



H1N1 2009 Pandemic Human Swine Influenza

What the government **can** do ?

未有流感疫苗前
香港可以怎麼辦



Summary I

- © The 2009 H1N1 Human Swine Influenza has a high attack rate among children.
- © The mortality rate would increase 10 times in the presence of bacterial co-infection.
- © 30-80% of bacterial co-infection are related to pneumococcus and Haemophilus influenza which are vaccine preventable.
- © **The government should prevent such complication by immunization program**

Age Group	Male (%)	Female(%)	Total(%)
<1	91.2	73.7	83.9
1-4	66.2	66.1	58.1
5-14	49.7	66.3	57.7



Summary II

- © Many of our frontline staffs who are working mothers and fathers have increased nasal colonization with pneumococcus
- © Elderly (age >65) has increased cardiovascular and pneumonic mortality related to pneumococcal co-infection during influenza period.
- © Chronic smokers and patient with diabetes mellitus have increased risk of pneumococcal co-infection during influenza virus infection.
- © Hong Kong pneumococcal population has high rate of penicillin resistance.
- © **The government should prepare the above at risk populations against pneumococcal co-infection by vaccination program before pandemic.**

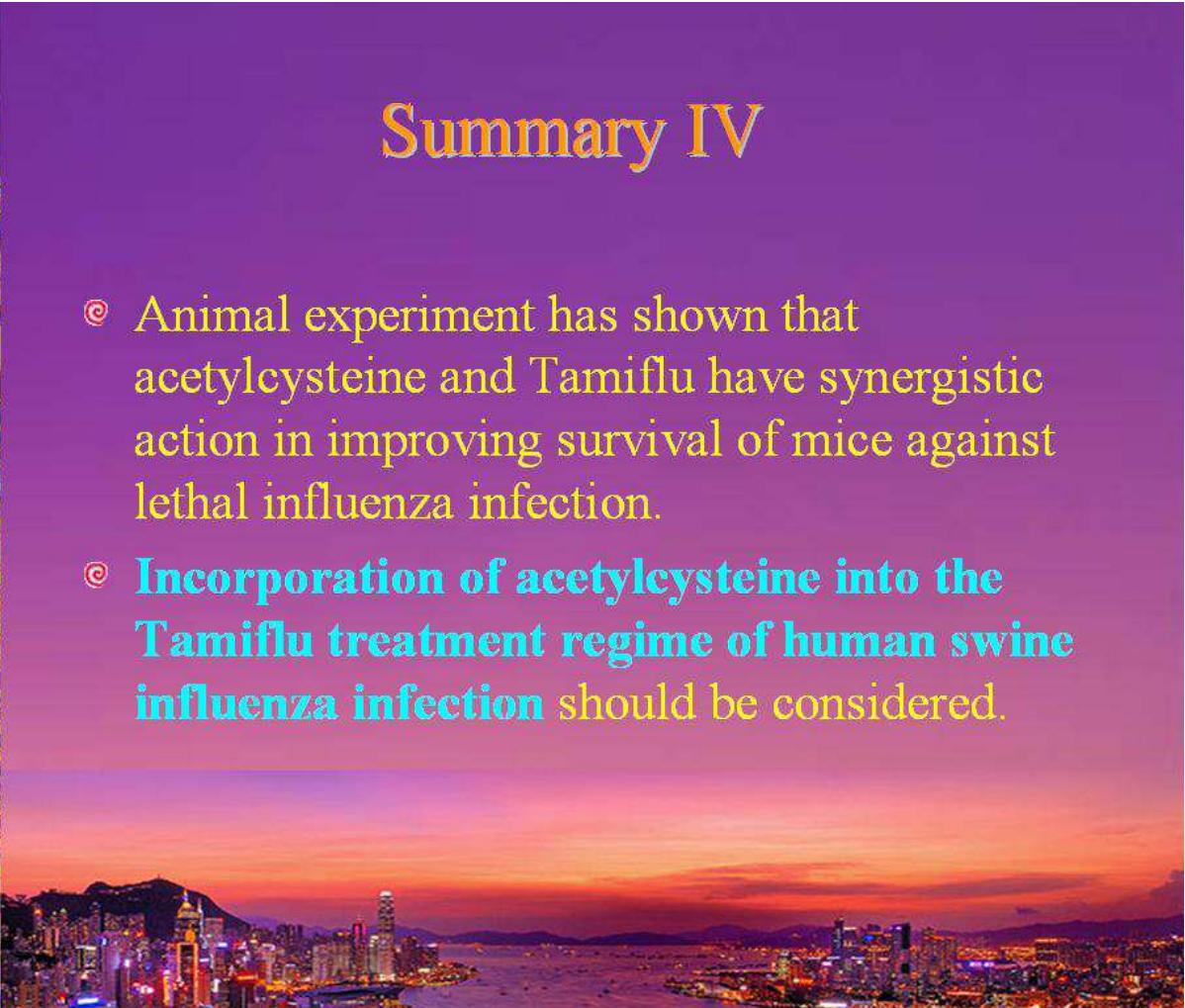


Summary III

- ② Acetylcysteine 600mg b.d. has been shown to reduce symptomatic influenza from 79% to 25% in elderly population.
 - ② Before vaccine are available, **acetylcysteine prophylaxis** is an attractive option in conserving the existing workforce during an pandemic outbreak.
- 



Summary IV

- © Animal experiment has shown that acetylcysteine and Tamiflu have synergistic action in improving survival of mice against lethal influenza infection.
 - © **Incorporation of acetylcysteine into the Tamiflu treatment regime of human swine influenza infection** should be considered.
- 

[illegible]

於此時期是臺灣經濟起飛的主要階段之一，而內政部人口調查所也於此時大舉引進人口調查技術與人才，當時以內政部調查所為首，其他如「行政院人口調查委員會」、「僑務委員會」、「經濟委員會」、「糧食委員會」、「衛生委員會」等中央級政府機關，以及省、市、縣、鎮、鄉、鎮公所等地方級政府機關，均先後成立人口調查所（AICP），組織臺灣人口調查的行政體系與技術支援體系（圖 1-1-1）。而內政部人口調查所也於此時開始以「戶籍法」為基礎，以戶籍調查為主要工作，並開始以戶籍調查為基礎，進行人口統計工作。而內政部人口調查所也於此時開始以「戶籍法」為基礎，以戶籍調查為主要工作，並開始以戶籍調查為基礎，進行人口統計工作。

與其前往內城區一處，都使補助作用，這不能保證100%保護環境也。

一般而論，上述兩端均與當前中國社會的具體現實相連，因而其研究也應與社會現實相連。

◎「第23條」的結合就是第23條有什麼不對？

在综合判断的基础上，对案件事实作出认定，并据以作出裁判。所谓综合判断，是指法官在认定事实时，应当综合全案证据，进行整体性、全局性的判断，而不能仅凭个别证据或孤立地进行判断。所谓据以作出裁判，是指法官在认定事实的基础上，应当根据法律规定的裁判规则，作出最终的裁判结论。这一过程体现了法官在认定事实时的主动性和创造性，也是法官行使自由裁量权的重要体现。



7面 2面

滿地可程比價一般稍低及廉！請到加心網或：

依據這組小數，估計數量或反應的穩定性較少數。



Sep.8, 2008

Sep 8, 2008

黎鏡堯醫生
伊利沙伯醫院



墨西哥的疫情對中國的啓示

- ◎ 從基因測試 2009 H1N1 豬流感是綜合病毒，含有四種不同的流感病毒基因，其中包括：北美洲的豬流感、歐亞型的豬流感、北美洲型的禽流感、及人類流感。其中 HA, NS1 and NP 則是於1918年傳入北美豬隻。因此我們現今第一波時實已處身於1918年的第二波。
- ◎ 15歲以下小童染病率為 61%，15歲以上為 29%。但小童死亡率未有預期高。小童流感死亡率多因細菌混合感染併發症。流感的細菌混合感染三成至六成為肺炎鏈球菌及嗜血桿菌。墨西哥早於1999年已為小童提供免費 b 型嗜血桿菌疫苗。及後更於2006為兩歲以下小童免費提供肺炎鏈球菌疫苗。因此現時四歲以下小童已為疫苗保障。
- ◎ 吸煙是流感死亡高危因素之一。因吸煙會令血小板活化因數增加，增加肺炎鏈球菌感染的機會。

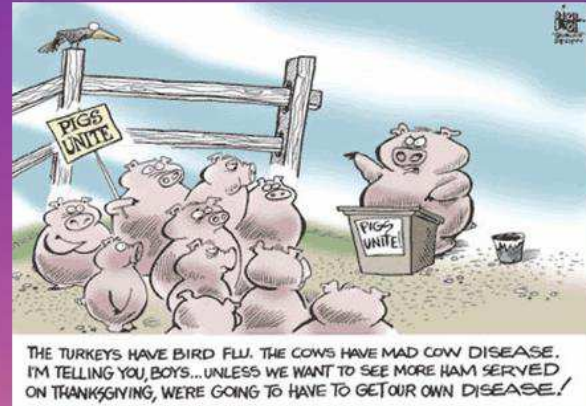
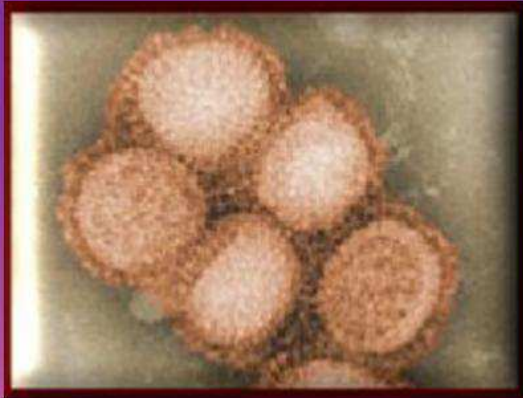
墨西哥的疫情對中國的啓示

中國的嬰兒死亡率與孕婦死亡率與墨西哥基本相近。墨西哥的疫情可於中國重演。但中國小童並沒b型嗜血桿菌和肺炎鏈球菌疫苗保障及中國成年人煙民數目及比例爲世界之冠。因此疫情可能比墨西哥嚴峻。



◎ 中國因此應盡速爲小童提供免費 b型嗜血桿菌和肺炎鏈球菌疫苗及呼籲成年煙民自行接種肺炎鏈球菌疫苗。

Human Swine Influenza



Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital

Mexican Flu, Swine Flu, H1N1 Pandemic Pandemonium Origin

La Gloria



- © It is believed that a five year old boy in La Gloria, Mexico was the very first person that tested positive for the Mexican Flu.



- © The outbreak may started as early as 15/2/2009



The grave of Maria Adela Gutierrez in Oaxaca Mexico

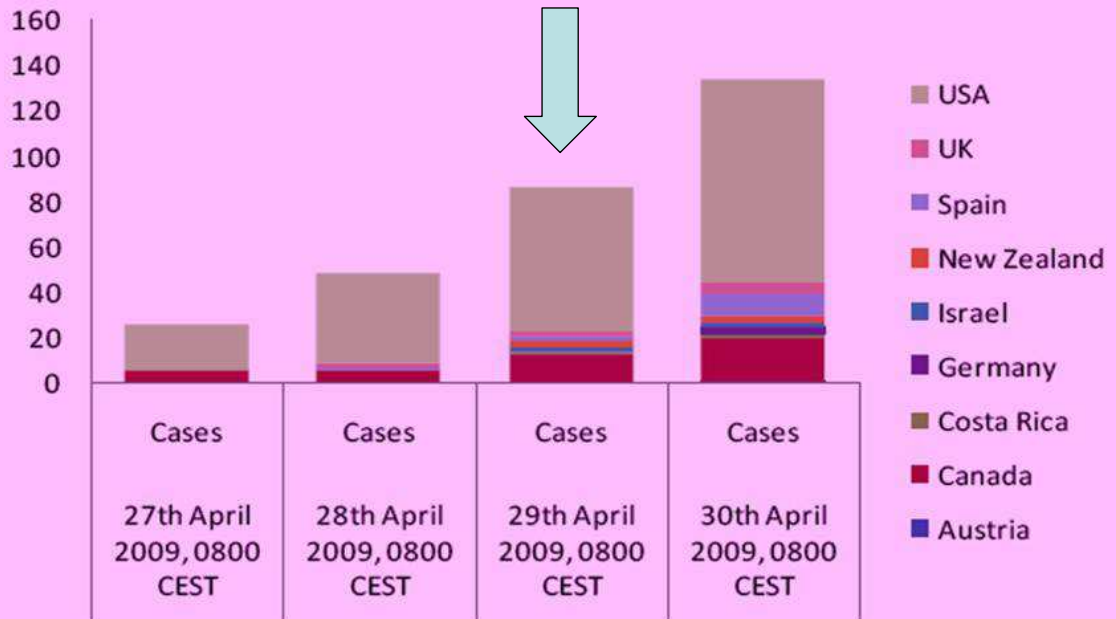


Mexico's first swine flu case surfaced in 17/3/09

The first swine flu fatality was a 39 year old Mexican door to door tax inspector (? Census taker) Maria Adela Gutierrez who had come into contact with at least 300 people when the virus was at its most infectious. She was admitted on 8/4/09 and died 5 days later



WHO Influenza pandemic alert phase 4 → phase 5



Rapid Spread to Countries Outside Mexico

Pigs in Canada were diagnosed with H1N1 on 2/5/2009



- A hog farm in Alberta is under quarantine after Canadian pigs caught the Hybrid H1N1 Flu from a farm worker. The pigs were exposed to the virus after a worker at a family-run farm returned from Mexico with flu symptoms. This is the first time the new H1N1 influenza strain has been found in pigs.

Farm Worker Gives H1N1 (Swine) Flu To . . . Pigs

Human Swine Influenza Virus



- © The first US case was in a 9-year-old girl in Imperial County, Calif., who got sick with a fever on Mar 28.
- © The second US case involved a 10-year-old boy in neighboring San Diego County who fell ill on Mar 30.
- © Pregnant women died of swine influenza 6/5/2009 in U.S.A.



Mortality (Age Distribution and Sex Ratio)

Mexico



N = 80

		%
< a 1	2	2.5%
1 a 4	2	2.5%
5 a 9	3	3.8%
10 a 14	3	3.8%
15 a 19	1	1.3%
20 a 24	11	13.8%
25 a 29	12	15.0%
30 a 34	8	10.0%
35 a 39	11	13.8%
40 a 44	6	7.5%
45 a 49	7	8.8%
50 a 54	7	8.8%
55 a 59	3	3.8%
60 a 64	1	1.3%
65 a 69	0	0.0%
70 a 74	1	1.3%
75 y más	2	2.5%
Totales	80	100.0%

77.5%



Mortality rate according to Age

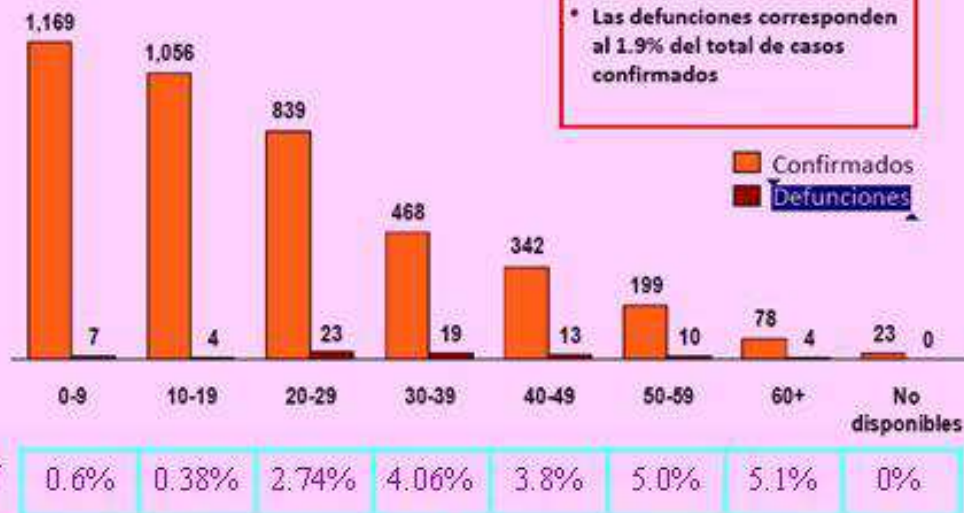
Mexico



Casos confirmados y defunciones por grupos de edad

(4,174 casos confirmados y 80 defunciones)

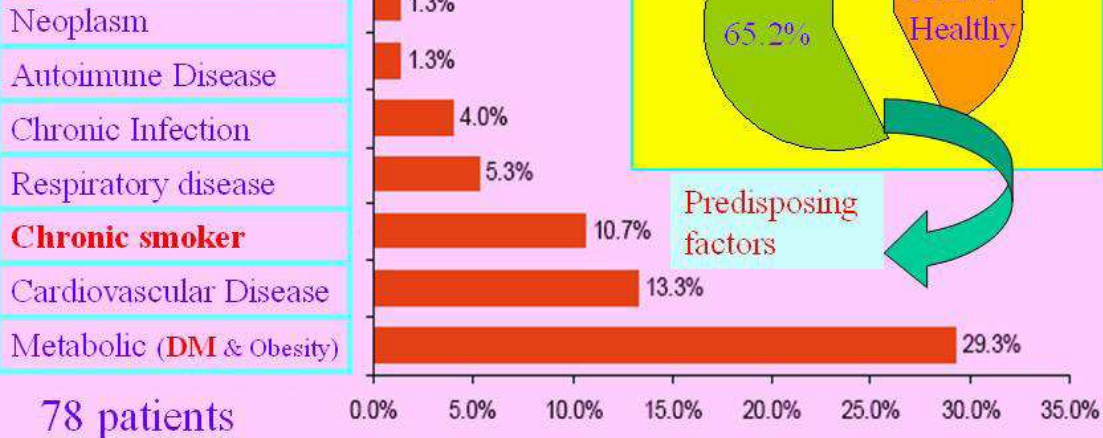
- 80 defunciones confirmadas
- Las defunciones corresponden al 1.9% del total de casos confirmados



