全球流感防疫總動員

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特別企劃

新型流行性感冒病毒一旦橫掃全球，
會奪走上百萬條人命，
這不是單一國家或地區的問題，
也沒有一個國家能夠置身事外。

人類，準備好了嗎？

全球流感防疫總動員

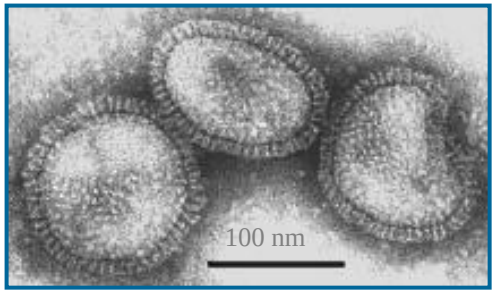
撰文 吉布斯（W. Wayt Gibbs）
索拉斯（Christine Soares）
翻譯 涂可欣

什麼是流感?

- 因流感病毒引起之急性呼吸道疾病
- 需要經由實驗室証明才能跟其他急性呼吸道疾病區分
- 經由飛沫傳染
- 全球各年齡層都會受到感染
- 疫苗是預防流感最經濟的一個方法

流感病毒傳染途徑:飛沫傳染

A型與B型流感病毒



Viral Genome:

8 Negative-Sense RNA Segments

Viral Non-Envelope Proteins:

PB1, PB2, PA Polymerase Complex

NP

Matrix (M1)

血球凝集素

Hemagglutinin (HA)

Neuraminidase (NA)

神經胺酸酶

M2 Ion Channel

PB2

PB1

PA

HA

NP

NA

M

NS

Non-Structural Proteins:

NS1, NS2

Table 1 Influenza viral genes and their functions

Influenza gene segment and protein(s)	Function(s)
1. PB2; 2. PB1; 3. PA	Viral replication and transcription, in a complex of these three proteins. Replicate the viral RNA in a complex with NP. PB2 may be host specific in replication.
4. HA 血球凝集素	Viral binding to SA (and other?) receptors. Induces virus entry by endocytosis and causes fusion of the viral envelope and the endosomal membrane. Specific HA sequences and structures control the binding to specific sialic acids and linkages. Must be proteolytically cleaved to be fusion-active. Major target of neutralizing antibody responses, variation results in evasion of the antibody responses.
5. NP	Role in controlling the replication of the viral RNA, in a complex with PB2, PB1, and PA.
6. NA 神經胺酸酶	Enzyme that cleaves the terminal SAs from cell surface glycoproteins and also from the viral glycoconjugates. Both the specificity for specific SA linkages and the level of activity may vary but are determined by mutations in the enzymatic active site and by the length of the stalk holding it above the membrane. Cleaving the SA from the viral HA can prevent virion aggregations. A target of antibody responses, some antigenic variation is selected.
7. M1/M2	M1: controls the transport of viral ribonucleoprotein complexes into and out of the nucleus. Involved in the budding of the RNPs at the plasma membrane during virion formation. M2: forms ion channel in virion to allow H+ ions to enter the virion and allow M/NP to dissociate, enabling the RNP to travel to the nucleus; modulates the pH of the Golgi to allow acid-sensitive HA molecules to pass to the cell surface intact.
8. NS1/NS2	NS1: binds and sequesters RNA, prevents activation of PKA, and prevents cellular apoptosis. NS2: involved in the nuclear export of viral RNPs.

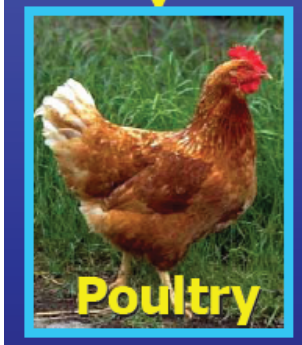
Influenza Types

- Three influenza virus types
  - Influenza A; hosts are man, birds, horses, pigs, etc.
  - Influenza B; hosts are man
  - Influenza C; hosts are man
  - Types A and B are the major pathogenic types

按一下可跳至文件下一頁

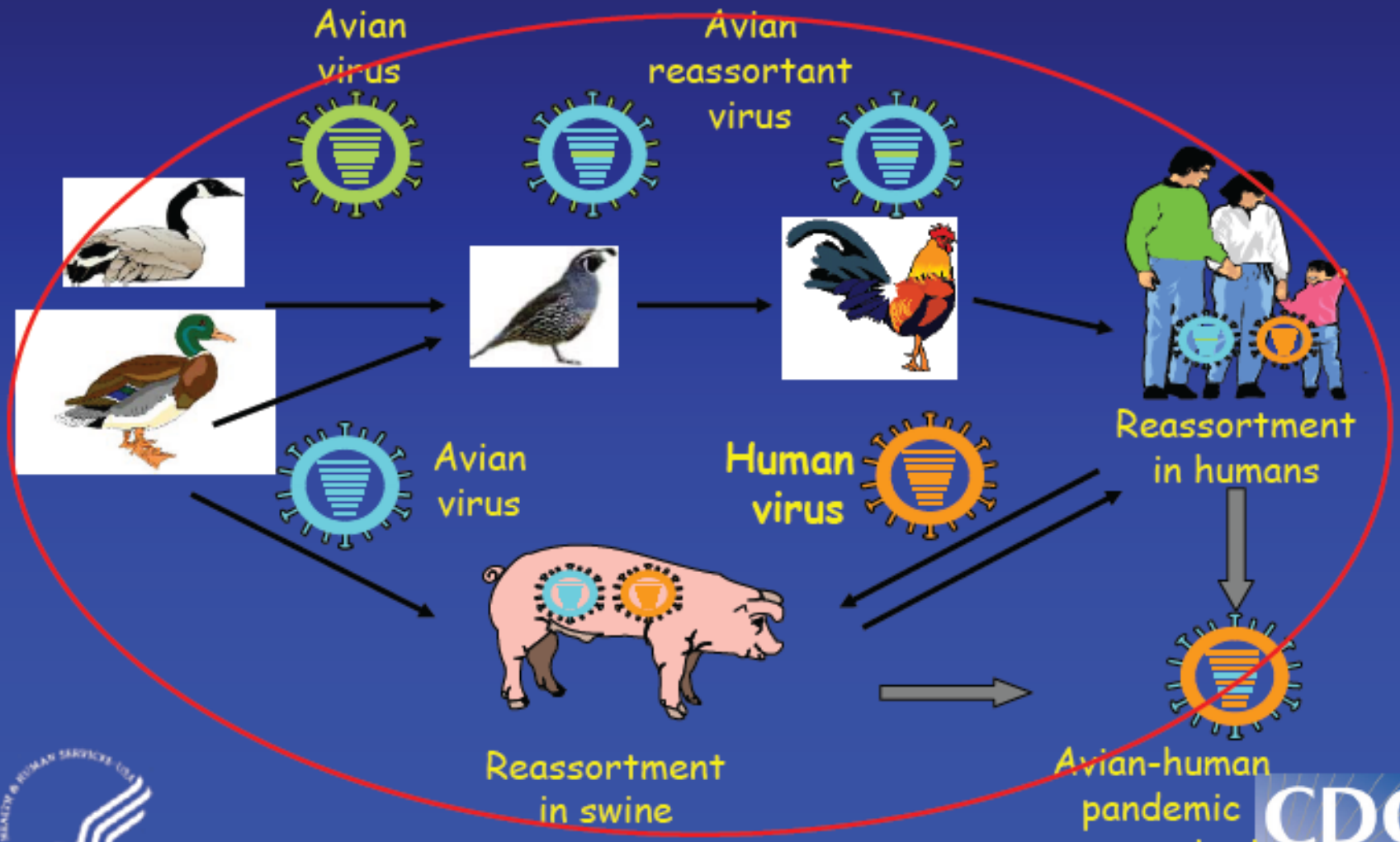
Influenza A Viruses

- **Aquatic birds - reservoir for all HA and NA subtypes:**
  - **H1 - H16**
  - **N1 - N9**



CDC

Possible Pathways for Generation Pandemic Influenza Viruses

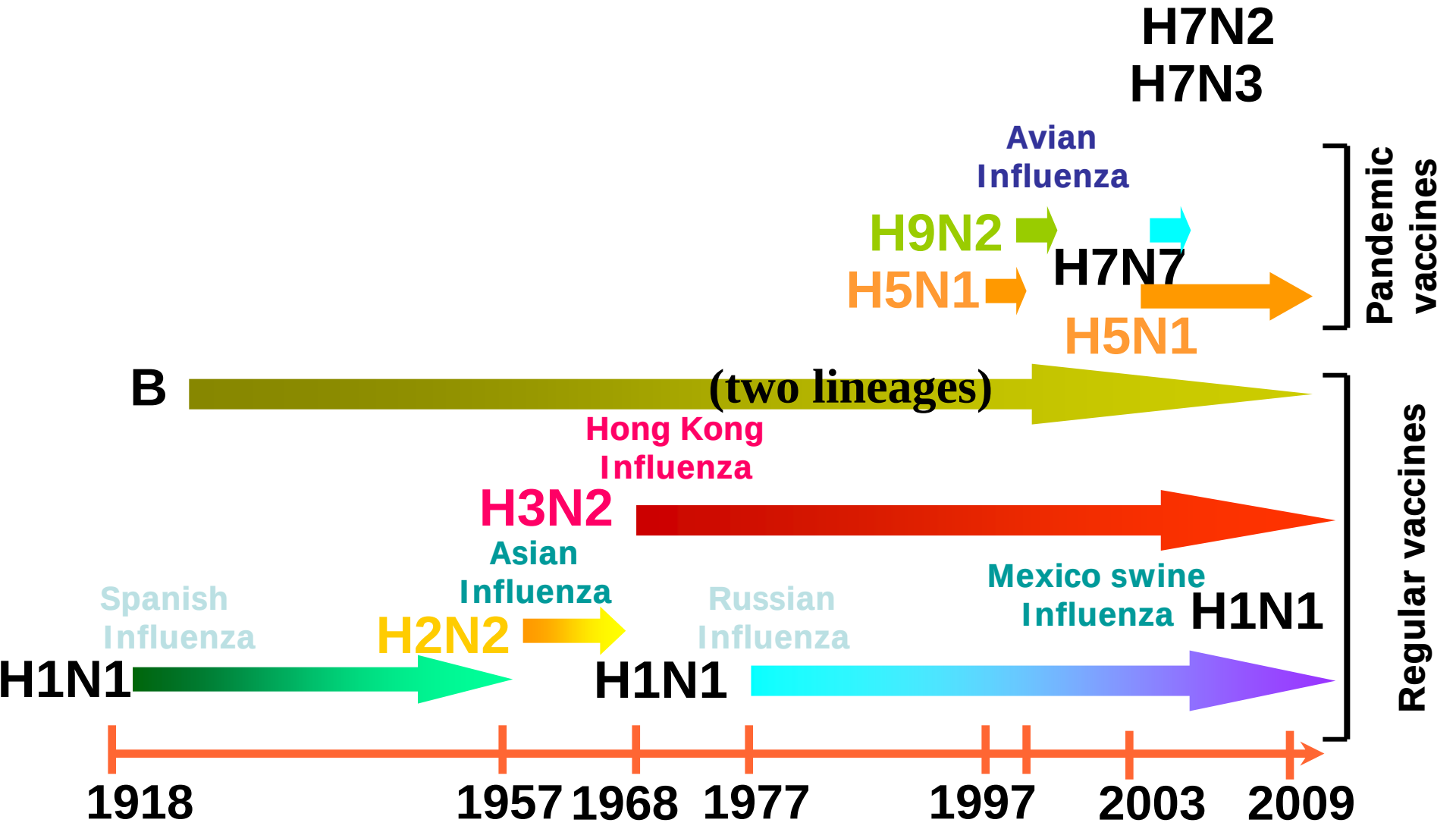


CDC
INFLUENZA DIVISION

A 型流感病毒亞型的自然宿主
Natural Hosts of Influenza A Subtypes

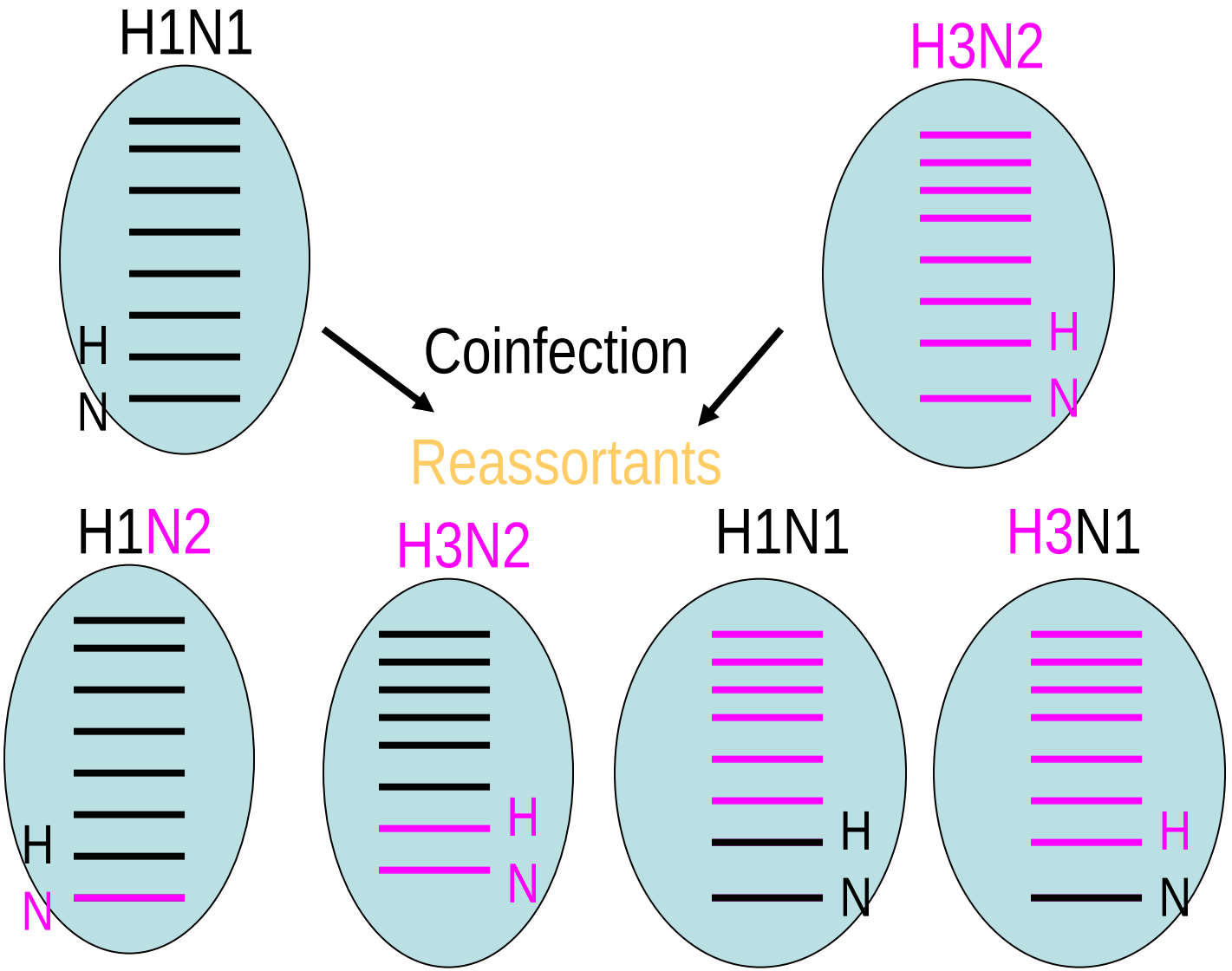
Host	HA subtypes	NA subtypes
Avian	H1~H16	N1~N9
Human	H1, H2, H3	N1, N2
Swine	H1, H3	N1, N2
Horse	H3, H7	N7, N8

