pandemic Without Interventions

WORLD FLU PANDEMIC DEATHS



Much more death than SARS



Roscoe Vaughn

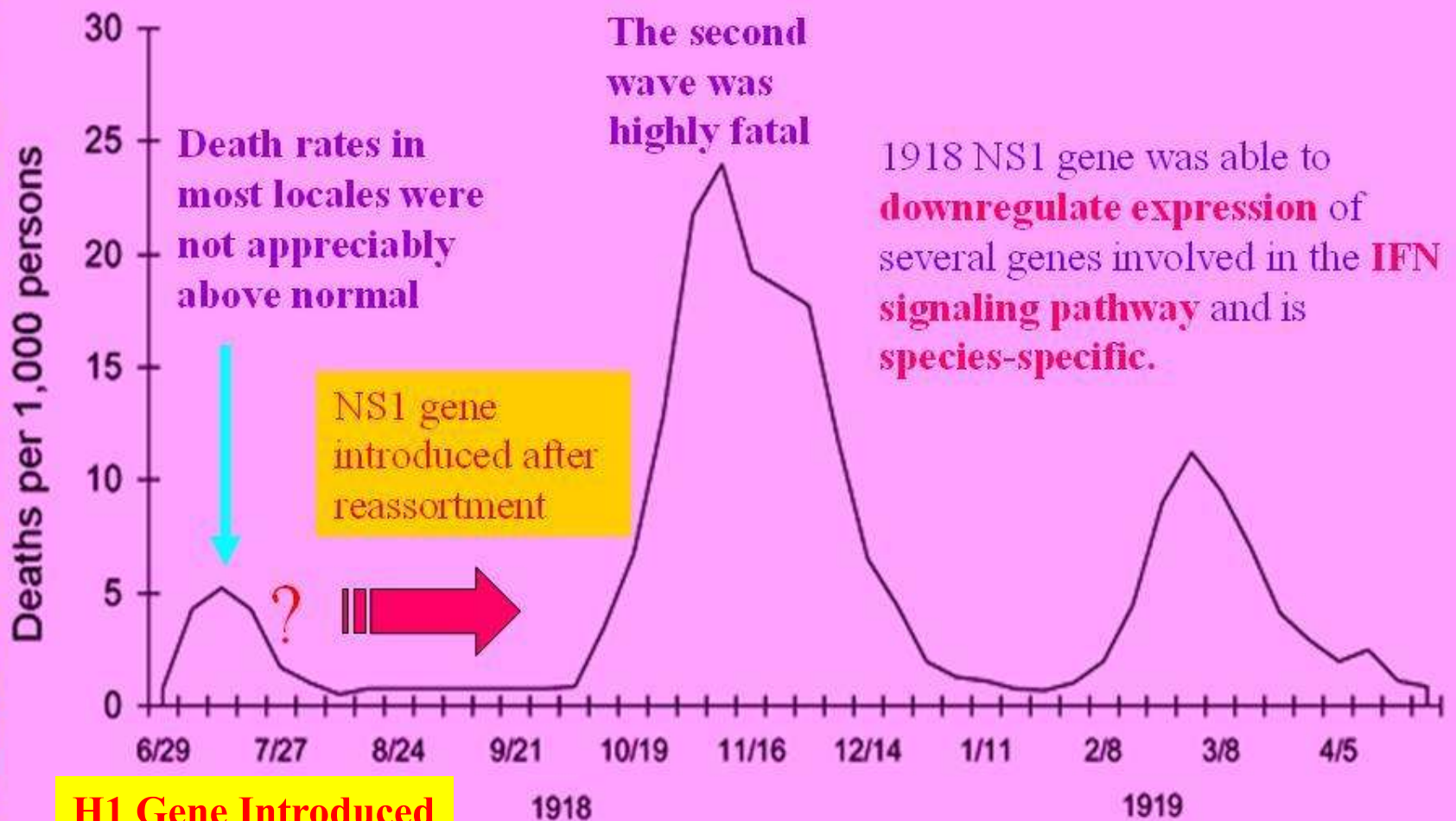
James Downs

Lucy

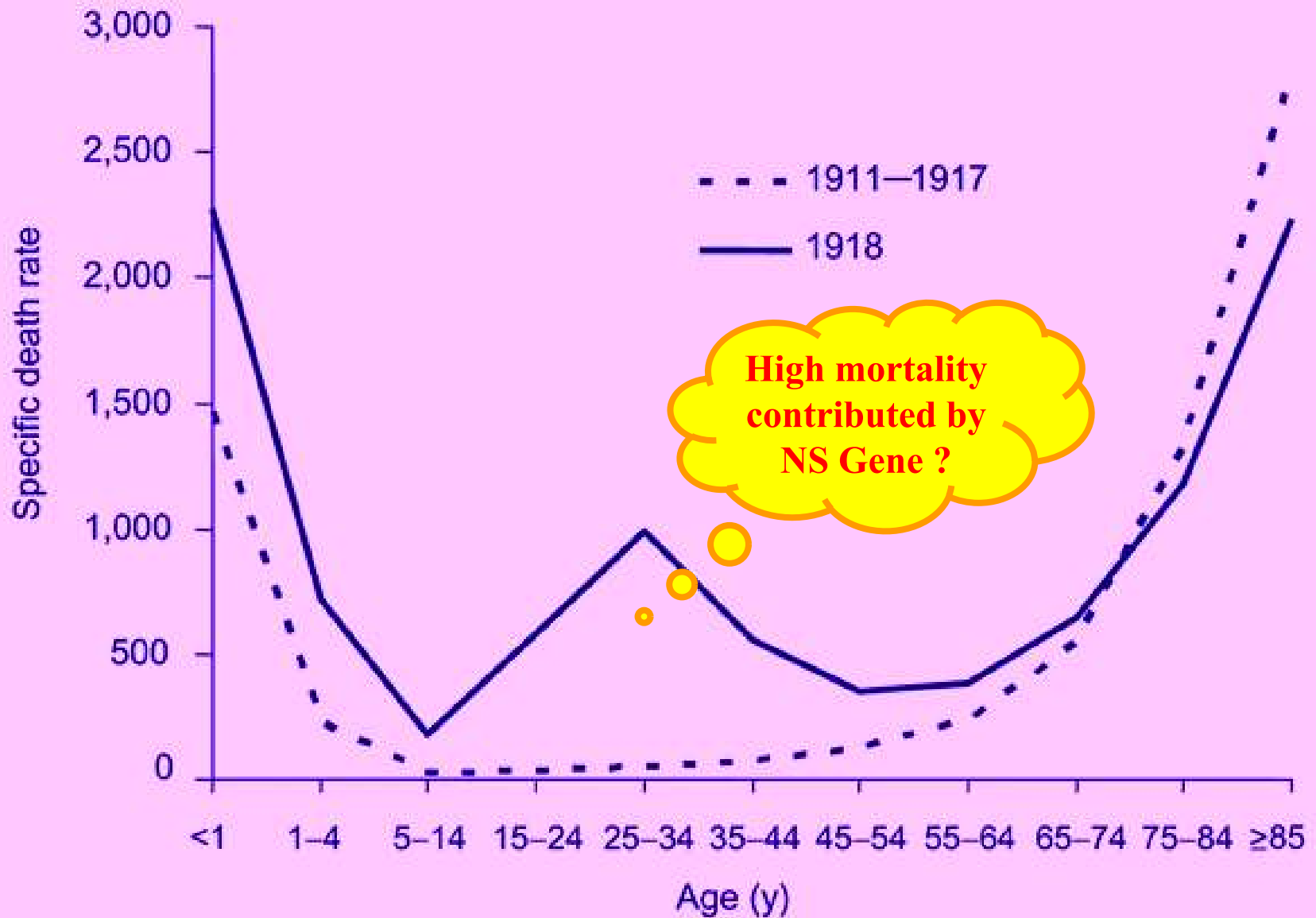


NS contributed to the virulence
of 1918 Pandemic virus

Jeffery K. Taubenberger of the National Institutes of Health
Reconstruct the 1918 H1N1 Spanish Influenza Virus in 1997 from tissues
recovered from victim buried in the Alaskan permafrost and samples
preserved from American soldiers.

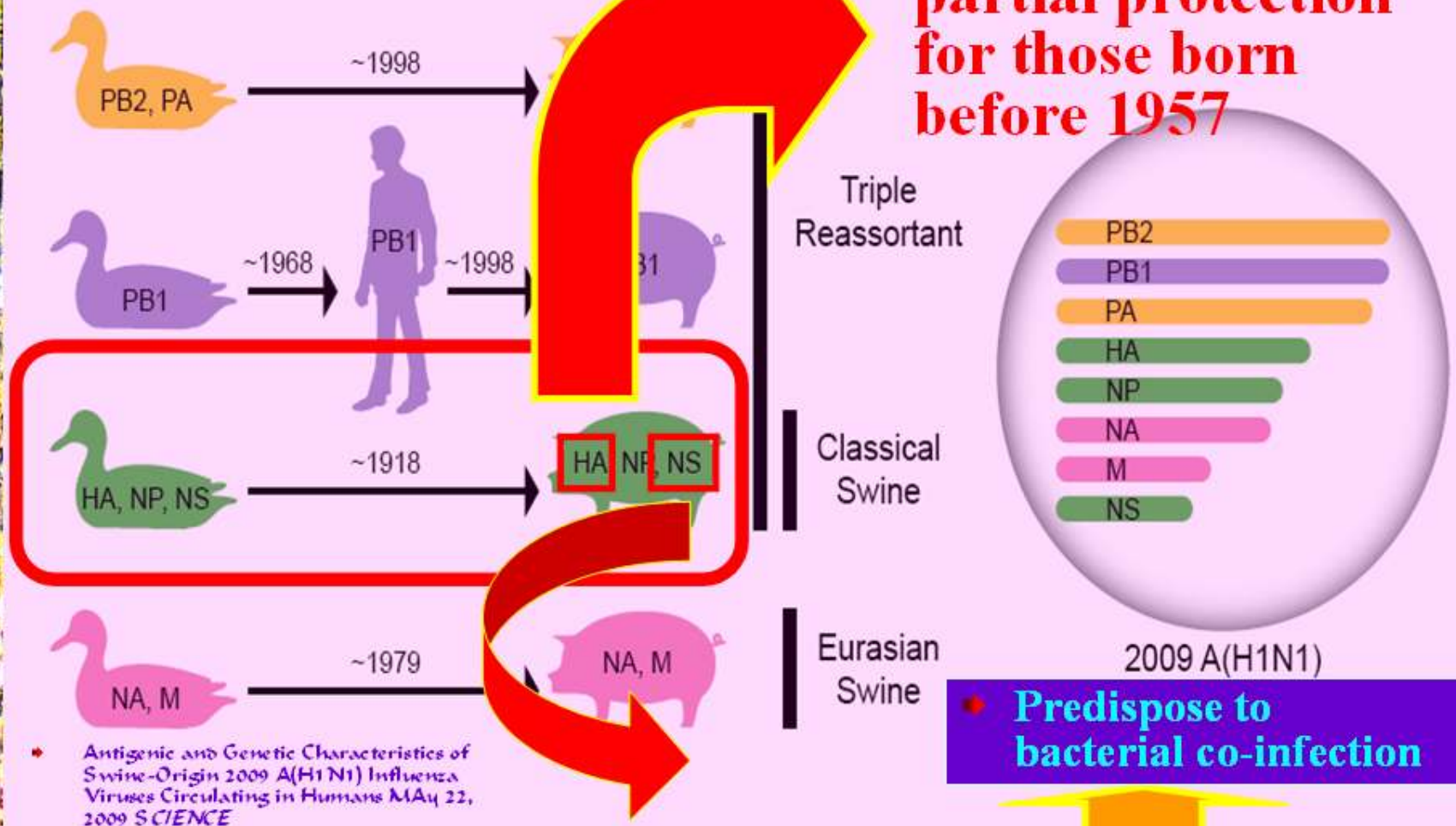


Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919

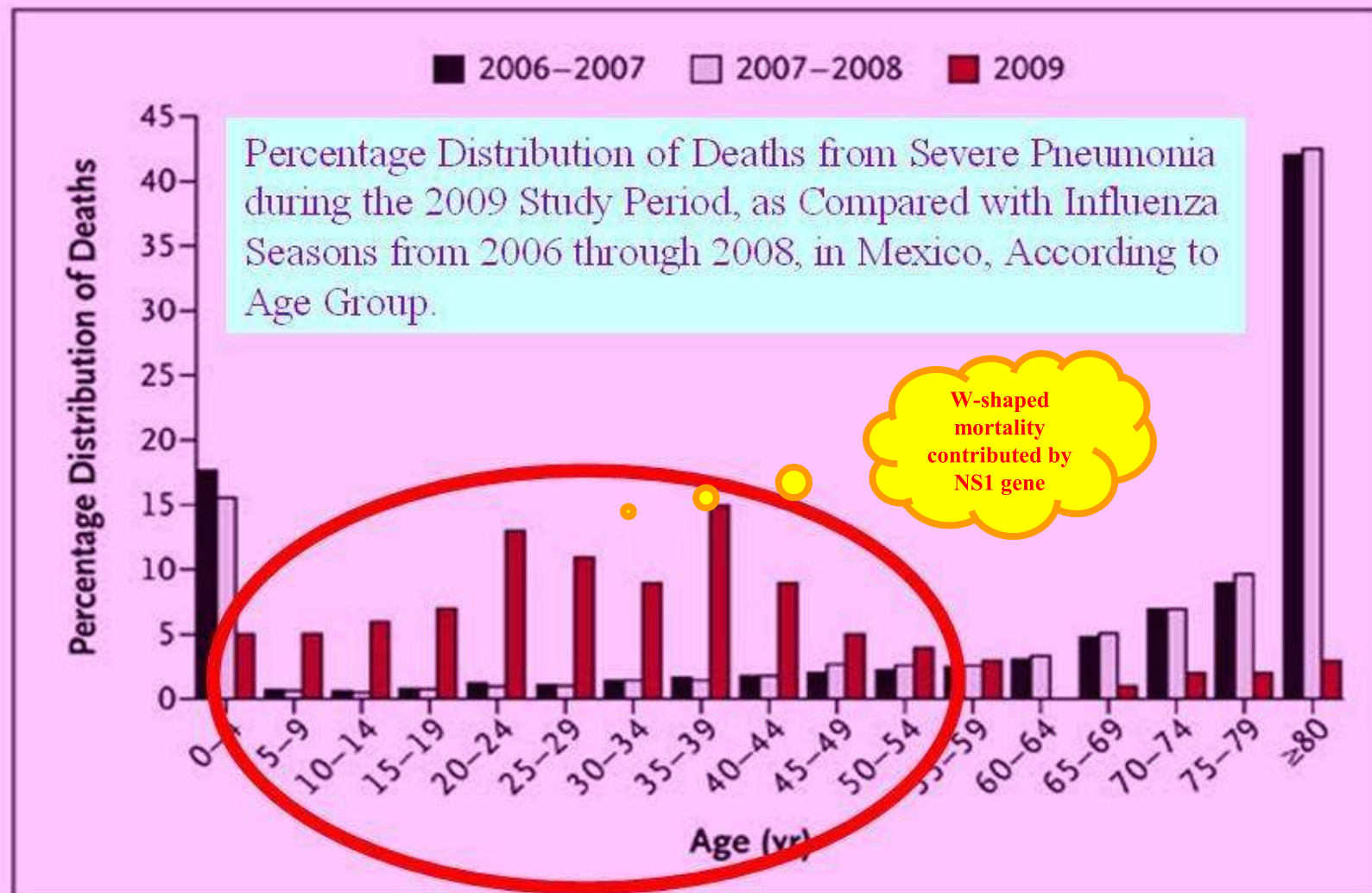


**U shape Mortality Rate of Seasonal Influenza
Vs W shaped Mortality Rate of H1N1**

Gene Segments, Hosts,
and Years of Introduction



■ **Suppression of innate immune response leading to initial rapid proliferation of influenza virus and severe mucosal damage**



March 24 to April 29, 2009, a total of 2155 cases of severe pneumonia, involving 821 hospitalizations and 100 deaths

Severe Respiratory Disease Concurrent with the Circulation of H1N1 Influenza Gerardo Chowell, Ph.D., Stefano M. Bertozzi, NEJM June 29 2009



IFN- β	Constitutive IFN- β inhibition	Inducible IFN- β inhibition		Mortality
		Pre-transcriptional	Post-transcriptional (Optimal human CPSF30 binding)	
H2N2 or H3N2	✗	✗	✓	<0.1%
2009PV	?	✓	✗	<0.1%
1918PV	?	✓	✓	~2.5%
H5N1 (1997)	✓	✓	✗	33%
H7N9 (2013)	?	✓	✗	33%
H5N1 (2003-	✓	✓	✓	~60%

IFN- β is encoded by a single gene, while both the human and mouse genomes contain 13 functional IFN- α genes

As opposed to H2N2 and H3N2, the NS1 proteins of 1918PV, HPAIV and some H1N1 viruses (except 1940-1957 and 1977-1990) block the activation of IRF3 and interferon- β transcription.

Kuo, R.L. et al. Influenza A virus strains that circulate in humans differ in the ability of their NS1 proteins to block the activation of IRF3 and interferon- β transcription. *Virology*; 408, 146-58 (2010).

PRISMA Study 2005

Influenza vaccination	Reduction in hospitalization	Reduction in mortality
Age < 65 with high risk factor	87%	78%
Age > 65	48%	50%

High-risk medical condition including chronic bronchitis, emphysema, asthma, other respiratory diseases, acute or chronic ischemic heart disease, heart failure, atrial fibrillation, other heart disease, cerebrovascular disease, diabetes mellitus, chronic renal disease, chronic staphylococcal infection, and immune-related diseases.

Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. Hak E, Buskens E, van Essen GA, et al. Arch Intern Med 2005;165:274-80.