Mortality Rate

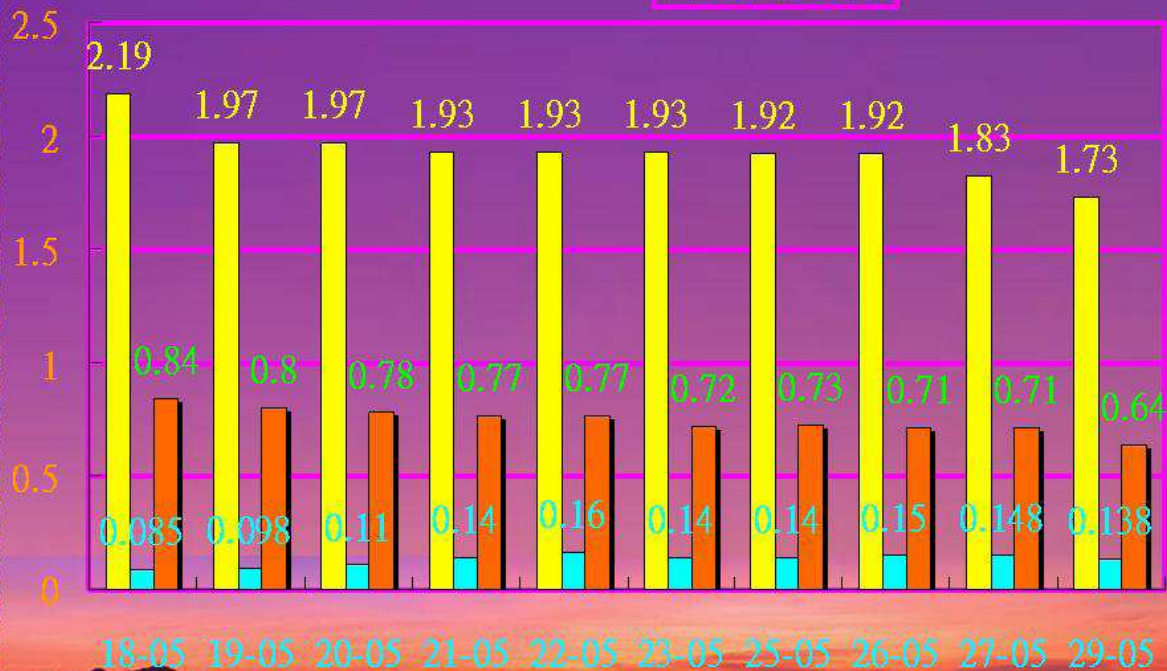
Antecedentes Patológicos

Mexico



Chronic smokers and diabetic patients have increased risk of death from HSI H1N1 2009

Mortality rate (%)



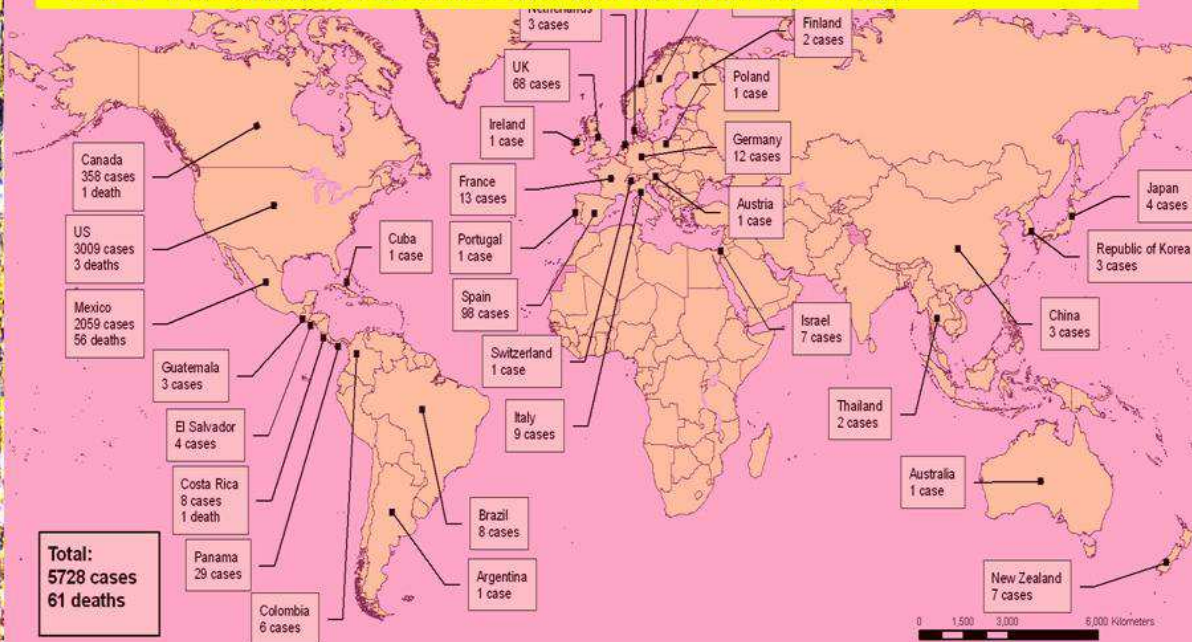
香港政府的應變系統及 醫管局應變系統

	Alert 戒備應變級別	Serious 嚴重應變級別		Emergency 緊急應變級別	
		S1	S2	E1	E2
概況	香港 境外 證實在 家禽 中爆發高致病性禽流感；香港 境內 證實在檢疫中的入口禽鳥、野生禽鳥、休憩公園、寵物店或自然環境中出現高致病性禽流感個案；在香港 境外 證實出現 人類 感染禽流感的個案。	香港 境內 證實在 家 禽所處環境或在零售市場、批發市場或農場中 家禽 爆發高致病性禽流感。	香港 境內 證實出現 人類 感染禽流感的個案，但 無 證據顯示病毒有效在 人與人之間 傳播。	有證據確定 外地或本港 出現 有效 在 人與人之間 傳播的 新型 流感	世衛宣告流感大流行發生

New Influenza A (H1N1),
Number of laboratory confirmed cases and deaths as reported to WHO

Status as of 13 May 2009
06:00 GMT

每日過關人多難堵截轉打社區戰 11/5/09



- ◎ 陸路口岸每日約有30 萬人次過關。
- ◎ 每日從美加直接飛抵本港的旅客多達4800 人，這還未計及由世界各地轉機來港的美加旅客。

豬流感研究發現

(Pandemic Potential of a Strain of Influenza A (H1N1) : Early Findings
Christophe FRASER Science 10.1126 science.1176062 2009)

- ◎ 死亡率為 0.4%
- ◎ 平均傳染機率為 1.4 至 1.6，即 1 人染病後可傳染 1.6 人
- ◎ 病毒人傳人次數最多為 73 次，即 1 個患者將病毒傳給第 2 個人，第 2 人傳第 3 人，如此衍生下，最多可傳 73 人
- ◎ 15 歲以下小童染病率為 61%，15 歲以上為 29%



Frequency of reported symptoms amongst 556/616 (90%) of cases

Symptom	Frequency (%)
Cough	456 (82.0%)
Fever	378 (68.0%)
Hyaline rhinorrhea	340 (61.2%)
Painful swallowing	279 (50.2%)
Headache	188 (33.8%)
Arthralgia	122 (21.9%)
Generally unwell	117 (21.0%)
Chills	110 (19.8%)
Malaise	109 (19.6%)
Nasal congestion	95 (17.1%)
Abdominal pain	53 (9.5%)
Conjunctivitis	50 (9.0%)
Prostration	40 (7.2%)

Impossible to
screen for
asymptomatic
carrier at
airport



(Pandemic Potential of a Strain of Influenza A (H1N1) : Early Findings
Christophe FRASER Science 10.1126 science.1176062 2009)

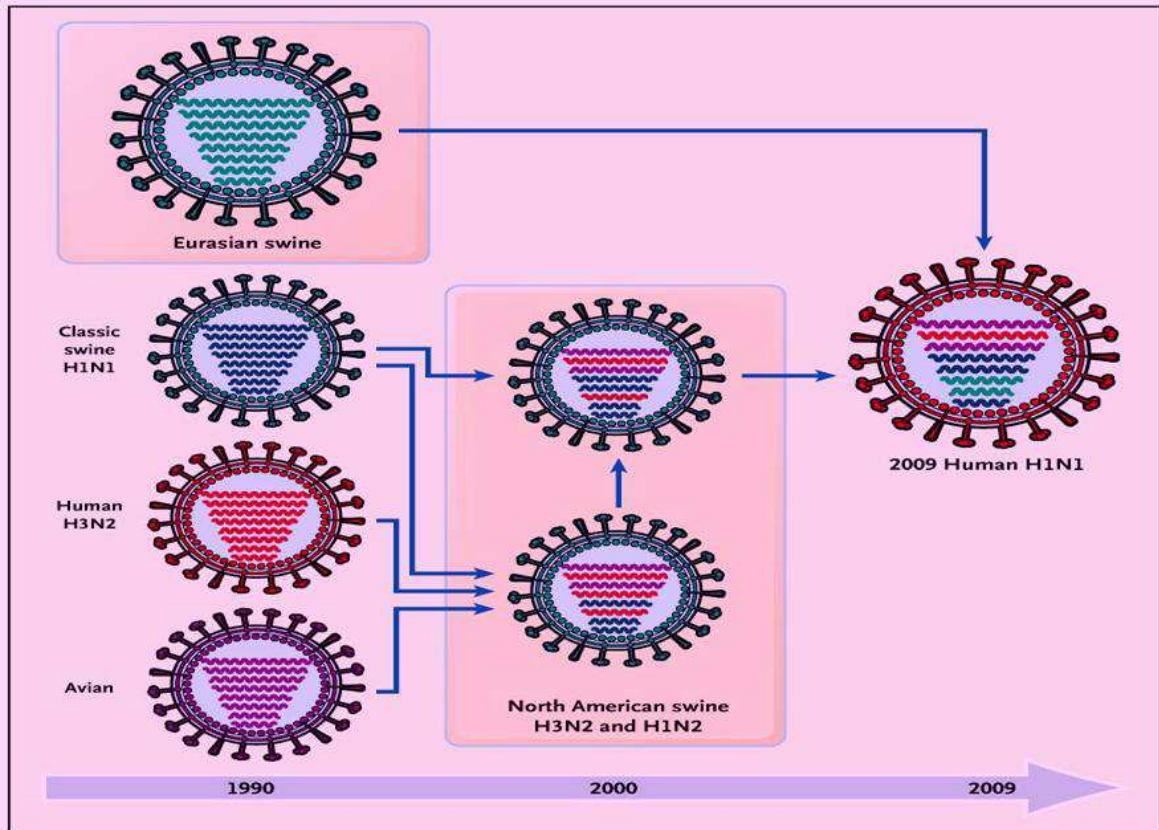




La Gloria clinical attack rates by age and gender

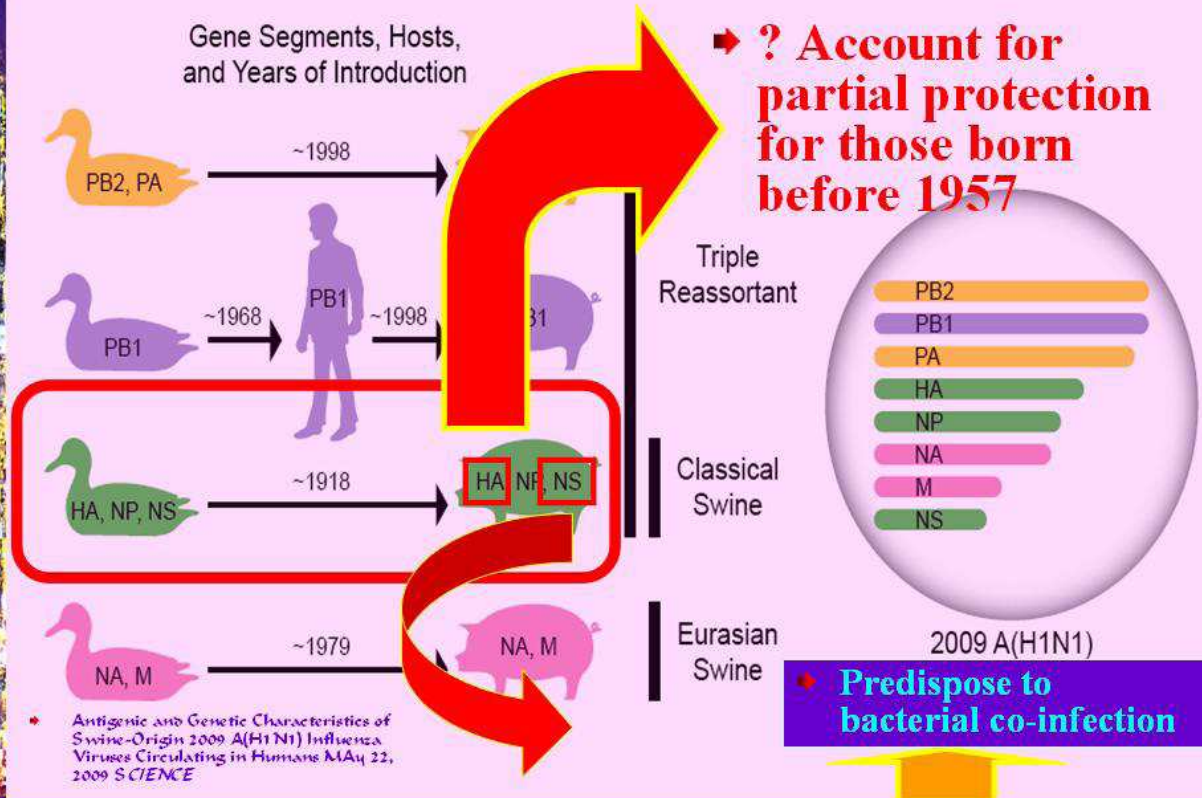
Age Group	Male (%)	Female(%)	Total(%)
<1	91.2	73.7	83.9
1-4	66.2	66.1	58.1
5-14	49.7	66.3	57.7
15-24	25.6	28.2	27.0
25-44	22.8	39.4	31.6
45-64	18.4	42.7	29.6
65+	17.5	25.7	22.0
Total	33.5	44.6	39.1

**High Clinical Attack Rate Among Children
especially those < 1 year of age**



Human Swine Influenza appears to be a combination of segments from four different viruses from three continents, including a human segment, 2 avian segment and 5 pig segments. (NEJM May 28 2009)

Gene Segments, Hosts,
and Years of Introduction



➔ ? Account for
partial protection
for those born
before 1957

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



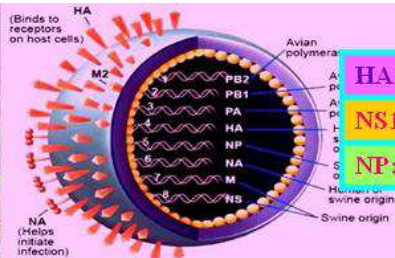
Human Swine Influenza Genome

Triple-Reassortant Swine Influenza A Viruses

- © The NA and M gene segments are in the Eurasian swine genetic lineage
 - ◆ Viruses with NA and M gene segments in this lineage, were originally derived from a wholly avian influenza virus and thought to have entered the Eurasian swine population in 1979, continue to circulate throughout Eurasia, and have not been previously reported outside Eurasia.
- © The HA, NP, and NS gene segments are in the classical swine lineage
 - ◆ Viruses that seeded this lineage are thought to have **entered pigs around 1918** (account for partial immunity for person born before 1957) and subsequently circulated in classical swine viruses and triple reassortant swine viruses.
- © The PB2 and PA gene segments are in the swine triple reassortant lineage
 - ◆ Viruses that seeded this lineage, originally of avian origin, entered pigs in North America around 1998.
- © The **PB1** gene segment is in the swine triple reassortant lineage.
 - ◆ This lineage of PB1 was seeded in swine from humans at the time of the North American swine triple reassortment events, and was itself seeded from **birds around 1968**.

Key differences between the new influenza A (H1N1) virus from this 2009 outbreak and the usual yearly (seasonal) human influenza A (H1N1) virus

	New Influenza A H1N1 (2009)	Yearly Influenza A H1N1
Oseltamivir (Tamiflu) sensitive?	<i>YES</i>	No
Vaccine Exists?	No	<i>YES</i>
Human Immunity?	No	<i>YES</i>
Human Infections known prior to 2009	No	<i>YES</i>
Hemagglutinin (H1) origin	Swine influenza virus	Human Influenza virus



HA: 1918 Swine

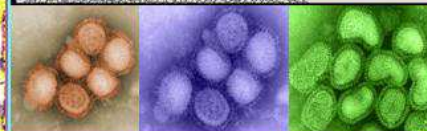
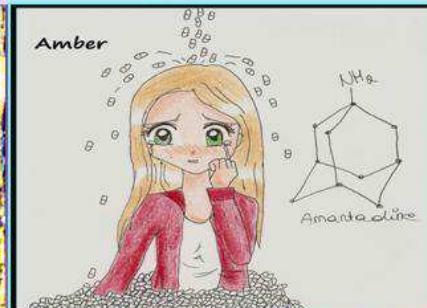
NS1: 1918 Swine

NP: 1918 Swine

Drug Sensitivity

Human H1N1

Human Swine Influenza



Amantadine/
Rimantadine

Tamiflu
(Oseltamivir)

Relenza
(Zanamivir)

Human H1N1

Sensitive

Resistant

Sensitive

Human Swine H1N1

Resistant

Sensitive

Sensitive

Human Swine Influenza appears to be a combination of segments from four different viruses from three continents, including a human segment, 2 avian segments and 5 pig segments.