流感病毒在人群流行的時程



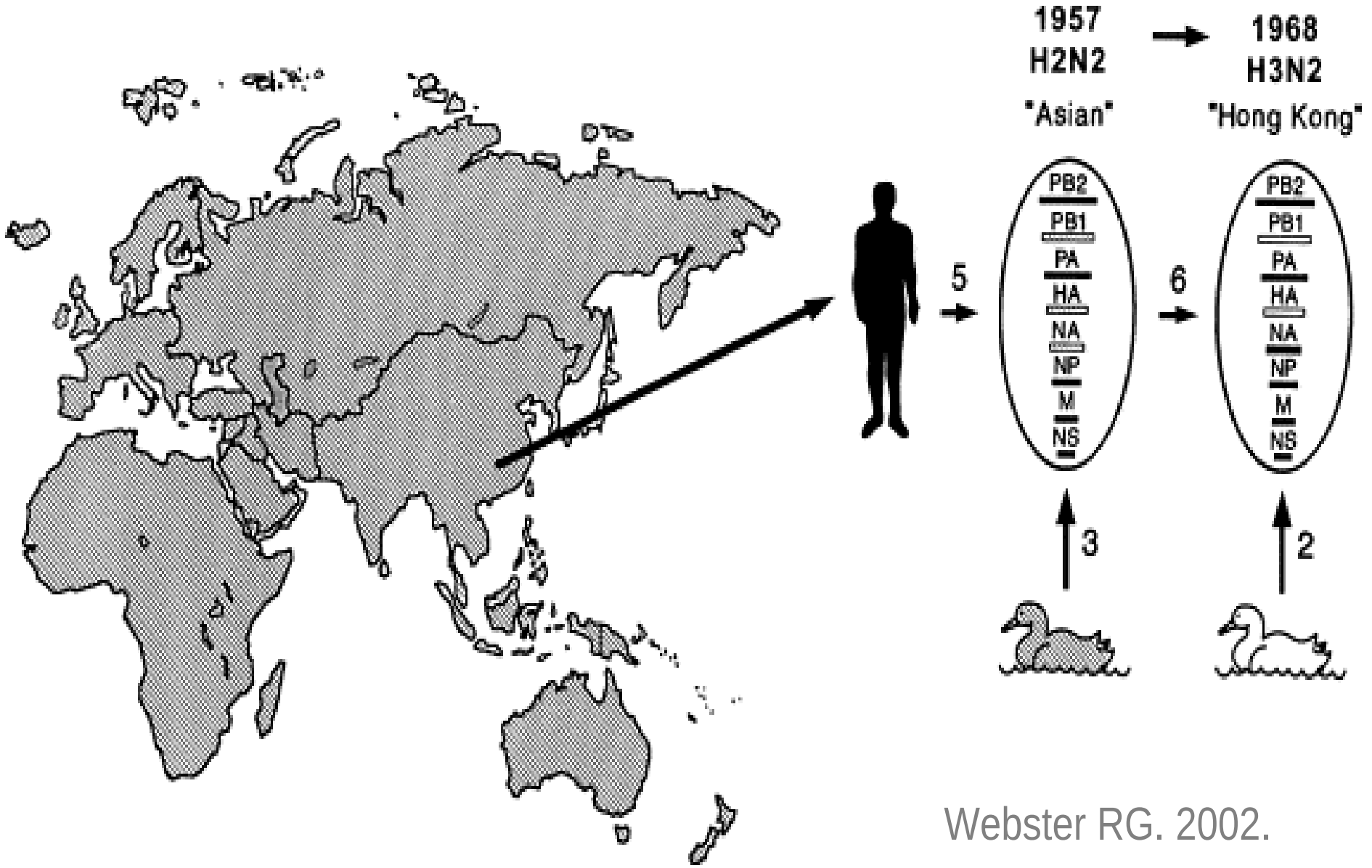
流感病毒的致命武器：
抗原轉移與抗原漂移

流感病毒的基因重排
Reassortment of Influenza Viruses



Kilbourne et al. 1960; 1969.

流感病毒透過基因重排造成抗原轉移
（Antigenic Shift）



Webster RG. 2002.

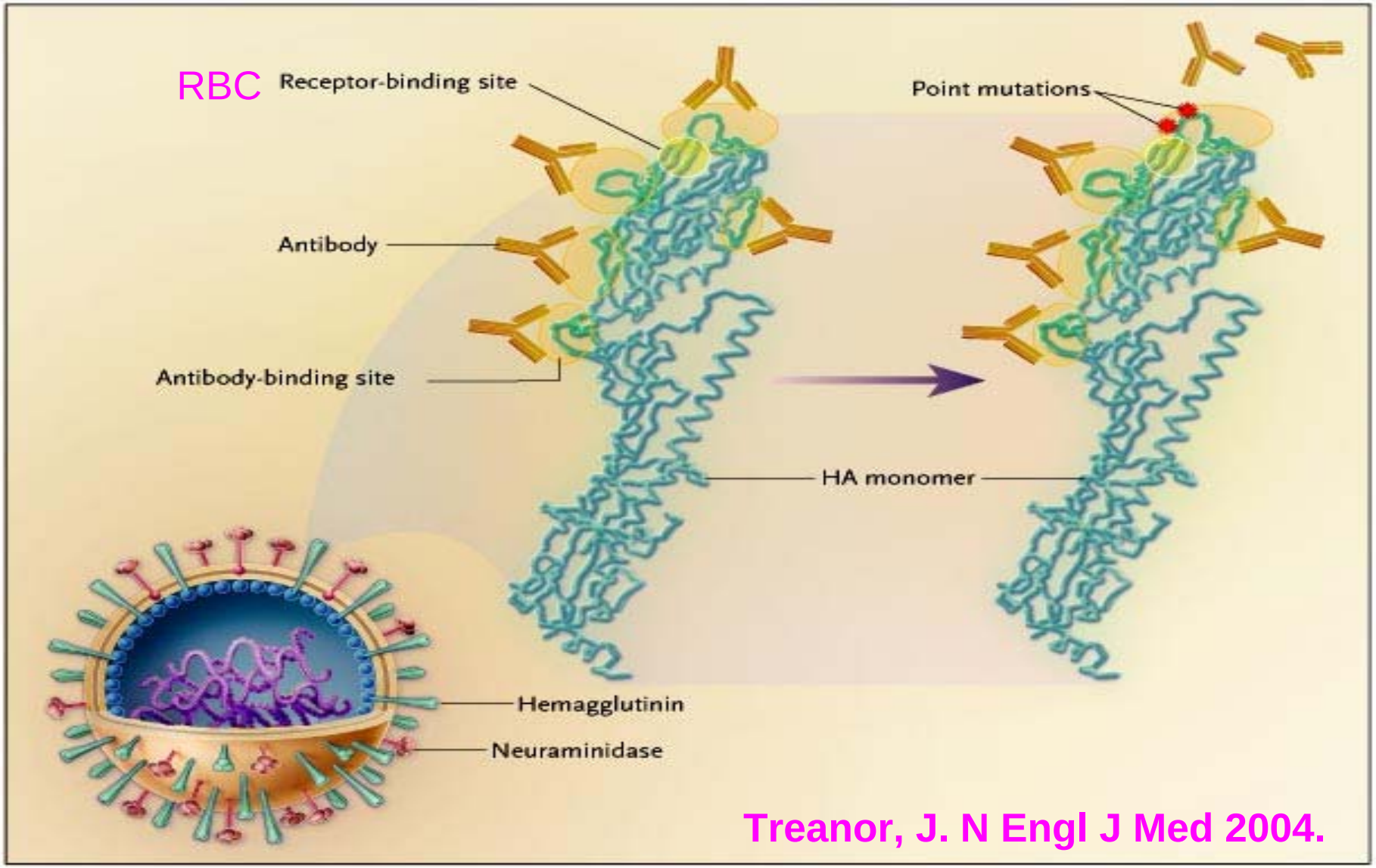
過去一百年發生過的人流感大流行

Antigenic Shift for Flu Outbreaks

Year	Strain	Mortality
1918-20	H1N1 (Spanish flu)	>20 million
1957-58	H2N2 (Asian flu)	>1 million
1968-69	H3N2 (Hong Kong flu)	<1 million
1977-78	H1N1 (Russia flu)	<1 million

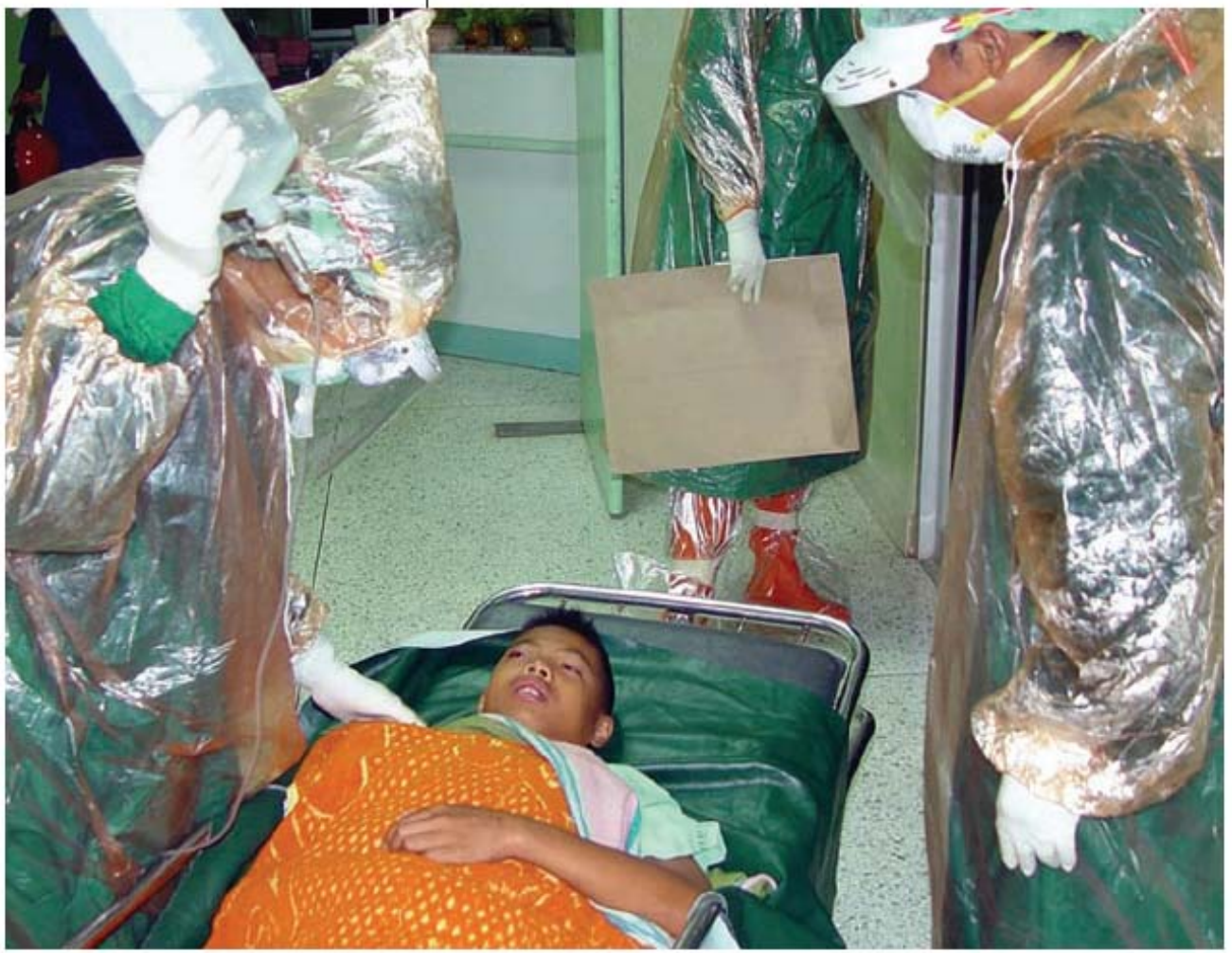
Textbook of Influenza. Chapter 1 & 41.

流感病毒透過基因突變造成抗原漂移
Antigenic Drift in Influenza Viruses



Treanor, J. N Engl J Med 2004.

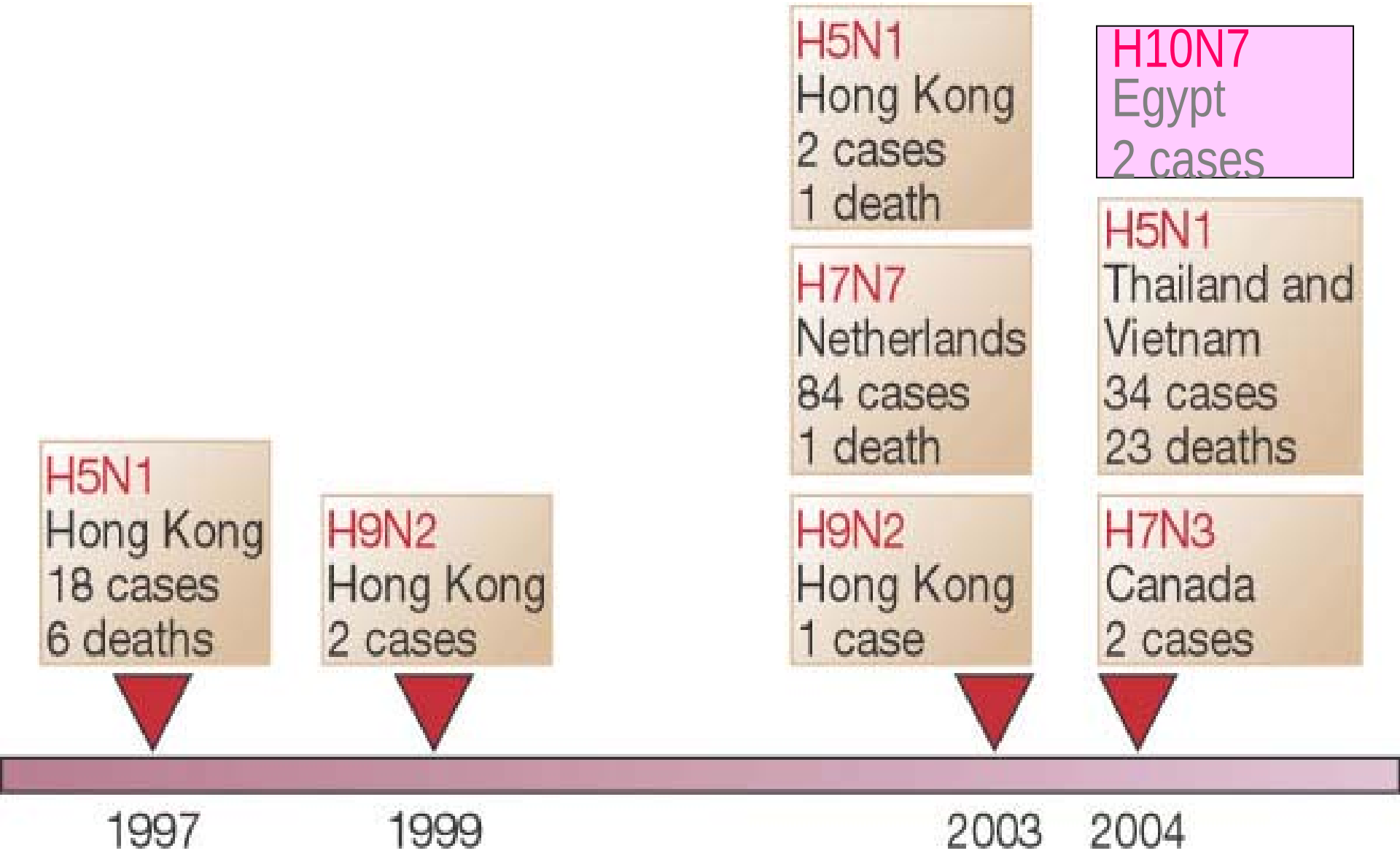
另一類可怕的流感:高致病型禽流感



警訊：一名13歲的男孩在2004年10月時感染了H5N1禽流感，而送至泰國曼谷北邊的一所醫院隔離。目前越南、柬埔寨和泰國，總共出現了71起禽流感病例，其中一例確定是人與人之間的傳播。