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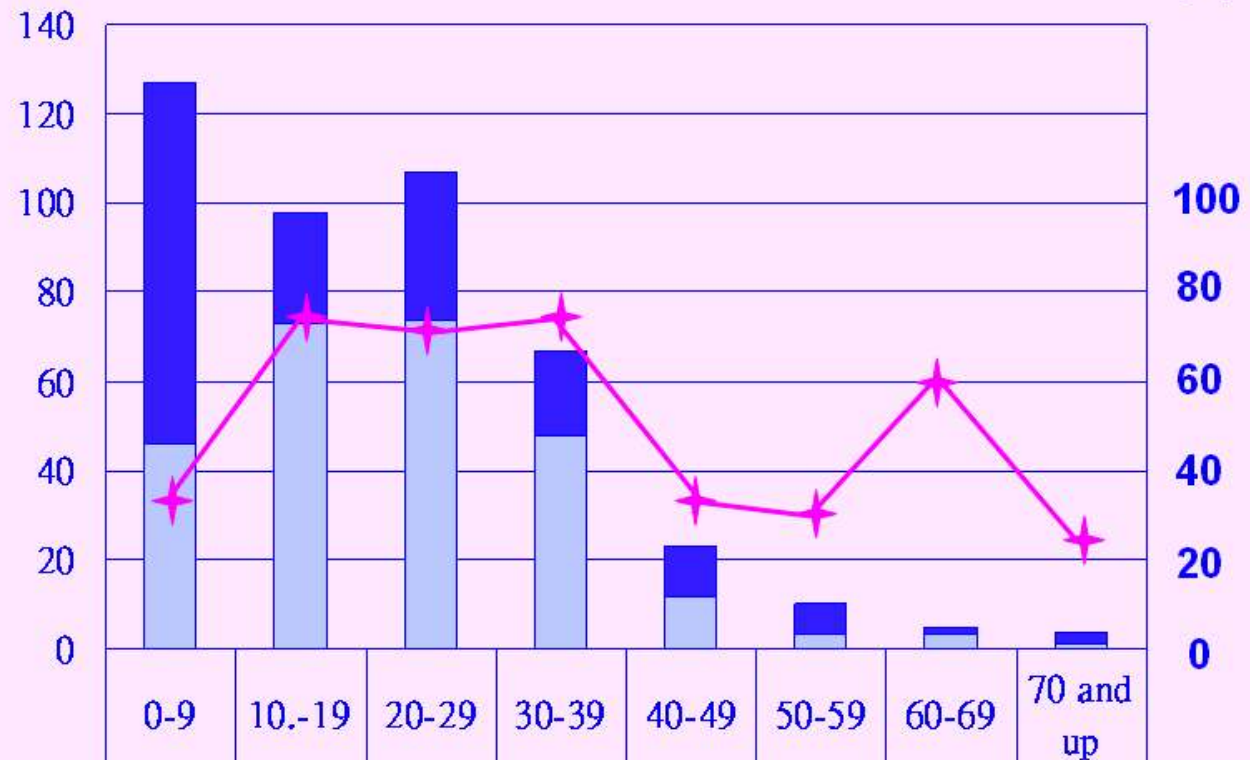
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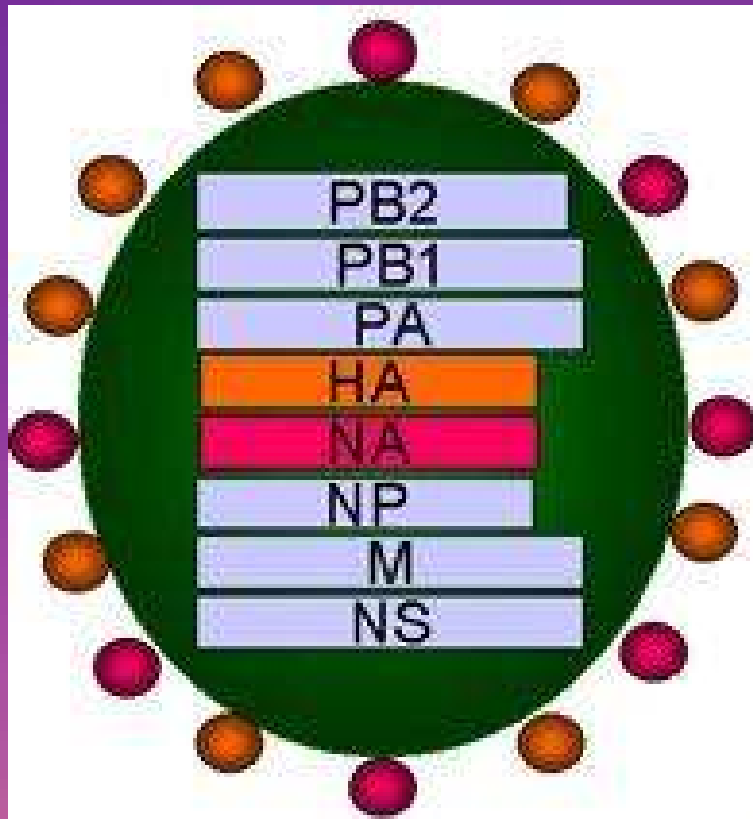
Human Avian Influenza A (H5N1) Cases by Age Group and Outcome (N=441) (As of 8th February 2010) (World Health Organization)

Number of cases

Mortality (%)

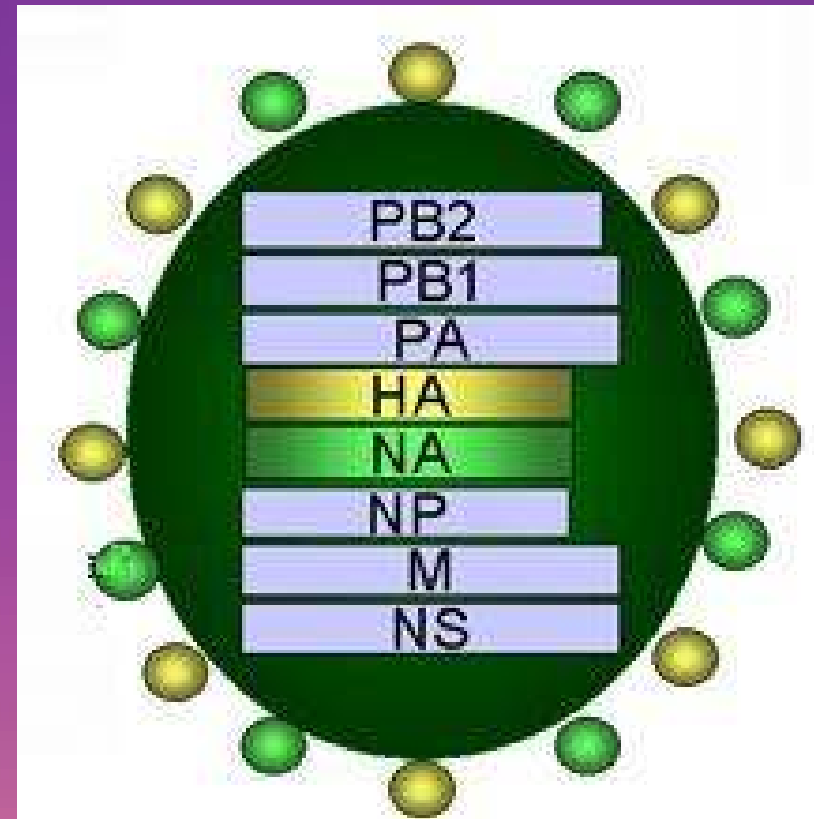
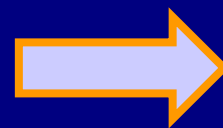


■ Alive (N=181)	81	25	33	19	11	7	2	3
■ Dead (N=260)	46	73	74	48	12	3	3	1
★ Mortality (%)	36	74	69	72	36	30	60	25



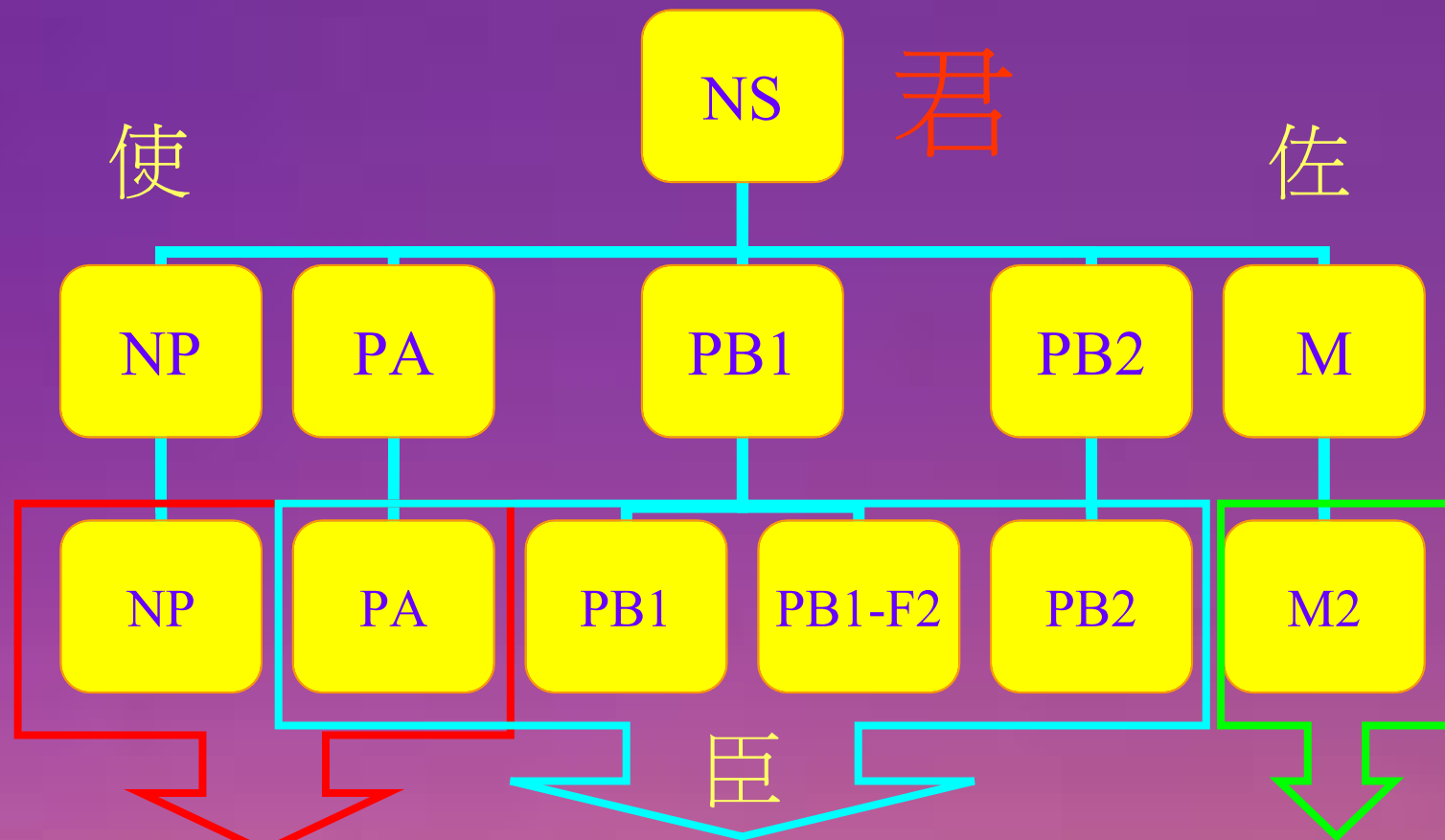
H9N2

(NS, NP, PA,
PB1, PB2, M)

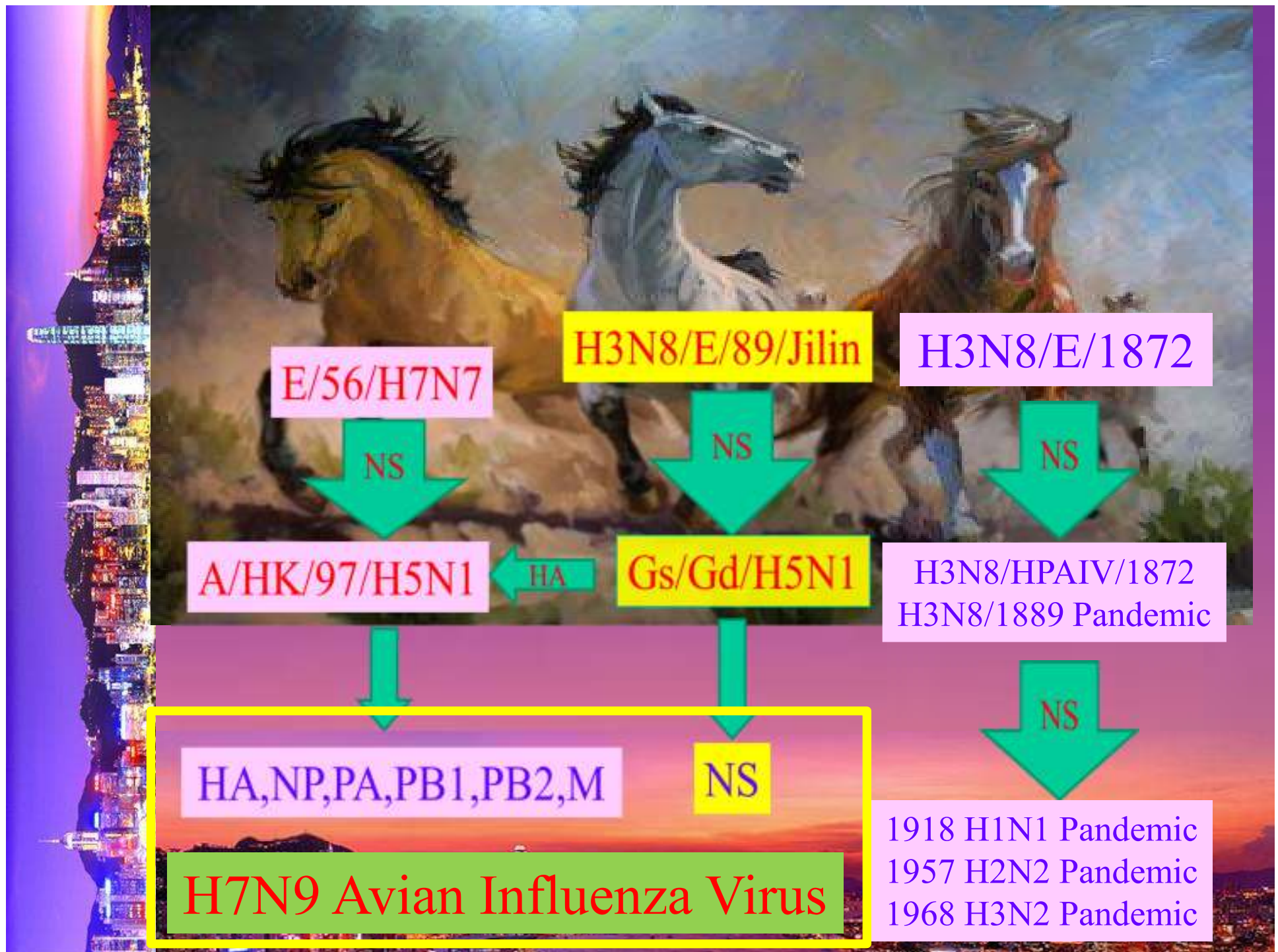


H5N1/H7N9

(NS, NP, PA,
PB1, PB2, M)



↑Viral Load, Cytokine Dysregulation, ↑Mortality





Live poultry trade in Southern China provinces and HPAIV H5N1 infection in humans and poultry: the role of Chinese New Year festivities.

Soares Magalhães RJ, et al. PLoS One. 2012;7:e49712.

Human H5N1 risks rise in Vietnam and Cambodia as Chinese New Year approaches when poultry movement and sales grow exponentially.

http://www.who.int/influenza/resources/documents/H5N1_Update_April_2010.pdf

Outbreak of H7N9 at “Chinese New Year”



The Live Poultry Market of China

Emergence, spread, amplification and maintenance of pathogenic reassortant influenza viruses.

H5N1

Avian Flu

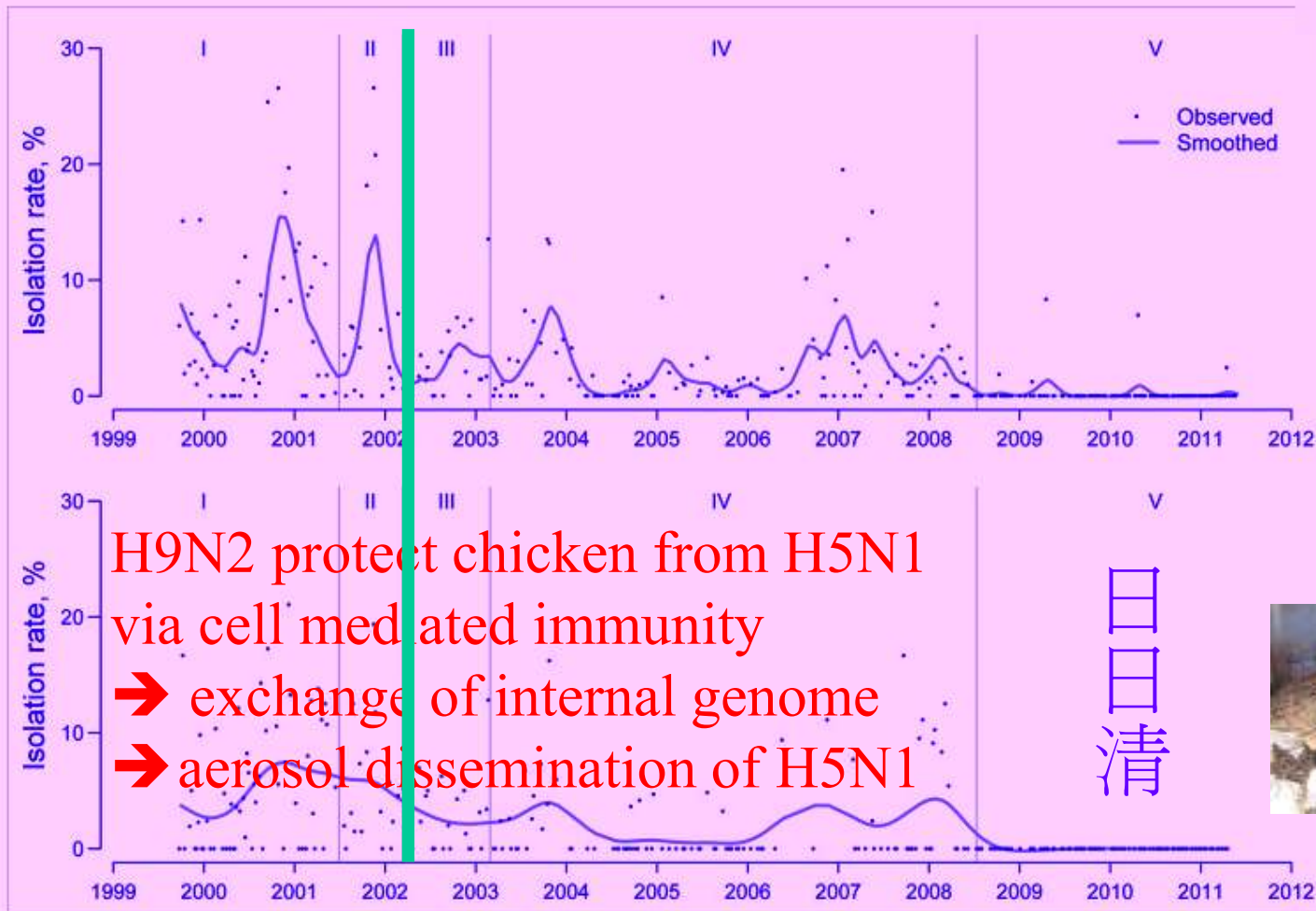
H9N2



Gary Kiesel
THE HUNTER'S SHIP
©2005 CREATORS SYND.
— APPLIES TO WARNER BROS.

H5N1 and H9N2

Cell-mediated immunity against H9N2 protect chicken from death of H5N1
=> Spread of H5N1 in poultry market via aerosol through chicken and quail



H9N2 protect chicken from H5N1
via cell mediated immunity
→ exchange of internal genome
→ aerosol dissemination of H5N1

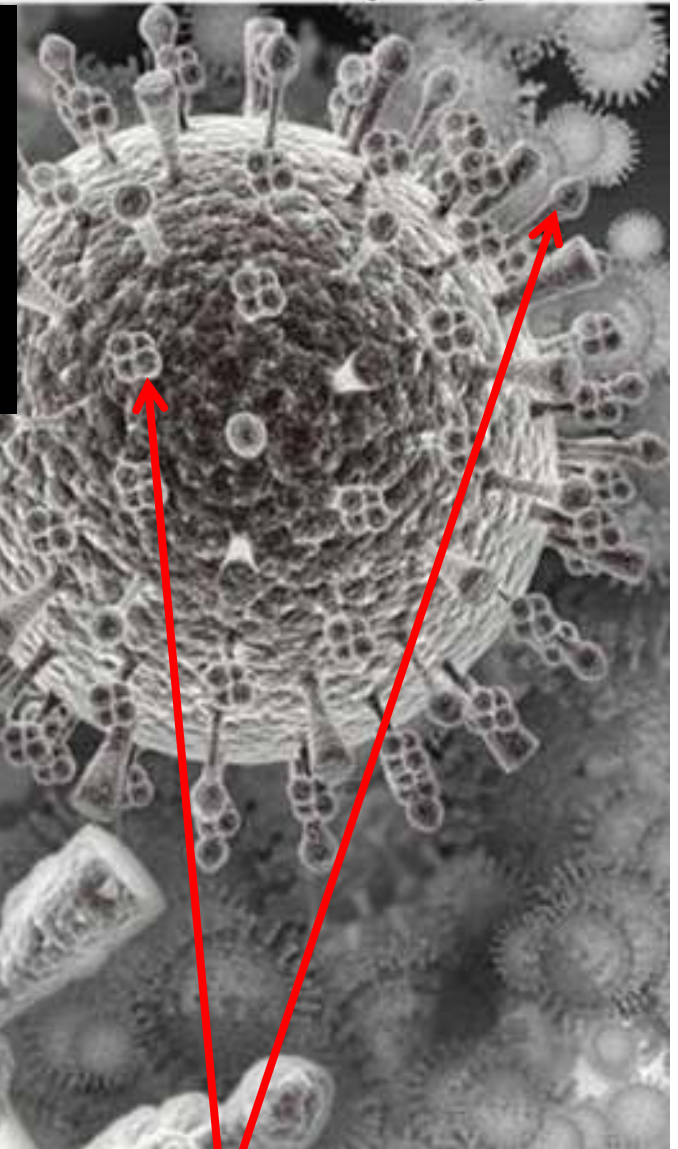
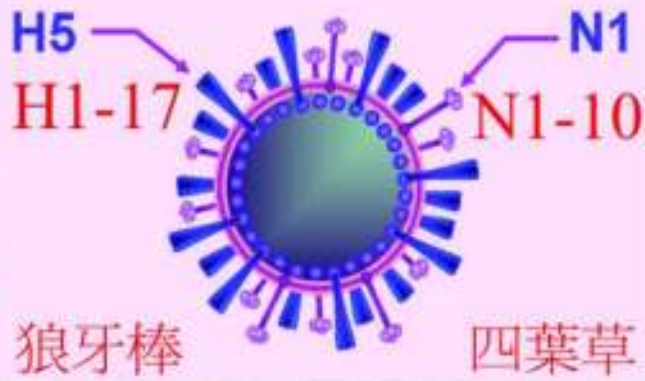
日日清

Weekly influenza virus A (H9N2) isolation rates for chickens (A) and minor poultry (B) in live poultry markets, Hong Kong, September 1999–May 2011. Vertical lines denote periods for different interventions: I, no rest day; II, 1 monthly rest day with quail sold in live poultry markets; III, 1 monthly rest day with no sales of quail in live poultry markets; IV, 2 monthly rest days; V, ban on keeping live poultry overnight in live poultry markets.