Antiviral Agents for Influenza

	<i>Amantadine</i>	<i>Rimantadine</i>	<i>Zanamivir</i>	<i>Oseltamivir</i>
Protein target	M2	M2	Neuraminidase	Neuraminidase
Activity	A only	A only	A and B	A and B
Side effects	CNS (13%) GI (3%)	GI (6%) GI (3%)	?Bronchospasm	GI (9%)
Metabolism	None	Multiple (hepatic)	None	Hepatic
Excretion	Renal	Renal + others	Renal	Renal (tubular secretion)
Drug interactions	Antihistamines, anticholinergics	None	None	Probenecid (increased levels of oseltamivir)
Dose adjustments needed	≥65 yr old CrCl < 50 mL/min	≥65 yr old CrCl < 10 mL/min	None	CrCl < 30 mL/min Severe liver dysfunction
Contraindications	Acute-angle glaucoma	Severe liver dysfunction	Underlying airways disease	
<i>FDA Approved Indications</i>				
Therapy	Adults and children ≥ year of age	Adults only	Adults and children ≥ 7 years of age	Adults and children ≥ 1 year of age
Prophylaxis	Yes	Yes	No	Adults and children ≥ 13 years of age
CNS, central nervous system; CrCl, creatinine clearance; FDA, U.S. Food and Drug Administration; GI, gastrointestinal.				

**Both Relenza
sensitive**



**Effective for Human
Influenza H1N1**

**Effective for Human Swine
Influenza H1N1 2009**

Pandemic Influenza: Preparedness



"For the first time in human history, we have a chance to prepare ourselves for a pandemic before it arrives...it is incumbent upon the global community to act now."

-Dr. Margaret Chan, WHO
Director General



Timeline of Emergence of Influenza A Viruses in Humans



Spanish Influenza

H1

1918

H2

1957

1968

1977

1997

2003

1998/9

Asian Influenza

H3

Russian Influenza

H1

Hong Kong Influenza

Avian Influenza

H9

H7

H5

H5

1918
Spanish
Influenza
H1N1

1957
Asian
Influenza
H2N2

1968
Hong Kong
Influenza
H3N2

Pandemic in the past

Pandemic Severity Index

Case
Fatality
Ratio

Projected
Number of Deaths*
Population of HKSAR 7 million

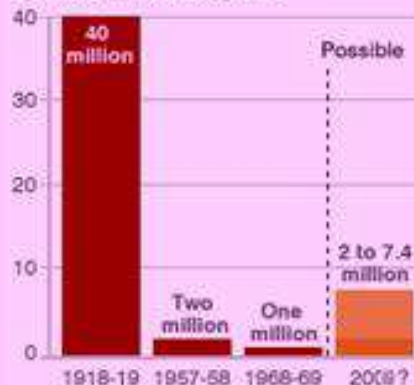
30% population = 2.1 million



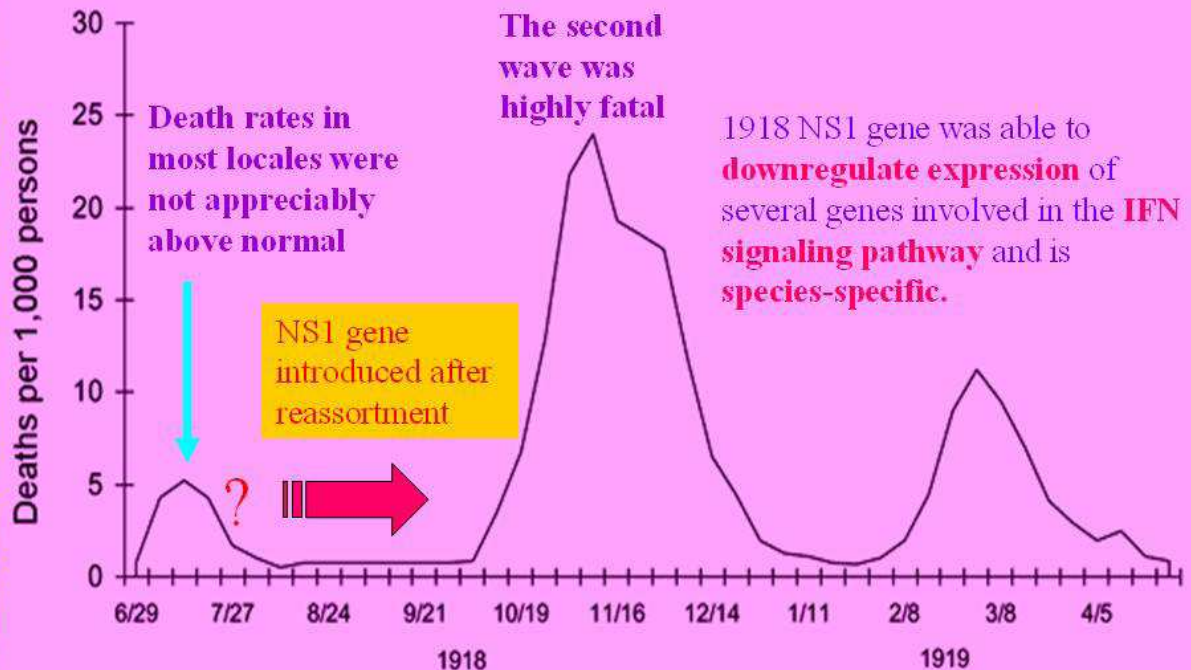
*Assumes 30% Gross Rate and Unmitigated
Pandemic Without Interventions

WORLD FLU PANDEMIC DEATHS

Estimated millions of deaths

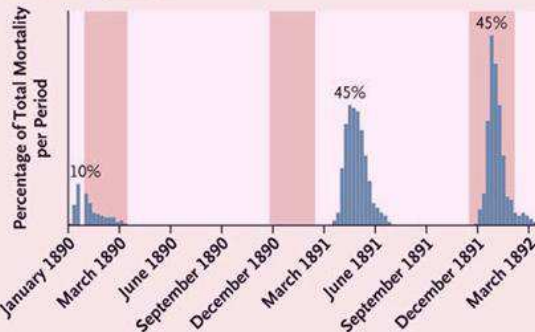


Much more death than SARS

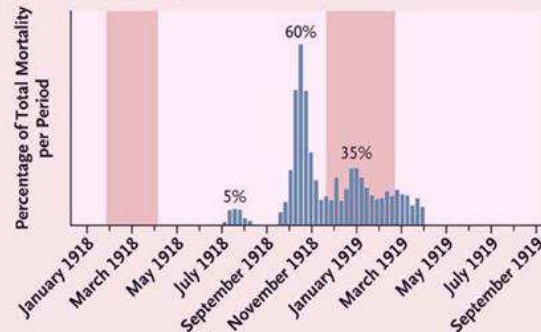


Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919

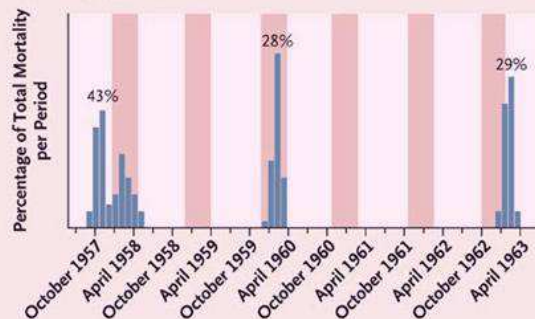
A 1889–1892, London



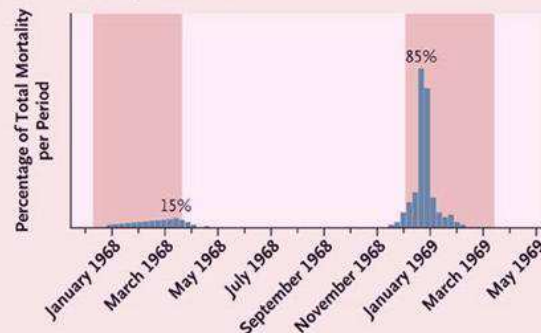
B 1918–1919, Copenhagen



C 1957–1963, United States



D 1968–1970, England and Wales



Mortality Distributions and Timing of Waves of Previous Influenza Pandemics May 28, 2009



"yup, sho nuff looks
like we'll have another
season of swine flew"

Make Preparation for the Second Wave





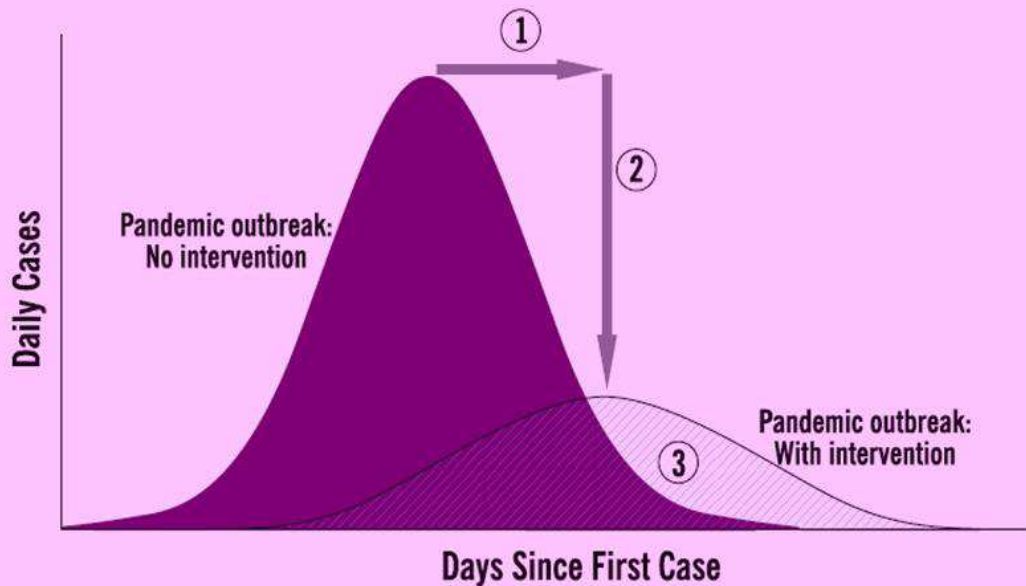
Pandemic would likely overwhelm our critical healthcare services and impose significant stress on our critical infrastructure.

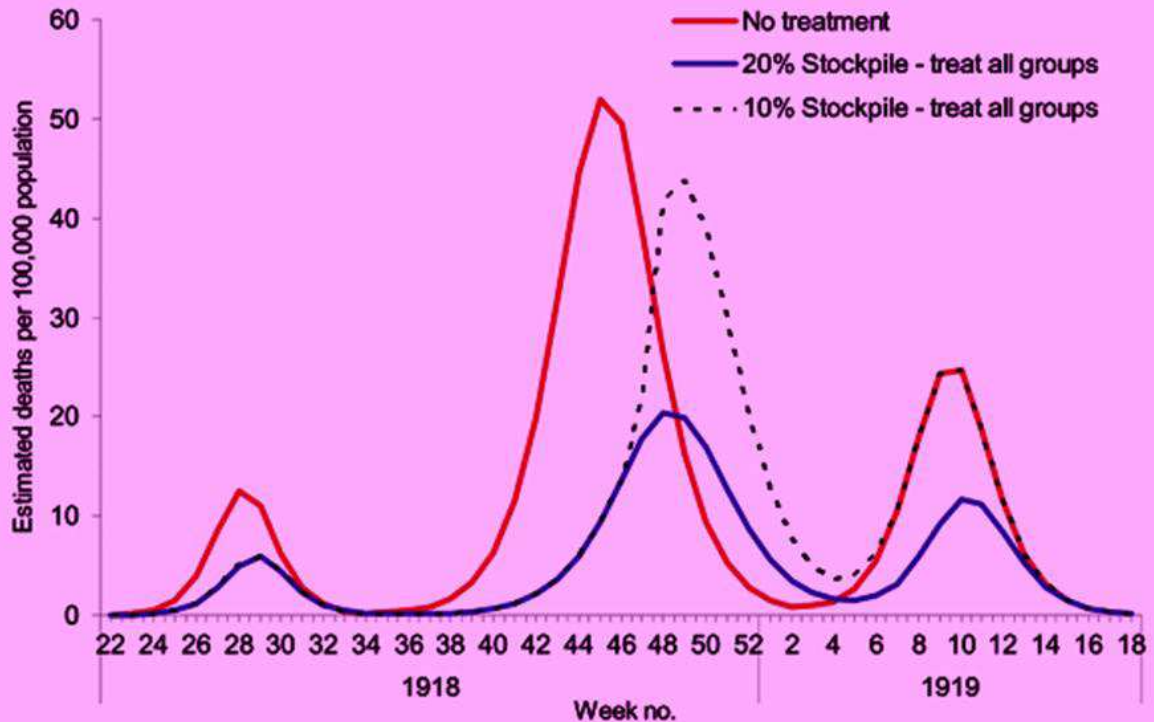
The goals of the Government's response to pandemic influenza are to limit the spread of a pandemic; mitigate disease, suffering, and death; and sustain infrastructure and lessen the impact on the economy and the functioning of society.



Goals of Community Mitigation

- ① Delay outbreak peak
- ② Decompress peak burden on hospitals / infrastructure
- ③ Diminish overall cases and health impacts





Potential Impact of Antiviral Drug Use during Influenza Pandemic

→ Current strain of Swine H1N1 is sensitive to **Zanamivir** and **Oseltamivir**

Should the government increase its stock of Zanamivir (Relenza) in preparation for the second wave ?

認識流行性感胃 Influenza



流行性感冒，是病毒引起傳染的疾病，每年的二、三及七月最常見。
流行性感冒病毒（尤其甲型）的特性是可造成不定期的流行性感冒，但生動且極，造成大規模流行性感冒。
Influenza is a viral infection mainly affects the respiratory tract. It is common in February, March and July.
Frequent mutation of genes of influenza A virus leads to the emergence of new variants and may cause epidemics.

靜養與健康生活方式能使人體力充沛，流行性感冒病毒對預防洗滌亦有一定功效。

A healthy life style can minimize the chance of getting influenza. Vaccination allows you to acquire the immunity against the prevalent enough of the viruses.

Vaccination : 6/12/2012 (9:00am - 1:00pm & 2:00pm - 5:00pm)

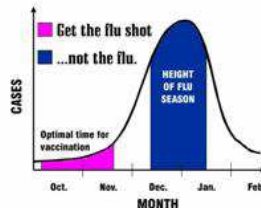
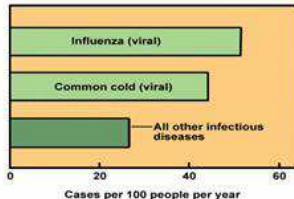
Venue : University Health Centre (1/F., Health Education Room (保健處1樓健康教育室))

Cost price : \$ 80

費用

Organized by :
University Health Services
中文大學醫務服務

香港中文大學
The Chinese University of Hong Kong



Vaccination

INFLUENZA: VACCINES



BEAT THE BUG

FLU SHOTS ARE AVAILABLE

STUDENTS: \$5.
STAFF: \$10.

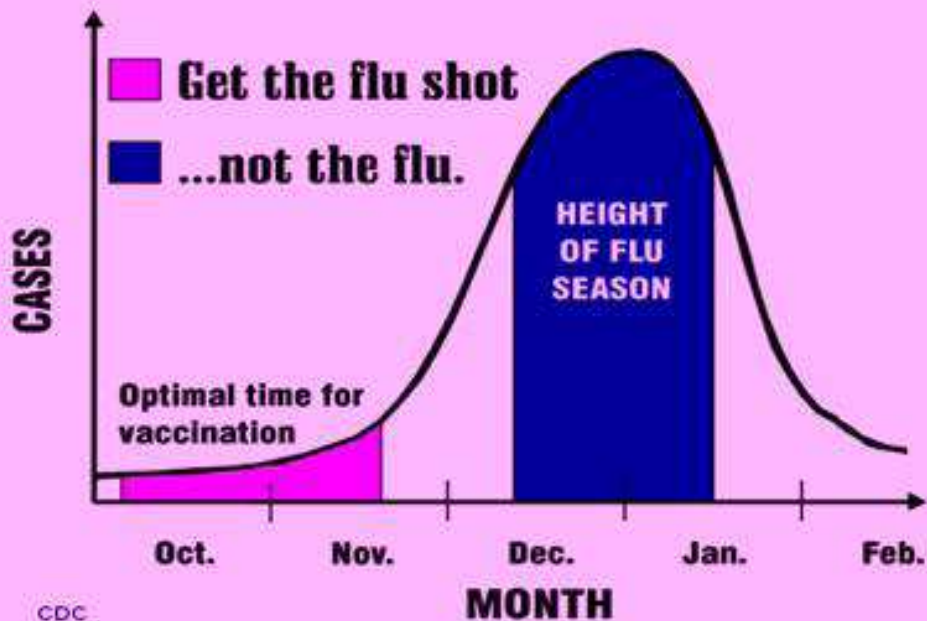
Call Health Services (x2823)
to make an appointment
for a flu shot.



Don't get the

The most important measure to protect population at large from pandemic influenza





Problem with vaccination

- There is a delay of 6 months before effective vaccine is available.
- There is limited capacity for vaccine production.
- Each person needs two vaccination for new antigen.



WHO Sees 4.9 Billion Pandemic Flu Shots in Best-Case

WHO Director-General Margaret Chan told reporters after her meeting with 30 pharmaceutical companies GENEVA (Reuters) May 19

It would be significantly lower if people need more than one injection to gain immunity against the strain or if seasonal flu vaccine-making continues.

Bringing a new pandemic vaccine to market - if it goes ahead - is expected to take 4-6 months, according to the WHO. It must be tested first on ferrets and then on humans in clinical trials before regulatory authorities can approve it.