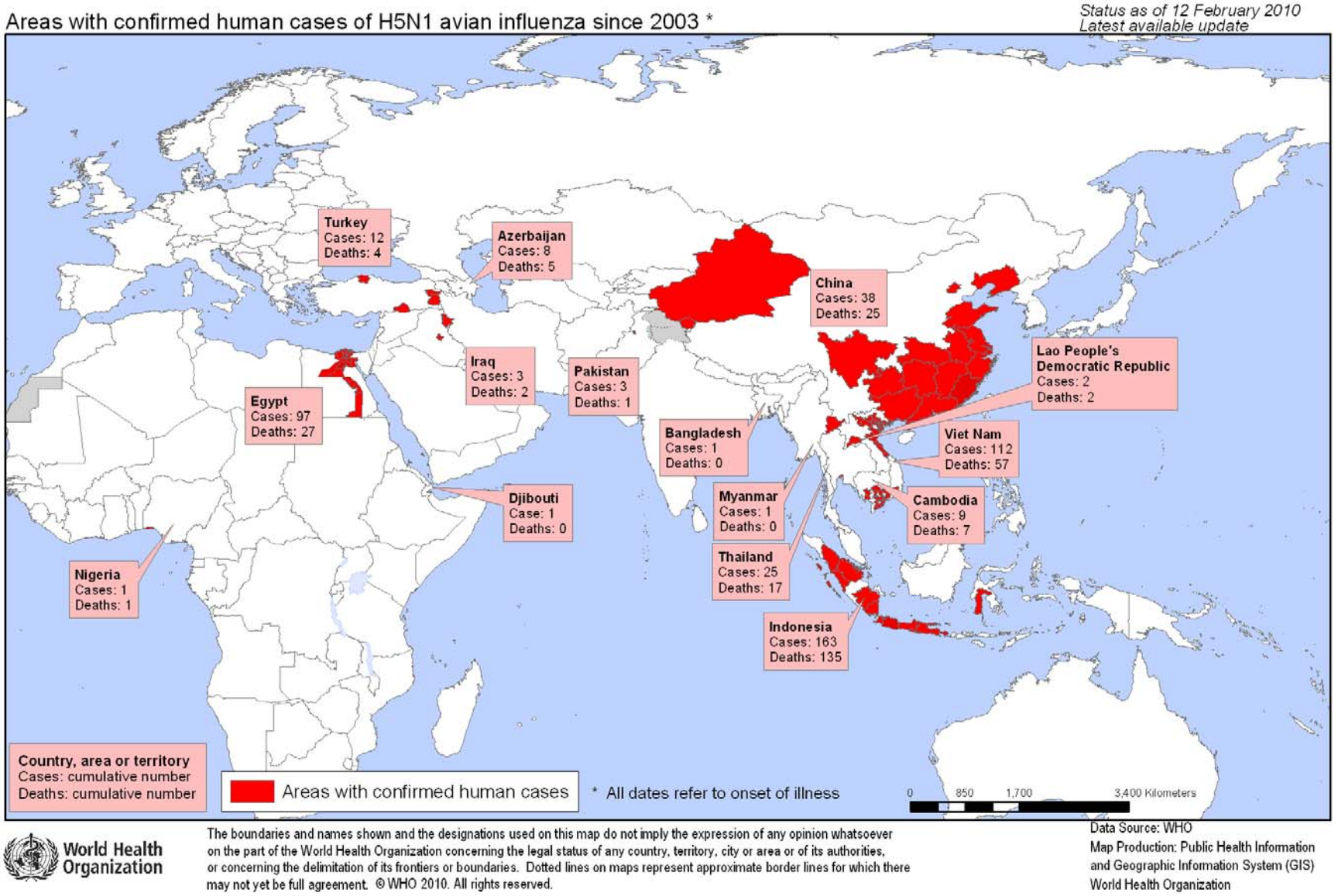
今年3月越南河內有兩名禽流感病患住院治療，分別是一名病情危急的21歲男子（左）和他的14歲妹妹。許多感染H5N1而出現嚴重症狀、甚至死亡的患者，都是原本健康的成人和兒童。

Avian Influenza in Humans, 1997-2004

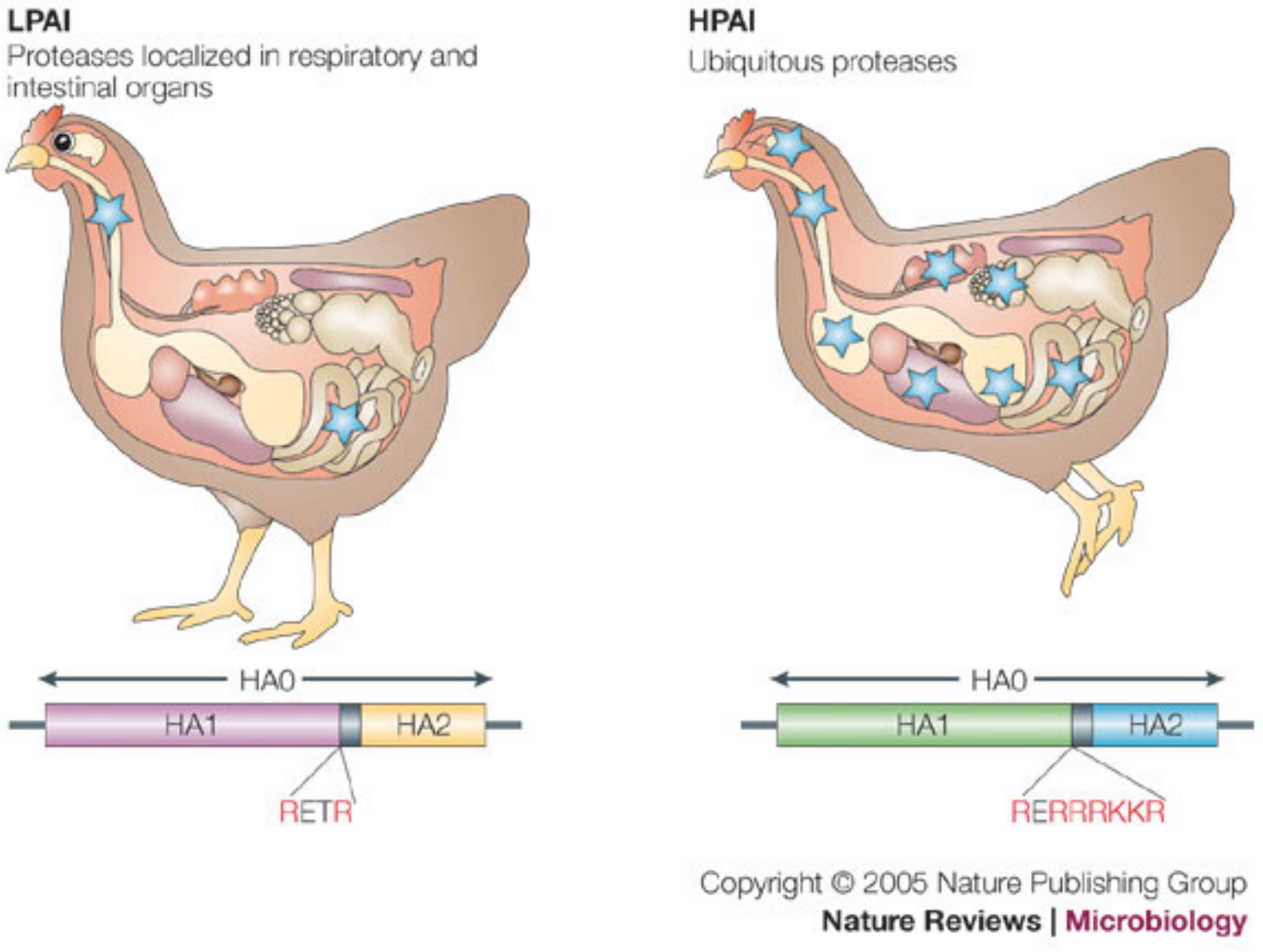


Stephenson et al. 2004

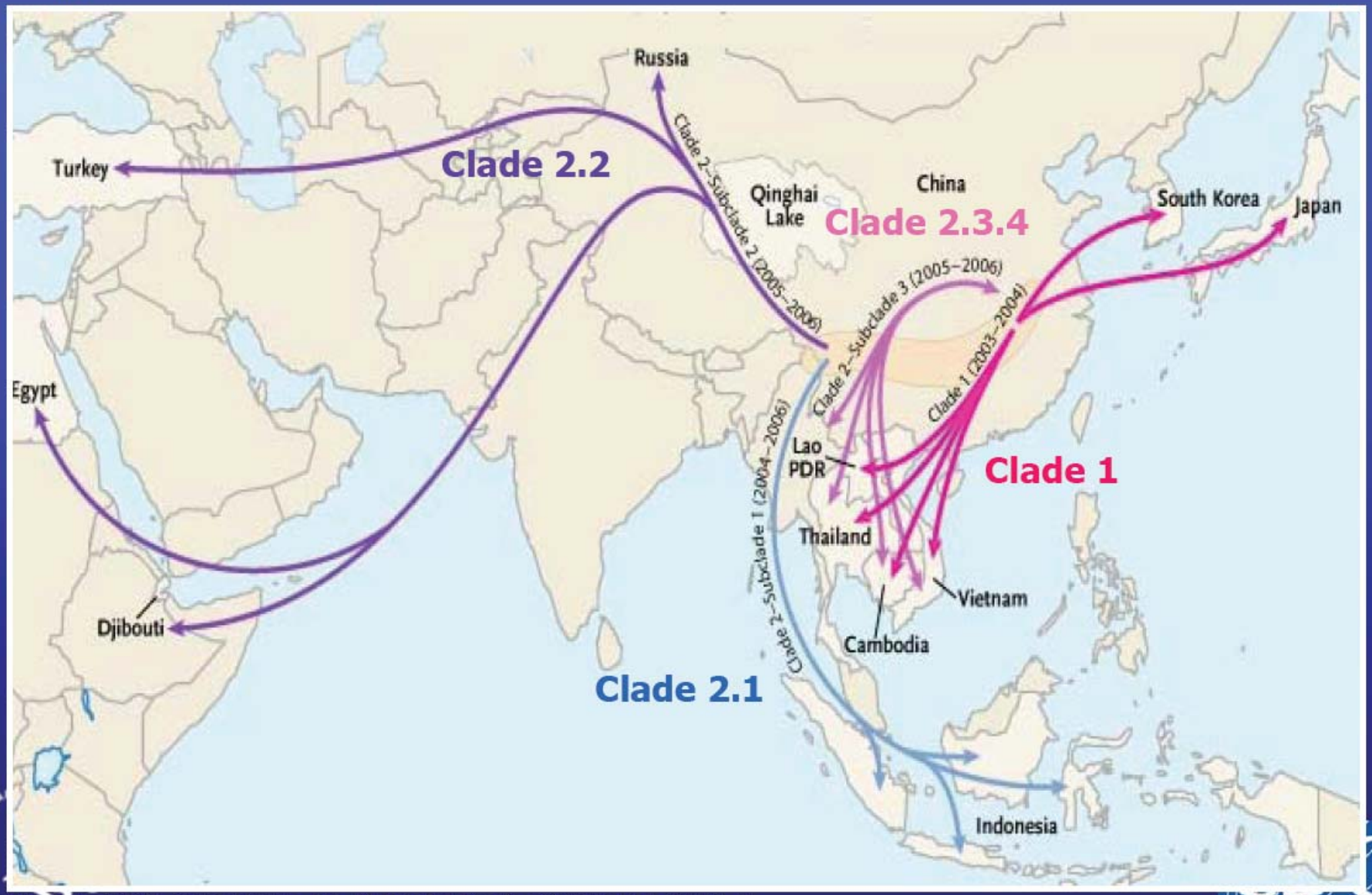
2003年至今人類感染H5N1確定病例數 - 387 cases, 245 deaths



High Pathogenic Avian Influenza



Spread of Influenza H5N1 Viruses

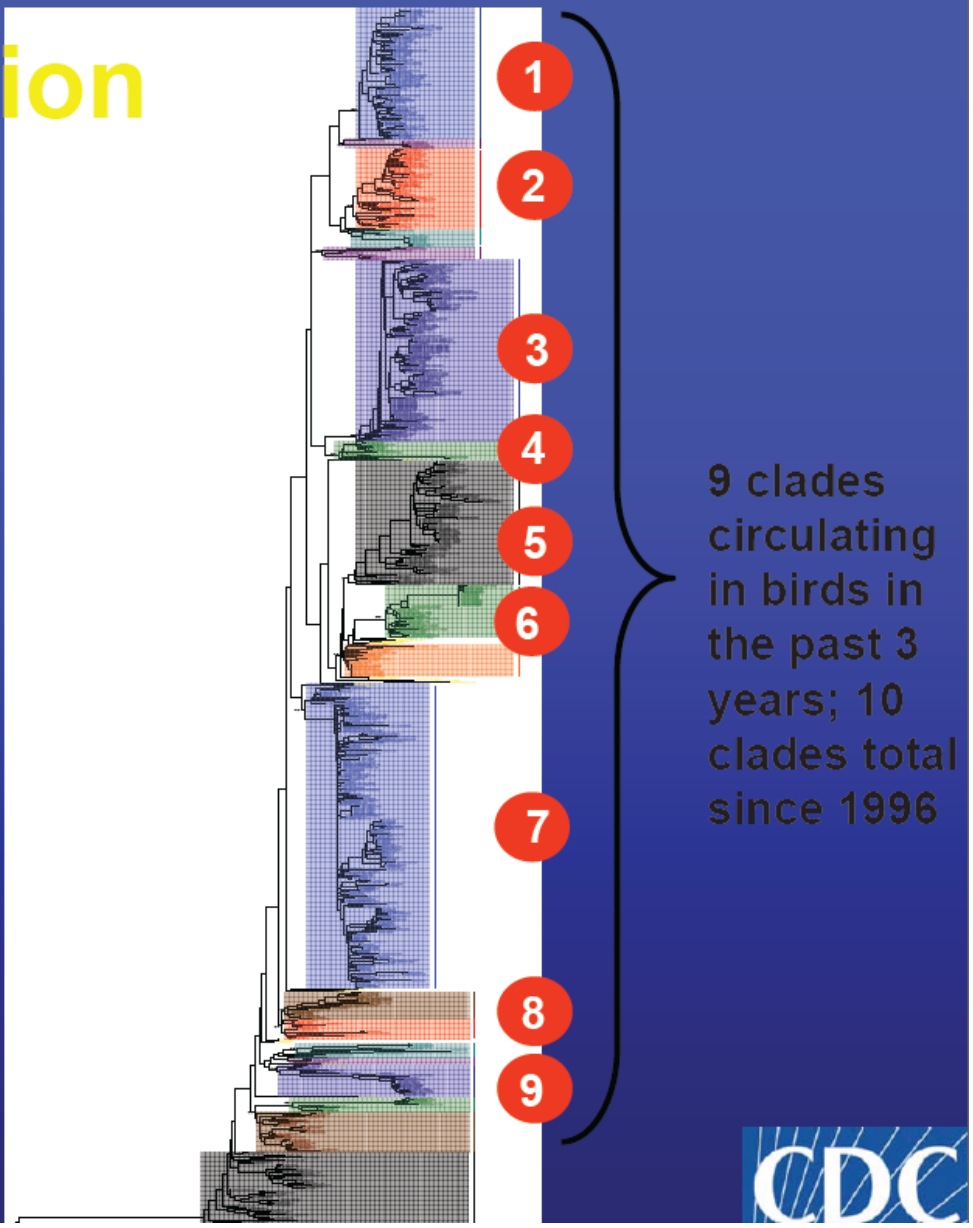


Webster RG, Govorkova EA. N Engl J Med. 2006; 355: 2174-7.

http://www.who.int/csr/disease/avian_influenza/guidelines/nomenclature/en

H5N1 circulation in birds

- Multiple clades and sub-clades circulate in birds
- Extensive genetic divergence since 1997