Leung, Y.H. et al. Avian influenza and ban on overnight poultry storage in live poultry markets, Hong Kong. *Emerg Infect Dis.* 2012 18, 1339-1341 (2012).

Virulence marker and pathogenic determinant	Pandemic virus				HPAI virus		Contemporary seasonal virus		LPAI virus
	1918 H1N1	1957 H2N2	1968 H3N2	2009 H1N1	H5N1	H7N7	H1N1	H3N2	H7N9
HA (binding and fusing with the host cell; antigenic determinant)									
Sialic acid linkage specificity	α -2,6 [*]	α -2,6 [†]	α -2,6 [‡]	α -2,6 and α -2,3 [§]	α -2,3	α -2,3	α -2,6	α -2,6	A-2,3
Residues involved in binding specificity¶	D190 and D225	Q226 and N186, or Q226 and S228	L226 and S228	D190 and D225 [§] ; K133 [#] , K145 [#] and K222 [#]	G143, T160, N186, Q196, Q226 and G228	Q226 ^{**}	D190 and D225	L226 ^{##} and S228	Q226L
Multibasic cleavage site	No	No	No	No	Yes	Yes	No	No	No
PB1-F2 (induction of apoptosis; promotion of secondary bacterial infection)									
S66 (associated with increased virulence), N66 or truncation	S66	N66	N66	Truncation	S66 or N66 ^{##}	N66	Truncation	N66	Unknown
PB2 (temperature-dependent replication competence)									
Adaptation to mammalian hosts	K627	K627	K627	R591	K627 or N701	K627 or N701	K627	K627	E627K/ D701N
NS1 (host antiviral response antagonist)									
PDZ domain-binding motif¶¶	KSEV	RSKV	RSKV	Truncated	ESEV or EPEV; ~3.3% of H5N1 isolates in 2003 were truncated	ESEV	RSEV	RSKV	truncated
CPSF30 binding	Yes	Yes ^{##}	Yes ^{##}	No	Yes ^{##}	Yes ^{***}	Yes	Yes	Unknown
E91 associated with virulence	No	No	No	No	Yes ⁺⁺⁺	No	No	No	Unknown
M2 (ion channel)									
Resistant to adamantanes (presence of N31)	No	No	No	Yes	Yes and no ^{§§§}	No	No	Yes	Yes
NA (receptor-destroying enzyme)									
Resistant to oseltamavir (presence of Y275 and S294)	No	No	No	No	No	No	Yes	No	5aa stalk deletion
CPSF30, cleavage and polyadenylation specificity factor 30 kDa subunit; HA, haemagglutinin; HPAI, highly pathogenic avian influenza; NA, neuraminidase; NS1, non-structural protein 1.									
*Some 1918 virus variants have differential receptor binding, allowing dual α -2,6-linked sialic acid (α -2,6-SA) and α -2,3-SA specificity (see main text for details).									

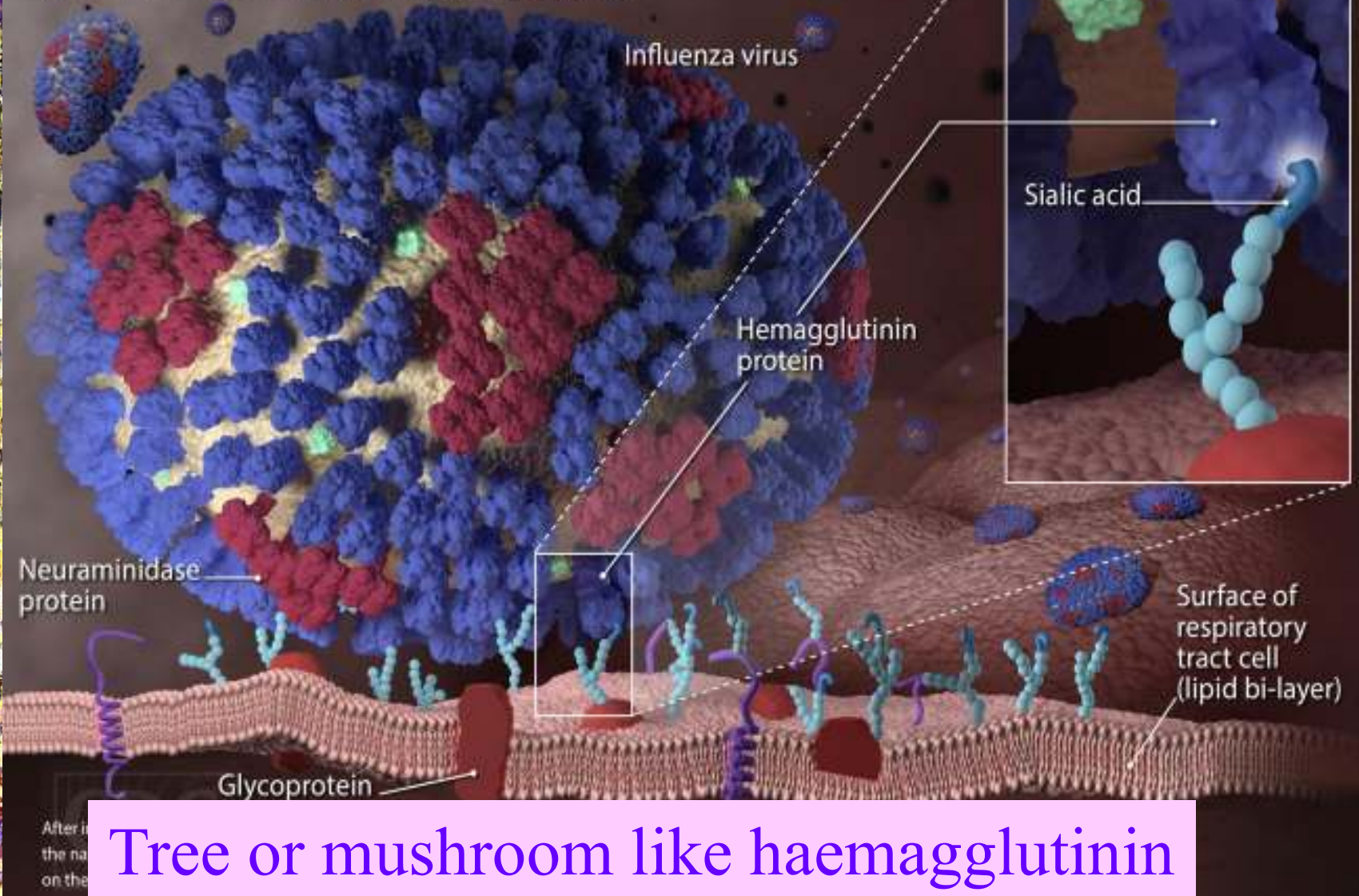
Image of Avian flu virus (H5N1)



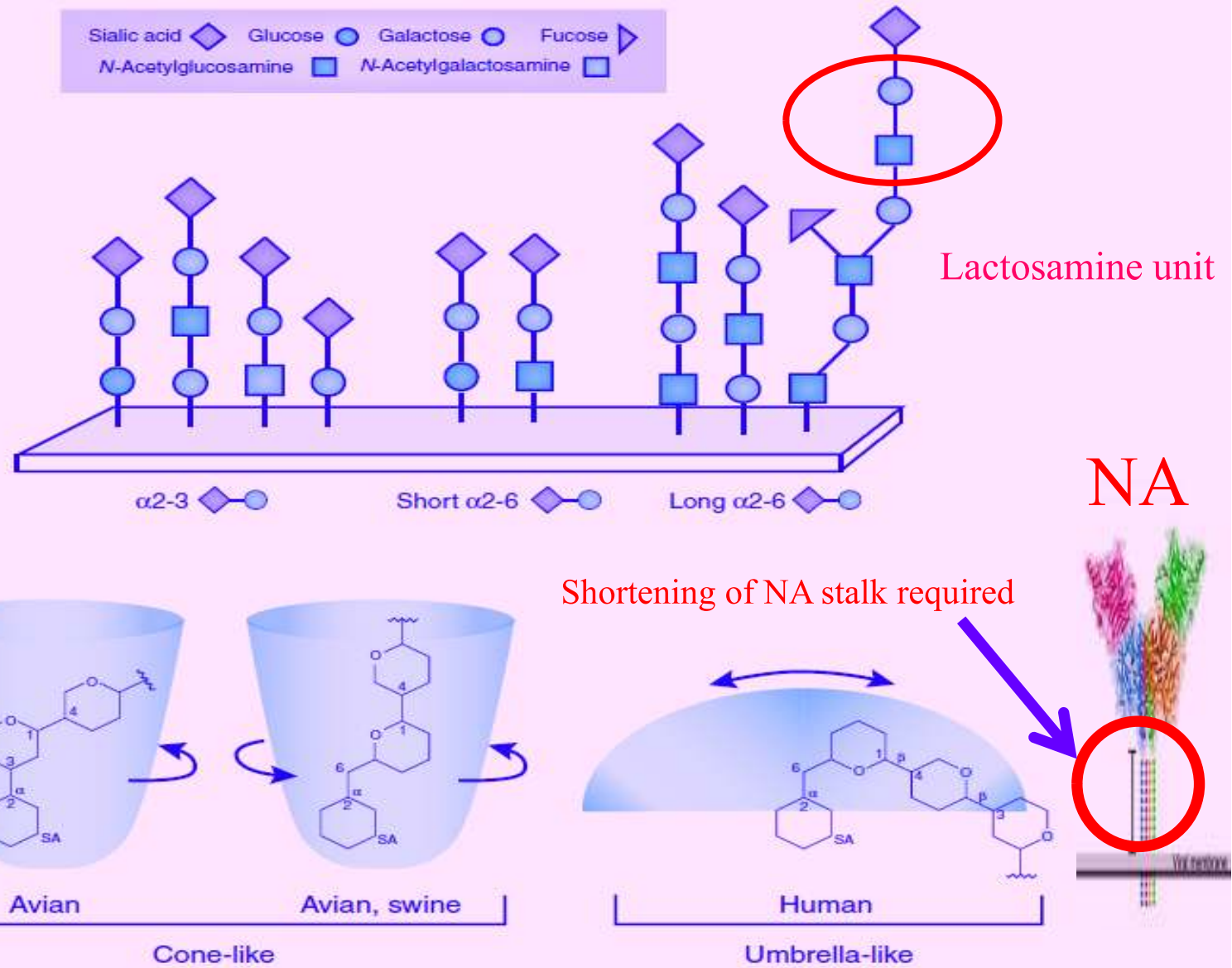
Haemagglutinin and Neuraminidase

Understanding Influenza (Flu) Infection:

An Influenza Virus Binds to a Respiratory Tract Cell



Umbrella-shaped HA of Seasonal Influenza

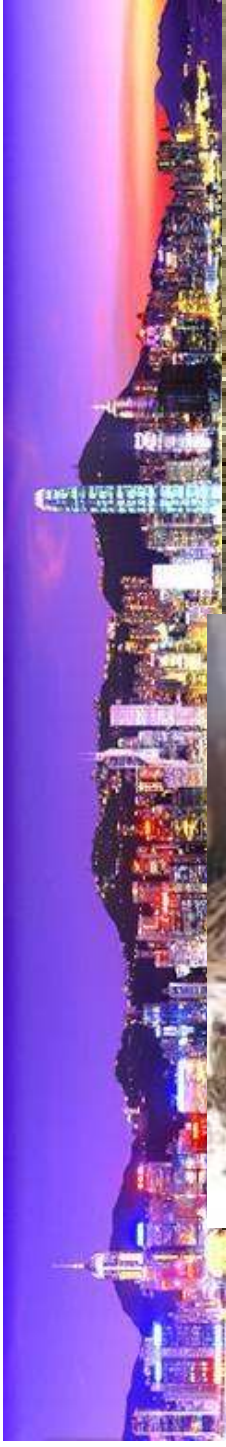


Bewley CA. Illuminating the switch in influenza viruses. *Nat Biotechnol.* 2008 Jan;26(1):60-2. doi: 10.1038/nbt0108-60.

INTERSPECIES TRANSMISSION OF INFLUENZA VIRUSES



Gln226→Leu and Gly228→Ser double *mutation*
(Q266L/G228S) is required for human adaptation



鸚鵡 Partridge



Quail 鸚鵡



火雞

These species have both SA- α 2,3-Gal (avian) and SA- α 2,6-Gal (human) receptor → H9N2, H7N2 and H7N7

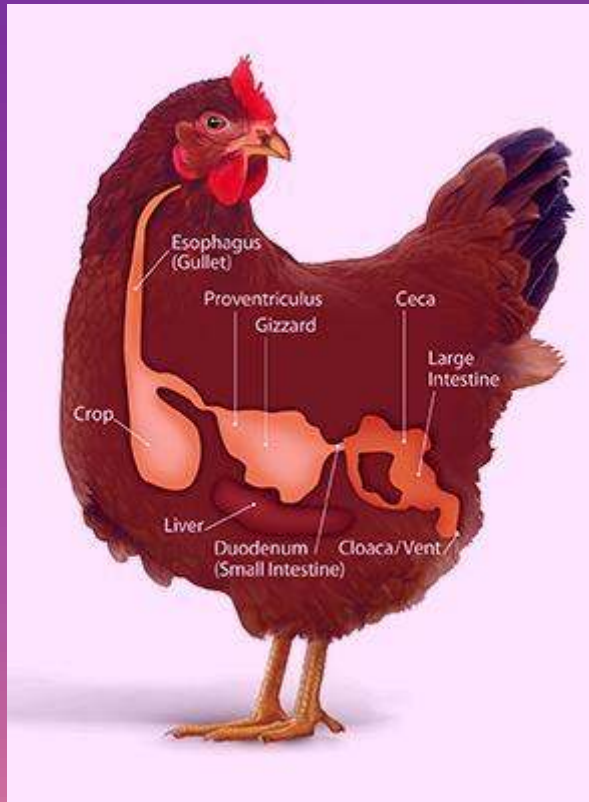
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Residues involved in binding specificity [¶]	D190 and D225	Q226 and N186, or Q226 and S228	L226 and S228	D190 and D225 [§] ; K133 [#] , K145 [#] and K222 [#]	G143, T160, N186, Q196, Q226 and G228	Q226 ^{**}	D190 and D225	L226 ^{##} and S228	Q226L
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*Some 1918 virus variants have differential receptor binding, allowing dual α -2,6-linked sialic acid (α -2,6-SA) and α -2,3-SA specificity (see main text for details)									

	Human (ZJ/DTID- ZJU01*)	Chicken (CK/ ZJ/DTID- ZJU01*)	Human (Shanghai/1†)	Human (Shanghai/2†)	Human (Anhui/1†)	Function
Haemagglutinin‡						
186	Val	Val	Gly	Val	Val	Gly186Val increases binding affinity for α -2,6-linked sialic acid receptor
226	Leu	Gln	Gln	Leu	Leu	Gln226Leu increases binding affinity for α -2,6-linked sialic acid receptor
Neuraminidase§						
292	Arg	Arg	Lys	Arg	Arg	Arg292Lys reduces susceptibility to oseltamivir and zanamivir
M2						
31	Asn	Asn	Asn	Asn	Asn	Ser31Asn causes resistance to adamantanes
PB2						
627	Glu	Glu	Lys	Lys	Lys	Glu627Lys results in mammalian host adaptation for viral RNA replication at 33°C
701	Asn	Asp	Asp	Asp	Asp	Asp701Asn enhances transmission in guinea pigs

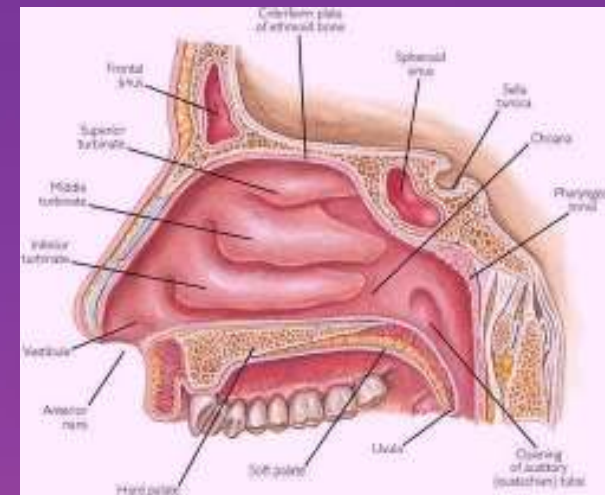
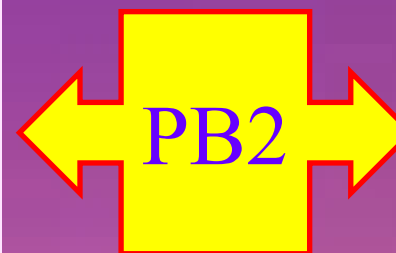
*Described in our study. †Described in another report.¹⁶ ‡H3 numbering. §N2 numbering.

PB2-E627K (Glutamic acid627Lysine) and PB2-D701N(Aspartic acid701Asparagine) mutants are **absents** in poultry (chicken, duck, quail, pigeon) isolated in the live poultry market !

聚合酶鹼性蛋白質 2 (Polymerase basic 2, *PB2*)



44° C



33° C

37° C

E627K

D701N

Mammals



PB2 627 amino acid composition for H5N1, H9N2, and H7N9 viruses.

Residue	Avian H5N1	Human H5N1	Avian/Human H9N2	Human H7N9
E	805	128	245	0
K	242	49	4	3
V	0	0	51	0
G	0	0	1	0
Total	1047	177	301	3
K Percentage	23.11%	27.68%	1.33%	100.00%

Chen GW, Lai MM, Wu SC, Chang SC, Huang LM, Shih SR. Is avian influenza A (H7N9) virus staggering its way to humans? J Formos Med Assoc. 2013 Jun;112(6):312-8. doi: 10.1016/j.jfma.2013.04.015.