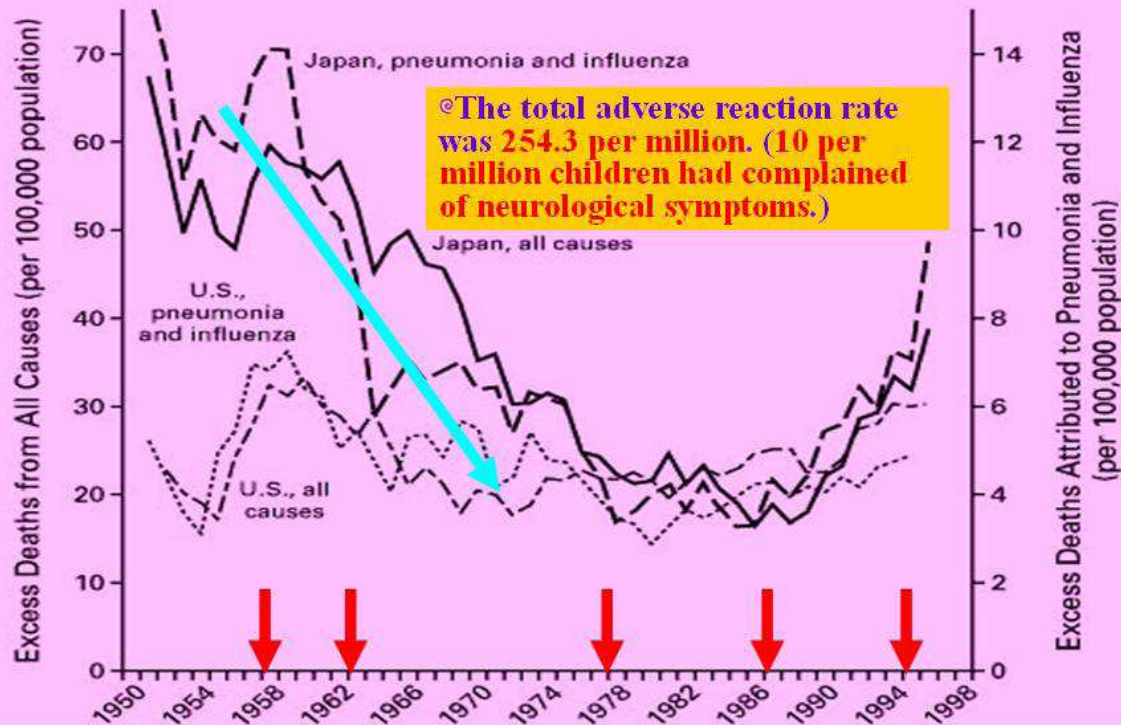




Gullain Barre Syndrome

1976 A/New Jersey mass vaccination in the USA.

- © **1976/1977 Swine Influenza Vaccine**
 - **35,000,000 dose**
 - **354 cases of GBS**
 - **28 GBS related death**
- © GBS occurred in 1.55/million, compared to 0.17 in non-vaccinated (9.11 times more frequent in those vaccinated). (Hennessen quotes different figures: 8.0/million in vaccinated compared to 1.8/million in non-vaccinated).
- © 31% of cases were over 60 years old. Only 12% occurred within 7 days after vaccination, 74% between 8 and 28 days, and 14% even after one month.



The Japanese Experience with Vaccinating Schoolchildren against Influenza N Engl J Med 344:889, March 22, 2001.

**1957 Asian
Influenza
Epidemic
claimed
8,000 lives**

**Program to
vaccinate
children
begins in
1962**

**Influenza
vaccination
mandatory
1977**

**Parents
allow to
refuse
vaccination
1987**

**The
government
lost the case
in the court
1992**

**Program
terminated
in 1994**



The Japanese Experience with Vaccinating Schoolchildren against Influenza

N Engl J Med 344:889, March 22, 2001

- © Vaccinating schoolchildren against influenza provides protection and reduces mortality from influenza among older persons.
 - © The vaccination of Japanese children prevented about 37,000 to 49,000 deaths per year, or about 1 death for every 420 children vaccinated.
 - © As the vaccination of schoolchildren was discontinued, the excess mortality rates in Japan increased.
- 

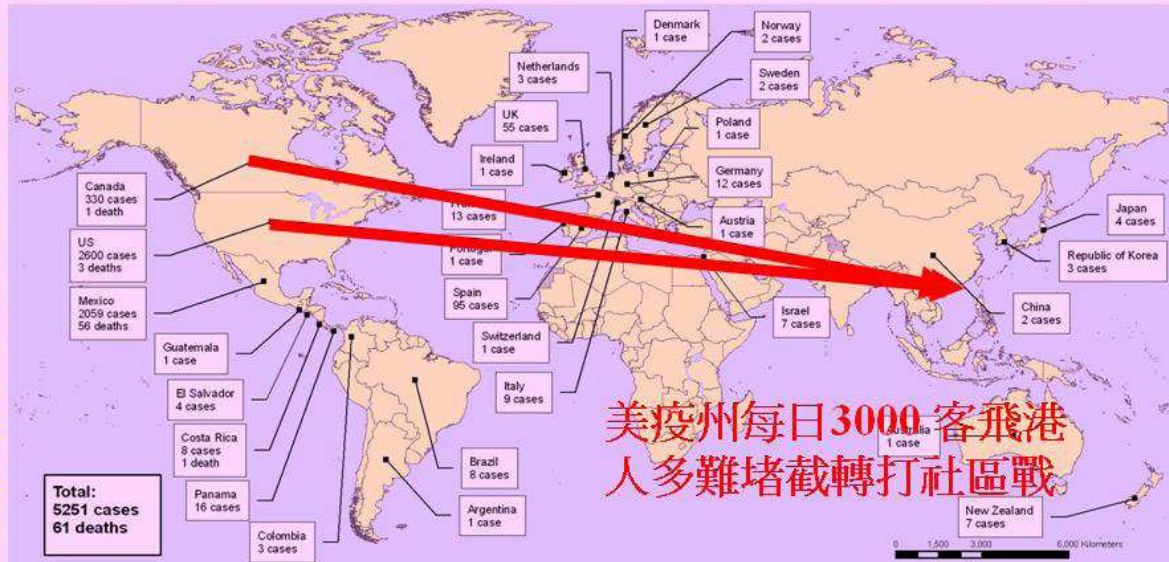


Influenza Vaccination Program for School children In Japan

- ◎ A mass study of adverse reactions against the influenza vaccine was conducted in 1987 involving about 400,000 children.
 - ◎ The total adverse reaction rate was 254.3 per million. (10 per million children had complained of neurological symptoms.)
 - ◎ This study was revealing, since from 1971 the government had changed the flu vaccine from a whole body type to a split particle type announcing that adverse reactions were almost nothing with the new one. The previous type, used in the 1960s had resulted in between 5-9 deaths occurring every year.
 - ◎ In 1987 the government changed the vaccine from compulsory to free choice.
 - ◎ From 1972 to 1979, a total number of 142 children and families sued the government for damages. The total number of deaths were 50, severe developmental retardation were 65, and intractable epilepsy were 35.
 - ◎ In 1992, the government lost the case in the court after about 20 years of legal proceedings.
- 

**New Influenza A (H1N1),
Number of laboratory confirmed cases and deaths as reported to WHO**

**Status as of 12 May 2009
06:00 GMT**



**美疫州每日3000 客飛港
人多難堵截轉打社區戰**

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**
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**Would H1N1 2009 outbreak occur
during the summer vacation in HK?**

The Worst Scenario !!!!!!!

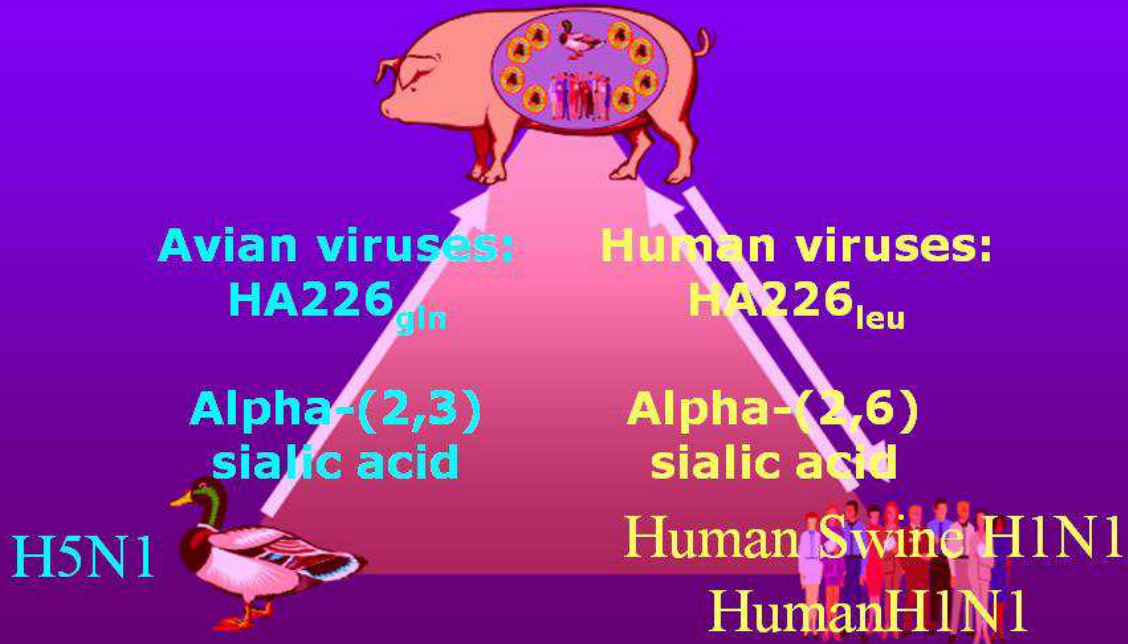


PIGS – INTERMEDIATE HOSTS
FOR PANDEMIC INFLUENZA

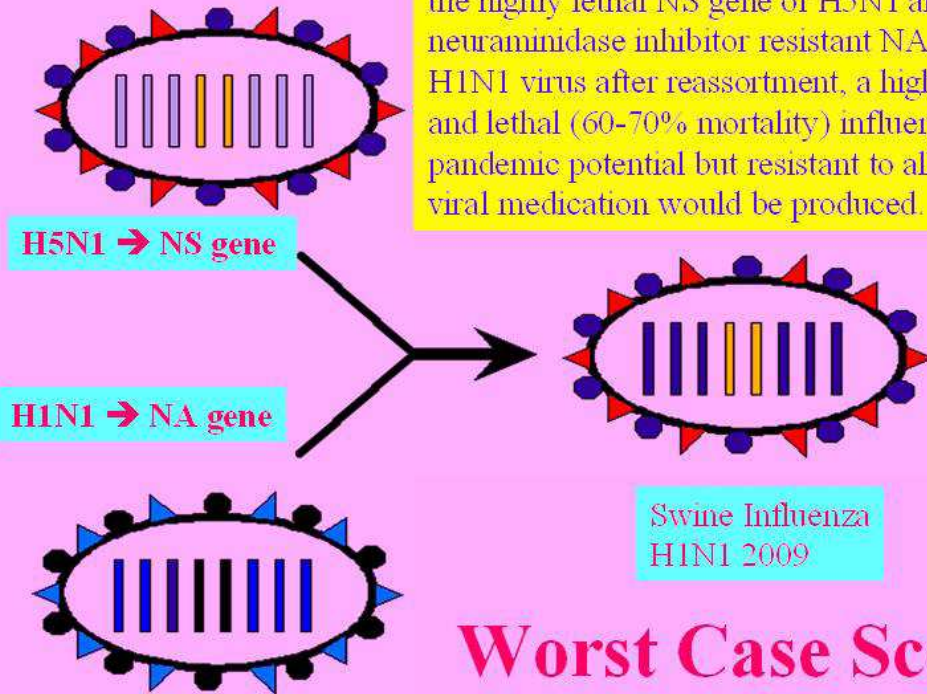


- © Two influenza viruses infecting the same cell can produce 256 different strains of viruses.
- © What would be the result of reassortment after swine flu spread to SEA and China where H5N1 is endemic and resistant to Oseltamivir?

INTERSPECIES TRANSMISSION OF INFLUENZA VIRUSES

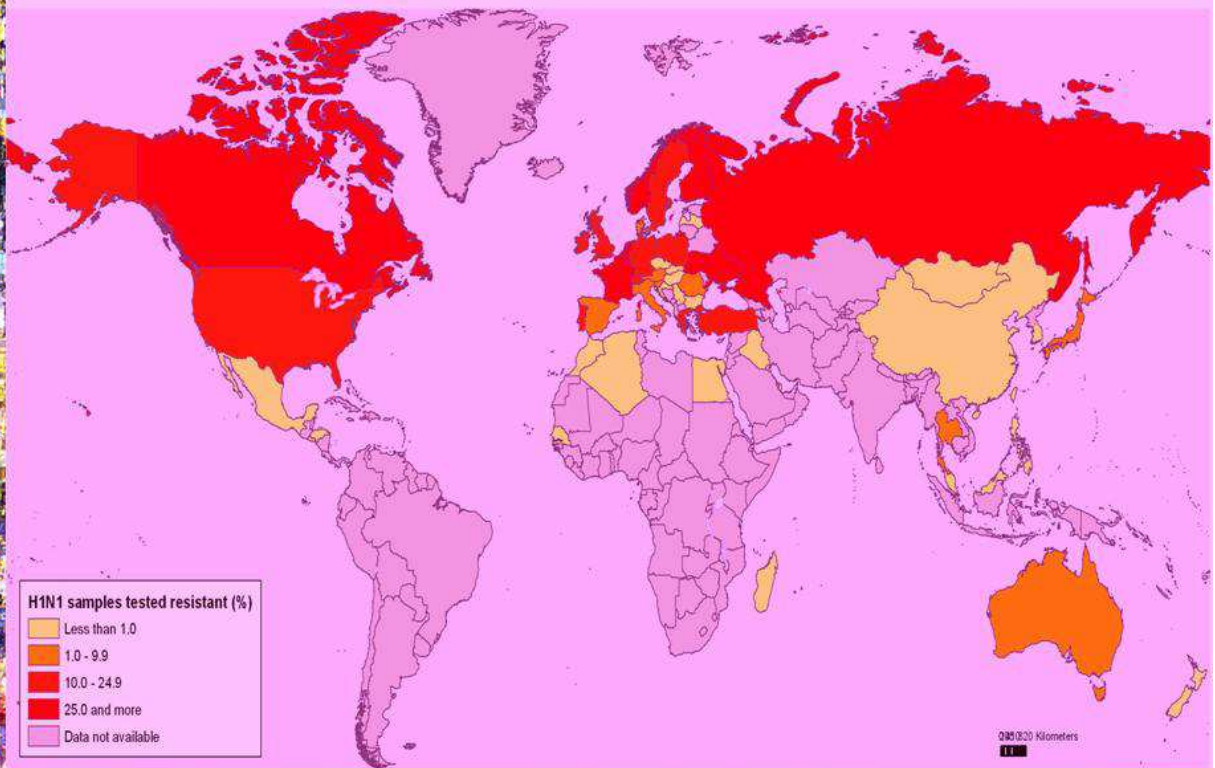


If the swine influenza H1N1 2009 virus has acquired the highly lethal NS gene of H5N1 and the neuraminidase inhibitor resistant NA gene of existing H1N1 virus after reassortment, a high transmissible and lethal (60-70% mortality) influenza virus with pandemic potential but resistant to all existing anti-viral medication would be produced.



Worst Case Scenario

Prevalence of Oseltamivir-resistant H1N1 viruses, as of 01 July 2008

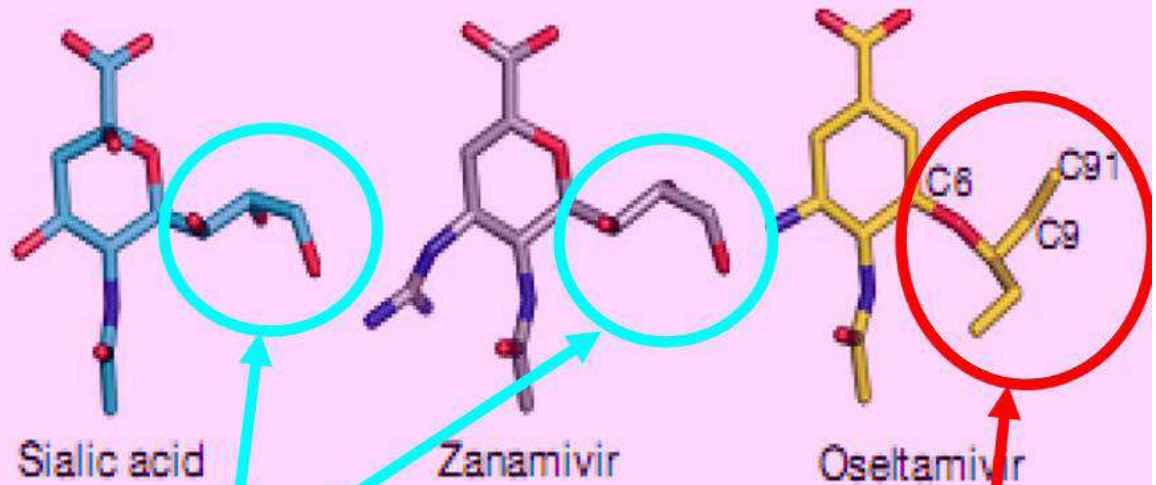


Reassortment with Tamiflu resistant NA gene would probably take place in U.S.A. Europe or U.S.S.R.