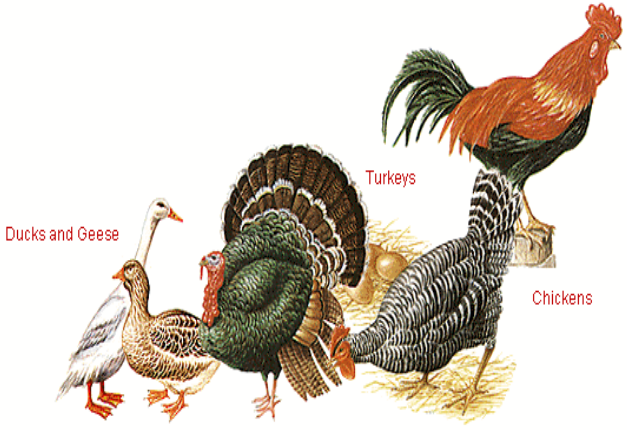


禽流感➡新型流感 (H5N1)➡流感大流行

1. 禽流感病毒 ➡ 輕易地人傳人 ➡ 流感大流行

2. 禽流感病毒&人流感病毒 ➡ 人 ➡ 輕易地人傳人 ➡ 流感大流行

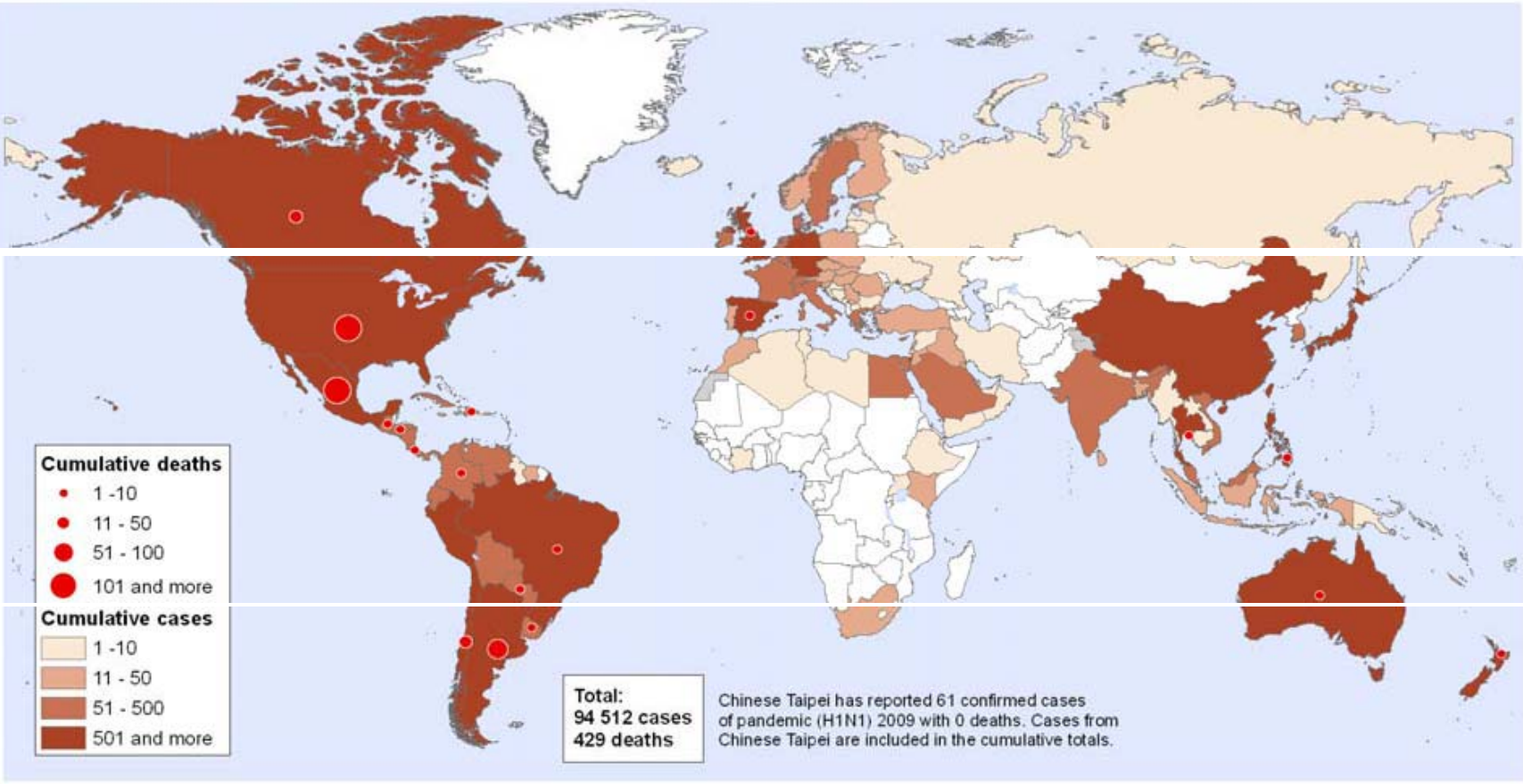
3. 禽流感病毒&人流感病毒 ➡ 豬 ➡ 輕易地人傳人 ➡ 流感大流行



2009 Mexico Swine Flu

Pandemic (H1N1) 2009,
Number of laboratory confirmed cases as reported to WHO

Status as of 06 July 2009
09:00 GMT



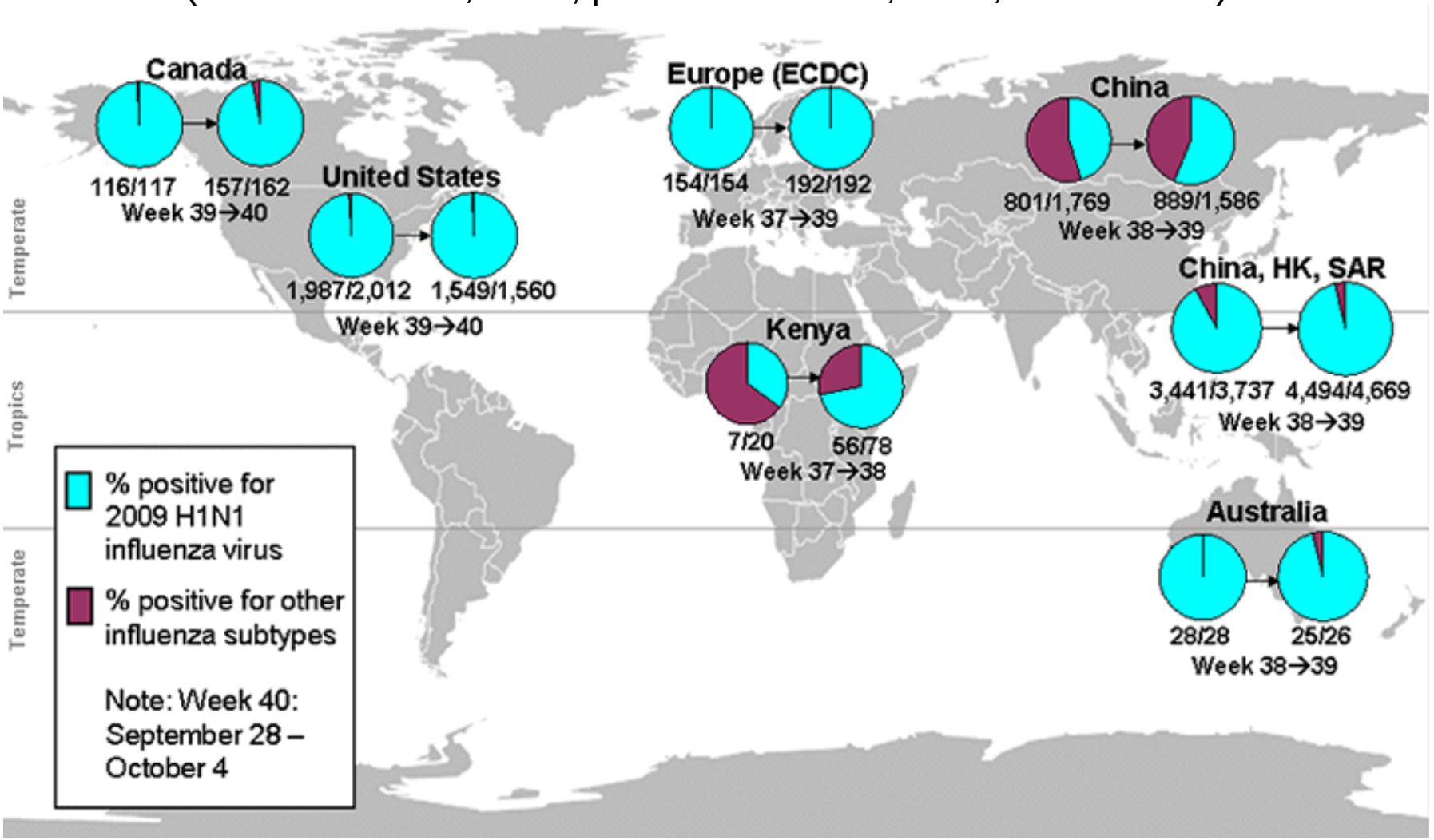
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

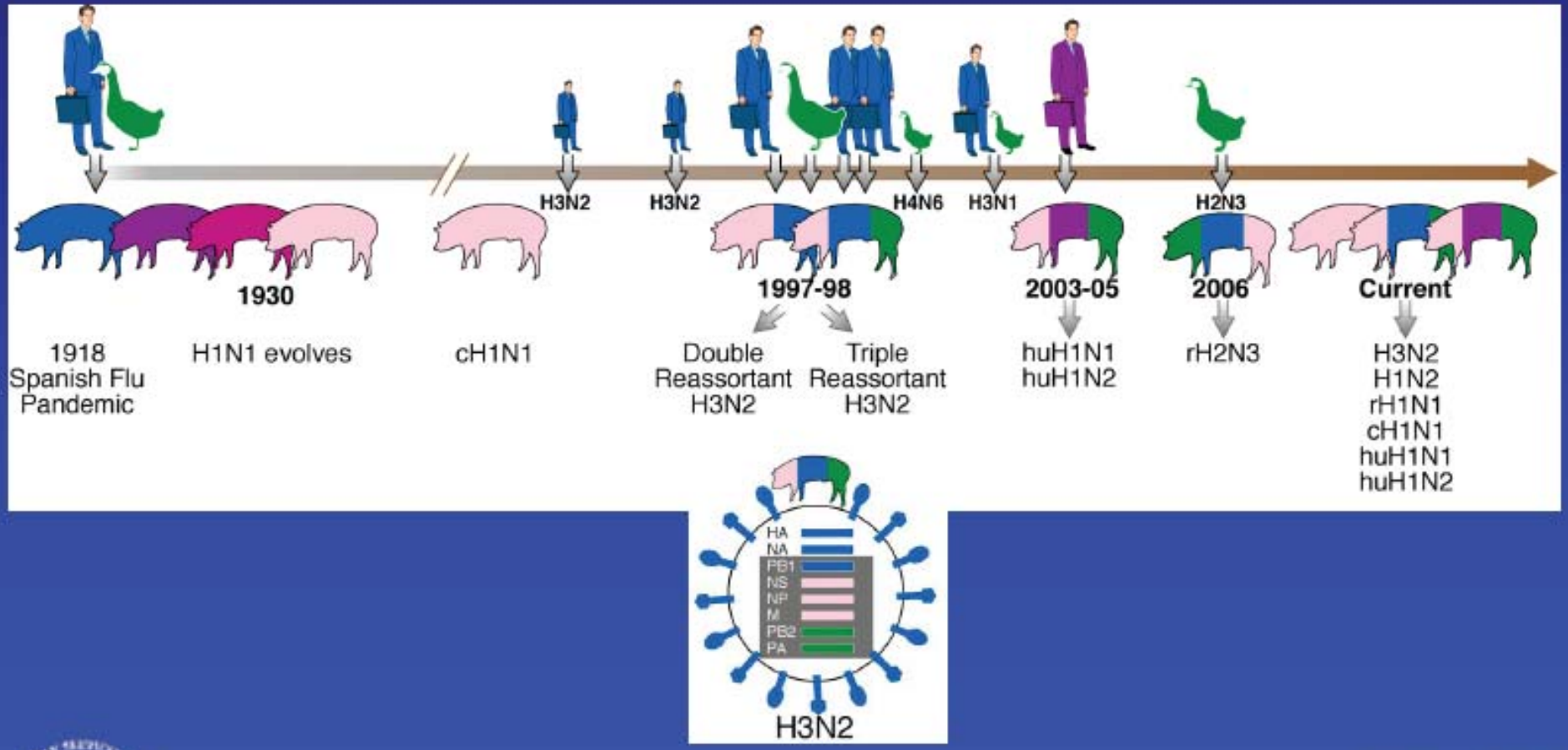
World Health Organization

Map produced: 06 July 2009 09:00 GMT

Map: International Co-circulation of 2009 H1N1 and Seasonal Influenza
(As of October 9, 2009; posted October 9, 2009, 3:00 PM ET)



Reassortant Events Among Swine Influenza Viruses (SIV) in North America



Slide courtesy of Dr. Amy Vincent, NADC, USDA

CDC
INFLUENZA DIVISION

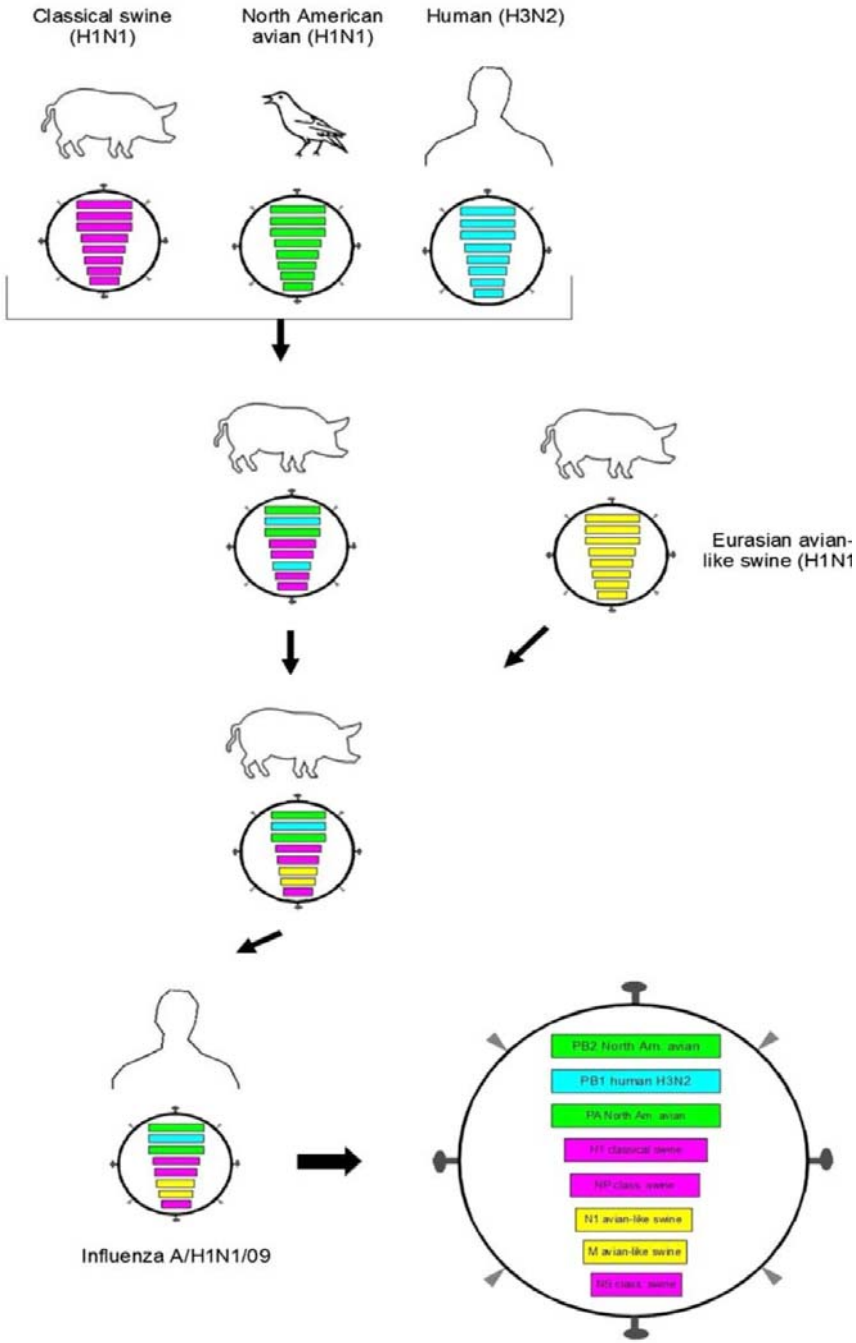
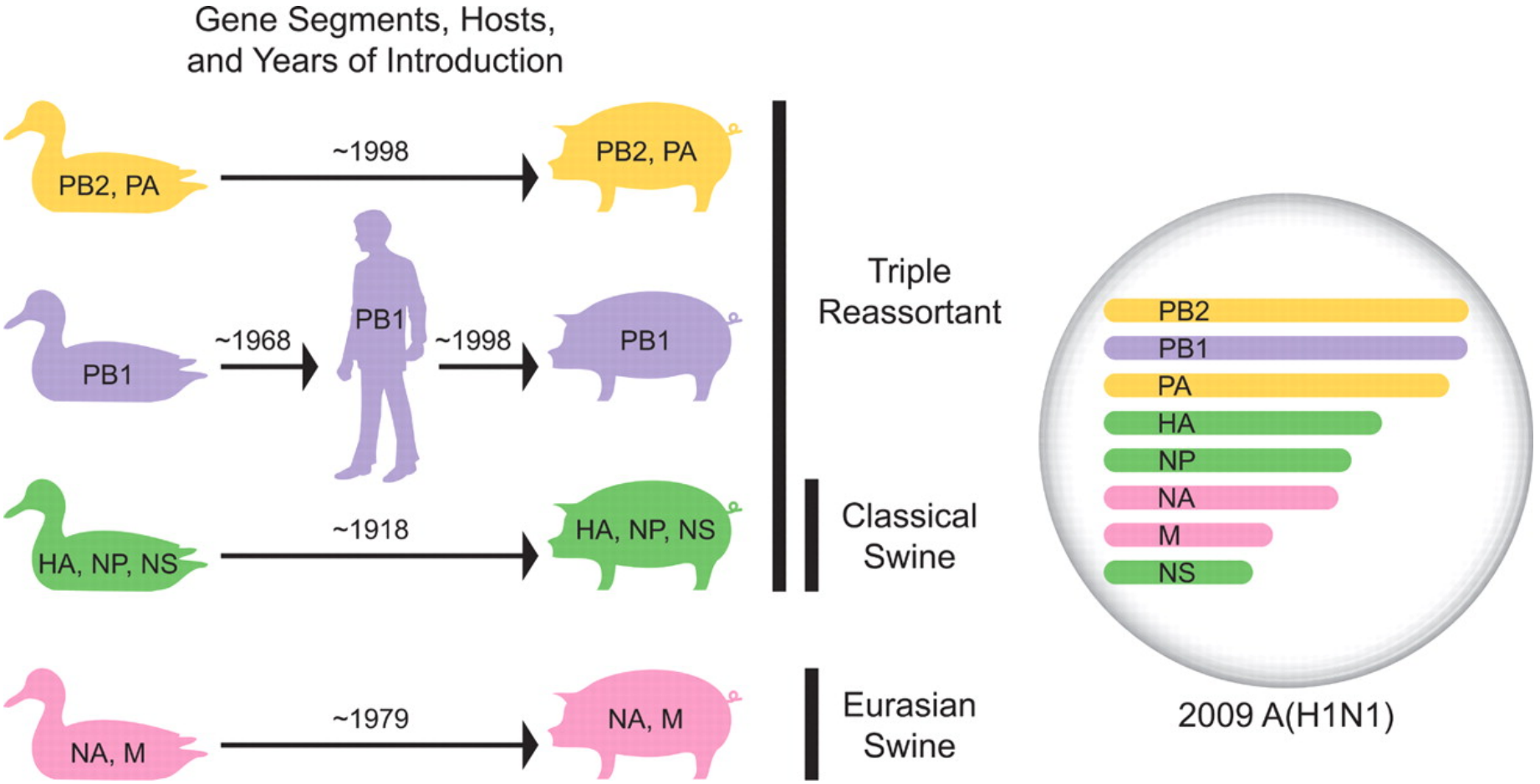