青海湖鳥島



青海湖

2005 H5N1
PB2-627Lys
(E627K)
33°C and 37°C
H7N7 only
human death is
associated with
E627K mutant



Struthio asiaticus was an ostrich of the Pliocene and Pleistocene

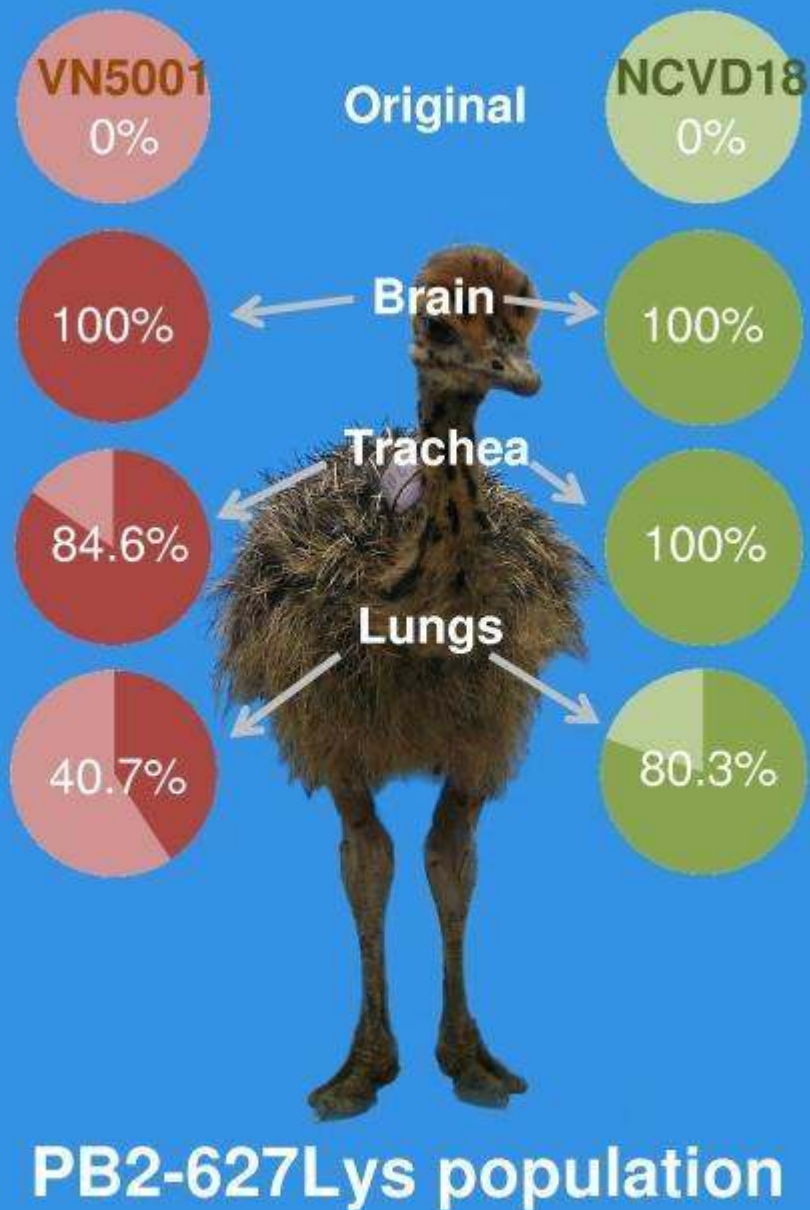
In China, ostriches are known to have become extinct only around or even after the end of the last ice age; images of ostriches have been found there on prehistoric pottery and as petroglyphs indicating that they were around at the same time as humans first reached China.

Number of avian virus isolates encoding mammalian-type amino acids at positions 627 and 701 in PB2 in the Influenza Virus Resource database^a

Avian species	No. of viruses possessing:		Total no. of viruses
	PB2-627Lys	PB2-701Asn	
Duck	1	1	375
Chicken	2	0	426
<i>Ratitae</i>			
Ostrich	2	0	6
Emu	2	1	4
Rhea	1	0	2

^a Numbers of viruses isolated prior to 2005 from duck, chicken, and three *Ratitae* species (ostrich, emu, and rhea) are shown.

Shinya, K. et al. Ostrich involvement in the selection of H5N1 influenza virus possessing mammalian-type amino acids in the PB2 protein. J Virol. 83, 13015-8 (2009).



PB2, 627Lys and 701Asn mutation in human H5N1 infection

(1) 701Asn mutation + in patient
(Lancet Yu Chen 25/4/13)

(2) 627Lys(K) mutation 3/3 patients
(NEJM Gao 11/4/2013)

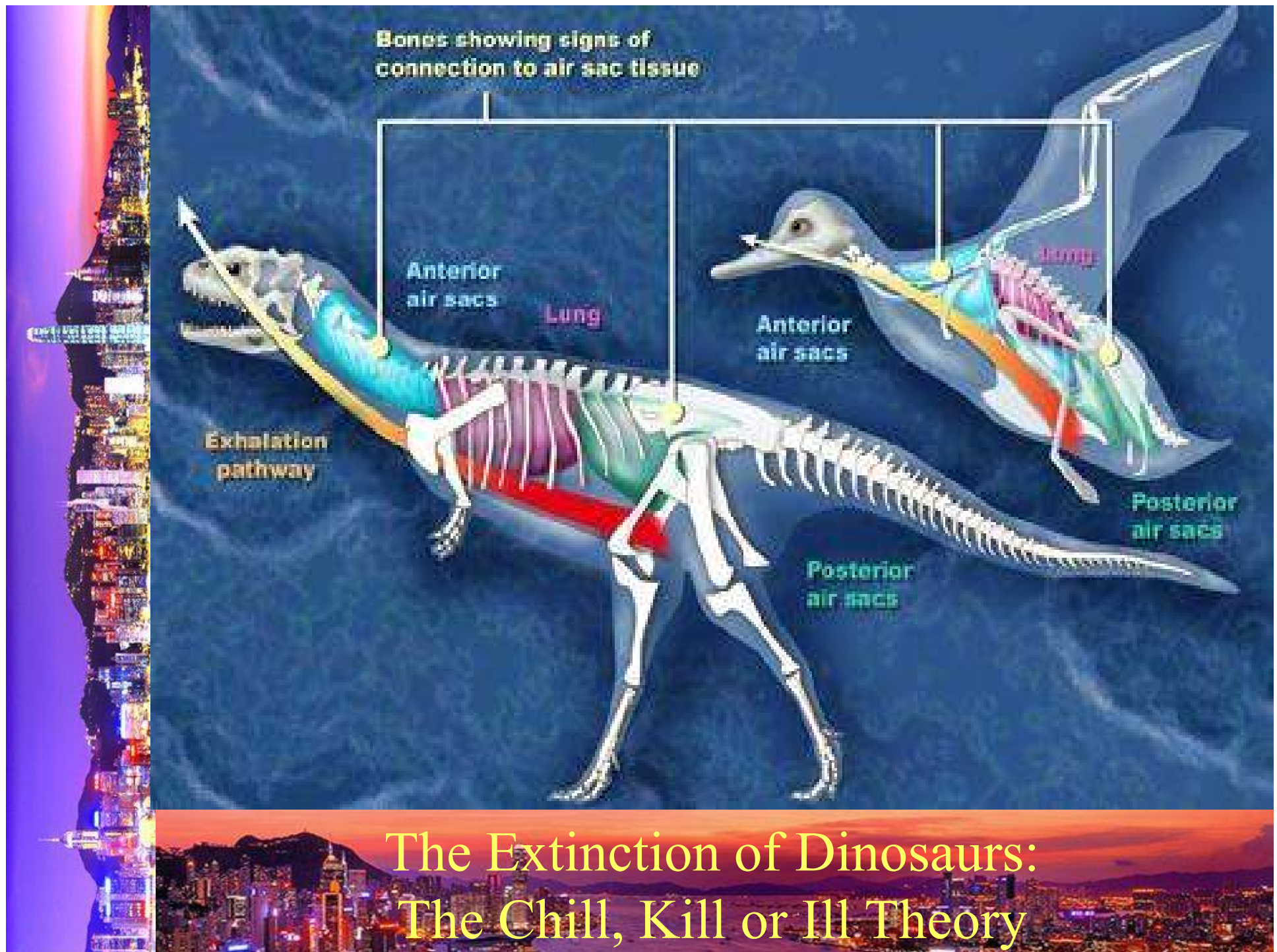
→ Simultaneous 627Lys and 701Asn mutation may allow efficient transmission among humans

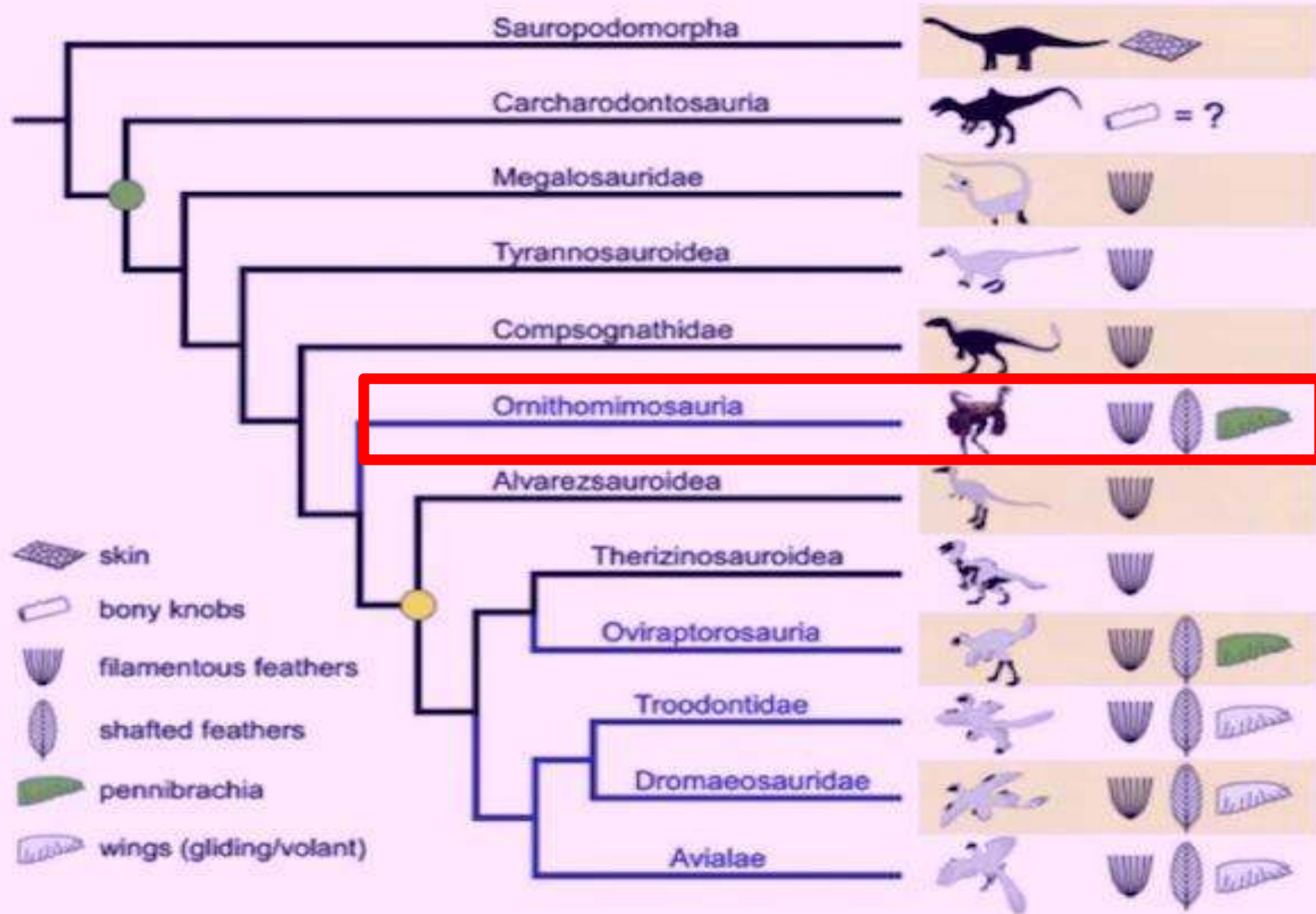
Infection of Ostrich by H5N1 can lead to the selection of these mutants.

China start ostrich farming since 1992 and becomes the largest ostrich raiser in Asia in 2004 and now ranks the fifth ostrich raiser in the world

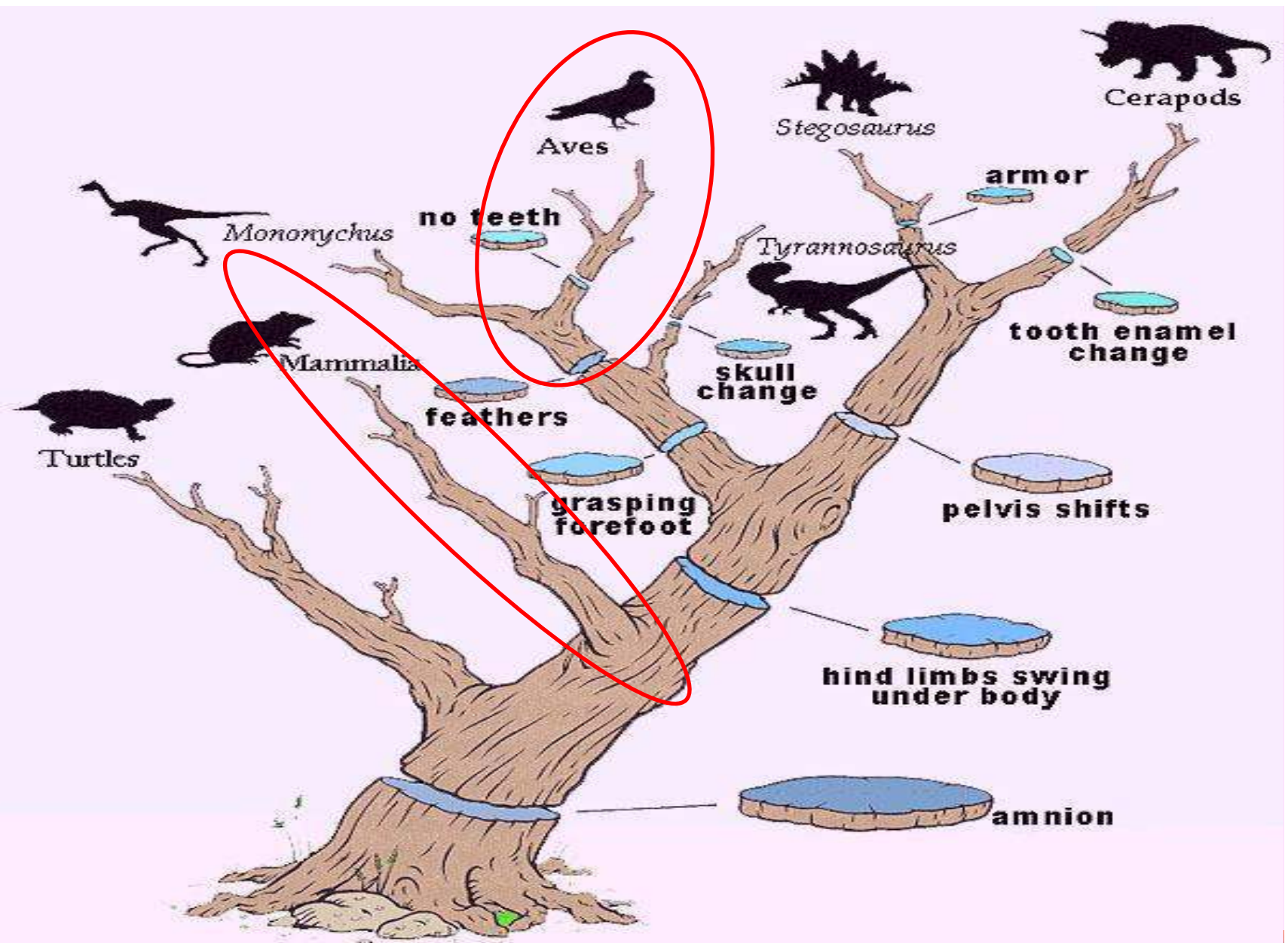
South Africa ostrich flock drop from a million ↓ to 250 000 due to outbreak of H5N2 in 2012 and H7N1 in 2013.

Shinya, K. et al. Ostrich involvement in the selection of H5N1 influenza virus possessing mammalian-type amino acids in the PB2 protein. J Virol. 83, 13015-8 (2009).





This phylogenetic tree represents the evolutionary view of dinosaur-to-bird evolution. Ornithomimids (貌似鸵鸟的「似鸟龙」) is between dinosaurs and birds and have filaments, feathers, and wings.



The Tree of Life

Avian Genetics – Gender Determination

Mammals
(e.g. man)

Male = XY
Female = XX

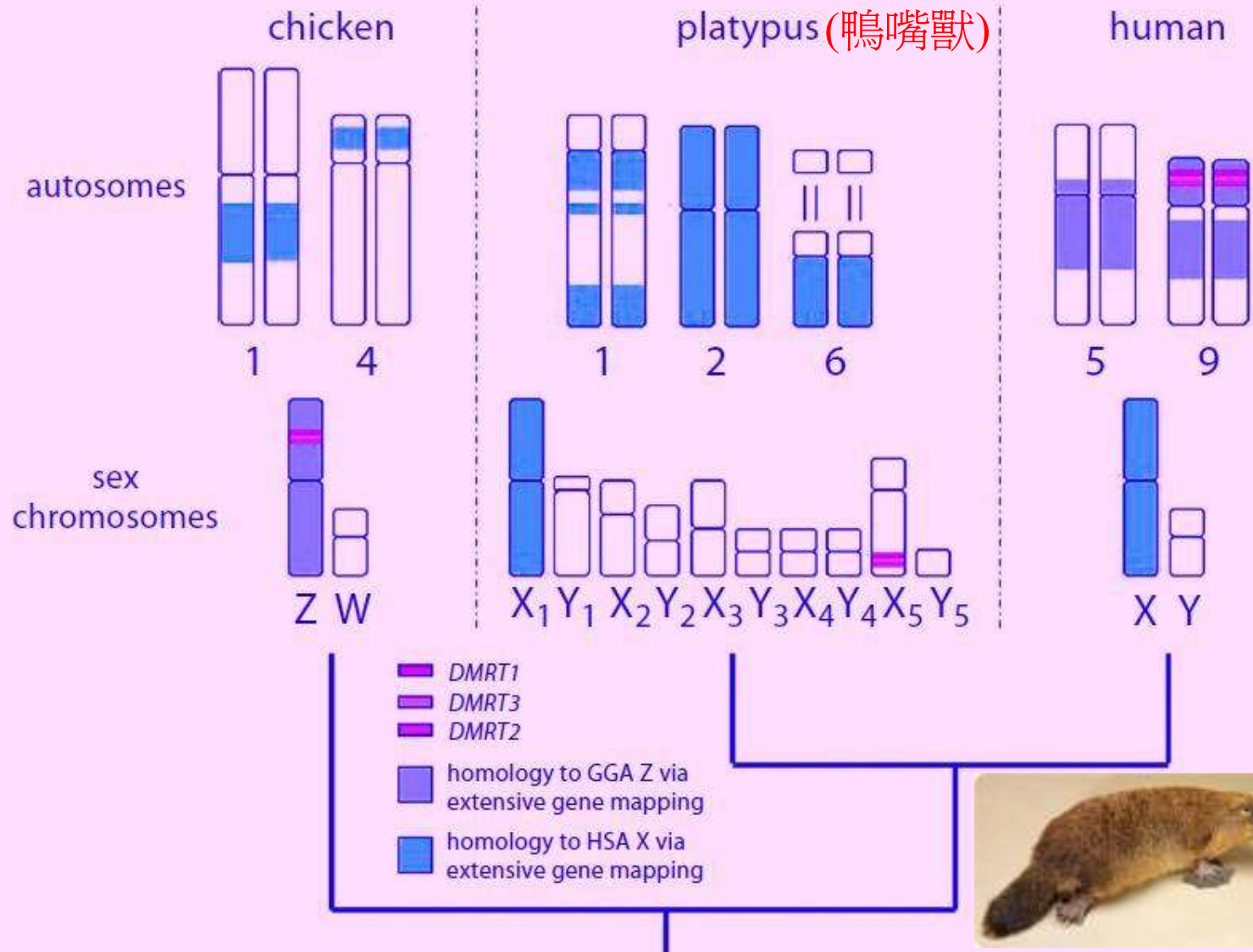
Male determine the sex of
offspring

Birds
(all poultry)

Male = ZZ
Female = ZW

Female determine the sex of
offspring

Human have an X and Y sex-determining chromosomes while birds has Z W sex-determining chromosomes. In contrast to humans, it is the female bird and not the male bird that has the two different types of sex chromosomes.