**Influenza A(H1N1) virus resistance to oseltamivir
(Fourth quarter 2008 - 31 January 2009) as of 18 Mar 2009**

Region	Country, area or territory	No. of H1N1 isolates tested	No. (%) of viruses tested positive for oseltamivir resistance
AFRO	Ghana	1	1
	Madagascar	7	0
	AFRO Total	8	1
AMRO	Argentina	1	0
	Canada	52	52 (100%)
	Costa Rica	1	0
	Mexico	5	4
	Puerto Rico	1	1
	United States of America	241	237 (98%)
AMRO Total		301	294 (98%)
EMRO	Marocco	10	10 (100%)
EMRO Total		10	10 (100%)
EURO	France	12	12 (100%)
	Germany	67	66 (99%)
	Greece	1	1
	Ireland	10	9 (90%)
	Israel	1	1
	Italy	16	16 (100%)
	Netherlands	4	4
	Norway	9	9
	Portugal	3	3
	Russian Federation	6	5
	Slovakia	1	1
	Spain	5	5
	Sweden	12	11 (92%)
	United Kingdom	62	61 (98%)
EURO Total		209	204 (98%)
SEARO	India	6	6
	Thailand	6	5
SEARO Total		12	11 (92%)
WPRO	China	44	6 (14%)
	China, Hong Kong SAR	80	72 (90%)
	Japan	422	420 (100%)
	Republic of Korea	269	268 (100%)
	Singapore	7	5
WPRO Total		822	771 (94%)
Grand Total		1362	1291 (95%)

HKSAR, Japan and Singapore have high rate of Tamiflu resistance among Human H1N1 influenza



Polar glycerol group in C6

**Hydrophobic
pentyloxy substituent
at C6**

Inhibitors that closely resemble the natural sialic acid substrate of NA are unlikely to select drug-resistant mutants that retain normal enzyme activity

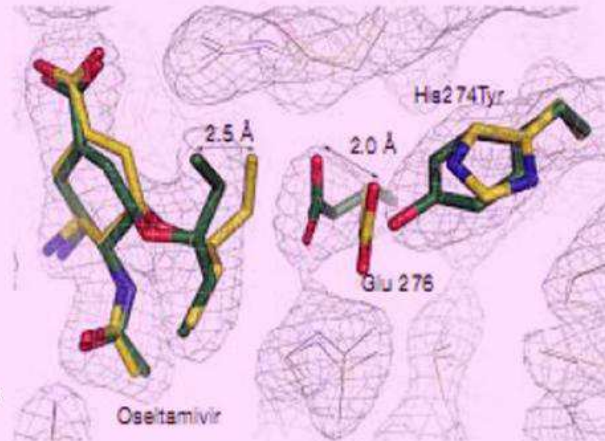
⇒ viruses that are resistant to such drugs must be less active

His274Tyr mutation:

oseltamivir has a hydrophobic pentyloxy substituent at the C6 position rather than a polar glycerol group in zanamivir and sialic acid substrate.

- ❖ Binding of oseltamivir to wild-type NA involves a conformational change in the side chain of Glu 276 relative to the ligand-free enzyme
- ❖ In its new conformation, the carboxyl group of Glu 276 is oriented away from the hydrophobic pentyloxy group of oseltamivir, the latter making hydrophobic contact with the C β methylene of Glu 276 .

➤ Histidine (H) to tyrosine (Y) mutation at at codon 274 in the neuraminidase (NA) gene

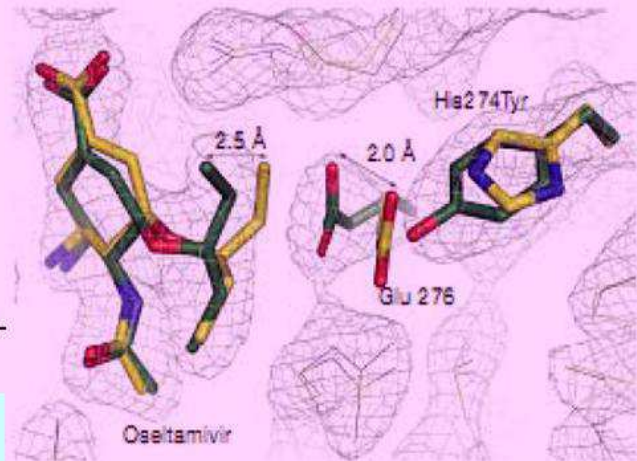


Tamiflu resistance can emerge during treatment by just single step mutations at the neuraminidase gene

❖ substitution by the bulkier tyrosine residue pushes the carboxyl group of Glu 276 2 Å farther into the binding site.

❖ the charged group disrupts the otherwise hydrophobic pocket that normally accommodates the pentyloxy substituent of oseltamivir and causes a change in the conformation of the inhibitor such that its C9 and C91 carbons move about 2.5 Å from their wild-type NA-bound position.

His274Tyr mutation:



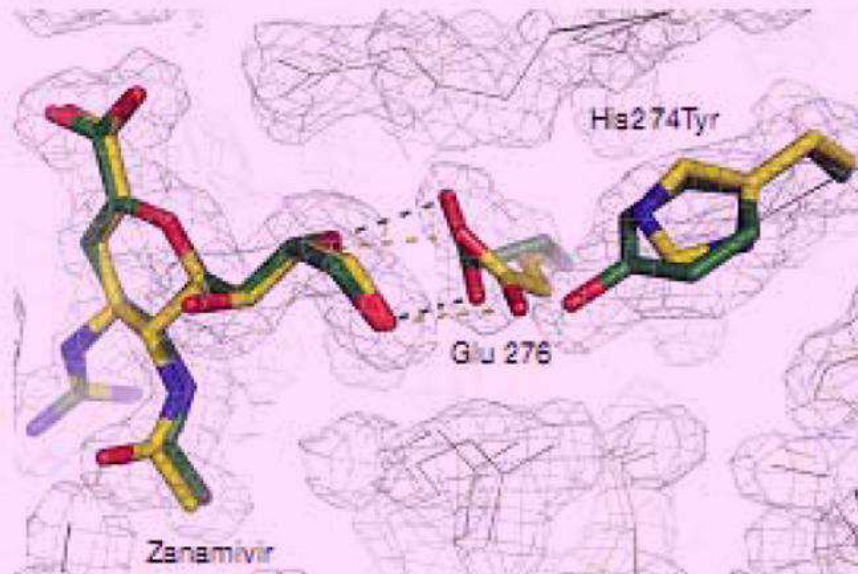
NA gene H274Y mutation

-Mutation specific to the N1 group16
-Oseltamivir (Tamiflu) resistant in Human H1N1

The mutant virus is compromised in its ability to replicate and exhibit attenuated pathogenicity, compromised transmission, and reduced lethality.

His274Tyr mutation:

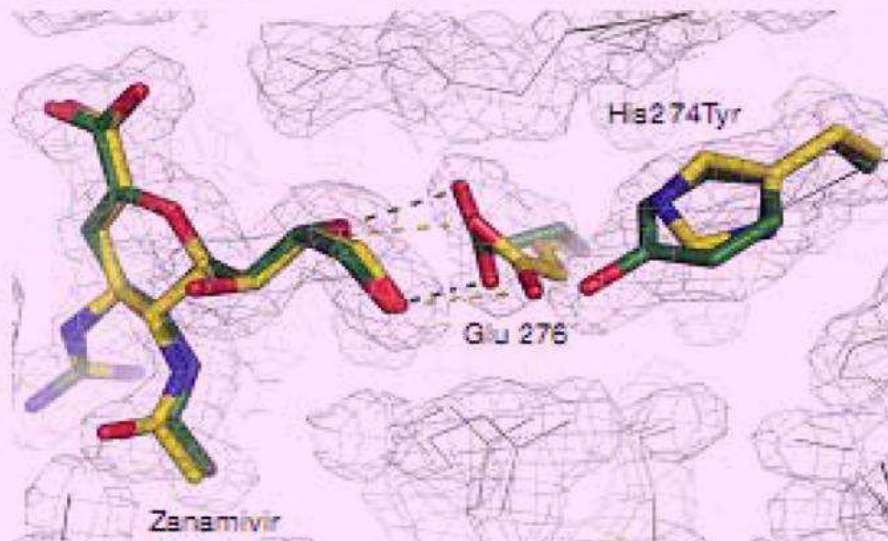
- Binding of zanamivir, like sialic acid²⁴ involves hydrogen-bond formation between the carboxyl group of Glu 276 and the 8- and 9-hydroxyl groups of the glycerol moiety of the inhibitor and requires no change in side-chain conformation.



The mutation had no impact on zanamivir susceptibility

His274Tyr mutation:

The structure of the His274Tyr–zanamivir complex shows the tyrosine residue is accommodated by a small movement in the side chain of Glu 276. Moreover, the adjustment is made without disrupting the hydrogen bonds made between zanamivir and Glu 276 in wild-type NA.



If His274Tyr mutation is anticipated, the government should increase its stock of Zanamivir (Relenza) in preparation for the second wave.

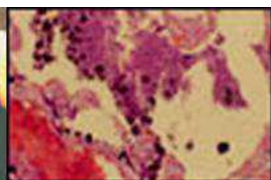
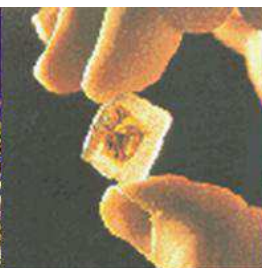
BIRD FLU OUTBREAKS AROUND THE WORLD



- Countries with outbreaks
- Countries with outbreaks including human cases

SOURCE: FAO/WHO

Reassortment with NS1 gene of H5N1 would probably take place in South East Asia



Lung tissue from 1918 influenza victim.

In March of 1997 Dr. Jeffery Taubenberger and colleagues, of the Armed Forces Institute of Pathology, announced in *Science* that they had recovered and analyzed fragments of the RNA genome of the virus responsible for the infamous 1918 Spanish Flu pandemic.

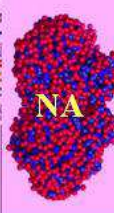


NS Protein

NS Protein's effectiveness in blocking the type I IFN system confer its ability to rapidly produce extensive damage to the respiratory epithelium.



HA



NA

In March of 1997 Avian flu outbreak among chicken farms in northwestern part of Hong Kong.

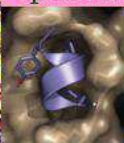


BIRD-FLU SCARE SWEEPS HONG KONG!

MILLION CHICKEN MASSACRE

6/18 = 33% mortality

F103 and M106 Increase mortality to 70%

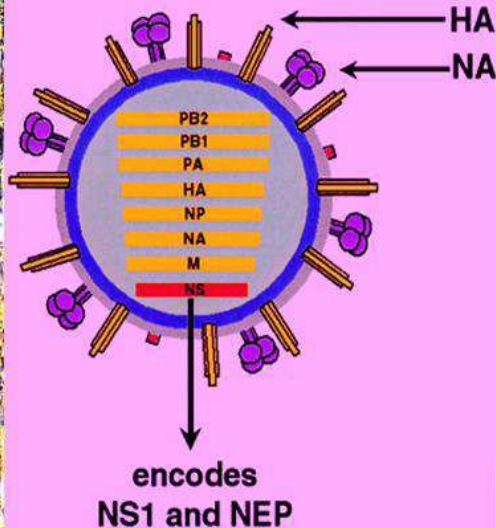


CPSF30-binding pocket
(30 kDa host protein cleavage and polyadenylation specificity factor)

流行性感冒病毒

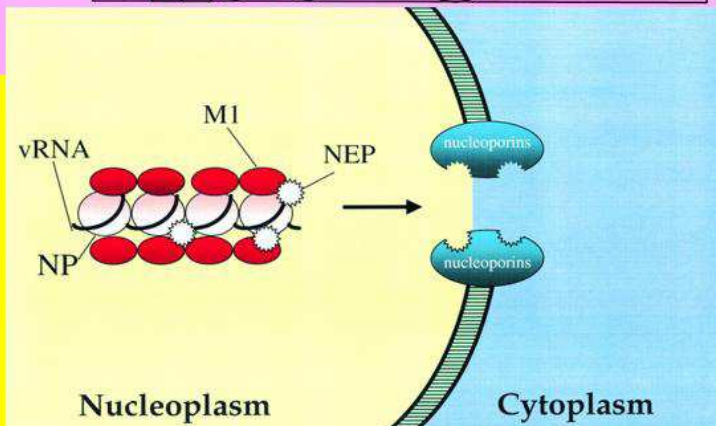
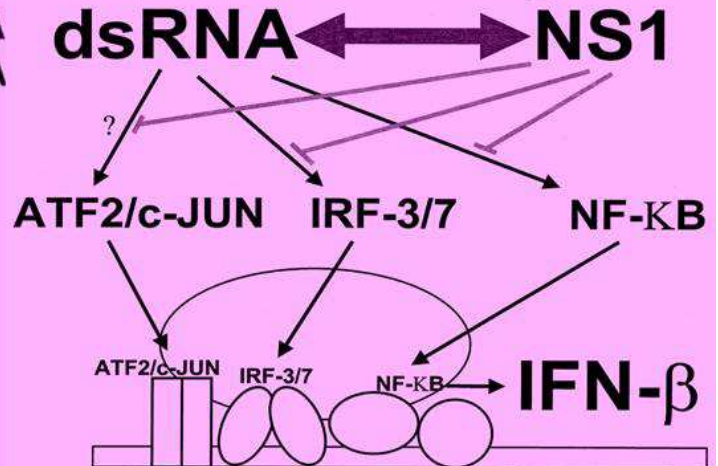
March 1997

INFLUENZA VIRUS

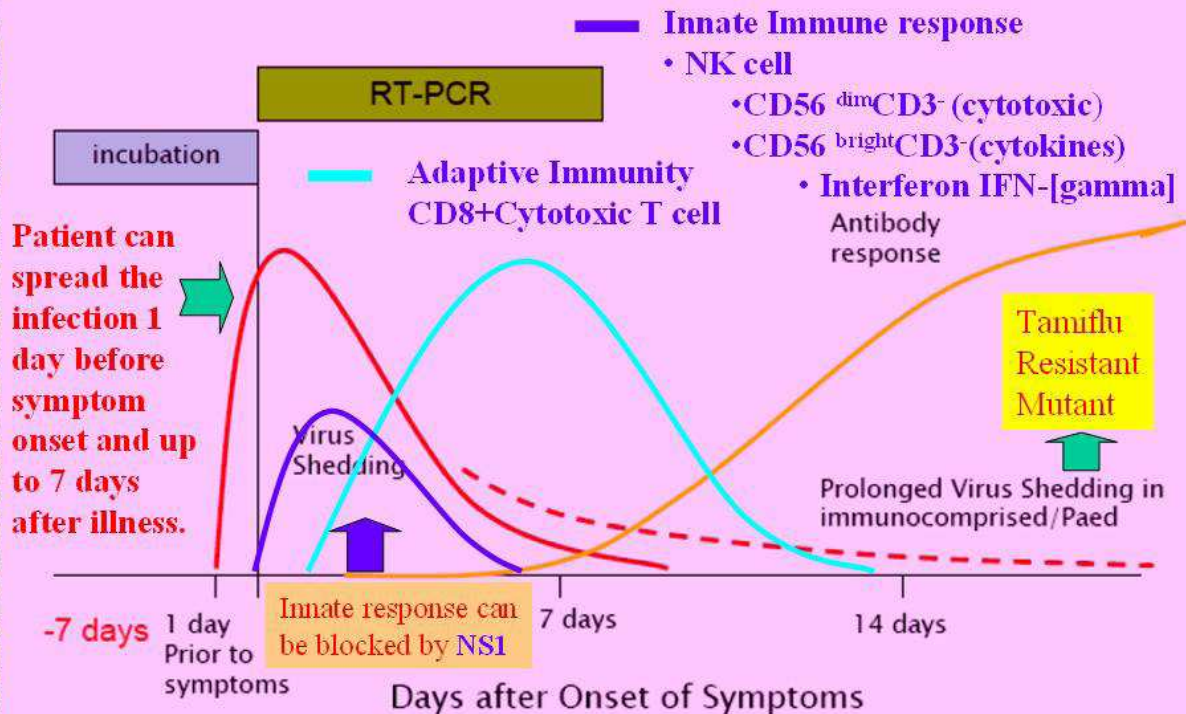


• The NS1 is an antagonist of the cellular type I interferon system, and the nuclear export protein (NEP) functions in viral assembly.

Influenza A virus



Virological Profile of Influenza



Depletion of NK cells abrogated fluA-specific CD8+ T cell responses both in vitro and in vivo. At an early stage of recurrent viral infection, NK-mediated innate immunity to the virus is enhanced by IL-2 production from preexisting virus-specific T cells

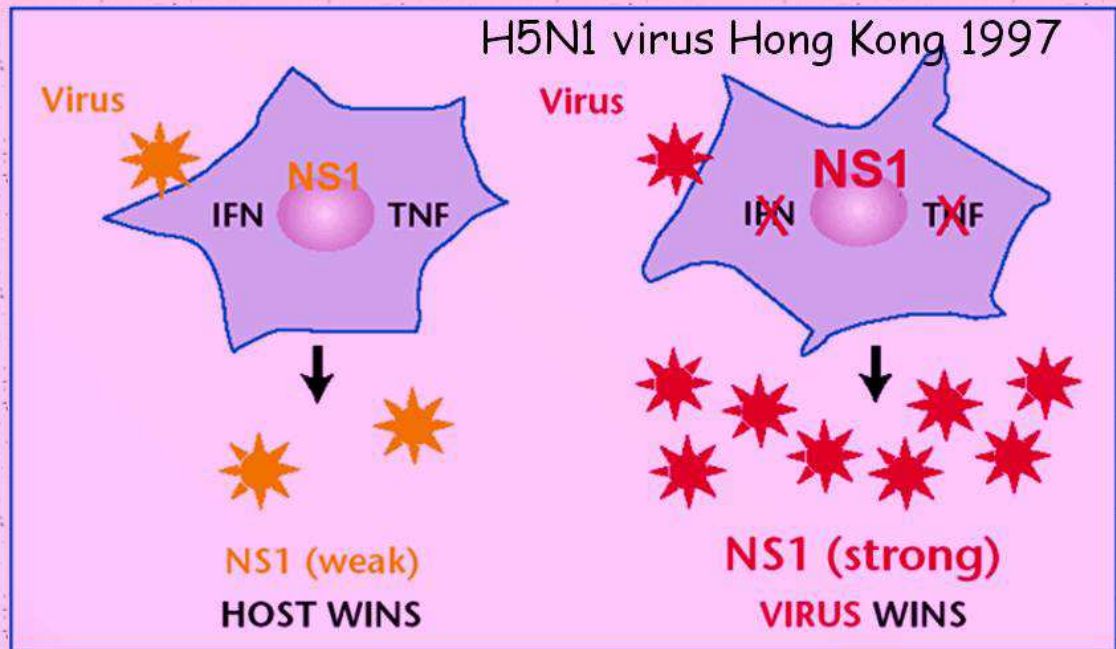


An influenza virus lacking the NS1 gene fails to prevent activation of the interferon regulatory factors IRF-3, IRF-7 and nuclear factor- B in infected cells.