Classical swine (H1N1)
North American avian (H1N1)
Human (H3N2)
Eurasian avian-like swine (H1N1
Influenza A/H1N1/09
PB2 North Am. avian
PB1 human H3N2
PA North Am. avian
N1 classical swine
NP class. swine
N1 avian-like swine
M avian-like swine
NS class. swine

Fig. 1 Host and lineage origins for the gene segments of the 2009 A(H1N1) virus: PB2, polymerase basic 2; PB1, polymerase basic 1; PA, polymerase acidic; HA, hemagglutinin; NP, nucleoprotein; NA, neuraminidase; M, matrix gene; NS, nonstructural gene

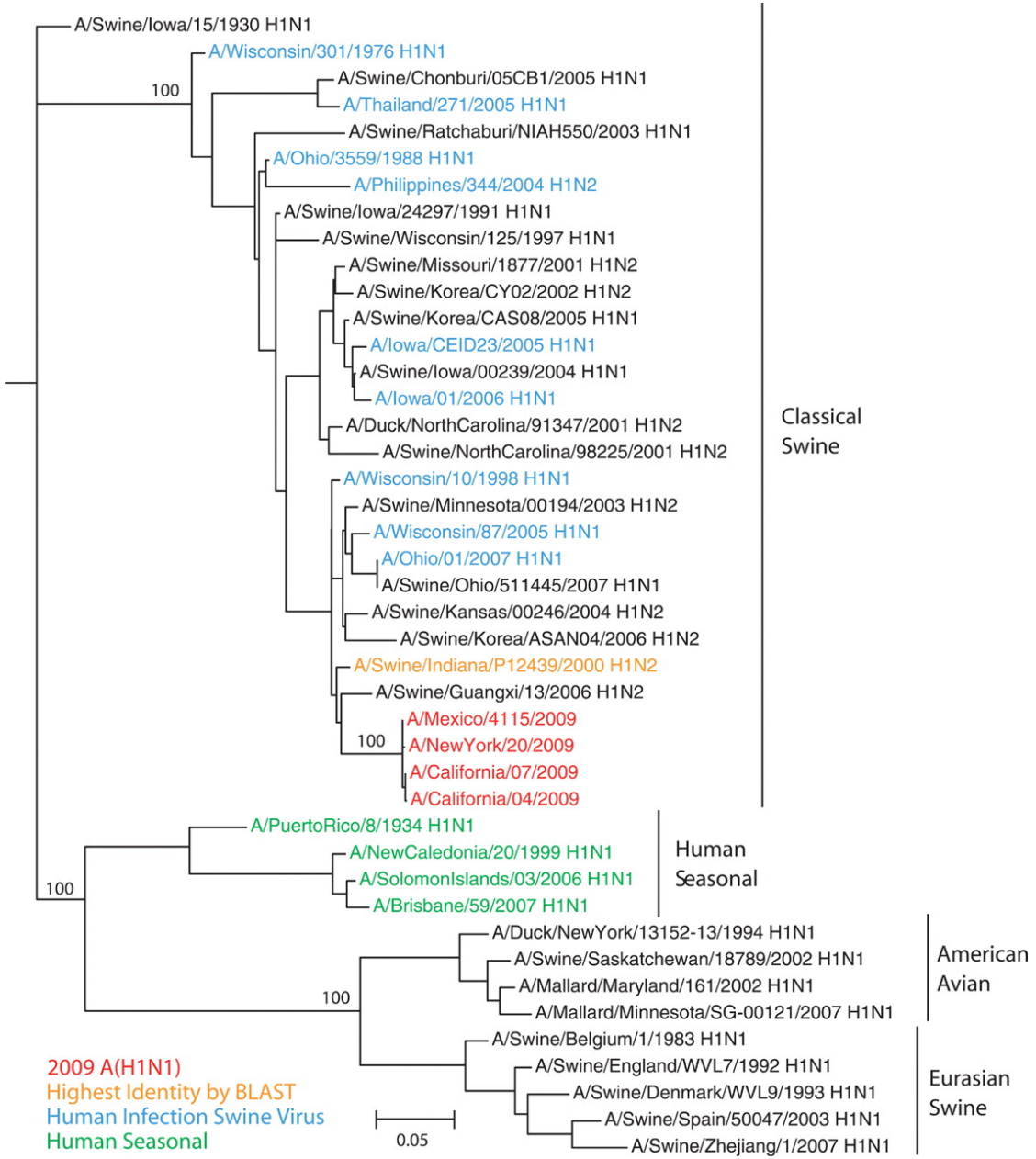


Published by AAAS

R. J. Garten et al., Science 325, 197 -201 (2009)

Science
AAAS

Fig. 2 A maximum likelihood phylogenetic tree for nucleotide sequences of the HA gene of selected influenza viruses



Published by AAAS

R. J. Garten et al., Science 325, 197 -201 (2009)

Science
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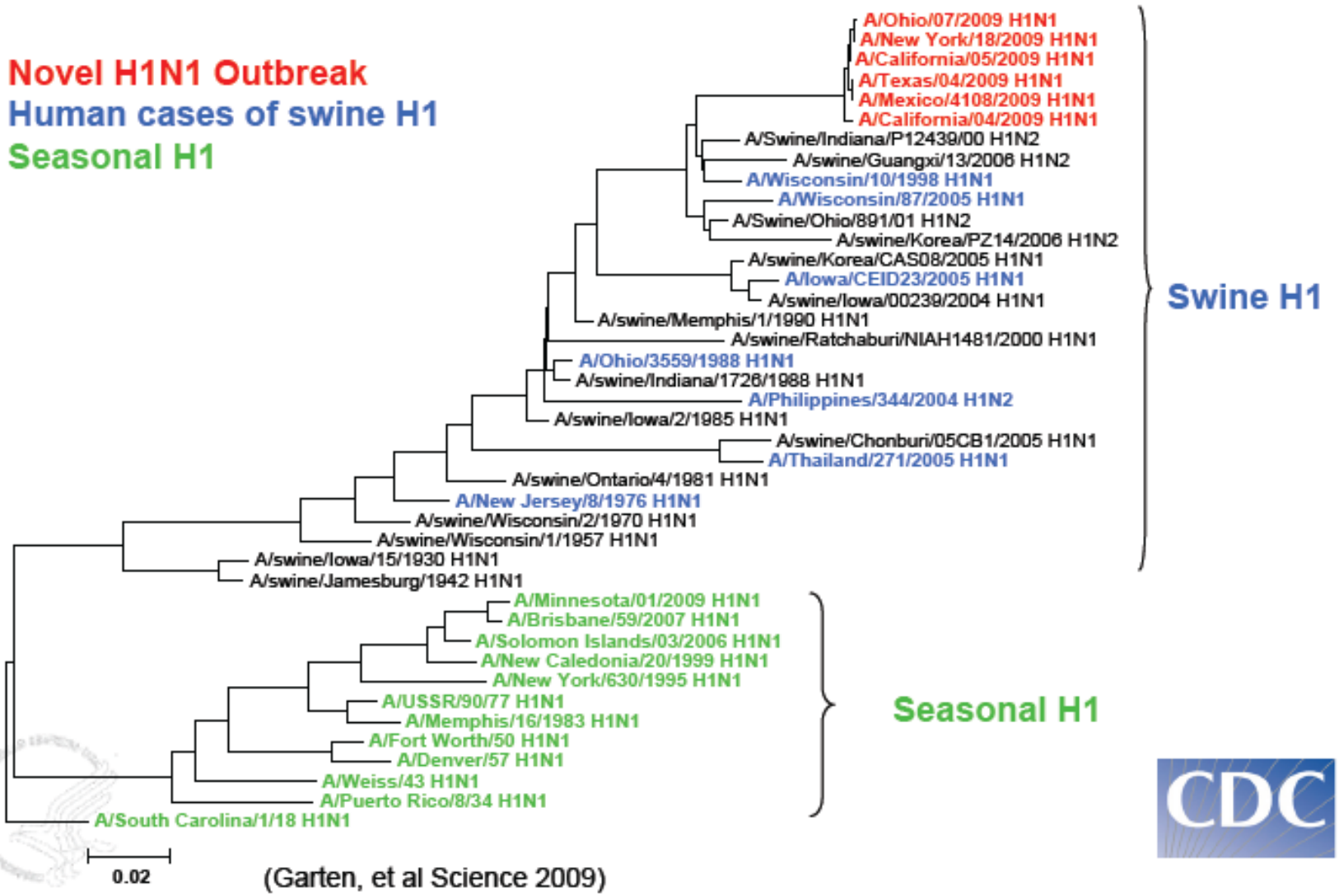
Phylogenetic Tree of Hemagglutinin H1: Swine vs. Seasonal

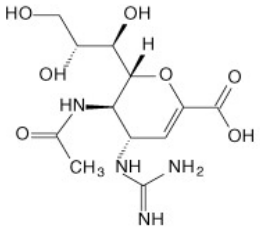


(Garten, et al Science 2009)

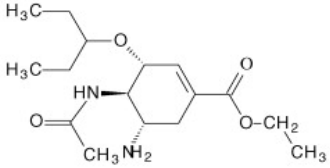
防治流感的抗病毒藥物

- M2 抑制劑（A 型有效)：金剛胺(amantadine)、金剛乙胺
- NA 抑制劑（A & B型有效）：克流感(oseltamivir)、瑞樂莎(zanamivir)

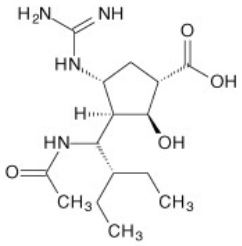
Neuraminidase inhibitors



Zanamivir
Relenza®

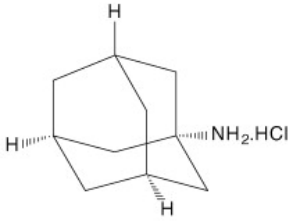


Oseltamivir
Tamiflu®

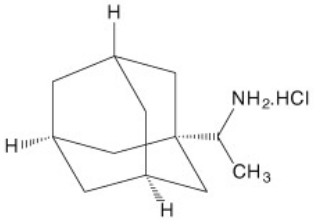


Peramivir

M2 ion channel blockers

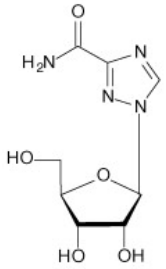


Amantadine
Symmetrel®, Mantadix®

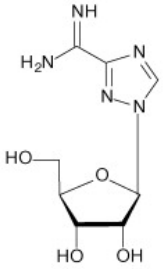


Rimantadine
Flumadin®

IMP dehydrogenase inhibitors

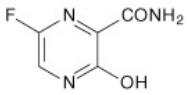


Ribavirin
Virazole®

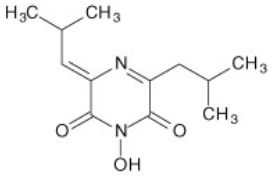


Viramidine (prodrug of ribavirin)

RNA polymerase (endonuclease) inhibitors



T705

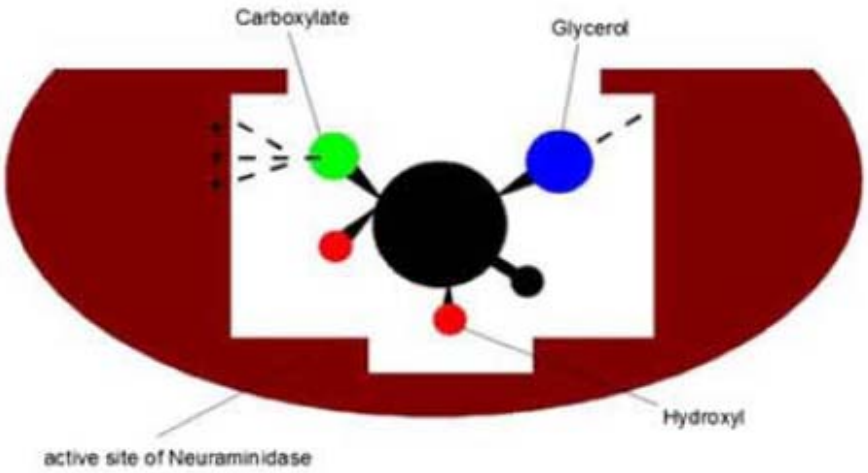


Flutimide

TRENDS in Pharmacological Sciences

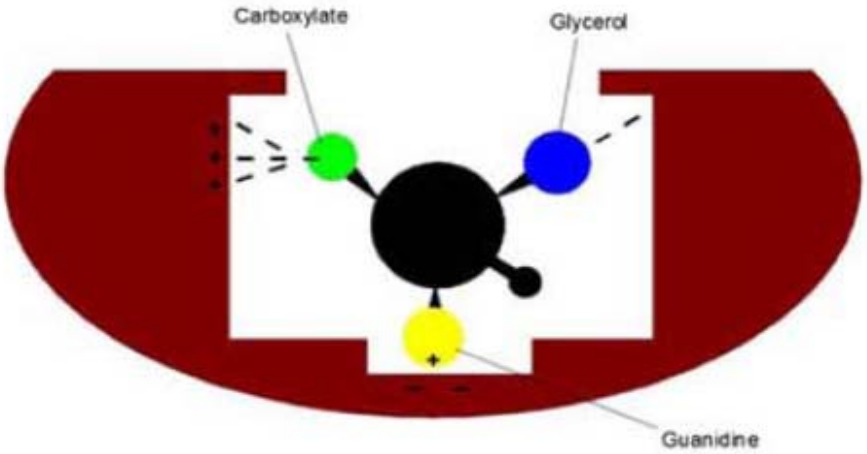
藥品名為克流感的奧斯他偉生產流程複雜，製程耗時一年。目前下的訂單需要數年才能交貨。即使在緊急狀況下，也很難製造出非專利性的同類藥物。

Sialic acid (N-Acetylneuraminic acid)