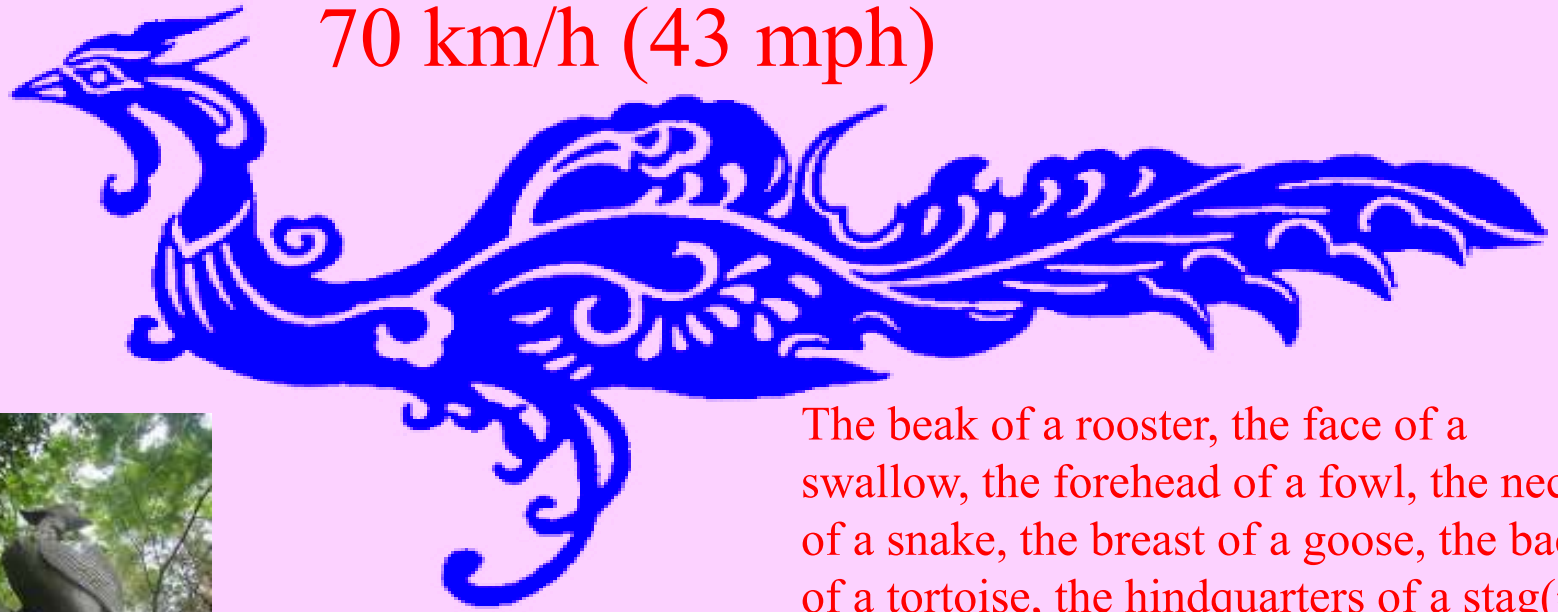


Stiglec, R. et al. A new look at the evolution of avian sex chromosomes. Cytogenet Genome Res. 117, 103-9 (2007).

Xinjiang Province *Struthio asiaticus*

在甲骨文中，鳳與風爲同字。

70 km/h (43 mph)



The beak of a rooster, the face of a swallow, the forehead of a fowl, the neck of a snake, the breast of a goose, the back of a tortoise, the hindquarters of a stag(牡鹿) and the tail of a fish.

Arabian Ostrich(-1966)



據《爾雅·釋鳥》郭璞注，鳳凰特徵是：「雞頭、燕頤、蛇頸、龜背、魚尾、五彩色，高六尺許」。

Was the Chinese Phoenix (鳳凰) actually an Ostrich?

H7N3



Shanghai City and
Anhui Province



PB2-627Lys

H9N2 (chicken)
NS Jiangsu
NP,PA,PB1,PB2,M
Shanghai



H10N9
chicken in
Jiangsu



Zhejiang



PB2-701Asn

H7N9
(NS, NP, PA,
PB1,PB2,M)



HA Q226L



Ostrich



Emu



LPAIV

H7N9
(NS, NP, PA,
PB1, PB2, M)

HPAIV

HA Arg/Lys



Chicken, common quail, red-
legged partridge, turkey, and
golden pheasant

(SA- α 2,6-Gal) + (SA- α 2,3-Gal)

Live Poultry
Market of
China



HA Q226L



Emu



Ostrich

PB2₆₂₇Lys/701 Asn

H7N9疑人傳人 廣州豆腐檔父女同中招

【本報訊】本地正值流感高峰期，再有兒童嚴重流感個案出現。一名健康一向良好的4歲女童，確診感染甲型H1N1流感，現時情況嚴重，在伊利沙伯醫院兒童深切治療部留醫，臨床診斷為肺炎，病童居住九龍城區，在何區就讀幼稚園，學校未有爆發流感；按近期亦未有接種流感疫苗。

港女童確診甲型H1 流感

衛生防護中心表示，患病女童以往健康良好，於15日起出現發燒和咳嗽。

17日被送入聖德肋撒醫院，翌日再轉送伊利沙伯醫院。

經化驗後證實女童的呼吸道樣本制H1N1病毒呈陽性反應，初步調查指她近日並無外遊，其家人亦無出現病徵。中心提醒市民要保持個人衛生等，以預防呼吸道感染。

此外，內地人感染H7N9禽流感疫情繼續肆虐。浙江連城第十一日有新增個案，昨新增的3宗病例，患者均為男性，年齡由53至61歲，兩人為杭州人，另一人是紹興人。當中一人危殆，

兩人嚴重，正在醫院接受治療。浙江省今年來確診個案增至23宗。

廣東省前日確診的83歲女病人陳波晨病逝，該名楊姓婆婆住在廣州荔灣區。她於本月2日發病，8日到醫院求診，延至昨日凌晨4時許，因呼吸系統衰竭不治，死者病發前曾多次前往菜市場；廣東感染H7N9死亡個案增至3宗。

至於前日廣州通報，居住於廣州市白雲區的5歲潘姓病童，其父為廣州首名確診H7N9病人，在天河區龍崗路沙東

市場經營豆腐檔，目前仍然留院。女童母親蘇女士表示，女兒曾跟隨父母前往菜市場，13日開始出現初步症狀，15日發現她發燒及咳嗽，繼而被轉送到醫院治療及確診。廣州市相關機構人員透露，女童病情較輕，實驗室檢驗結果已轉為陰性，相信可盡快出院。

內地專家指，父女接連感染H7N9，但是否人傳人仍難以確定，因為女童曾到訪菜市場，感染途徑是有限度人傳人或是否直接市場感染，流行病學上尚難以分辨。



蘇女士

20/1/14

人傳人 恐慌

上海醫生染H7N9亡

醫院隔離搶救者 下封口令派「解毒

21/1/14

浙三口家確診 掀人傳人疑

29/1/14



The Perspective of H5N1/H7N9 Avian Influenza Pandemic

- ④ In the event of a human H7N9/H5N1 avian influenza pandemic that carries a mortality of over 30%, more than 85% of the world's population will not have meaningful access to pandemic vaccines or antiviral agents.
 - ④ From the experience of the novel H1N1 pandemic, pandemic vaccines are unlikely to be available for effective prevention during the first wave of a pandemic , and non-pharmaceutical interventions such as quarantine and containment failed to contain the pandemic in the initial mitigation phase even in developed countries.
 - ④ The number of casualty will overwhelm the medical system and other essential medications and supportive equipment (e.g. ECMO accessories) may not be available during pandemic.
- 



Our Preparedness and Response Plan for Avian Influenza Pandemic Are Too Hospital Focused

Our public antiviral and vaccine stockpile program has no effective delivery program to the public!

Tamiflu®
Oseltamivir
75 mg

*Logistics Aspects of H5N1/H7N9
Avian Influenza Pandemic in Hong Kong*

The Perspective of H5N1/H7N9 Avian Influenza Pandemic



Unless we can achieve **successful home therapy** of H7N9/H5N1 infection, human society cannot survive this pandemic.



*“And I looked, and behold a pale horse:
and his name that sat on him was Death,
and Hell followed with him.”*

Revelation 6:8



And power was given unto them over the fourth part of the earth, to kill with **sword**, and with **hunger**, and with **death**, and with the **beasts** of the earth.



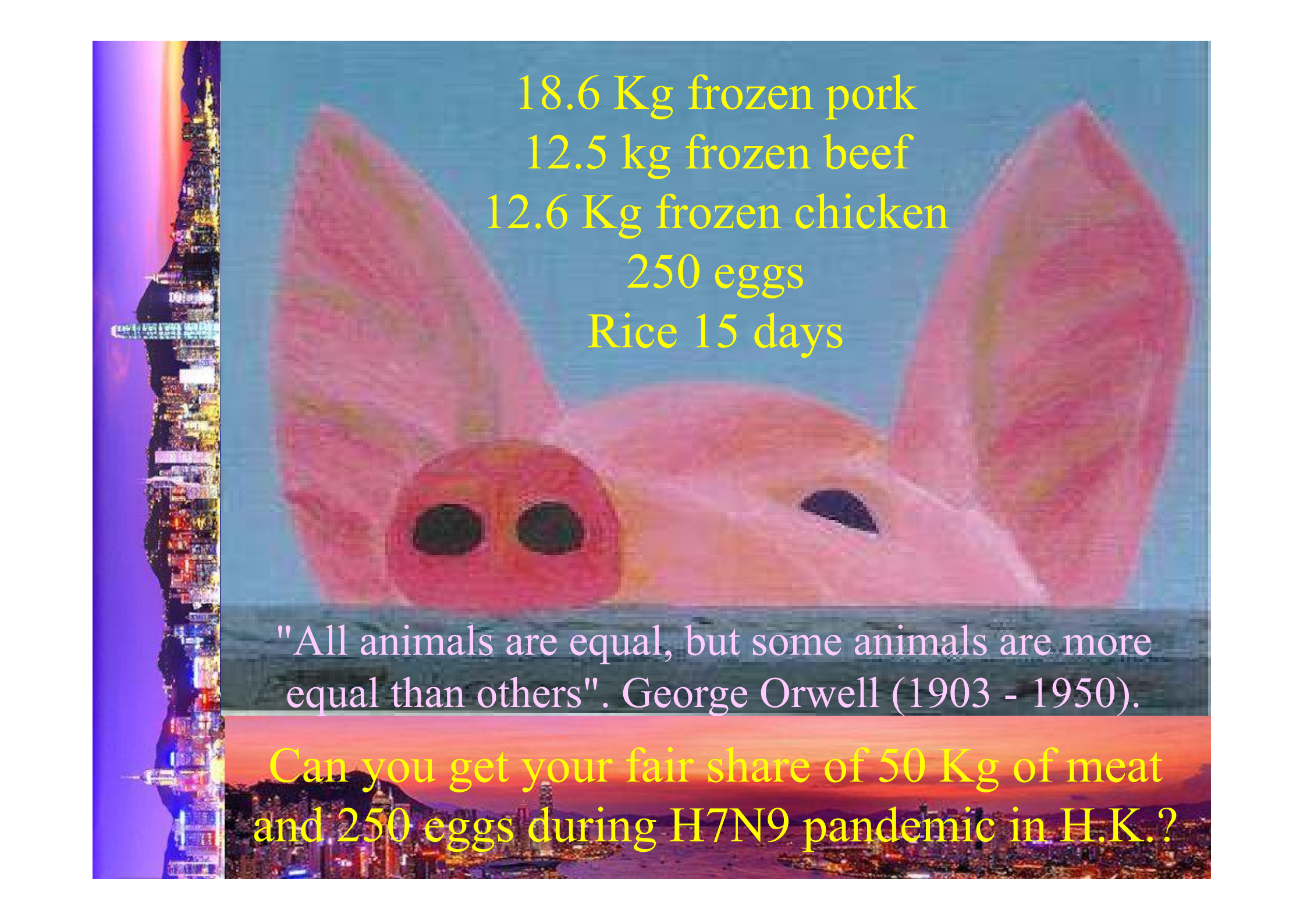
*Our survival is
dependent on
each other.*

Human H7N9 Pandemic

**We May Be Facing A Total Disintegration of
Global Economy and Collapse of Civilization**

*Without the string,
the necklace will
fall apart.*



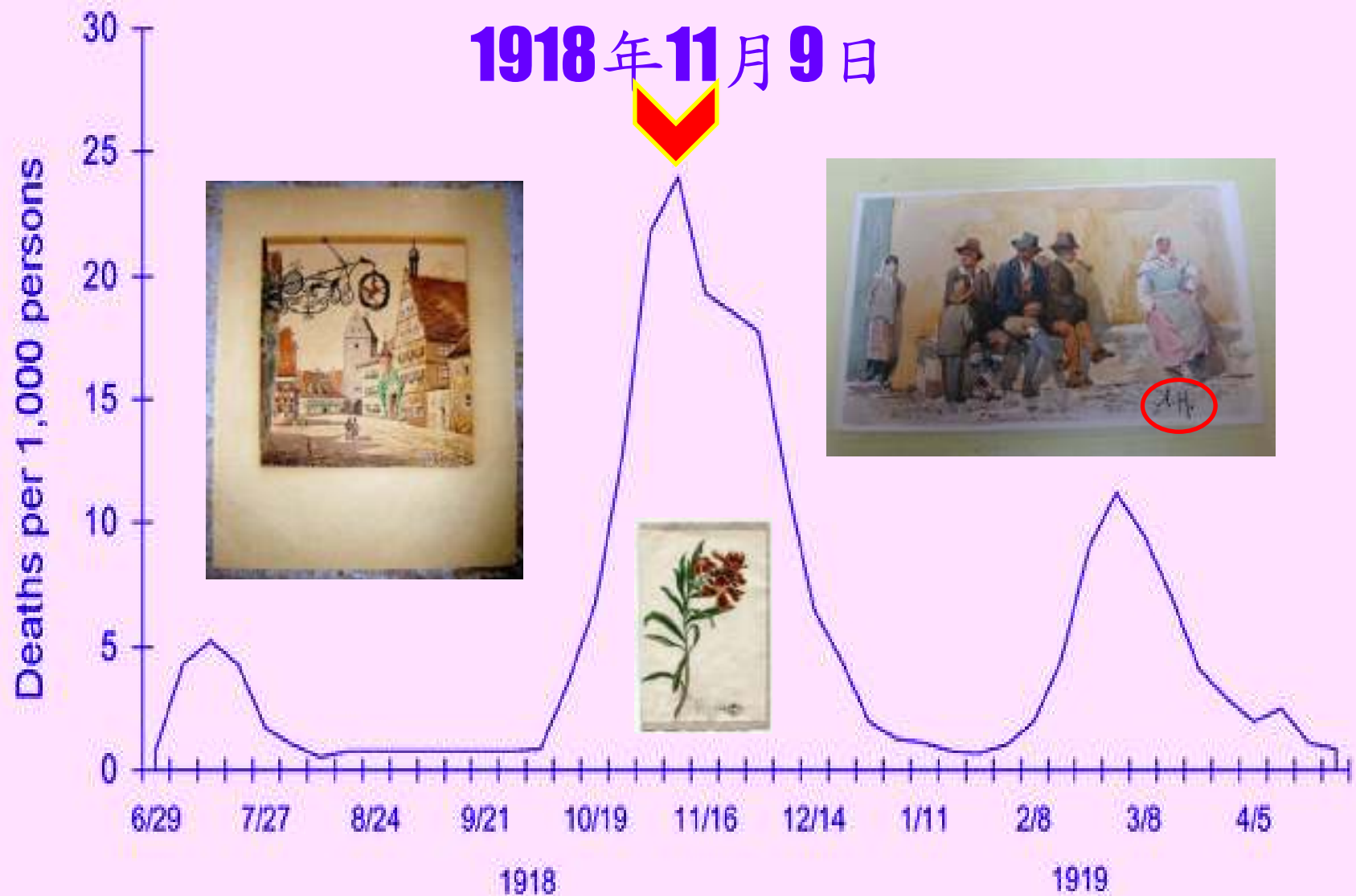


18.6 Kg frozen pork
12.5 kg frozen beef
12.6 Kg frozen chicken
250 eggs
Rice 15 days

"All animals are equal, but some animals are more equal than others". George Orwell (1903 - 1950).

Can you get your fair share of 50 Kg of meat and 250 eggs during H7N9 pandemic in H.K.?

1918年11月9日

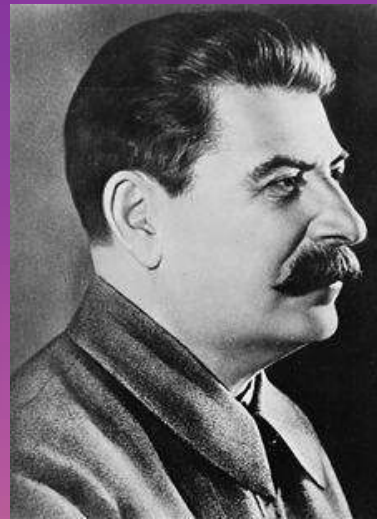


This day marks the end of the first German empire and first world war.
1918年11月9日年輕的“小素描畫家和水彩畫家”靠藝術吃飯的夢想幻滅。

天心莫測，劫隨心轉。

Encephalitis Lethargica
Neuropsychiatric manifestations
?Emotional Lability

Joseph Stalin



Adolf Hitler



Violent and aggressive behaviour and
gesticulation of Hitler may have been due,
at least partly to Encephalitis Lethargica !

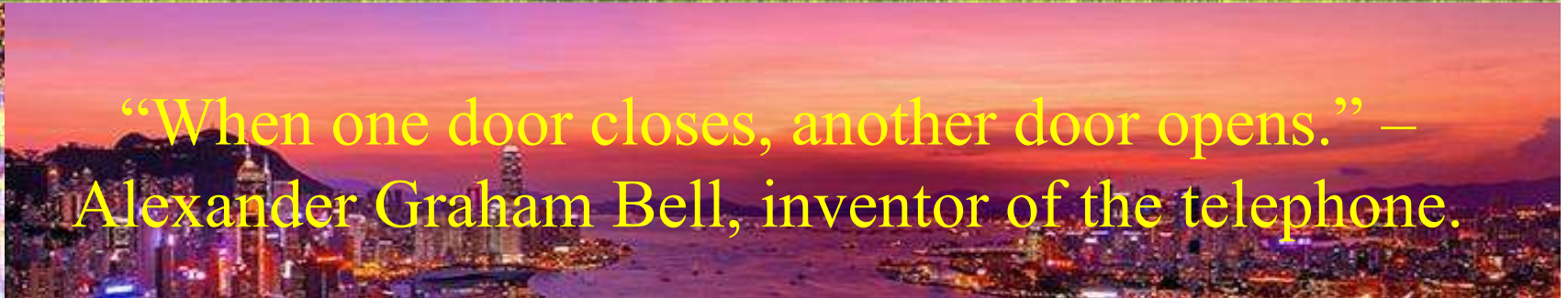
Lancet Editorial. Anon. 1981; ii : 1396–1397.

Was encephalitis lethargica a post-influenzal or some other phenomenon? Time to re-examine the
problem P. P. MORTIMER^{a1} Health Protection Agency Centre for Infections, London, UK



Revelation 3:8

Behold, I have set before
you an open door, which
no one is able to shut.

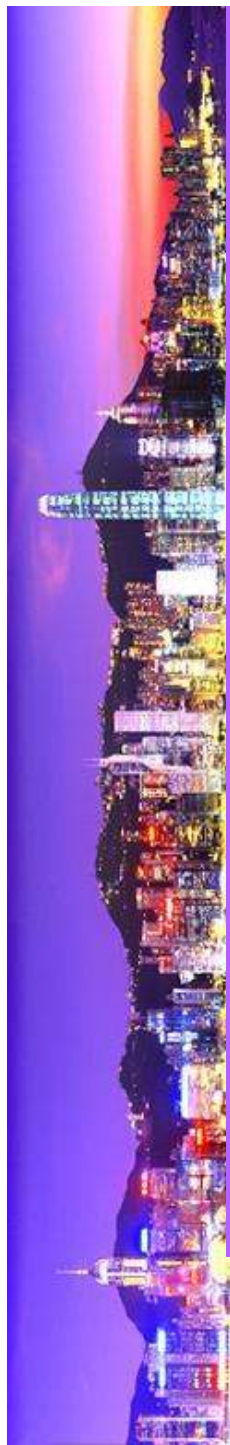


“When one door closes, another door opens.” —
Alexander Graham Bell, inventor of the telephone.