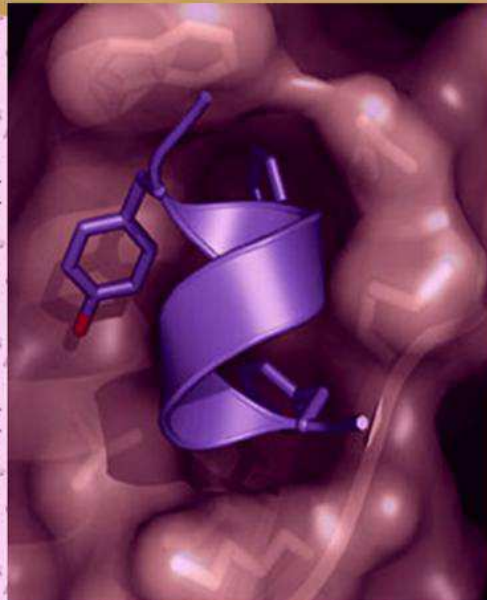
Viruses lacking the NS1 gene or having mutations abrogating its activity were also unable to prevent the activation of the dsRNA-dependent protein kinase (PKR), one of the most important effector antiviral molecules induced by IFNs.

IFN antagonists (NS1) in viral pathogenesis

(*Nature Medicine* 8, 927 - 928 (2002))



The hydrophobic pocket on the surface of the influenza A protein NS1A (brown) interacts with a fragment of the human CPSF30 protein (blue).



The amino acids in the CPSF30-binding pocket are highly conserved among human influenza A viruses, including H5N1 viruses isolated from humans and the pandemic 1918 strain.

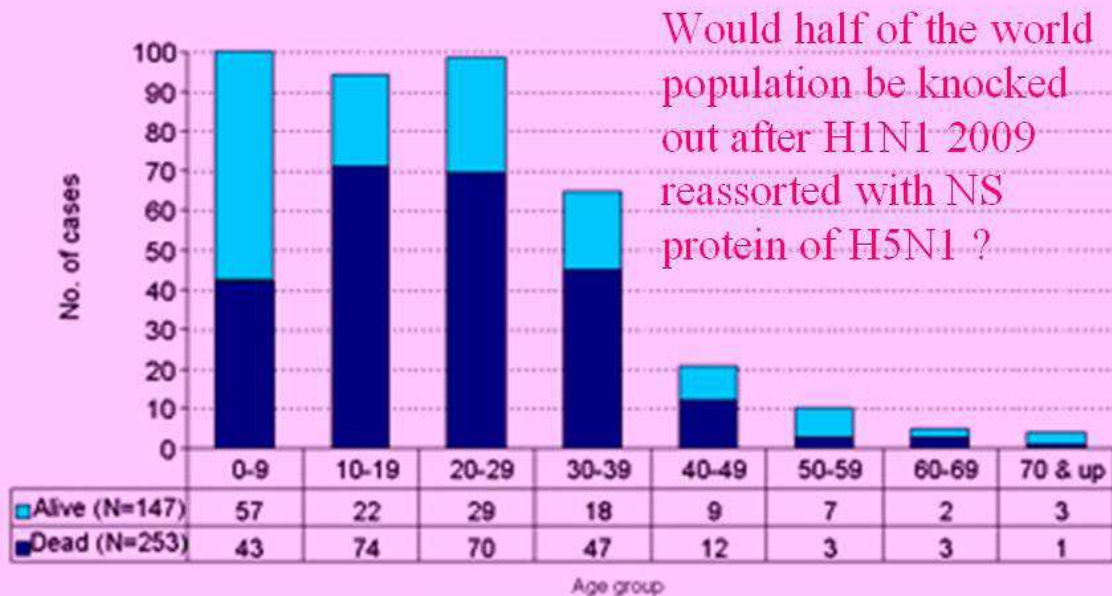
- # In infected cells, double-stranded RNA produced by the virus usually triggers the production of interferon- β , a cytokine with antiproliferative and antiviral activities.
- # But influenza A avoids this response by producing the virulence factor **NS1A**, which **inhibits the production of interferon- β by binding to CPSF30 protein.**
- # 30 kDa host protein cleavage and polyadenylation specificity factor (CPSF30) is required for all 3' end processing of pre-mRNAs, including interferon- β mRNA.

CPSF30 binding by the H5N1 HK97 virus is suboptimal for virulence: changing L103 to F and I106 to M results in not only a **20-fold enhancement in virus replication** in tissue culture, but also an even larger **250-fold, enhancement of virulence in mice**.



Unlike the NS1A protein of the HK97 virus, **all of the NS1A proteins of H5N1 viruses isolated from humans since 2003 contain the optimum F103 and M106 amino acids**

Human Avian Influenza A (H5N1) Cases by Age Group and Outcome (n=400) (as of 23 March 2009)



Worst Scenario Estimation after Swine H1N1 2009 spread to SEA and China and mix with H5N1.



What should be our strategy before effective vaccine is available and Swine H1N1 has mutated to a malignant strain with high mortality rate and show some degree of resistant to oseltamivir ?

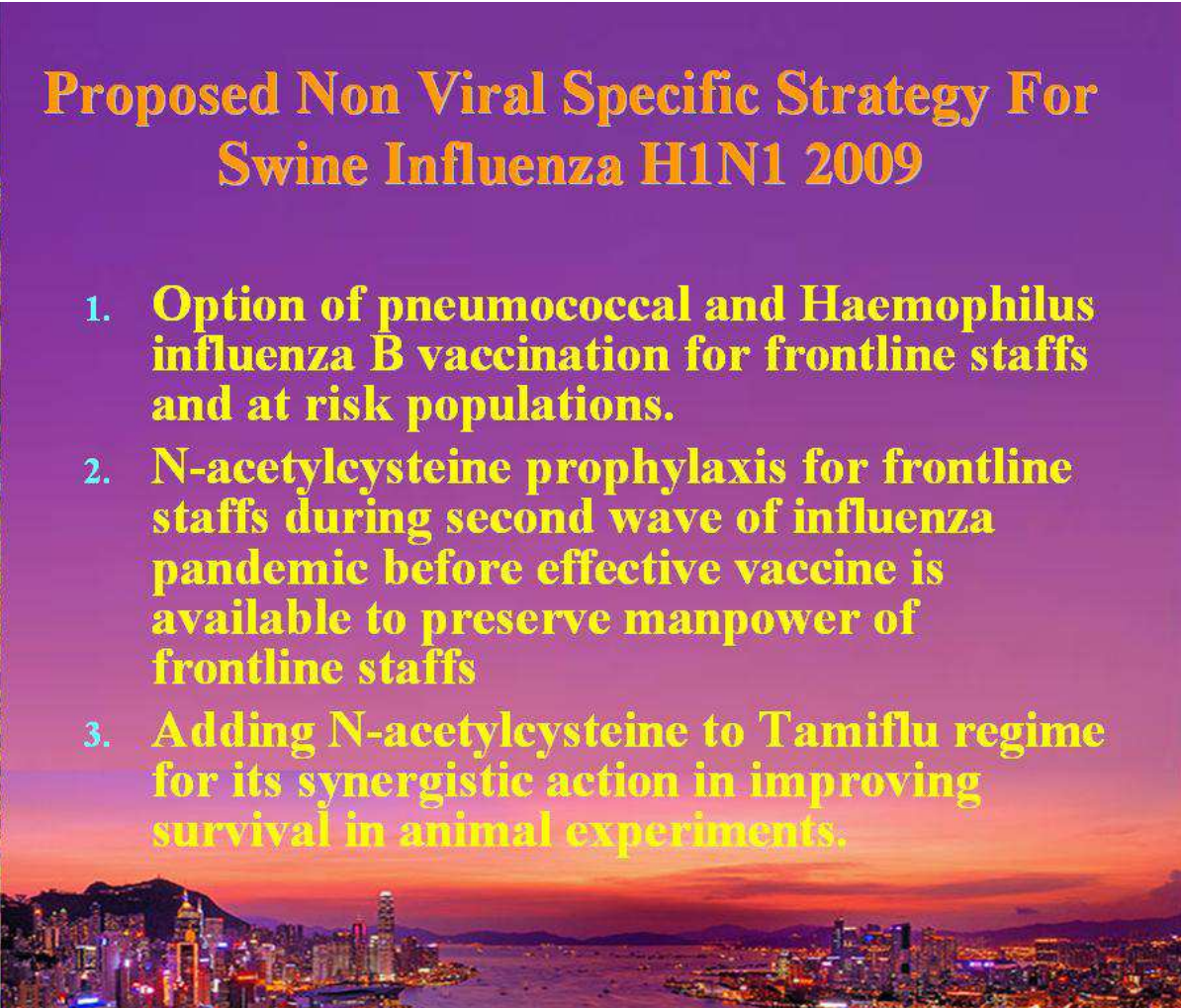
Non Viral Specific Strategy For Swine Influenza H1N1 2009

Dr. Lai Kang Yiu
Intensive Care Unit
Queem Elizabeth Hospital





Proposed Non Viral Specific Strategy For Swine Influenza H1N1 2009

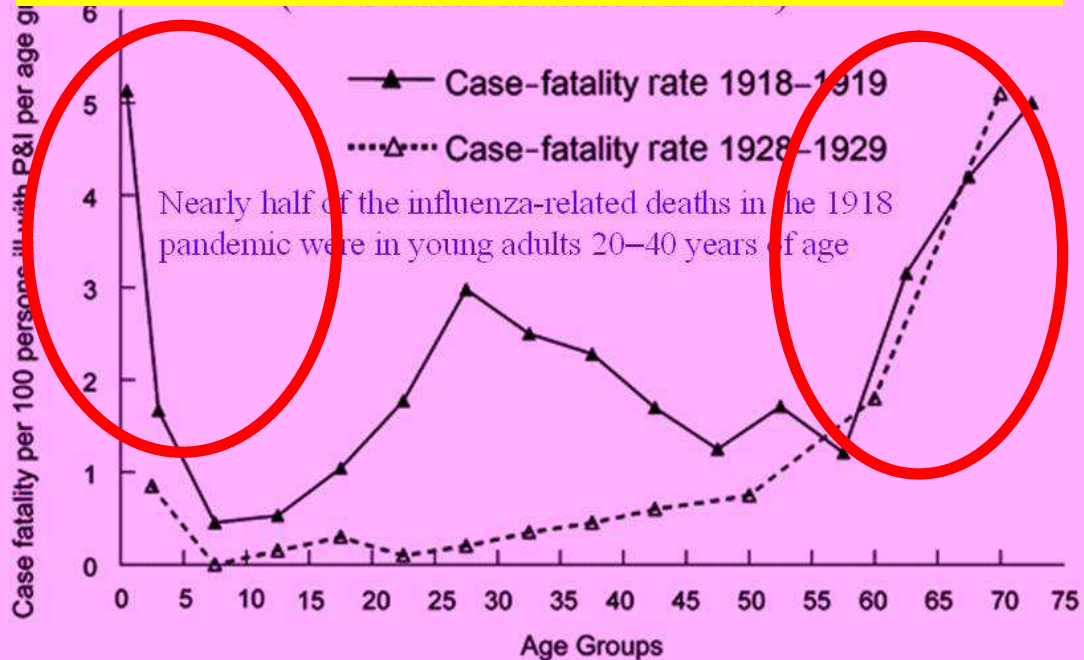
- 1. Option of pneumococcal and Haemophilus influenza B vaccination for frontline staffs and at risk populations.**
 - 2. N-acetylcysteine prophylaxis for frontline staffs during second wave of influenza pandemic before effective vaccine is available to preserve manpower of frontline staffs**
 - 3. Adding N-acetylcysteine to Tamiflu regime for its synergistic action in improving survival in animal experiments.**
- 

**Pneumococcal and Haemophilus
influenza B vaccination for frontline
staffs and at risk population**

**Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital**



Case Fatality is highest at extremes of age



How can we reduce this mortality ?

Bacterial co-infection →

(a) NA facilitate bacterial adhesion and invasion.

(b) Cleavage activation of HA by bacteria amplify virus replication

Cytokine storm → NS protein suppress IFN production



**Over 50% of influenza death were reported to have died
with the pneumococcal complications**

Pneumococci do not mutate like the influenza virus

We have effective vaccine for pneumococcus

Preparing for the influenza pandemic:
remember its ally the pneumococcus

Clinical Medicine. London: Jun 2007. Vol. 7,
Iss. 3; p. 309





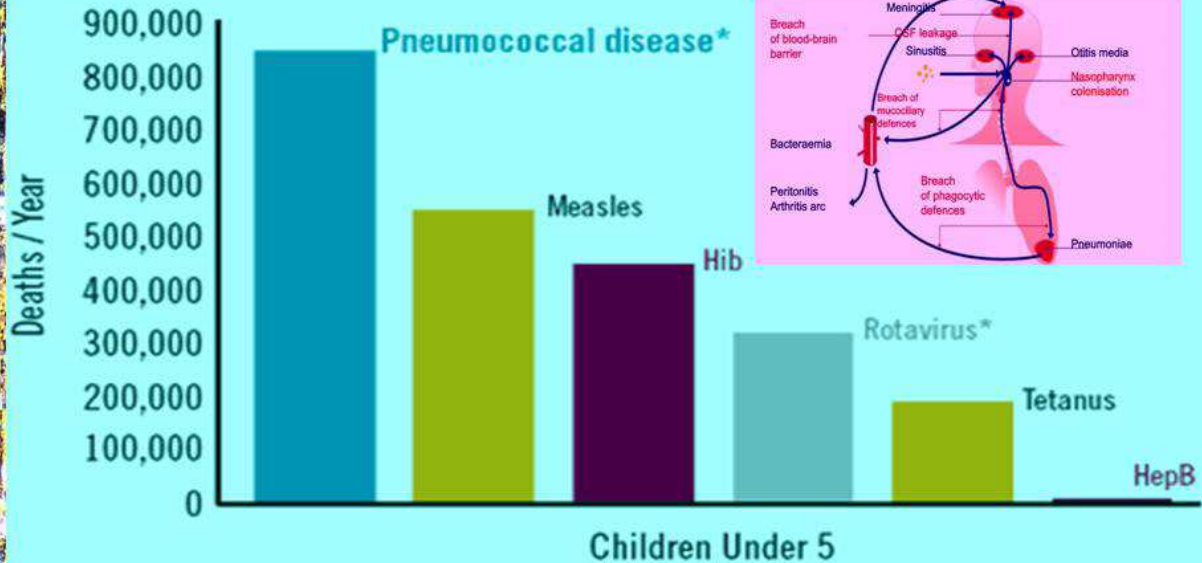
W.H.O.

Reducing excess mortality from common illnesses during an influenza pandemic

WHO guidelines for emergency health interventions in community settings Geneva, 2008

- ©Pneumonia is one of the most common causes of morbidity and mortality for adults and children
- ©The burden of disease is highest in children under 5 years of age; pneumonia is responsible for more childhood deaths than any other illness.
- ©Majority of of secondary bacterial pneumonias were associated with *Streptococcus pneumoniae* and *Staphylococcus aureus*, and *Haemophilus influenzae*.

Leading Causes of Vaccine-Preventable Death in Children <5 Years Old



Source: WHO official mortality rates — June 2003

* Provisional estimates

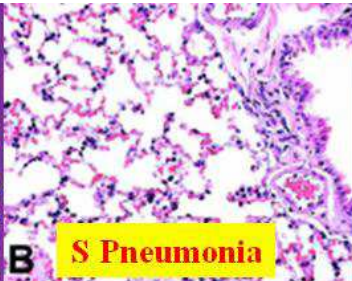
Pneumococcal infection is the leading vaccine preventable death in children < 5 years old

Comparative Features of Pulmonary Complications of Influenza

	Primary Viral Pneumonia	Secondary Bacterial Pneumonia	Mixed Viral and Bacterial Pneumonia	Localized Viral Pneumonia
Setting	Cardiovascular disease; pregnancy; young adult (Hsw1N1)	Age >65 yr; pulmonary disease	Any associated with A or B	?Normal
Clinical history	Relentless progression from classic 3-day influenza	Improvement, then worsening after 3-day influenza	Features of both primary and secondary pneumonia	Continuation of classic 3-day syndrome
Physical examination	Bilateral findings, no consolidation	Consolidation	Consolidation	Area of rales
Sputum bacteriology	Normal flora	<i>Pneumococcus</i> , <i>Staphylococcus</i> , <i>Haemophilus influenzae</i>	<i>Pneumococcus</i> , <i>Staphylococcus</i> , <i>H. influenzae</i>	Normal flora
Chest radiography	Bilateral findings	Consolidation	Consolidation	Segmental infiltrate
White blood cell count	Leukocytosis with a shift to the left	Leukocytosis with a shift to the left	Leukocytosis with a shift to the left	Usually normal
Isolation of influenza virus	Yes	No	Yes	Yes
Response to antibiotics	No	Yes	Often	No
Mortality	High	Low	Variable	Very low

A highly virulent virus would produce early death

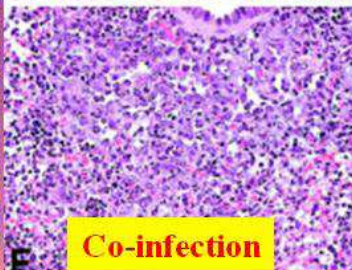
The median time of death in 1918 pandemic is 7-10 days suggesting mixed or secondary bacterial infection play a major role.