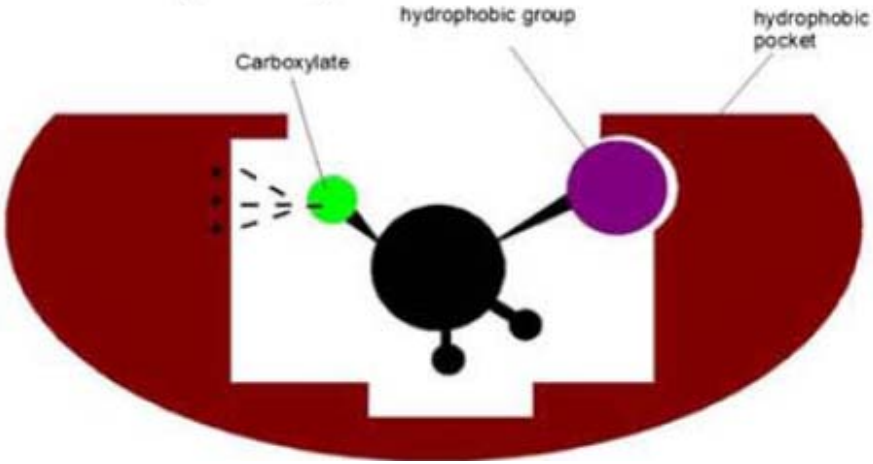


active center of Neuraminidase

Zanamivir (Relenza®)



Oseltamivir (Tamiflu®)



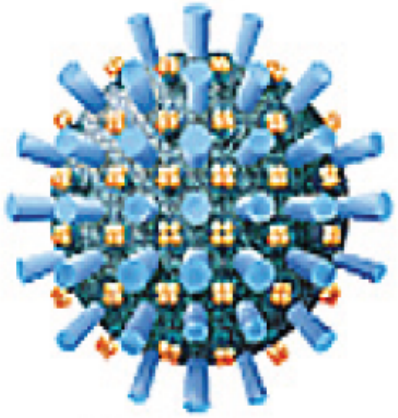
新流感藥物

現有的抗流感病毒藥物會抑制病毒表面上的特定蛋白質，像金剛胺（amantadine）這種藥物會抑制M2蛋白質；札納米偉（zanamivir）和奧斯他偉（oseltamivir）則會抑制神經胺酸酶。目前開發的新藥中，有些是改良過的神經胺酸酶抑制劑，其他還有些是全新的做法，例如防止病毒進入細胞，或阻斷它們在細胞內的功能。

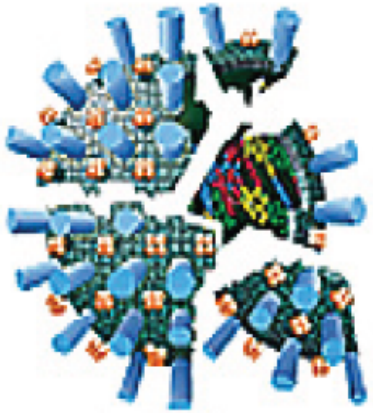
方法	藥物名（公司名）	優點	開發現況
抑制神經胺酸酶（病毒利用這種蛋白質從一個細胞中釋出，而去感染其他細胞）	帕拉米偉（生物水晶公司）；CS-8958（生物群／三共）	神經胺酸酶抑制劑副作用較小，較不會像金剛胺類舊型藥物引發病毒的抗藥性。CS-8958則是一種長效性藥物，可附著在肺部長達一星期。	藥丸型式的帕拉米偉在臨床試驗時無法有效抵達肺部，2006年將測試靜脈注射的方式。CS-8958已完成初步安全測試
抑制病毒黏附在細胞上	流感酶（NexBio）	由於這種藥物可阻斷流感病毒進入細胞時利用的唾液酸受體，流感酶應對所有的流感病毒株都同樣有效。	計畫在2006年展開臨床試驗
刺激RNA干擾機制	G00101（葛藍尼亞公司）；未命名藥物（阿尼藍製藥公司）	利用DNA活化細胞內原本就有的防衛機制，將病毒的指令加上摧毀的標記。小鼠實驗顯示G001498對H5型禽流感和H7型流感病毒有效。	預計在18個月內會展開臨床試驗
可阻斷病毒基因的反義DNA	中和基因（AVI 生物製藥）	合成的DNA可和病毒RNA結合，使病毒無法命令宿主細胞製造更多的病毒，這型策略應對所有病毒株都有效。	預計2006年將展開動物試驗

流感疫苗

seasonal influenza vaccine formulations

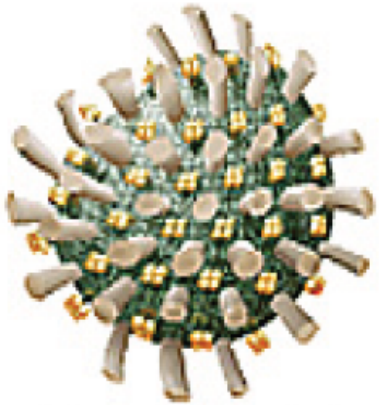


Whole virus



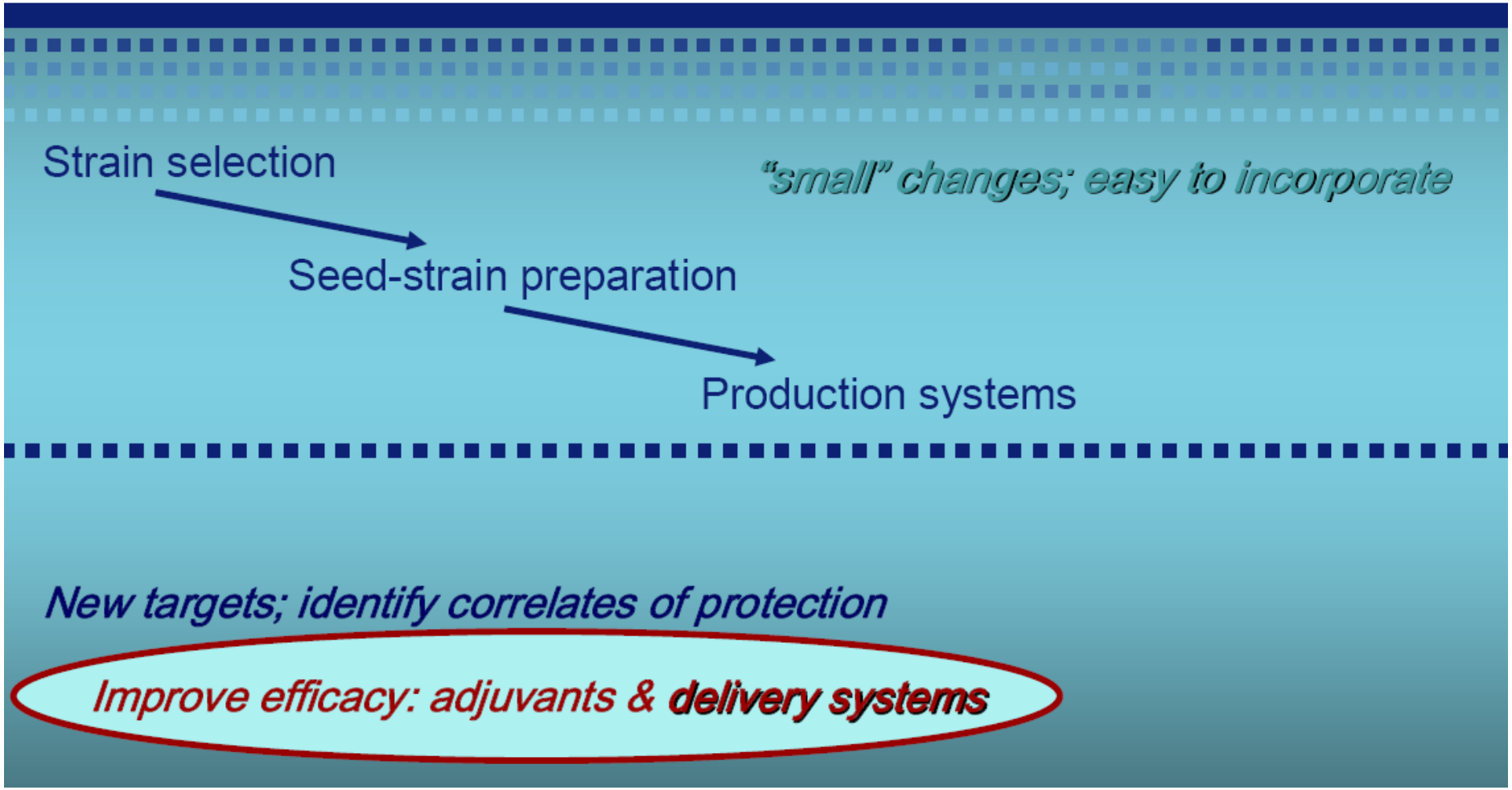
Split virus

Subunit
(surface antigen)



Live attenuated

Pandemic Influenza Vaccines



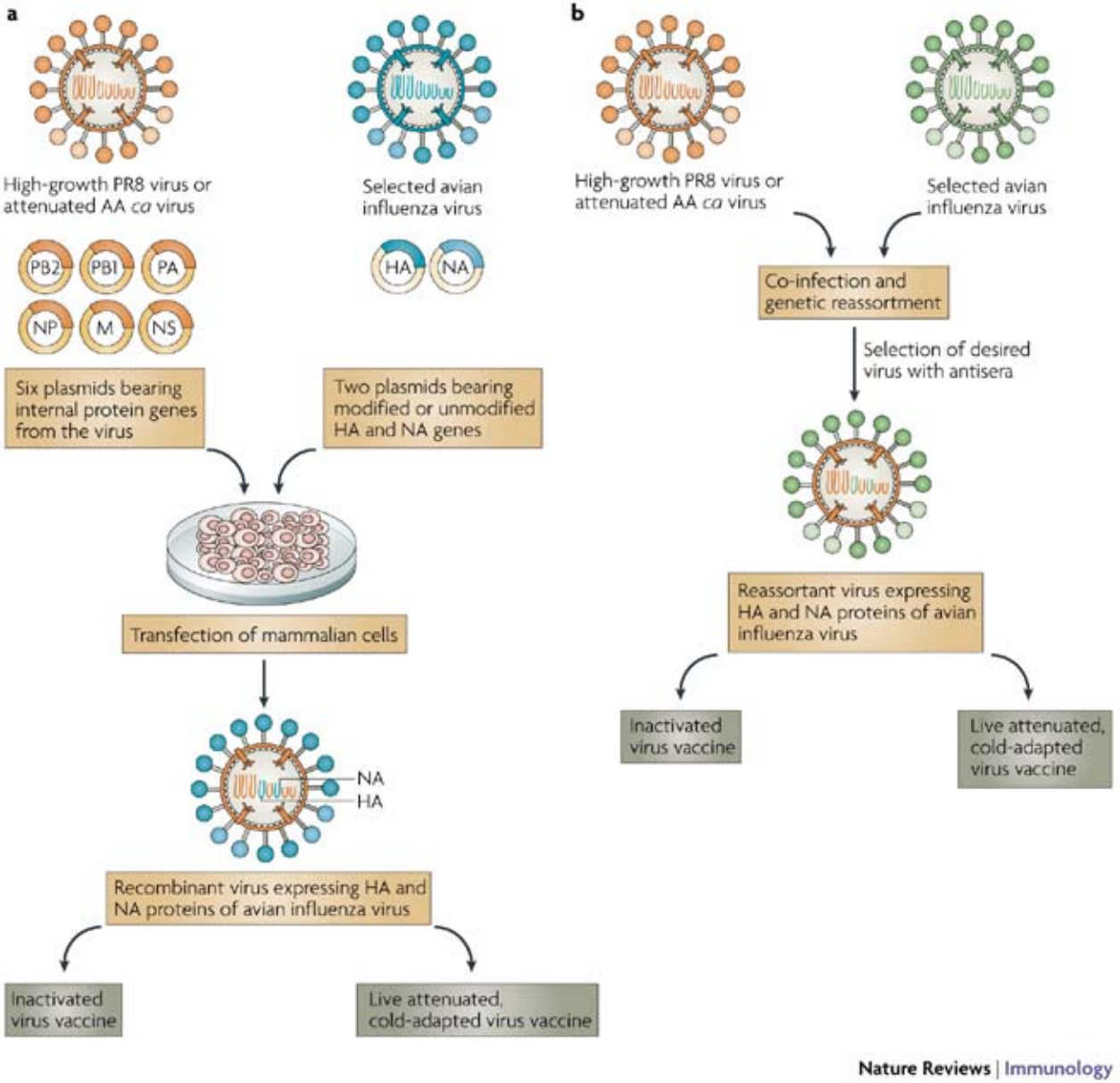
禽流感疫苗之開發現況

新疫苗技術

工業界和學術界的研究人員正試驗新預防接種方法，或許可以增加疫苗供應量，讓更多人受到保護。他們也正開發需求急迫時可加快疫苗生產的技術。

新技術	優點	目前進度	公司
皮下注射	將疫苗注射到皮下而非肌肉，可以讓每次所需劑量只需原來的1/5。	臨床試驗顯示其可行性，但很少護士和醫生熟悉這個步驟。	艾歐邁（Iomai）、葛蘭素史克
佐劑	疫苗內的化學添加物可增強免疫反應，因此每次注射所需的抗原蛋白質用量較低。	歐洲已核准了一種疫苗，其他疫苗正積極開發中。	艾歐邁、開隆、葛蘭素史克
細胞培養疫苗	利用培養在生物反應器內的細胞來繁殖流感病毒（而非雞胚），可在全球流感爆發時加速疫苗的生產。	開隆正在歐洲進行大規模試驗，賽諾菲巴斯德和庫賽爾（Crucell）則為美國開發此種技術。	開隆、百特、賽諾菲巴斯德、庫賽爾、蛋白質科學
DNA疫苗	將覆有病毒DNA的金質微粒以空氣束注射到皮下。針對新病毒株的DNA疫苗可以在數週內製成，而不需要等待數月。成品不需冷藏且可保存數年。	目前尚未證實DNA疫苗對人類有效。粉末醫學公司（PowderMed）預估在2006年底可獲得H5N1 DNA疫苗的小型臨床試驗結果。	粉末醫學公司、凡科（Vical）
萬能流感疫苗	針對流感病毒鮮少突變的蛋白質而開發的疫苗，將可讓接種者對所有流感病毒株都免疫。儲備這種疫苗將可有效防禦全球流感。	阿坎比斯（Acambis）公司今年夏天開始開發針對M2e抗原的疫苗。	阿坎比斯

Eight-plasmid 反式遺傳學技術 禽流感病毒疫苗株的製備

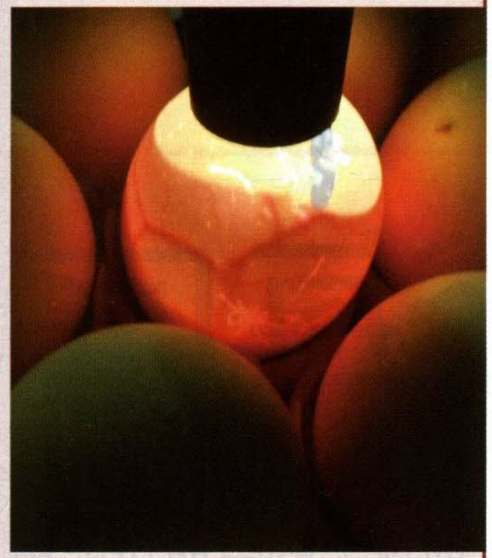


Nature Reviews | Immunology

流感疫苗製造流程

世界衛生組織每年2月會公佈當年年底全球可能流行的流感病毒株，各大藥廠隨即開始找尋和世衛公佈病毒株具有相同抗原性、但比較適合培養的疫苗株，確認疫苗株未受到污染之後，就可生產疫苗。由於世衛所公佈該年年底可能流行的季節性流感皆包含三種可能病毒，因此各大藥廠都必須做出三種疫苗，檢驗每一劑所含抗原量，並將三種疫苗調配起來，得到最後抗原量夠高、足以刺激人體產生抗體的疫苗。

疫苗的製造方式是將病毒注入已受精的雞蛋，在雞胚胎中複製出大量病毒，之後再抽取含有病毒的尿囊液，將病毒裂解、去活化（即殺死病毒）並進行純化，取出病毒抗原以製造疫苗。這也是為什麼對雞蛋過敏的人不適合注射流感疫苗。



製造新流感疫苗所用的雞蛋，事先會先經過人工抽驗，圖為被抽驗的雞蛋在照蛋機的強光照射下，顯露出雞胚胎的血管。

在利用雞胚製造流感疫苗的過程中，有一些瓶頸使得全球流感疫苗的生產時間需要六個月或更久，屆時將面臨嚴重的供不應求。

Cell Culture-based Flu Vaccines

Madin-Darby canine kidney (MDCK) cells

- first extracted in 1958 from a healthy cocker spaniel and subsequently "immortalized" through growth in culture
- Such cells prove to be "highly permissive" for growing the influenza virus
- Whether MDCK cells are *tumorigenic* and *oncogenic* ?