"When one door of happiness closes, another opens, but often we look so long at the closed door that we do not see the one that has been opened for us."



-Helen Keller



一心法界，無盡緣起。

NS

(非結構性蛋白)

M

(子通道蛋白)

NP

(核蛋白質)

dsRNA
雙股RNA

(雙鏈感應把關受體)

TLR3

PB2

(聚合酶鹼
性蛋白質)

(神經氨酸)

NA

(聚合酶鹼
性蛋白)

PB1

(聚合酶酸性蛋白)

PA

ER-
overload

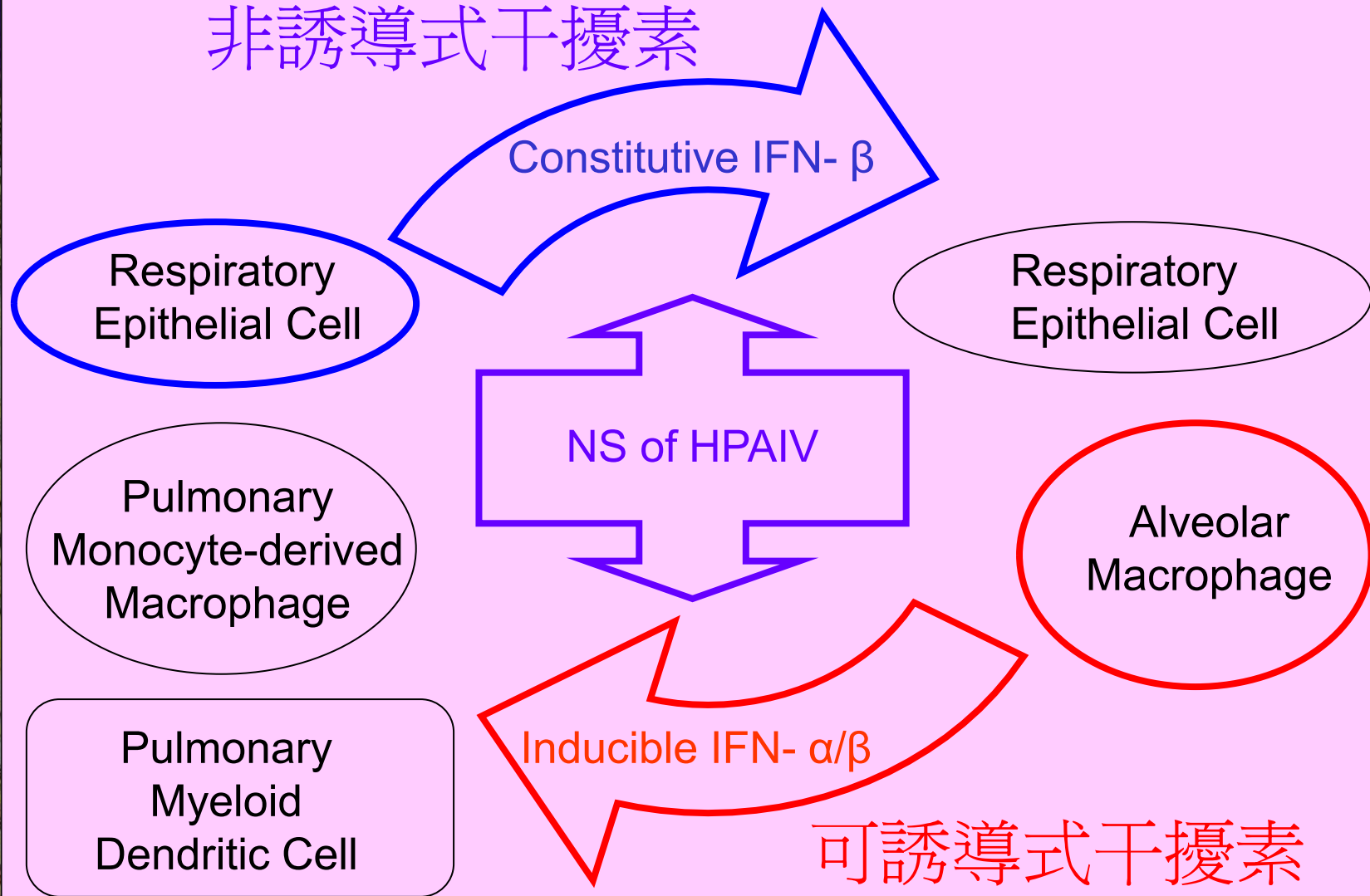
(血凝素)

HA

ROS

(活性含氧物種)

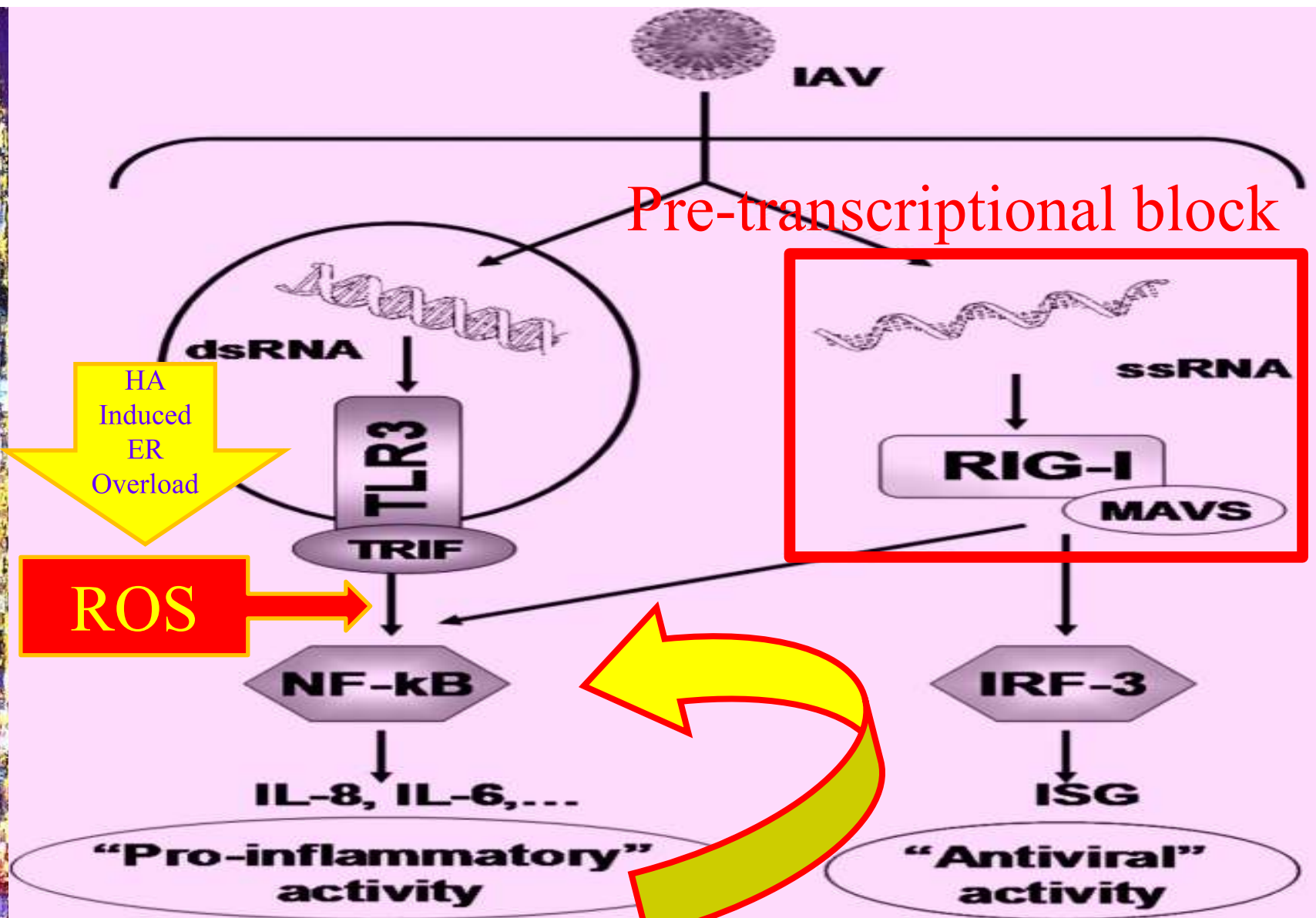
非誘導式干擾素



可誘導式干擾素

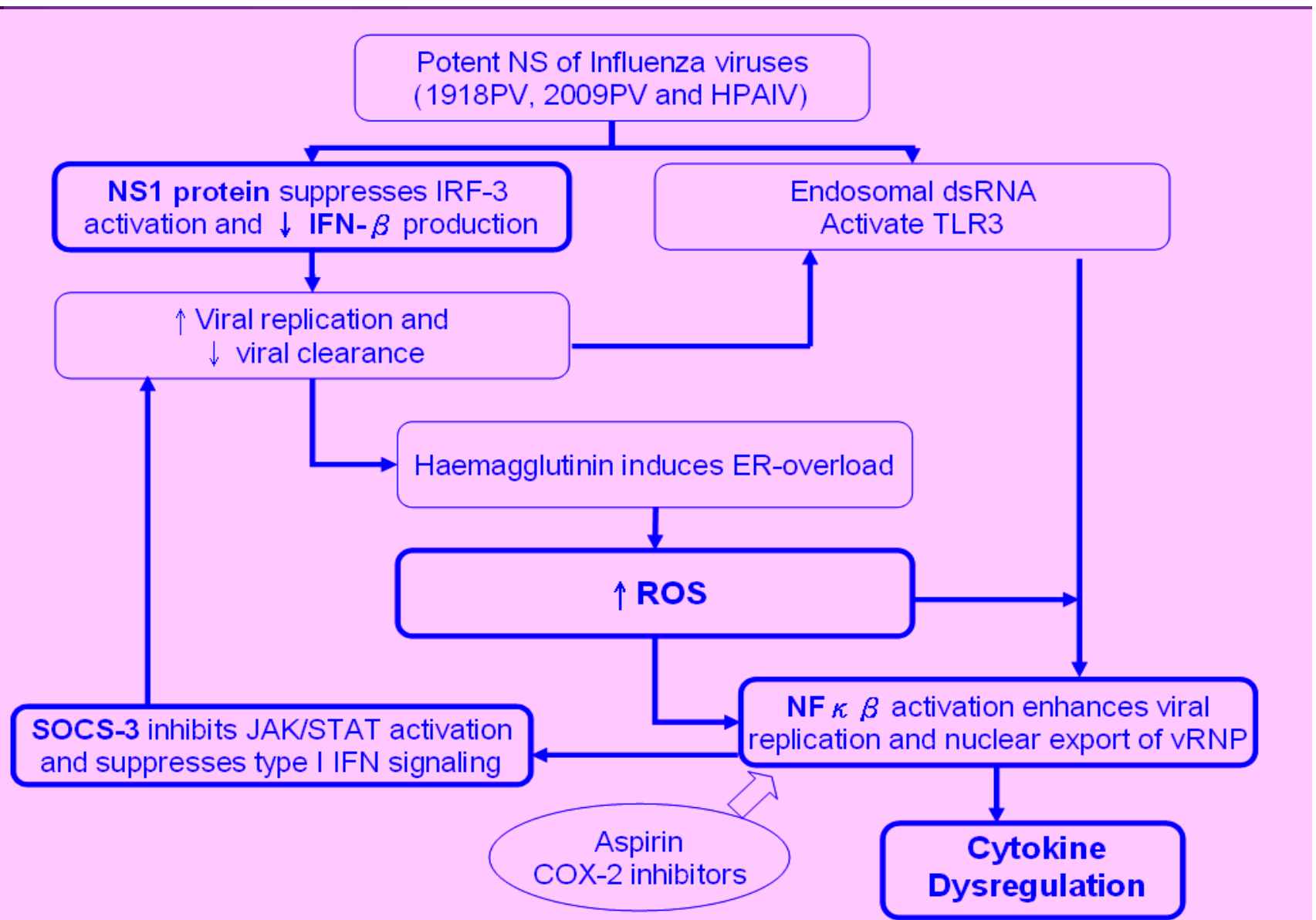
All Influenza Virus Is Susceptible to Interferon.
Interferon Is Useful In Preventing Influenza Infection In Uninfected Cells

Constitutive and Inducible IFN- β

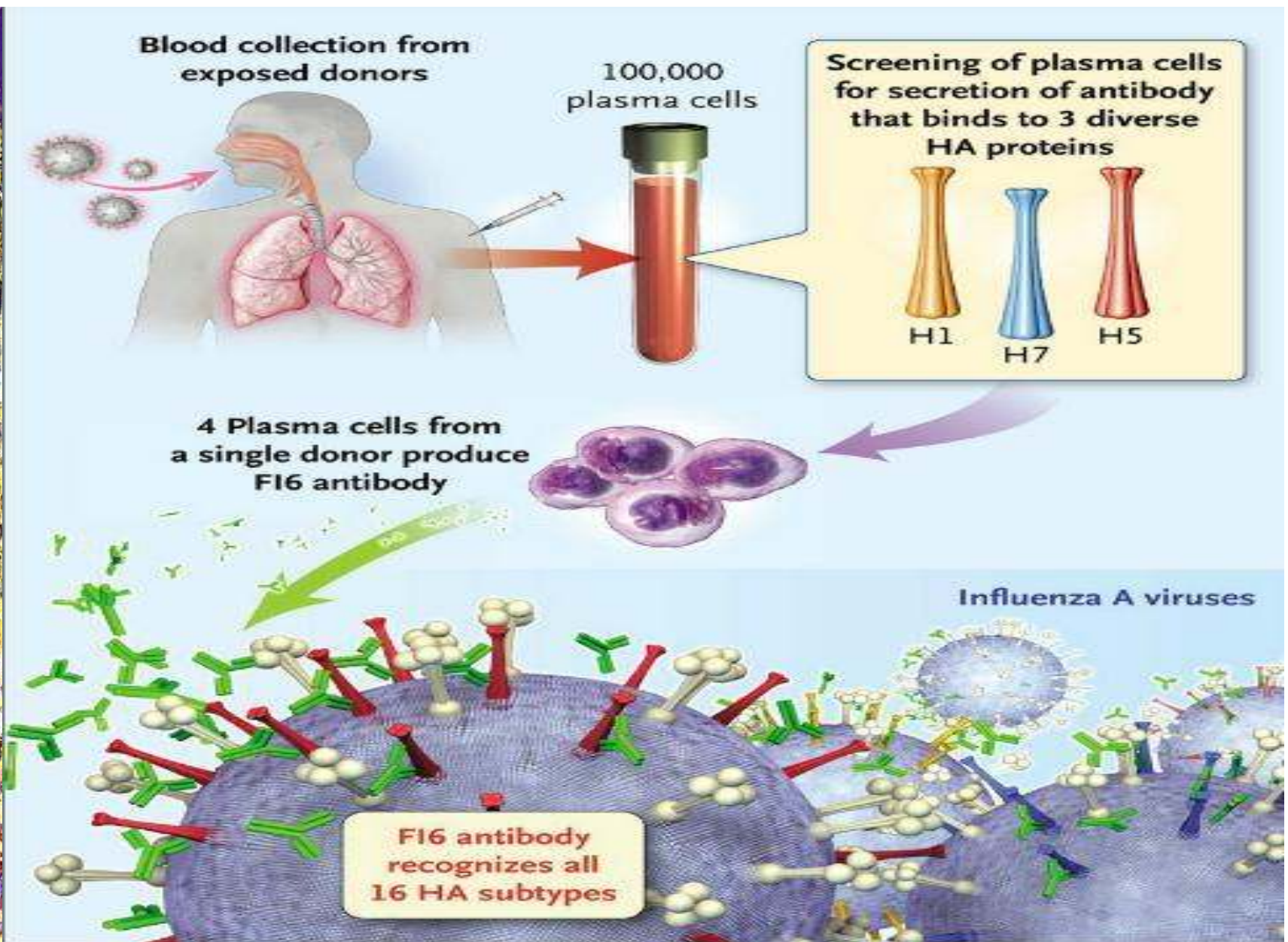


➤ Cytokine storm can be blocked without affecting anti-viral activity.

Cutting Edge: Influenza A Virus Activates TLR3-Dependent Inflammatory and RIG-I-Dependent Antiviral Responses in Human Lung Epithelial Cells
Ronan Le Goffic *The Journal of Immunology*, 2007, 178: 3368-3372.



NFκB activation Is A Pre-requisite of Influenza Infection and Cytokine Dysregulation



Russell CJ. Stalking influenza diversity with a universal antibody.
N Engl J Med. 2011 Oct 20;365(16):1541-2.

CDC

Patient Safety

CLEAN HANDS SAVE LIVES

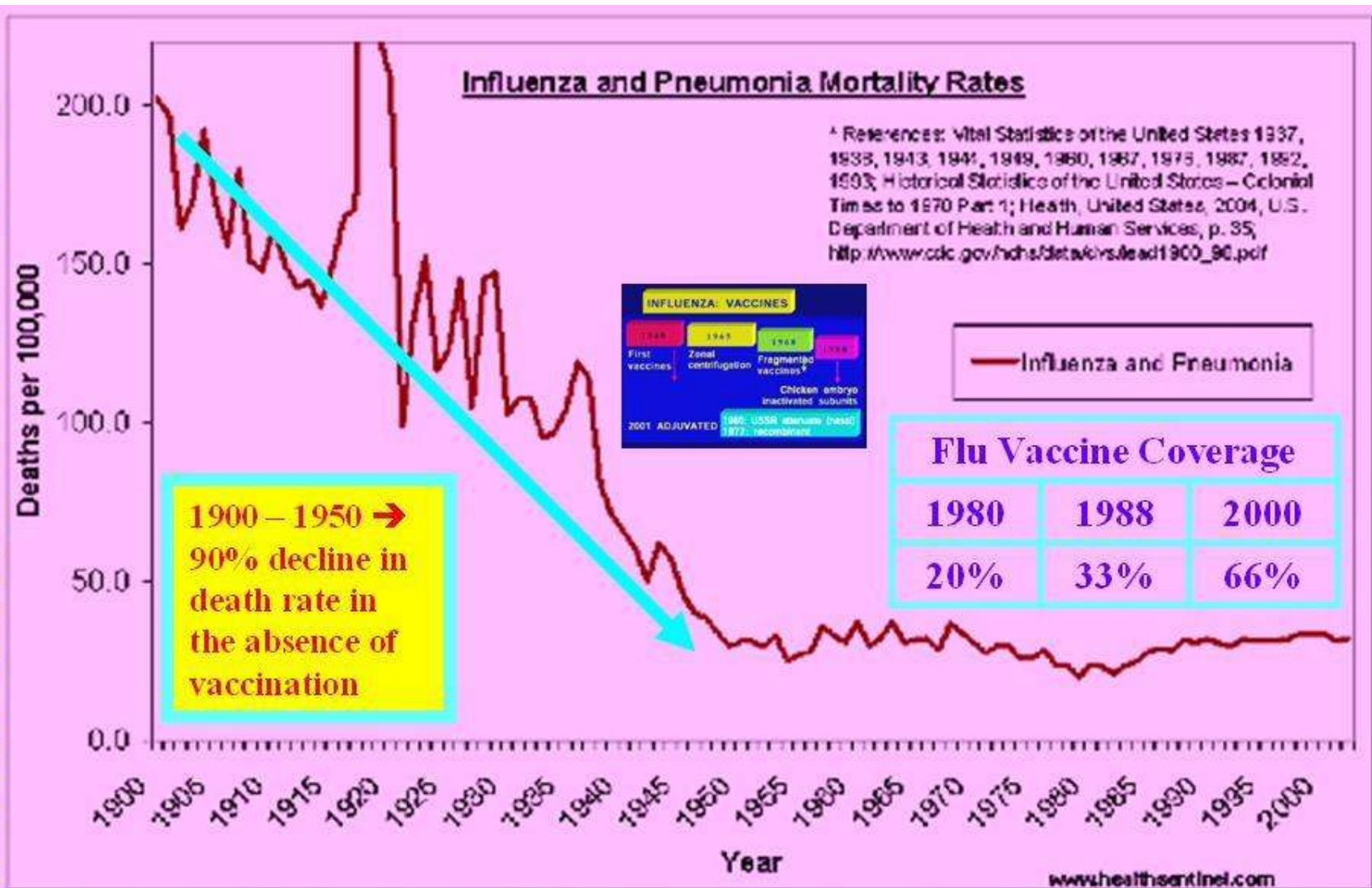
Protect patients, protect yourself



Alcohol-rub or wash
before and after *EVERY* contact.