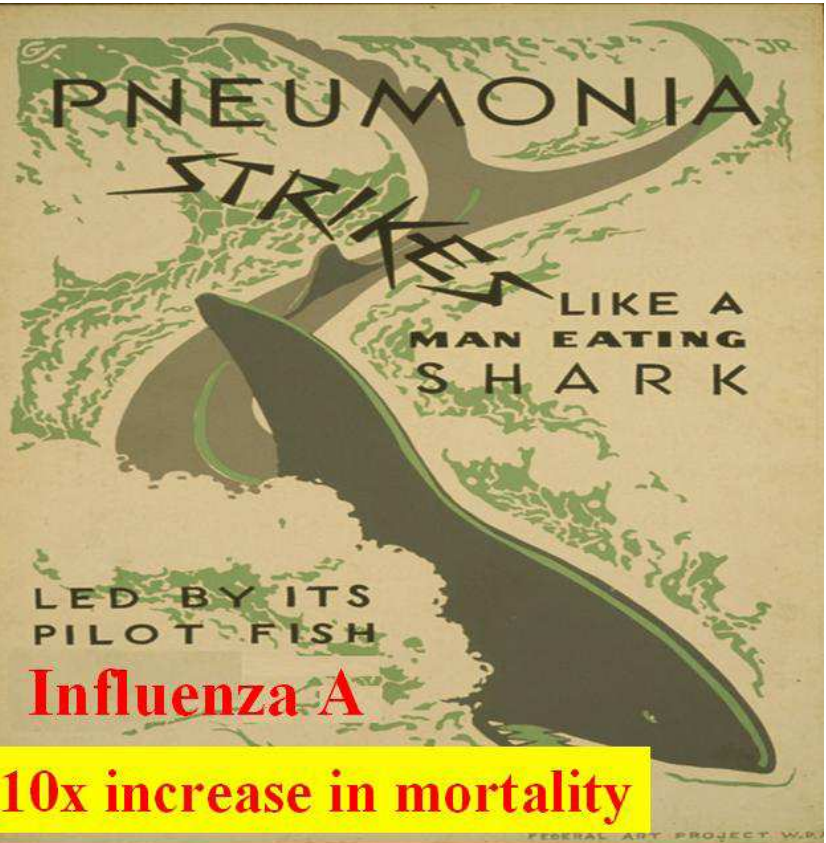
S Pneumonia



Influenza A



Co-infection



10x increase in mortality



Predominant Role of Bacterial Pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness
(Morens J infect Dis 2008;198:962-970)

Bacterial culture results in lung tissues from 5226 victims of the 1918-1919 influenza pandemic from 96 autopsy series

Bacterial pathogens	% of culture from which organism was recovered
Streptococcus pneumoniae	24%
Streptococcus pyogenes	17%
Haemophilus influenza	10%
Staphylococcus aureus	8%
Mixed growth	21%
Others	16%
No growth	4%

Case-fatality ratio of 20-30% (10x) when there is secondary bacterial infection

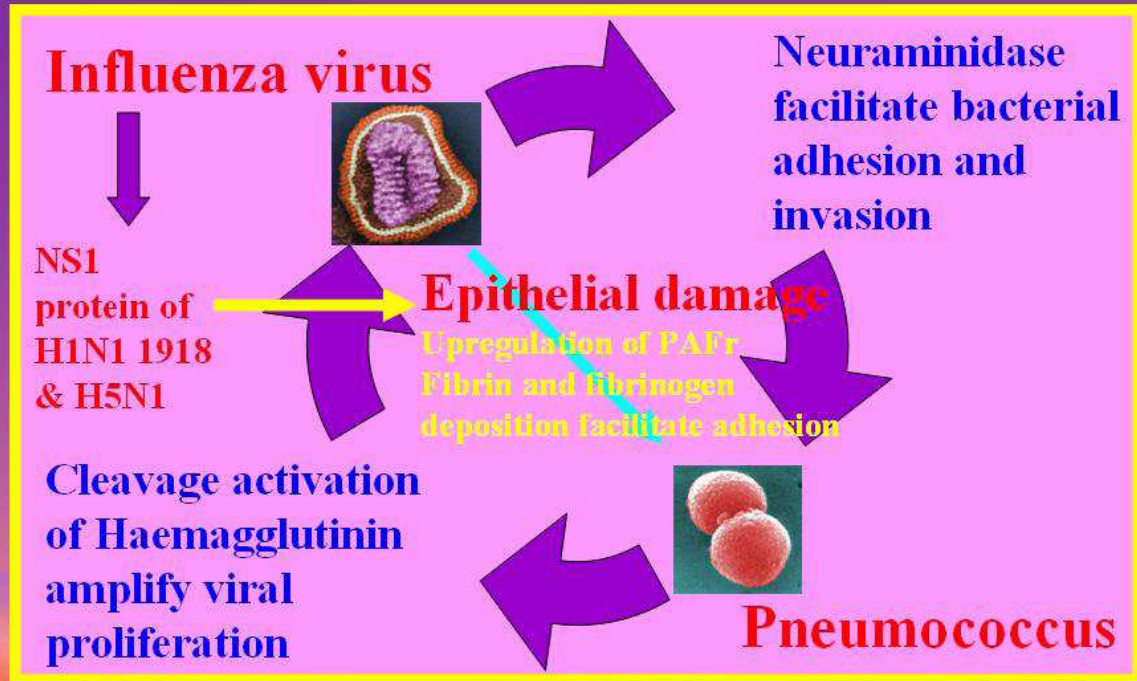
Predominant pathogens responsible for bacterial co-infection during pandemic

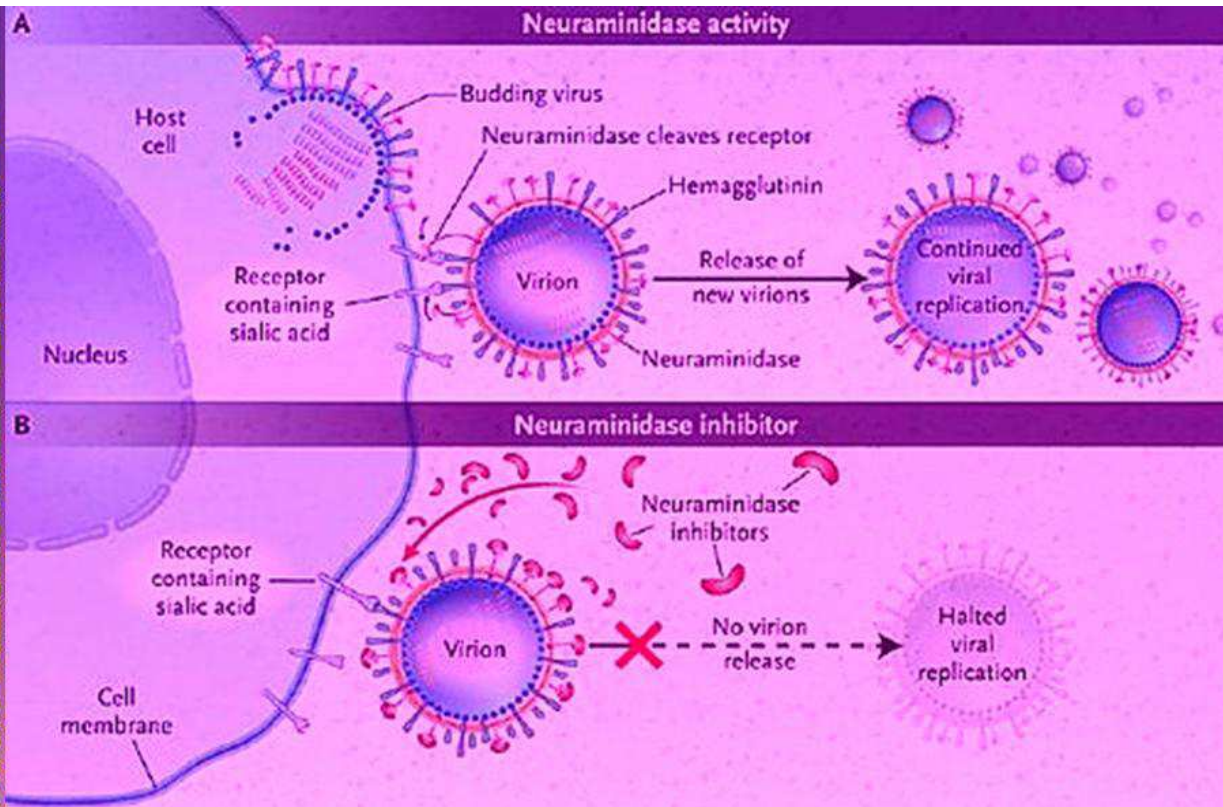
Pandemic	Predominant pathogen for bacterial co-infection
1918	S pneumonia, H. influenza and S pyogenes
1957	S. Aureus (69%)
1968	S. Pneumoniae (48%) S. Aureus (26%) H. Influenza (11%)

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.

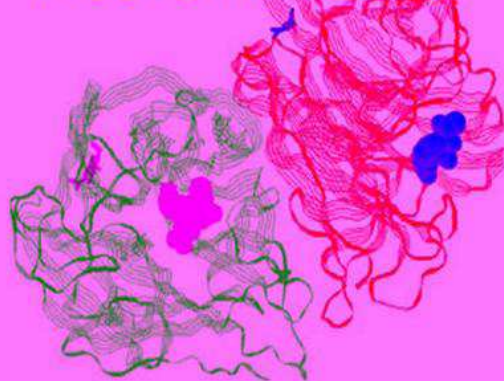
Bacteria and Virus Synergism



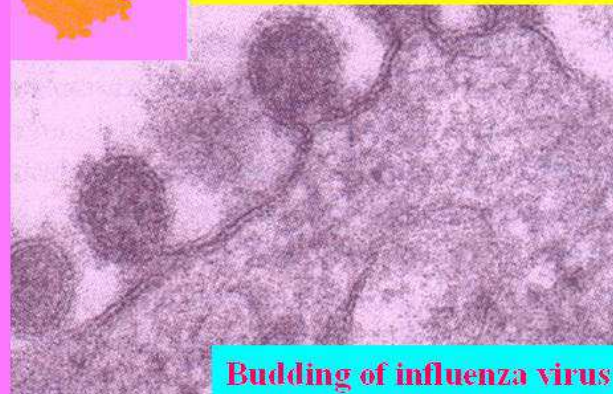


Neuraminidase: Role in Budding

Neuraminidase



Zanamivir at the active site in a cleft on the surface of Neuraminidase.



Budding of influenza virus

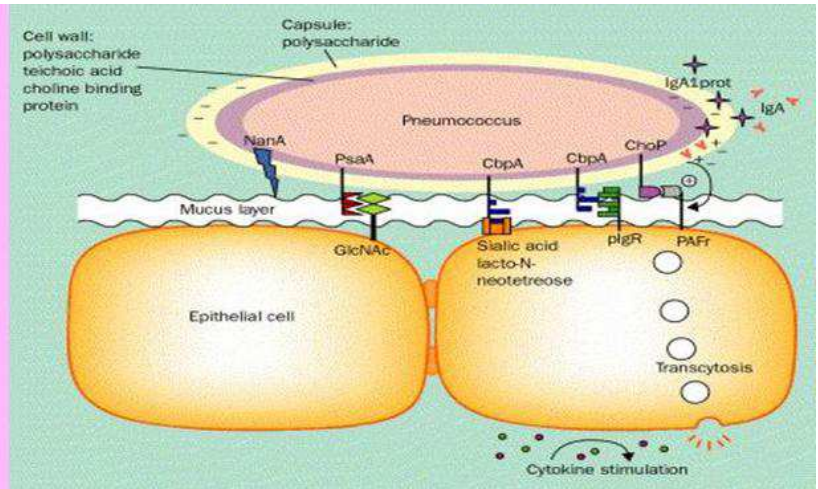
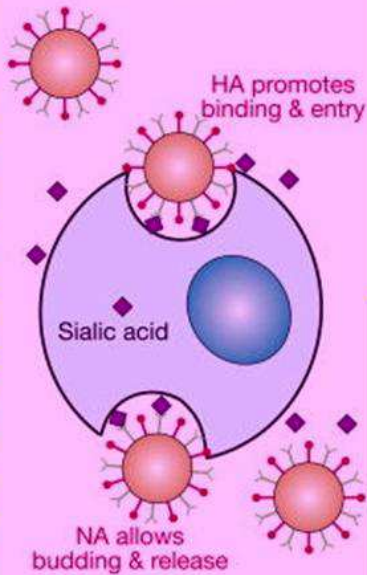
Ville The Journal of Infectious Diseases 2005;192:249–257

Comparison of neuraminidase (NA) activity with excess mortality from influenza.

Season	Circulating influenza virus	NA activity, ^a %	Deaths ^b	Excess mortality/100,000 persons
1957–1958	Sing57	100	66,000	39
1962–1963	Eng62	24	46,000	25
1968–1969	HK68	12	28,100	14
1972–1973	Mem72	37	20,700	10
1987–1988	Len86	41	30,800	13
1997–1998	Syd97	71	72,400	27

Influenza Viruses

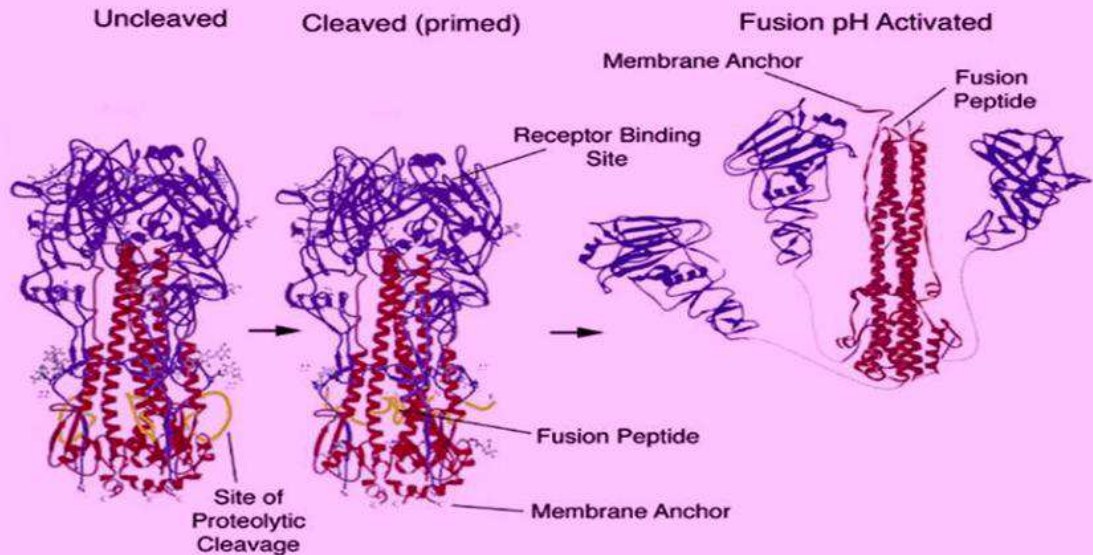
- Neuraminidase (NA)
- Hemagglutinin (HA)



Interaction between *S. pneumoniae* and epithelial cells. Neuraminidase (NanA) decreases the viscosity of the mucus and exposes the N-acetyl-glycosamine (GlcNAc) receptors on the epithelial cells, which can interact with pneumococcal surface-associated proteins such as PsaA. In response to cytokine stimulation, host epithelial cells upregulate the platelet-activating-factor receptors (PAfr). The pneumococcus has increased affinity via its cell-wall phosphocholine (ChoP) for PAfr. Moreover, a second choline-binding protein, CbpA, shows increased affinity for immobilised sialic acid and lacto-N-neotetraose, and binds directly to the polymeric Ig receptor (pIgR), which increases migration through the mucosal barrier (transcytosis). Pneumococcal IgA1 protease cleaves opsonising IgA, which results in a change (neutralisation) of surface charge and increases the physical proximity of ChoP to the PAfr.

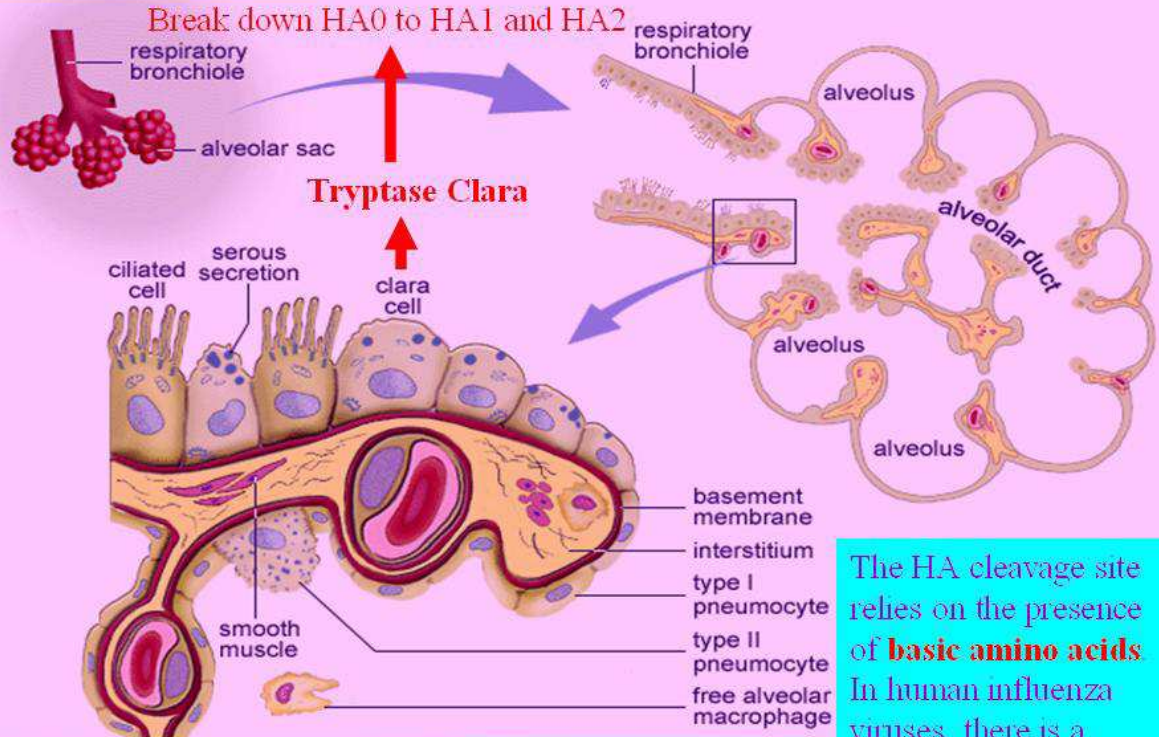
High NA activity increase mortality rate during influenza epidemic. Oseltamivir treatment prevents secondary bacterial pneumonia **even if administered late** during the course of the influenza infection.