Cell Culture Flu Vaccines

- Solvay
  - **MDCK** cells grown on microcarriers within bioreactors
- Nobilon
  - **MDCK** cells grown on microcarriers within bioreactors
- Chiron
  - **MDCK** cells adapted to grow in suspension
- Baxter
  - **Vero** cells grown on microcarriers within bioreactors (Vaccine 2007)

- both types of cells can **induce tumors** when administered to immunosuppressed mice
- post-MDCK vaccine-manufacturing procedures entail **extensive purification and inactivation steps to reduce the risk that any intact MDCK cells or cell-derived neoplastic agents could be found in the final vaccine product.**
- Solvay's Medema estimates a greater than **10^21 clearance factor** for removing MDCK cells from finished vaccine, while Chiron's cell-removal estimates extend higher.

以佐劑對抗流感

新流感疫情蔓延，世界衛生組織建議在疫苗中添加佐劑，以有效利用有限的疫苗。佐劑為何有這種功效？台灣也有研發佐劑嗎？

撰文／黃明熙、周愛湘、蕭佳欣、劉士任、莊再成

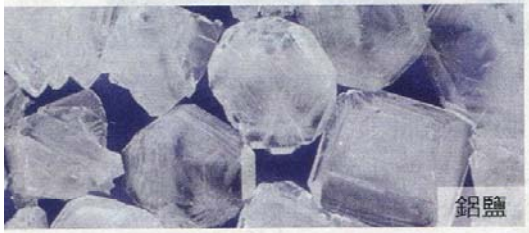
乳化劑型佐劑的比較

佐劑名稱	開發單位	組成成份			製造程序
		核心油脂	疏水性乳化劑	親水性乳化劑	
MF59	諾華（Novartis）	角鯊烯	Span 85	Tween 80	單一乳化程序
AS03	葛蘭素史克（GSK）	角鯊烯／維生素E	—	Tween 80	乳化分散兩階段
PELC	國衛院疫苗中心	角鯊烯	Span 85	生物可吸收式高分子	乳化分散兩階段

新舊佐劑

核可疫苗裡的佐劑

- 鋁鹽
- 水包油與油包水乳化液
- 微脂體（脂質微粒）
- 仿病毒顆粒（由脂質與病毒蛋白所構成）
- 維生素 E
- 單磷酸脂質 A（MPL），這是一種純化的細菌脂多醣成份。



鋁鹽

研發中的佐劑

- CpG，未甲基化的細菌 DNA 片段（甲基化是人類 DNA 的特質）。
- 皂素（植物萃取物）：
  - QS21
  - Quil A
  - 免疫刺激複合體（皂素與脂質籠）
- 利用病毒做為抗原載體：
  - 禽痘病毒
  - 牛痘病毒
  - 金絲雀痘病毒
- 類病毒粒子，自動組裝的病毒外殼，缺少遺傳物質。
- 介白素與其他細胞訊號分子

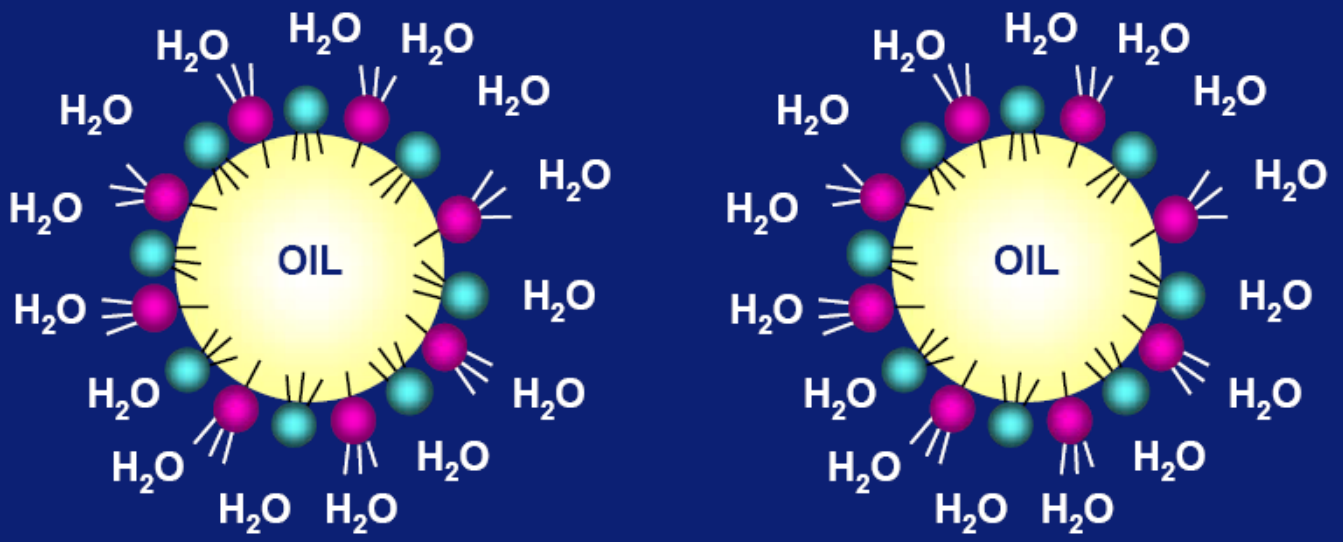
Assessment of pre-pandemic H5N1 clinical trials

Type of vaccine	Compliance with EU licensing criteria
Split vaccine no adjuvant	Need two doses of 90 µg
Split/subunit vaccine with alum	Need two doses of 30-45 µg
Whole virus (egg) with alum	Need two doses of 10-15 µg
Subunit with MF59 adjuvant	Need two doses of 7.5 µg
Whole virus Vero cell culture, no adjuvant	Need two doses of 7.5 µg
Split vaccine with AS adjuvant	Need two doses of 3.8 µg

Data presented at WHO meeting, February 2007
(Sanofi Pasteur, 4 Companies in Jp, CSL, Microgen, Sinovac, GSK, Novartis,Baxter)

MF59 - o/w emulsion adjuvant (Novartis)

Appearance: milky white oil in water (o/w emulsion)



Composition:

0.5% Polysorbate 80 water-soluble surfactant
0.5% Sorbitan Triolate oil-soluble surfactant
4.3% Squalene -oil
Water for injection
10 nM Na-citrate buffer

Density: 0.9963 g/ml

Viscosity: close to water, easy to inject

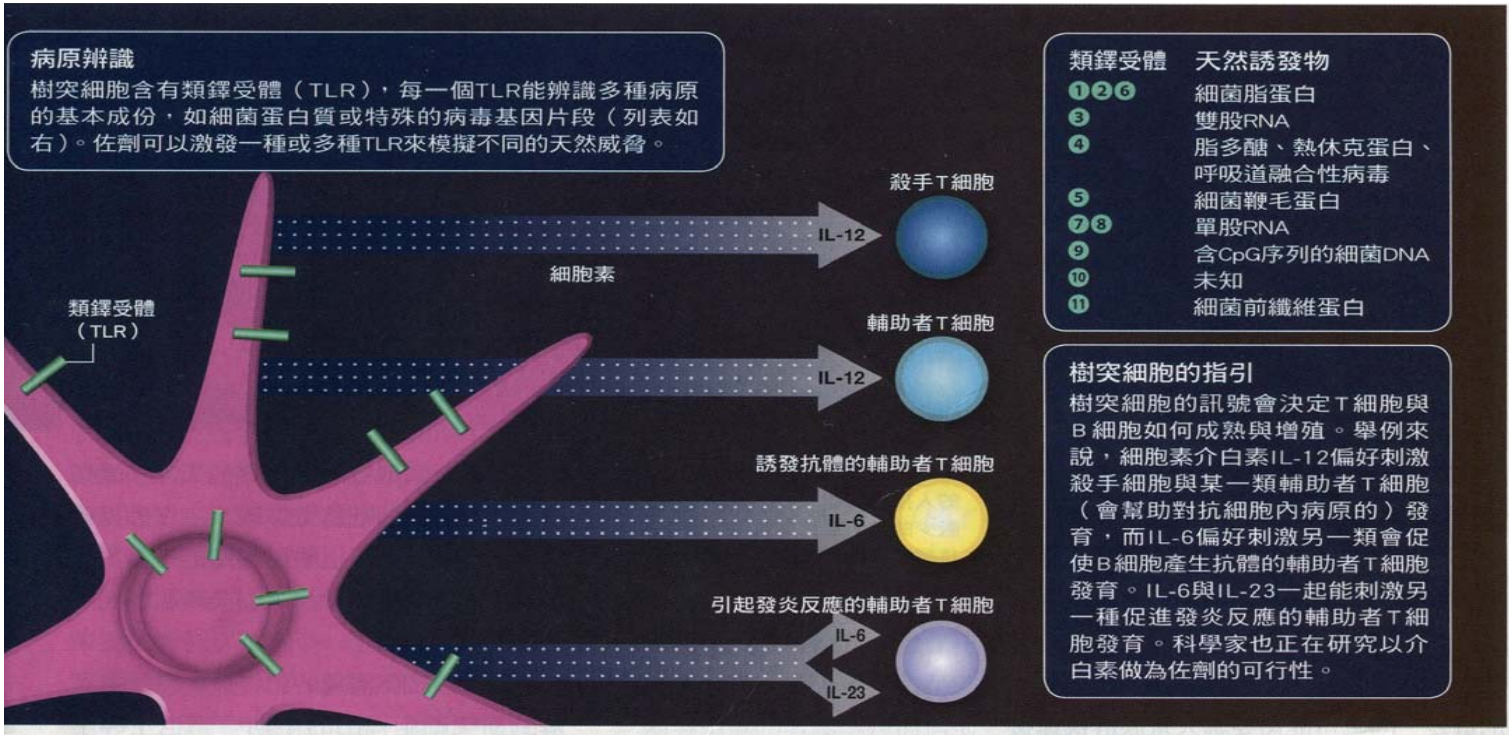
AS-03 adjuvant

- Oil-in-water emulsion (cf MF59): metaboliseable oil sterol (alpha-tocopherol) emulsifying agent
- Strong dose-reduction for pandemic vaccine
- Strong broadening of protective response

疫苗加強劑

佐劑的強化效用

佐劑有數種機制來增進免疫系統對疫苗抗原的反應，但是其中最有效的方式，可能是經由活化樹突細胞上的微生物辨識受體。樹突細胞會根據它們感知到的威脅型式，來引導其他免疫細胞以不同方式反應。疫苗研發者可以運用這些知識來選擇佐劑，因此不只可以增進免疫反應，也能著重加強需要的反應。



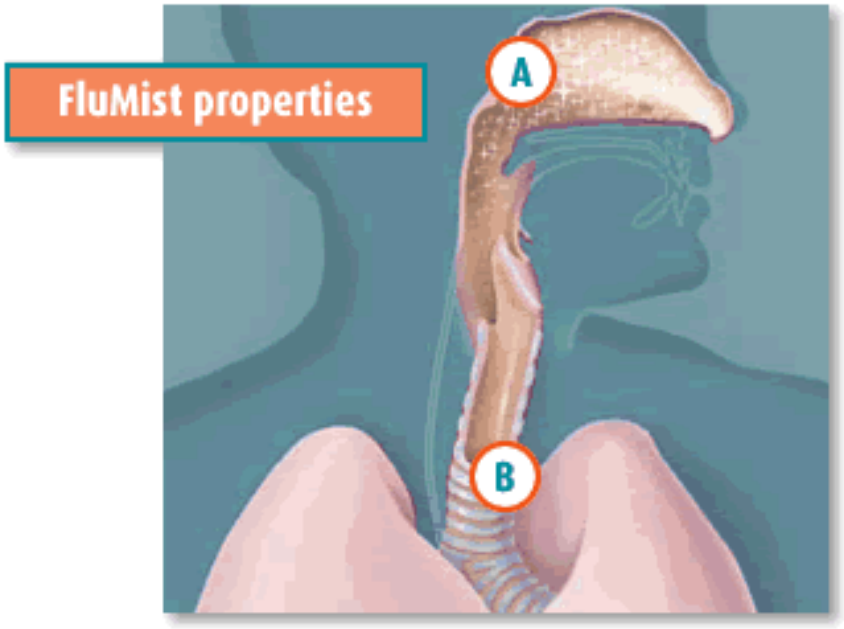
進行中的研究

新一代疫苗

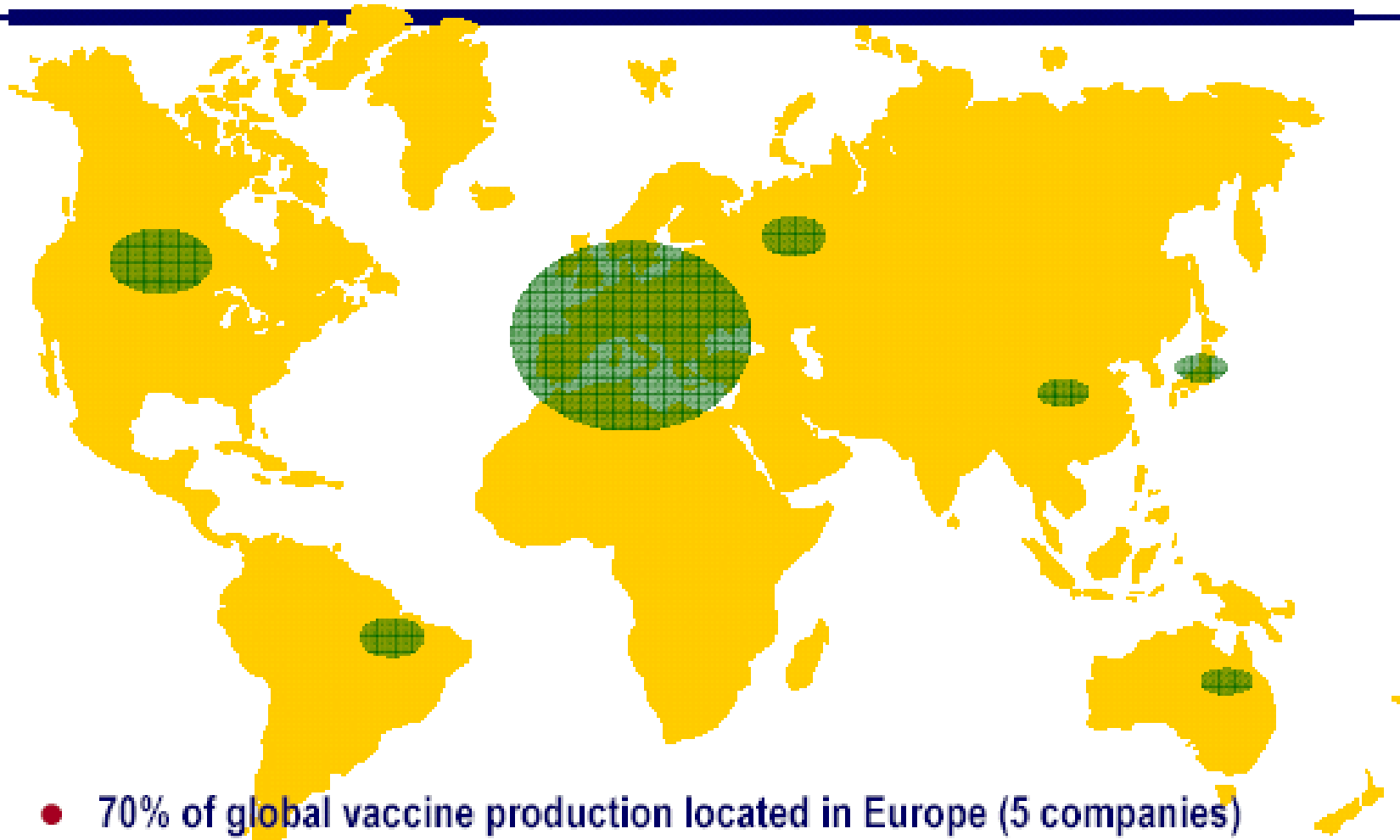
下表列出的疫苗添加了嶄新的佐劑，有些已經被部份國家核准，有些正在進行人體試驗後期（第三期）。

疾病	疫苗	佐劑成份	發展階段	公司
A型肝炎	Epaxal	仿病毒顆粒	歐洲核准	庫賽爾生技
B型肝炎	Fendrix	AS04（鋁鹽、MPL）	歐洲核准	葛蘭素史克藥廠
	Supervax	RC-529（合成的MPL）	阿根廷核准	Dynavax生技
	Heplisav	CpG	試驗第三期	Dynavax生技
人類乳頭瘤病毒	Cervarix	AS04	96個國家核准	葛蘭素史克藥廠
流行性感冒（季節性與大流行性）	Fluad, Focetria	MF59（水包油乳化液）	歐洲核准	諾華藥廠
	Inflexal V	仿病毒顆粒	歐洲核准	庫賽爾生技
	Prepandrix, Pandemrix	AS03（水包油乳化液與維生素E）	歐洲核准	葛蘭素史克藥廠
	季節性流感老人疫苗	AS03	試驗第三期	葛蘭素史克藥廠
瘧疾	Mosquirix	AS01（微脂體、MPL與QS21）	試驗第三期	葛蘭素史克藥廠
非小細胞肺癌	Mage 3	AS15（微脂體、MPL、QS21與CpG）	試驗第三期	葛蘭素史克藥廠
	CimaVax EGF	Montanide ISA-51（水包油乳化液）	古巴與智利核准	Bioven生技

MedImmune FluMist



Vaccine production capacities



- 70% of global vaccine production located in Europe (5 companies)
  - 50% of that production is exported outside of Europe

Source:EVM Press Release 30 April 2004

Influenza A (H1N1) 2009 Monovalent

- FDA approved these vaccines as a strain change to each manufacturer's seasonal influenza vaccine. There is considerable experience with seasonal influenza vaccine development and production and influenza vaccines produced by this technology have a long and successful track record of safety and effectiveness in the United States. The Influenza A (H1N1) 2009 Monovalent vaccines will undergo the usual testing and lot release procedures that are in place for seasonal influenza vaccines.