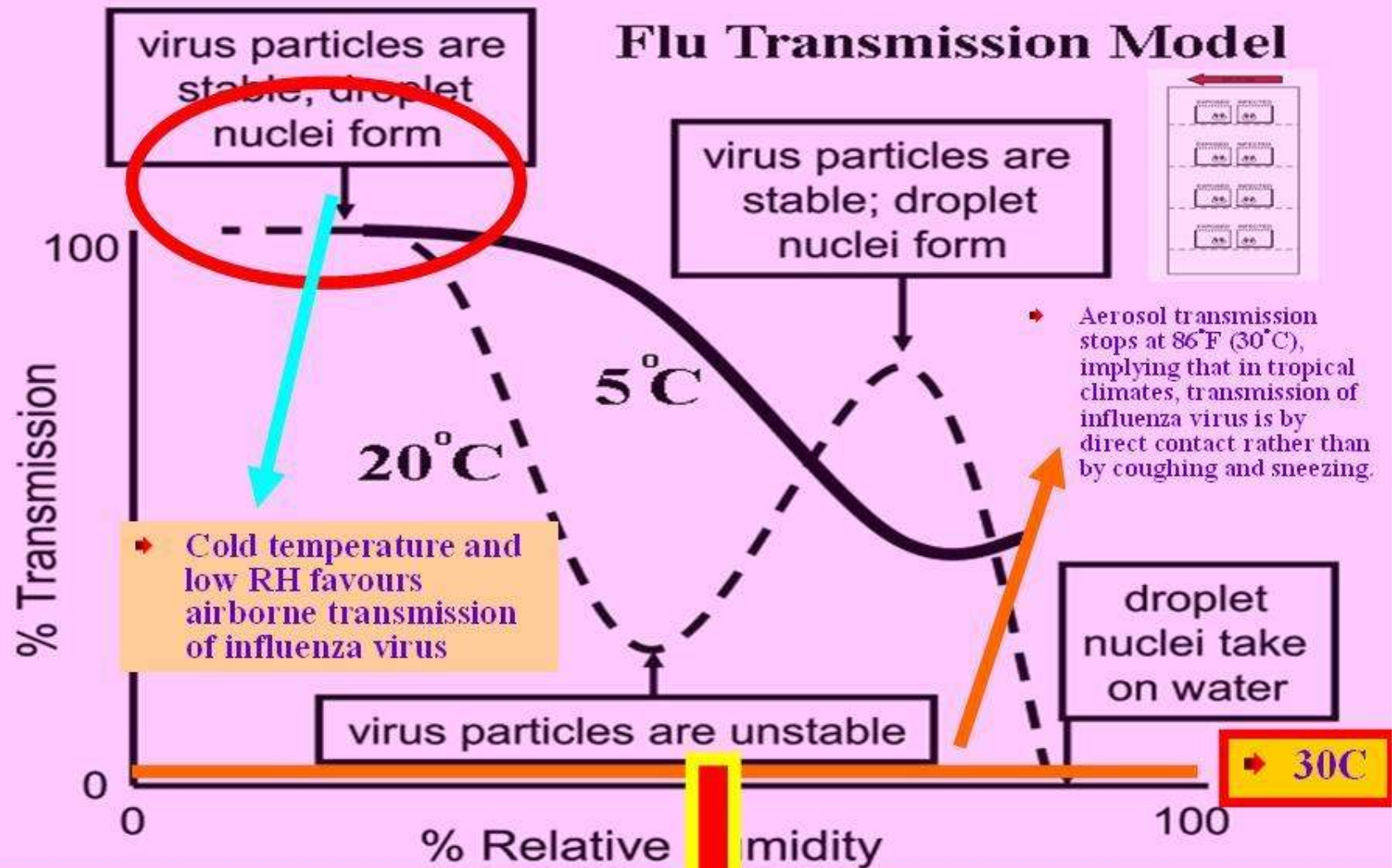
Clean Hand Habit Save Our Lives
During H7N9 Pandemic!!



**Major reduction in flu deaths depends on
sanitation, nutrition and basic healthcare**

Last But Most Important of ALL

Flu Transmission Model



- Lowen, A. C., S. Mubareka, J. Steel, and P. Palese, 2007, "Influenza Virus Transmission Is Highly Dependent on Relative Humidity and Temperature", PLoS Pathogens, October 2009, "High Temperature (30°C) Blocks Aerosol but Not Contact Transmission of Influenza Virus", Journal of Virology, June 2008, p. 5650-5652, Vol. 82,



Influenza virus transmission indoors could potentially be curtailed by simply maintaining room air at warm temperatures (>20 °C) and either intermediate (50%) or high (80%) RHs".

- In temperate region influenza spread by aerosols (dry and cool winter)



- In tropical region influenza spread by contact or formites

- Predominant mode of influenza virus spread differs between temperate and tropical regions: aerosol transmission plays a major role in temperate climates, while contact or close-range spread are more important in the tropics.
- Transmission by the aerosol route is sensitive to RH and temperature, contributing to increased influenza virus activity during the winter months in temperate zones; conversely, transmission by the contact route is insensitive to RH and temperature, with the result that influenza in the tropics may occur throughout the year or in sporadic outbreaks with no clearly defined seasonality.



An easily overlook source of formite transmission

When nasopharyngeal secretions of naturally infected children were used, influenza virus survived for at least 48 h in one-third of the cases. **Large inoculum in the presence of respiratory mucus can survive up to 17 days.** The unexpected stability of influenza virus in this nonbiological environment suggests that unusual environmental contamination should be considered in the setting of pandemic preparedness.

Journal of Virology, 2000, 74(10):2400-2404. DOI: 10.1128/JVI.74.10.2400-2404.2000

fight the flu



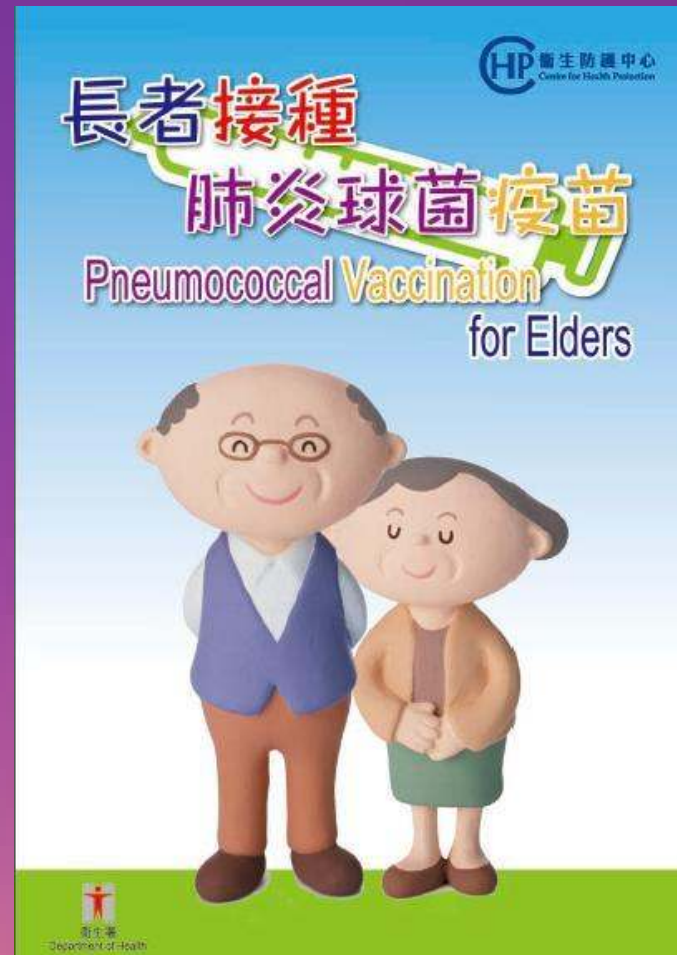
use soap and water for 15-20 seconds

wash your hands



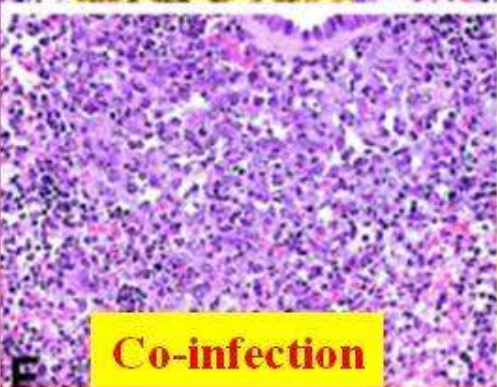
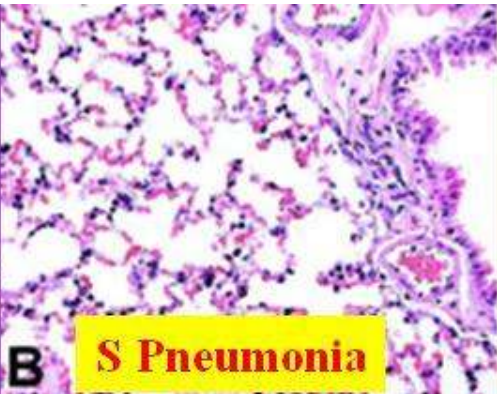
Hong Kong Childhood Immunisation Programme

AGE	Immunisation RECOMMENDED
Newborn	B.C.G. Vaccine Hepatitis B Vaccine - First dose
1 month	Hepatitis B Vaccine - Second dose
2 months	DTaP-IPV Vaccine - First Dose Pneumococcal Vaccine - First Dose
4 months	DTaP-IPV Vaccine - Second Dose Pneumococcal Vaccine - Second Dose
6 months	DTaP-IPV Vaccine - Third Dose Pneumococcal Vaccine - Third Dose Hepatitis B Vaccine - Third Dose
1 year	MMR Vaccine (Measles, Mumps & Rubella) - First Dose Pneumococcal Vaccine - Booster Dose
1 1/2 year	DTaP-IPV Vaccine - Booster Dose
Primary 1	MMR Vaccine (Measles, Mumps & Rubella) - Second Dose DTaP-IPV Vaccine - Booster Dose
Primary 6	dTap-IPV Vaccine - Booster Dose



The poster features a blue sky background with a green grassy area at the bottom. In the center, a cartoon illustration of an elderly man and woman are standing together. The man is wearing a blue vest over a white shirt and brown trousers, while the woman is wearing a brown jacket over a green skirt. Above them, the text '長者接種' (Elderly Vaccination) is written in large, stylized Chinese characters, followed by '肺炎球菌疫苗' (Pneumococcal Vaccine) in a similar style. Below this, the English text 'Pneumococcal Vaccination for Elders' is displayed. In the top right corner, the logo of the Centre for Health Protection (HP) is visible, and in the bottom left corner, the Department of Health logo is shown.

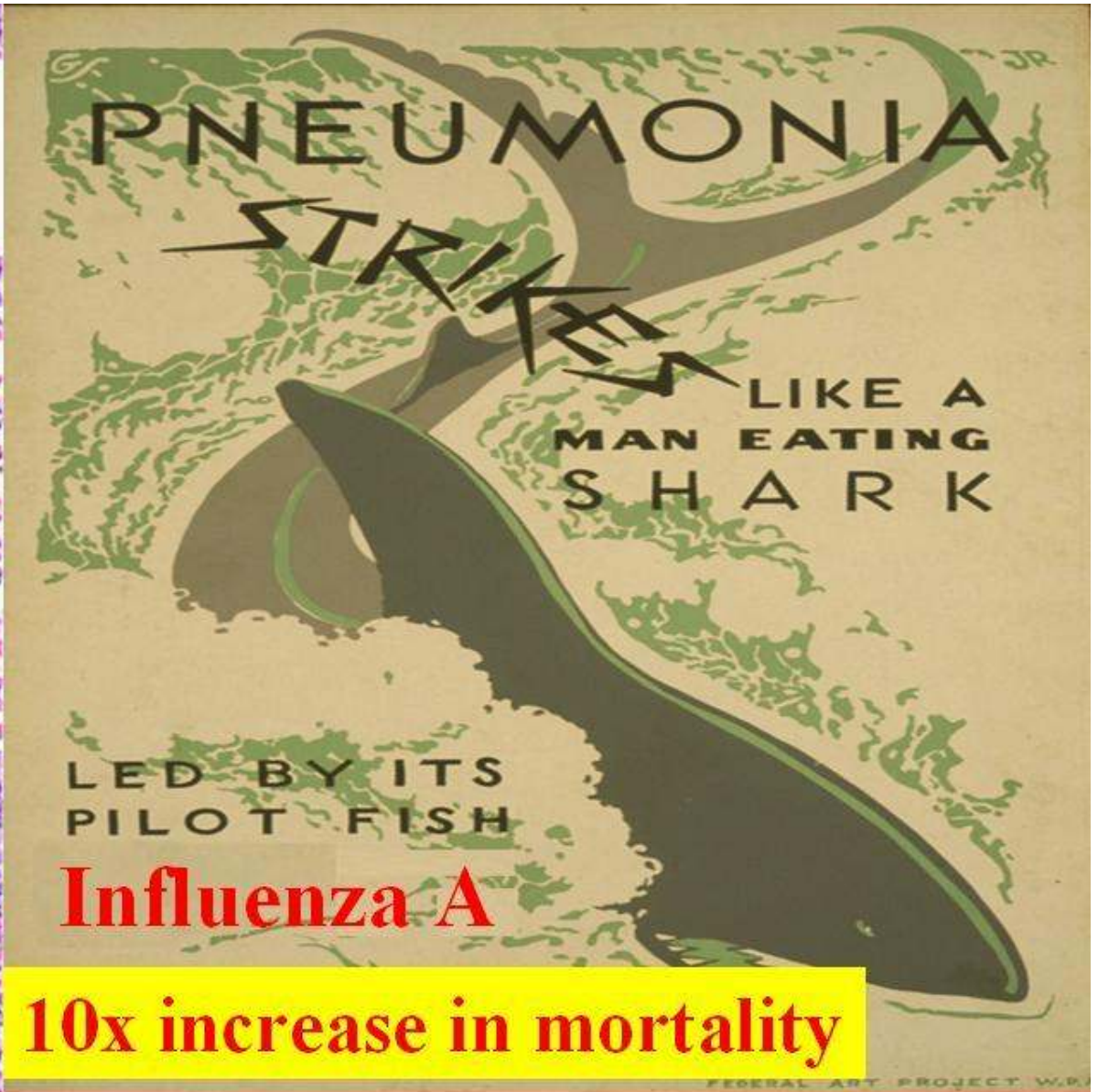
The Importance of Pneumococcal Vaccination



S Pneumonia

Influenza A

Co-infection



Influenza A

10x increase in mortality



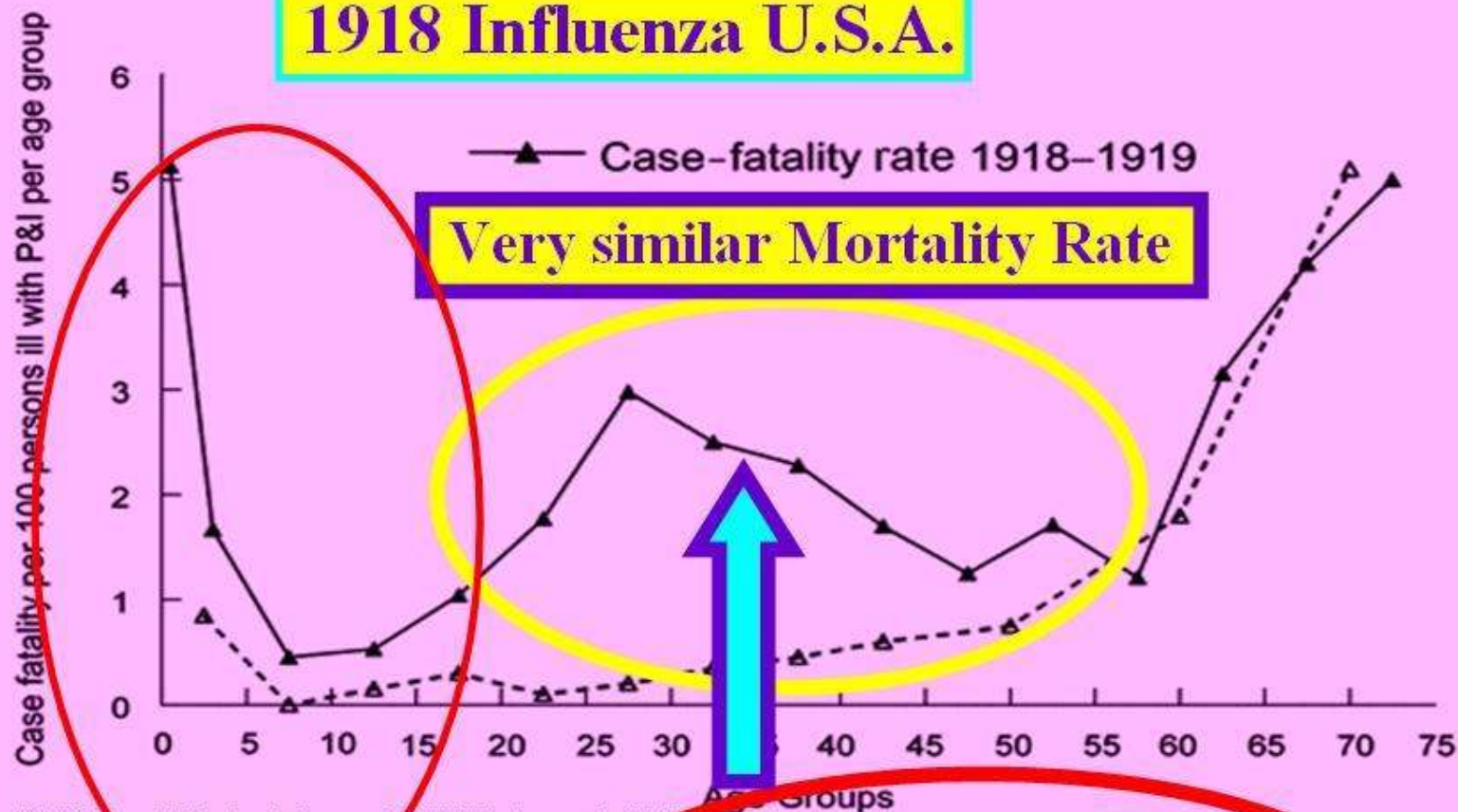
Predominant pathogens responsible for bacterial co-infection during pandemic

Pandemic	Predominant pathogen for bacterial co-infection
1918	<i>S pneumonia</i> (24%), <i>H. influenza</i> (10%) and <i>S pyogenes</i> (17%)
1957	<i>S. Aureus</i> (69%)
1968	<i>S. Pneumoniae</i> (48%) <i>S. Aureus</i> (26%) <i>H. Influenza</i> (11%)

Pandemic outbreak of Panton-Valentine leukocidin (PVL)-positive penicillin resistant *S. aureus* (Phage Type 80/81) in 1954- 1957 causing a high frequency of skin and soft tissue infections, sepsis and pneumonia in healthy children and young adults.

In the three pandemic of the 20th century, bacterial pneumonia was estimated to develop in 15-20% of influenza patients.

1918 Influenza U.S.A.



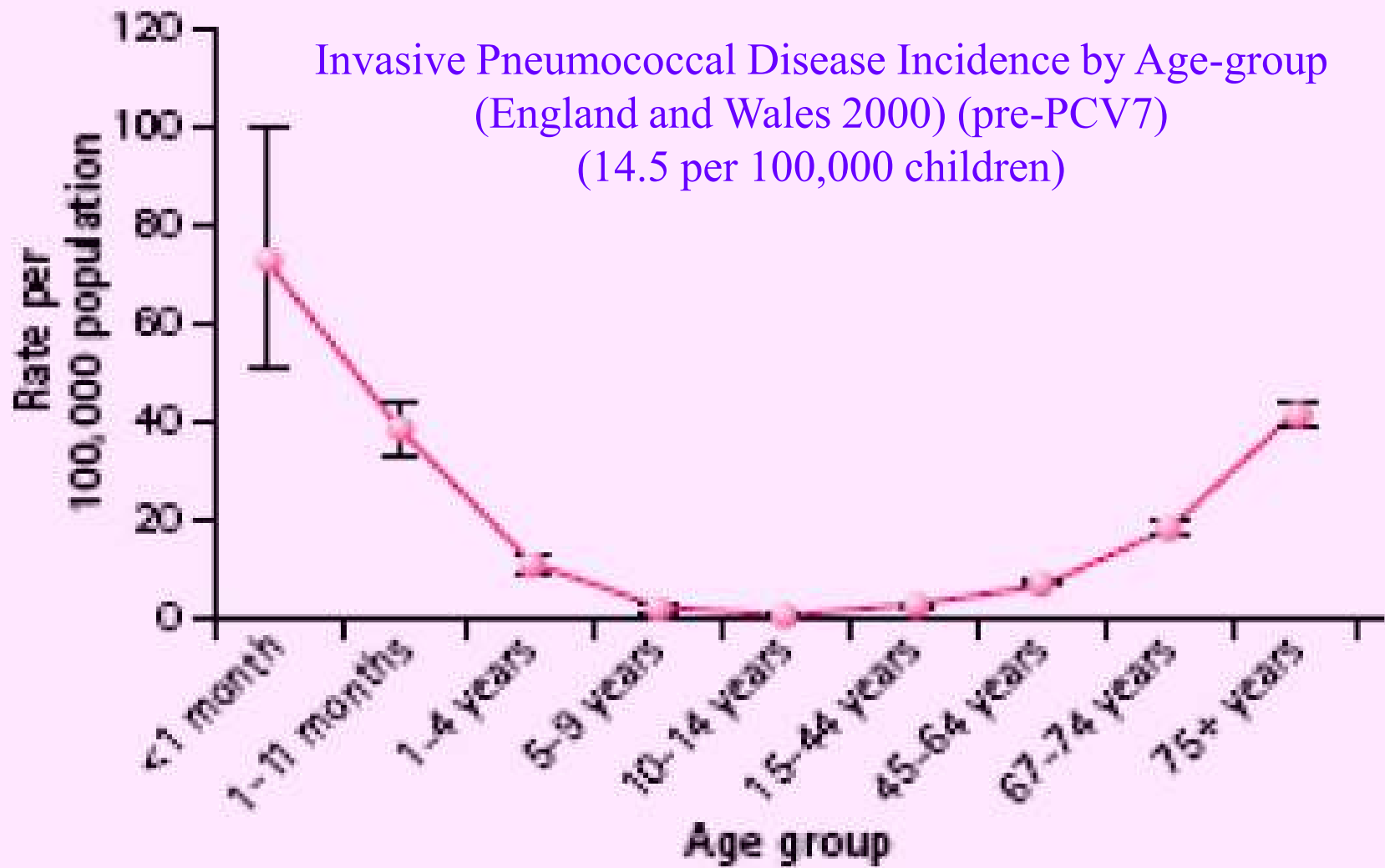
CDC Volume 12, Number 1, January 2006 1918 Influenza: the Mother of All Pandemics Jeffrey K. Taubenberger* and David M. Morens

Mexico	0.6%	0.38%	2.74%	4.06%	3.8%	5.0%	5.1%
Age	0-9	10-19	20-29	30-39	40-49	50-59	60+

? Protected by Immunization Program with major reduction in mortality

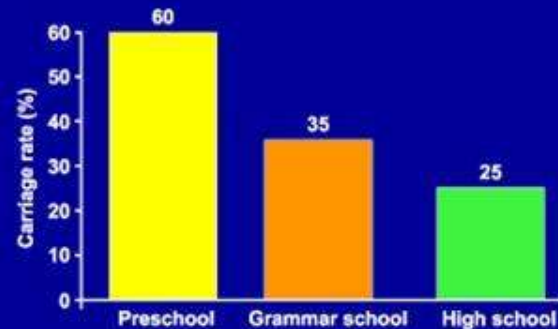
Born before 1957
Partially protected by previous exposure

Invasive Pneumococcal Disease Incidence by Age-group
(England and Wales 2000) (pre-PCV7)
(14.5 per 100,000 children)



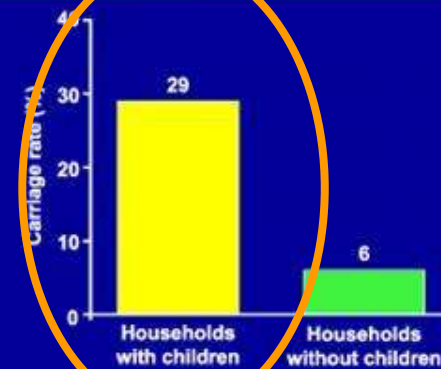
Nasopharyngeal carriage of pneumococcus

Paediatric Carriage Rates



Fedson DS et al. *Vaccine*. 3rd ed. Philadelphia, Pa: WB Saunders; 1999:553-607.

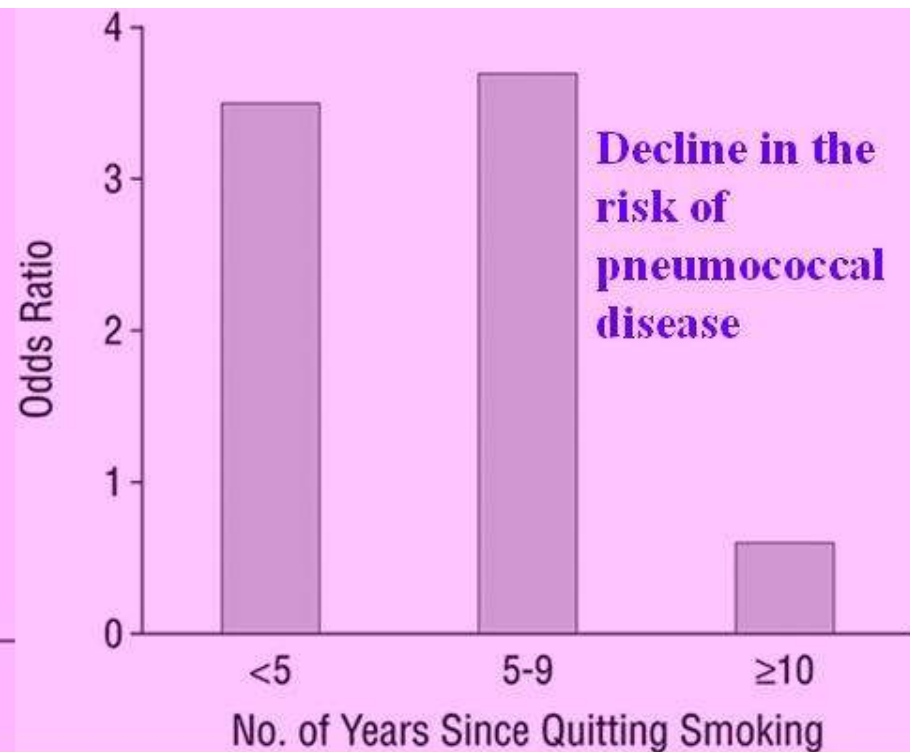
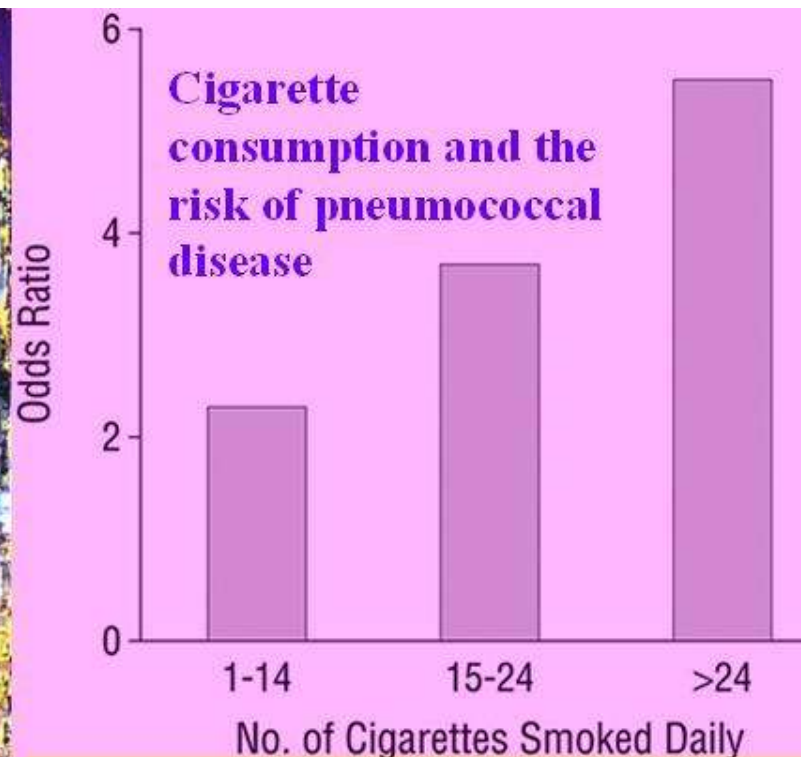
Adult NP Carriage Rate



Fedson DS et al. *Vaccine*. 3rd ed. Philadelphia, Pa: WB Saunders; 1999:553-607.

Patients with high risk of co-infection during pandemic influenza

Co-infection would increase mortality 10x



Nuorti JP, Butler JC, Farley MM, et al, Active Bacterial Core Surveillance Team. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med* 2000;342:681-689.

Cigarette smoking cause activation of platelet-activating factor facilitating attachment and invasion of cells by pneumococcal strains. This may contribute to the increased incidence of bacterial superinfection in people who develop influenza.



The additive benefits of influenza and pneumococcal vaccine during influenza seasons among elderly persons with chronic lung diseases. Nichol K.L. Vaccine 1999 17:S91-S93

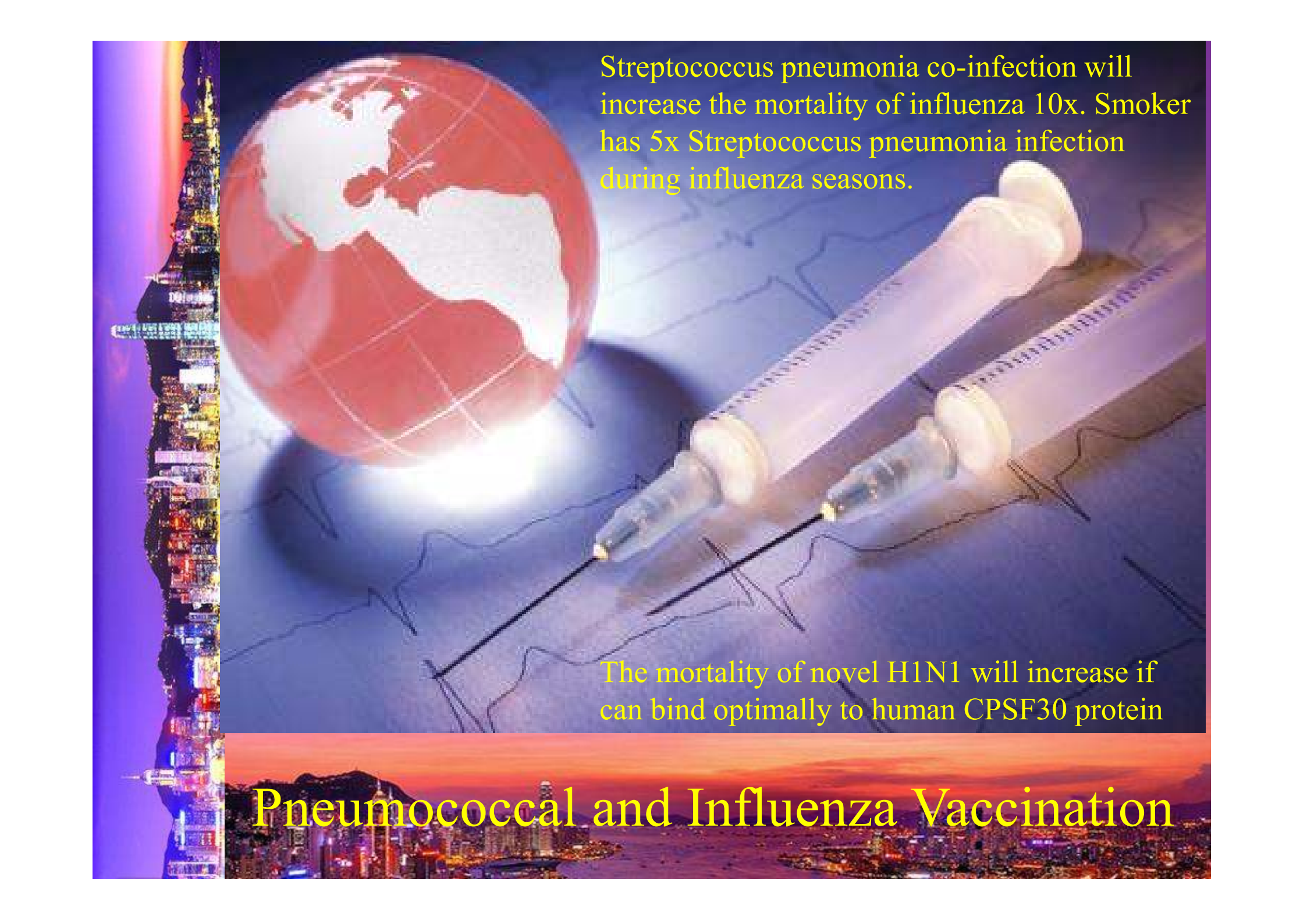
	Hospitalization (% reduction)	Death (% reduction)
Influenza Vaccine alone	52%	70%
Pneumococcal vaccine alone	27%	34%
Influenza + pneumococcal vaccine	64%	81%

You need Pneumococcal vaccination once.
You need Influenza vaccination yearly !



Preparation for H7N9 Pandemic

- © Keep a good personal hygiene and infection control measures
- © Pneumococcal vaccination
- © Since the mortality of novel H1N1 may escalate if it acquired the optimal structure for binding to human CPSF30 protein, yearly influenza vaccination is advisable.
- © Avoid visiting poultry market or crowded area
- © Hoard Soap/surgical mask at home
- © Check Your First Aid Kit: A thermometer and acetaminophen/high dose Vit C/NAC/Tamiflu/Augmentin/Klacid. Start Rx as early as possible.
- © Purchase Dried Grains/Procure Non-Perishable Proteins (dry bean/peanut butter)/Canned vegetables
- © Test Your Portable Radio with working battery
- © Make an Emergency Contact List (on Paper)
- © Stash Away Extra Prescriptions (1-3 month supply)

The image is a composite graphic. On the left, a vertical strip shows a city skyline at night with lights reflecting on water. The main background is a dark blue gradient. In the upper left, a red globe with white grid lines is shown. In the center, two medical syringes are depicted, one slightly behind the other, both pointing towards the bottom right. The syringes are white with clear barrels and black plungers. In the bottom right, a city skyline at sunset or sunrise is visible, with buildings and a bridge over water.

Streptococcus pneumonia co-infection will increase the mortality of influenza 10x. Smoker has 5x Streptococcus pneumonia infection during influenza seasons.

The mortality of novel H1N1 will increase if can bind optimally to human CPSF30 protein

Pneumococcal and Influenza Vaccination



Wash Your Hands.
Tell your friends to do the same.

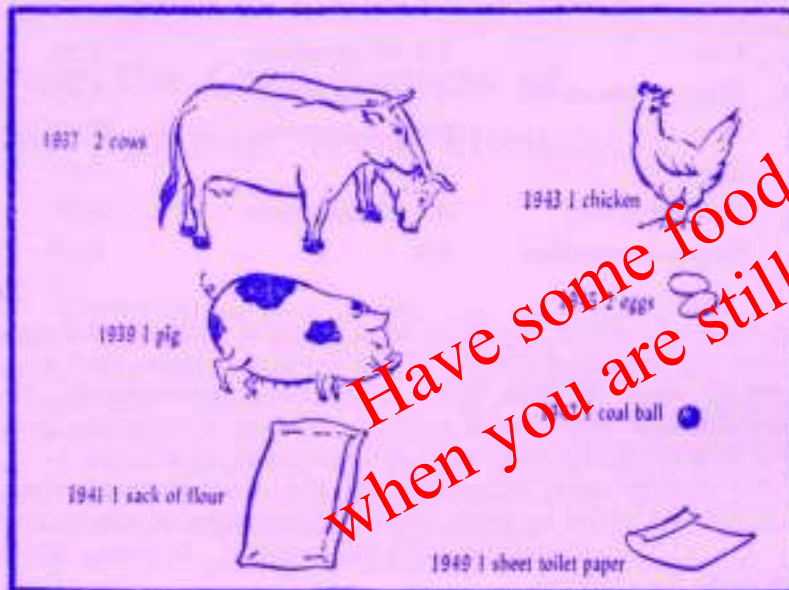
「疫情令人揪心。」

「千祈千祈千祈，洗手洗手洗手。」

Joseph and the Famine Genesis 47: 13-26

First Year	All the money
Second Year	All the livestock
Third Year	All the land
Fourth Year	Reduced the people to servitude
Fifth Year	Give a fifth of the crop to Pharaoh This is the beginning of taxation .

Decline of the Purchasing Power of 100 yuan
in Kuomintang Currency Before the Liberation



GERMANY

In the early years after 1870 some of the States retained their own currencies. Figures quoted here are for the mark of 100 pfennigs

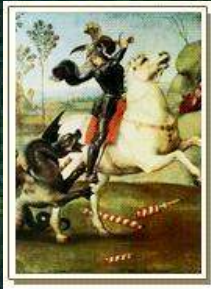
	MARKS TO £1	MARKS TO \$1
Pre-war parity	20.429	4.198
1913 - Jan	-	4.59
1914 - Jan	-	5.36
1914 - Oct	-	5.53
1920 - Jan	340	100.5
1920 - Oct	240	60.5
1921 - Jan	160	40.25
1921 - Oct	240	70.45
1921 - Jan	215 - 262	57 - 74
1921 - Jun	245 - 280	63 - 75
1921 - Oct	463 - 712	124 - 180
1922 - Jan	790 - 862	186 - 201
1922 - Feb	873 - 1009	204 - 227
1922 - Mar	1022 - 1485	250 - 338
1922 - Jul	1770 - 2975	402 - 670
1922 - Aug	2860 - 8850	644 - 1975
1922 - Oct	7925 - 20,350	1815 - 4500
1922 - Dec	31,000 - 39,000	6750 - 8470
1923 - Jan	32,000 - 225,000	6890 - 48,390
1923 - Jun	265,000 - 900,000	57,000 - 193,500
1923 - Aug	4.5 million - 52 million	900,000 - 11.4 million
1923 - Oct	1 milliard - 800 milliard	250 million - 170 milliard
1923 - Dec	15 billion - 25 billion	3.43 billion - 5.72 billion
1924 - Jan	19 billion	4.47 billion
	New currency introduced	
1925 - Jan	20	4.22

Have some food reserve
when you are still affordable!!

Happy Chinese New Year of The Horse 2014

Aerial view of the 3000 year old White Horse of Uffington

The Vale of White horse (Dragon Hill)



聖喬治大戰惡龍 (1505)
St. George and the Dragon
(Raphael 拉斐爾 1483-1520)



尤芬頓白馬是英國最古老的
山麓雕刻[青銅器時代(約1200BC-800BC)]

Thank You For Your Attention !