- **Injectable Vaccines**
  - Influenza A (H1N1) 2009 Monovalent Vaccine (CSL Limited)
  - Influenza A (H1N1) 2009 Monovalent Vaccine (Novartis Vaccines and Diagnostics Limited)
  - Influenza A (H1N1) 2009 Monovalent Vaccine (Sanofi Pasteur, Inc.)
- **Intranasal Vaccine**
  - Influenza A (H1N1) 2009 Monovalent Vaccine (MedImmune LLC)

Table 1: FDA Approved H1N1 Vaccines

Proper Name	Route of Administration	Virus	Manufacturer	How Supplied	Indication
Influenza A (H1N1) 2009 Monovalent Vaccine	Injectable	Inactivated	CSL Limited	0.5 mL preservative-free single-dose, prefilled syringe 5 mL multi-dose vial[1]	Active immunization of persons ages 18 years of age and older against influenza disease caused by pandemic (H1N1) 2009 virus.
Influenza A (H1N1) 2009 Monovalent Vaccine	Injectable	Inactivated	Novartis Vaccines and Diagnostics Limited	0.5 mL single-dose, prefilled syringe[2] 5 mL multi-dose vial[1]	Active immunization of persons 4 years of age and older against influenza disease caused by pandemic (H1N1) 2009 virus.
Influenza A (H1N1) 2009 Monovalent Vaccine	Injectable	Inactivated	Sanofi Pasteur, Inc.	0.25 mL preservative-free, single-dose, prefilled syringe and single-dose vial 0.5 mL preservative-free, single-dose, prefilled syringe and single-dose vial 5 mL multi-dose vial[1]	Active immunization of persons 6 months of age and older against influenza disease caused by pandemic (H1N1) 2009 virus.
Influenza A (H1N1) 2009 Monovalent Vaccine	Intranasal	Live, attenuated	MedImmune LLC	0.2 mL pre-filled, single-dose intranasal sprayer	Active immunization of individuals 2-49 years of age against influenza disease caused by pandemic (H1N1) 2009 virus.

[1] contains Thimerosal as preservative

[2] Thimerosal, a mercury derivative used during the manufacture, is removed by subsequent purification steps to a trace amount (≤ 1 mcg mercury per 0.5 mL dose)

ASPR

Total H1N1 Vaccine Products & Output


standard

or


standard

or


w/ adjuvant

CSL 18.7%


standard

MedImmune 5.8%


w/ adjuvant

GSK 3.4%


standard

or


standard

or


w/ adjuvant

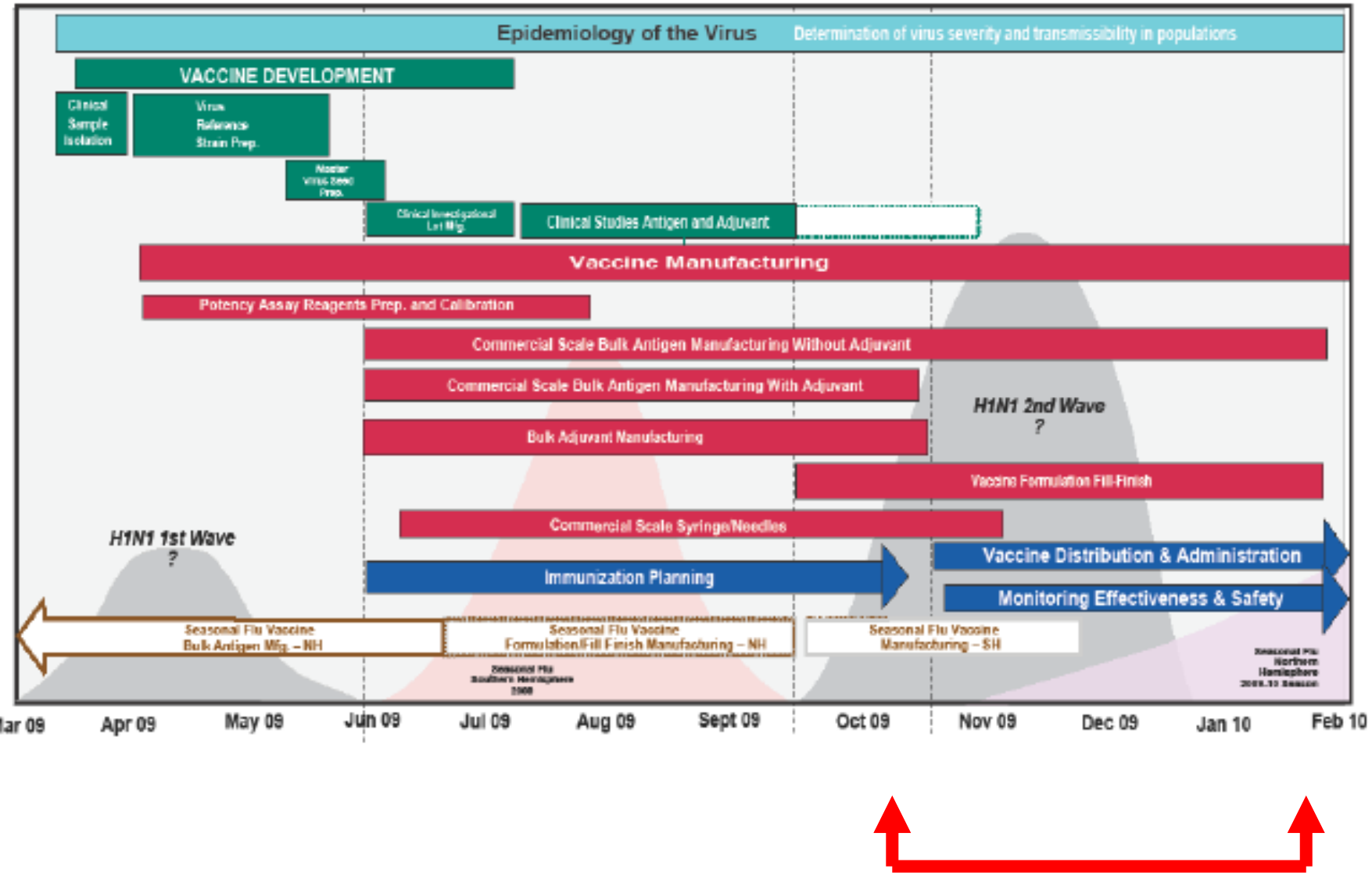
sanofi pastuer 26.4%


standard

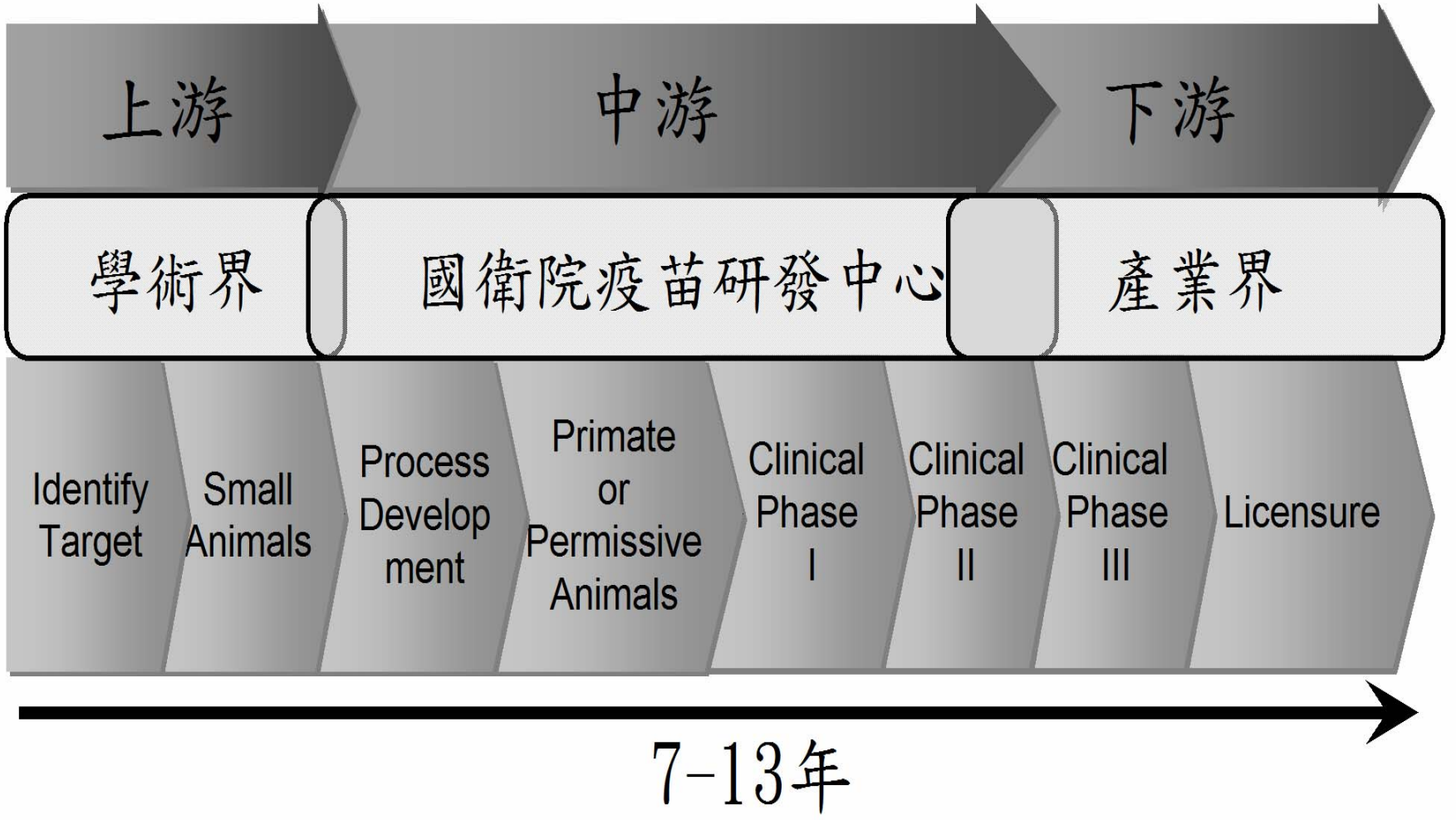

w/ adjuvant

Novartis Vaccines 45.7%

U.S. 2009-H1N1 Vaccine Strategy

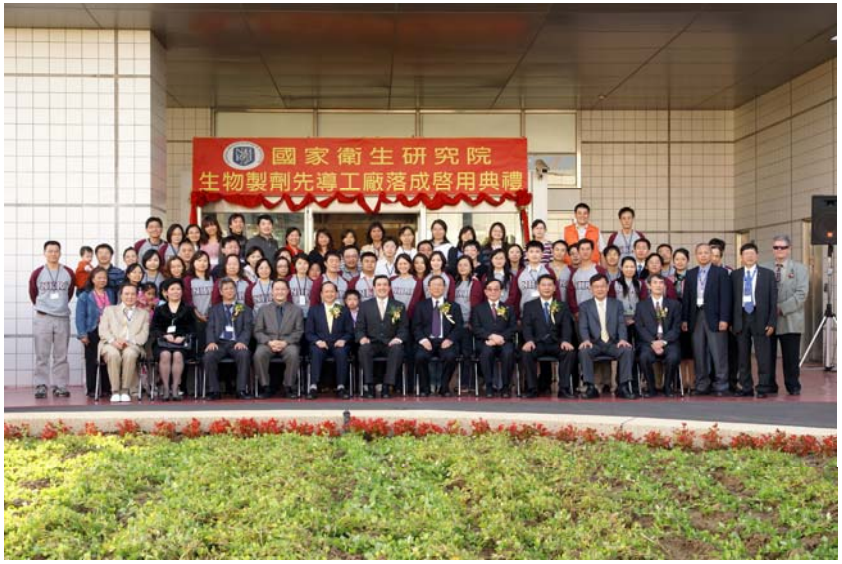


台灣疫苗開發分工體系


上游
中游
下游
學術界
國衛院疫苗研發中心
產業界
Identify Target
Small Animals
Process Development
Primate or Permissive Animals
Clinical Phase I
Clinical Phase II
Clinical Phase III
Licensure
7-13年

國家衛生研究院生物製劑先導工廠

（94年9月動土、96年完工、97年試產）



細菌性疫苗:b 型嗜血桿菌疫苗,卡介苗

開發新疫苗：腸病毒疫苗,H5N1及H1N1流感疫苗

國光生技公司完成國內首座符合歐盟標準的新疫苗廠，昨天下午由總統馬英九(左二)等人共同主持啟用典禮。2009/06/18 19:40》

國光生技新疫苗廠昨天啟用，將立即投入新流感疫苗研發產製。圖為國光生技員工正在篩選疫苗所需的雞胚胎蛋。（路透）2009/06/18 19:40》

新流感疫苗安全嗎？

當H1N1新流感陰影籠罩全世界時，注射疫苗成為最好的自保之道；但注射疫苗是否會產生副作用，卻人言言殊。從科學的觀點出發，施打新流感疫苗的風險究竟如何？

撰文／李名揚

國光疫苗純度

項目	國際標準	國光疫苗	臨床解釋
卵蛋白含量	≦2000奈克／毫升（歐盟）	1奈克／毫升	含量越低，發生過敏的機會越低
內毒素殘留	≦200單位／毫升	1單位／毫升	含量越低，發燒的機會越低
滲透壓	-	1：1（生理食鹽水）	滲透壓越接近生理食鹽水，注射時越不疼痛

各國新流感疫苗疑似不良反應通報率

每10萬劑	台灣	美國	加拿大	日本
疑似不良反應	11.7	7.1	21.5	12.1
疑似嚴重不良反應	3.3	0.4	0.7	1.9

註：美、日、加均以疫苗配送劑數來計算（即疫苗送到注射場所即視為已注射），台灣也換成相同算法，因此與51頁內文的數字不同。

國光與諾華疫苗的疑似不良反應通報率

每10萬劑	國光	諾華
疑似不良反應	17.6	18.2
疑似嚴重不良反應	5.5	3.3

註：醫療院所通報注射疫苗後造成的疑似不良反應時，有少數（約1/15）未註明疫苗的廠牌，因此表中數字比實際數字略低。

Vaccine Related Questions

- Thimerosal 硫柳汞
  - a mercury-based preservative that has been used for decades in the United States in multi-dose vials (vials containing more than one dose) of some vaccines to prevent the growth of microorganisms, such as bacteria and fungi, which may contaminate them.
- Guillain-Barré syndrome (GBS) 吉蘭–巴雷氏綜合症
  - 1976 swine flu vaccine in US
  - a higher risk for GBS than those who were not vaccinated (about 1 additional case occurred per 100,000 people vaccinated).