The Conformations of the Haemagglutinin



Influenza virus hemagglutinin HA0 required cleavage into HA1, HA2 during activation. Cleavage of HA0 is vital for the subsequent infection of new cells. Without proteolysis, the acid-triggered conformational change in HA to expose the fusion peptide cannot occur, and therefore the virus is essentially non-infectious.

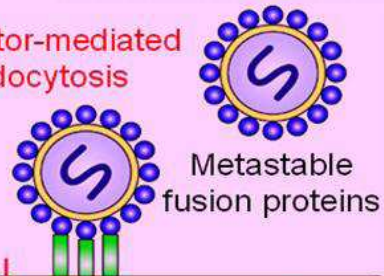
Respiratory Bronchiole



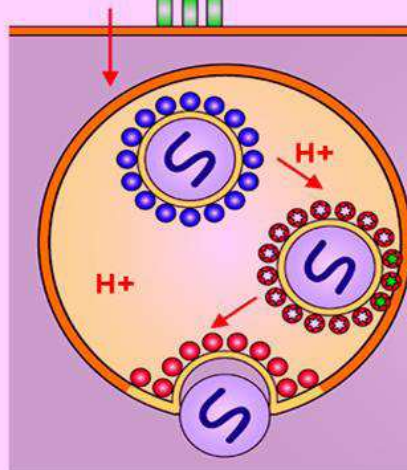
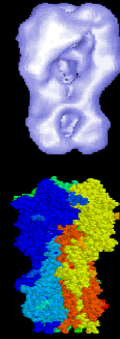
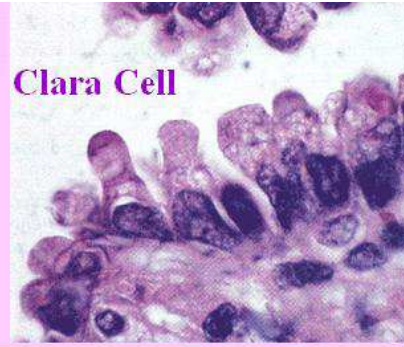
The cleavage site is specific and the protease has limited tissue distribution. Both of these features mean that influenza infections are generally limited to the upper respiratory tract.

The HA cleavage site relies on the presence of **basic amino acids**. In human influenza viruses, there is a single basic amino acid (arginine; R) at the site of cleavage (e.g. HA1-PSIQVR-GL-HA2).

Receptor-mediated
endocytosis



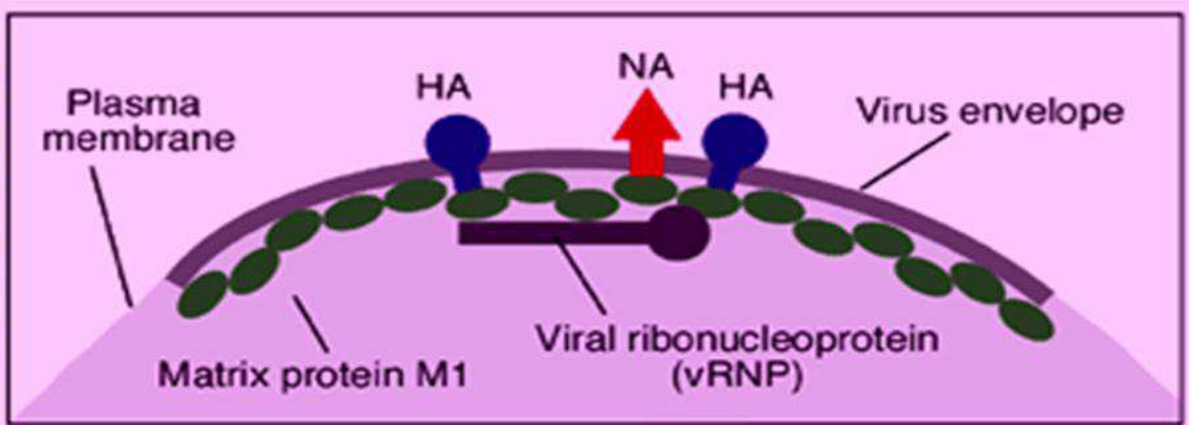
Clara Cell



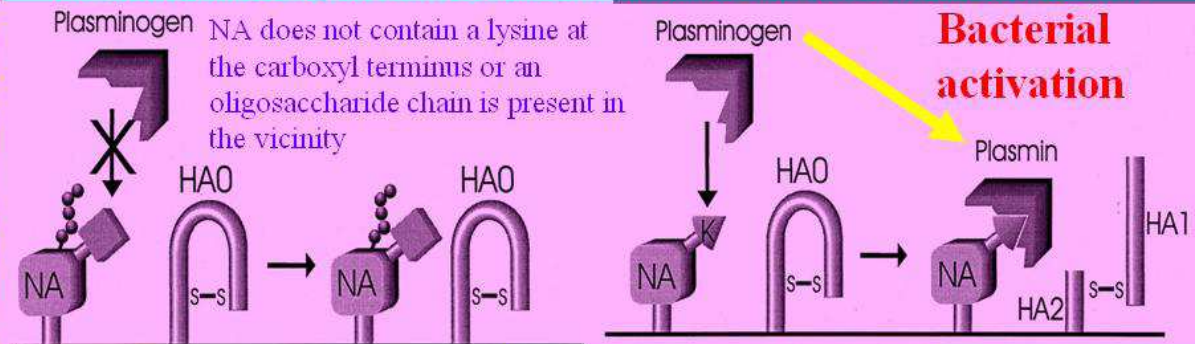
©Bacteria such as *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and various Gram-negative bacilli often produce *extracellular proteases* that can cleave monobasic cleavage sites on HA, **enhancing virus spread.**

Role of Secondary Bacterial Infection in HA0 Cleavage

[Tashiro, M. and Rott, R. (1996) The role of proteolytic cleavage of viral glycoproteins in the pathogenesis of influenza virus infections. *Seminars Virol* 7, 237-243]



Lysine at the carboxyl terminus of NA can lead to ubiquitous HA cleavage by plasmin



Lysine at the carboxyl terminus of NA

Goto, H. & Kawakita, Y. (1998) Proc. Natl. Acad. Sci. USA 95, 10224-10228

Estimated number of persons affected by pandemic influenza per 1000 population for resource-poor settings (W.H.O.)

Description	Estimated during pandemic	Estimates for crowded, low-resource settings	Number of persons affected over a 2–3 month pandemic wave
Ill from influenza	15–35% (of the general population)	Up to 50–60% (of the general population)	Up to 500–600
Secondary bacterial pneumonia (needing antibiotics)	2.5–5% (of those ill)	5–10% (of those ill)	25–60
Health-care seeking for influenza (outpatients)	30–50% (of those ill)	50–50% (of those ill)	150–300

Patient with potential need for hospitalization

A volume that cannot be handled by current resources of HA

Should we vaccinate our population at risk to reduce secondary bacterial pneumonia due to pneumococcus and haemophilus influenza co infection to reduce this potential volume load?



Haemophilus influenzae type b (Hib) is an important pathogen in children <5 years of age. The Hib conjugate vaccines were the first polysaccharide–protein conjugate vaccines to be used in routine childhood schedules. Their introduction in the UK in 1992 has resulted in the near elimination of Hib disease.

The UK Hib vaccine experience

P T Heath and J McVernon

Archives of Disease in Childhood 2002;86:396-399

Hi type b strain (Hib) was responsible for approximately 95% of all invasive Hi disease in children and 50% of all invasive Hi disease in adults.



Incidence of Hib disease in UK children < 5 years of age

The UK Hib vaccine experience

P T Heath and J McVernon Archives of Disease in Childhood 2002;86:396-399

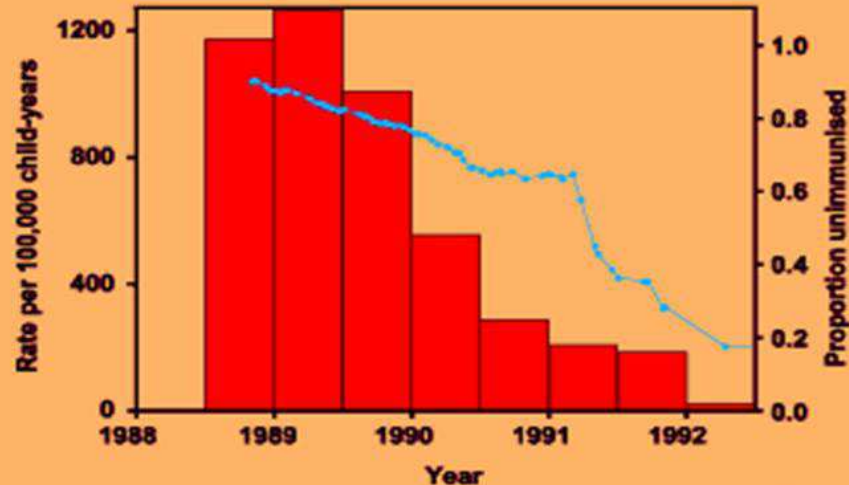
Year	Cases	Incidence rate per 105 (95% CI)
1980-1990	1500 © 900 meningitis © 60 death	21 – 44 © Mortality 2.3-4.3% © MR 6% © Seizure 6% © Deafness 7%
1996	31	0.83(0.53, 1.1)
1997	31	0.84(0.54, 1.1)
1998	23	0.63(0.37, 0.89)
1999	39	1.1(0.74, 1.4)
2000	66	1.8(1.4, 2.3)



Vaccination Program by N.H.S.

Age	Vaccine
Two months	DTaP/IPV/Hib + pneumococcal (PCV)
Three months	DTaP/IPV/Hib + MenC
Four months	DTaP/IPV/Hib + MenC and PCV
12 months	Hib/MenC
13 months	MMR + PCV

Indirect Effect of Community Wide Hib Conjugate Vaccination: Navajo Nation; 1988–92, Children < 2 yo



Moulton L, et al *Int J Epi*, August 2000

Significant drop even only 30% of population vaccinated



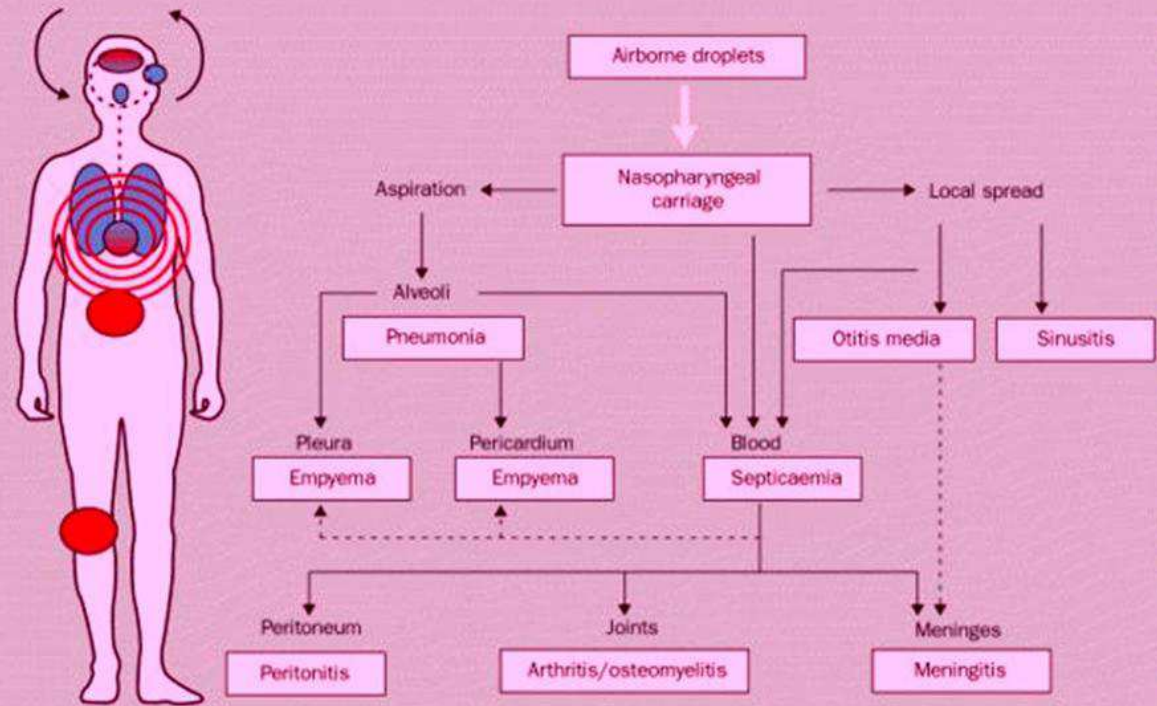
W.H.O.

Reducing excess mortality from common illnesses during an influenza pandemic

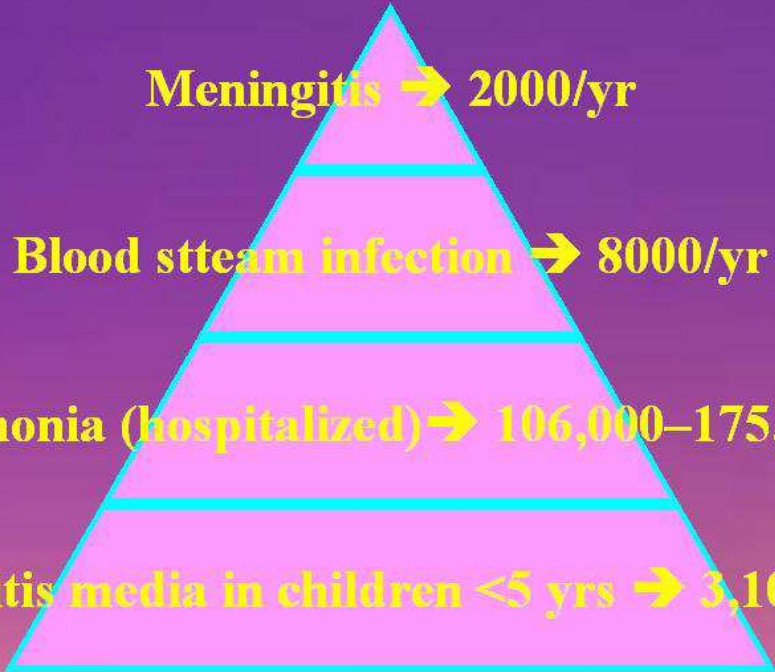
WHO guidelines for emergency health interventions in community settings Geneva, 2008

WHO recommends Hib vaccine for
infant immunization in **all**
countries.





Pathogenic route for *S. pneumoniae* infection
From nasopharyngeal colonisation to bacterial invasion



Meningitis → 2000/yr

Blood stream infection → 8000/yr

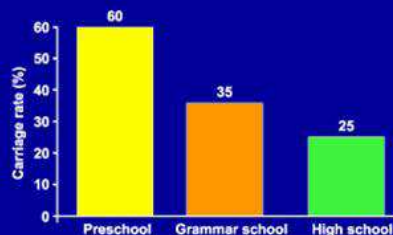
Pneumonia (hospitalized) → 106,000–175,000/yr

Acute otitis media in children <5 yrs → 3,100,000/yr

**Incidence of pneumococcal infections in the United States
(CDC)**

Nasopharyngeal carriage of pneumococcus

Paediatric Carriage Rates



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

Adult NP Carriage Rate



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

Patients with high risk of co-infection during pandemic influenza



How about Young Children in Hong Kong?

- In Hong Kong, the prevalence of nasopharyngeal carriage of *Streptococcus pneumoniae* is 19.4% (393 of 1978 children in 79 day care centers with age between 2-6 years from 1999 to 2000, study by Dr. Susan Chiu et al).
- Carriage of *S. pneumoniae* was more common at a younger age.

Age	Carriage rate (%)
2-6	19.4
2-3	28.8
4	32.6
5	20.1
6	15.2



香港兒科基金
The Hong Kong Paediatric Foundation

► **Nasopharyngeal carriage rate of *Streptococcus pneumoniae* in Hong Kong Paediatric Population**



Annual incidence of culture-confirmed IPD, Hong Kong Island,
by age, 1995-2004.



Invasive pneumococcal disease (IPD) based on all positive cultures (blood, CSF, body fluid) in two major hospitals (Queen Mary Hospital and PYH) representing 90% of all cases on Hong Kong island, 1995-2004. Population figures from sub-census in 1996 and 2001 used in calculation.

P L Ho, et al, The Paediatric Infection Disease Journal, Vol 25 (5) 454-455 May 2006

Population at Risk of Invasive Pneumococcal Disease



Risk for IPD

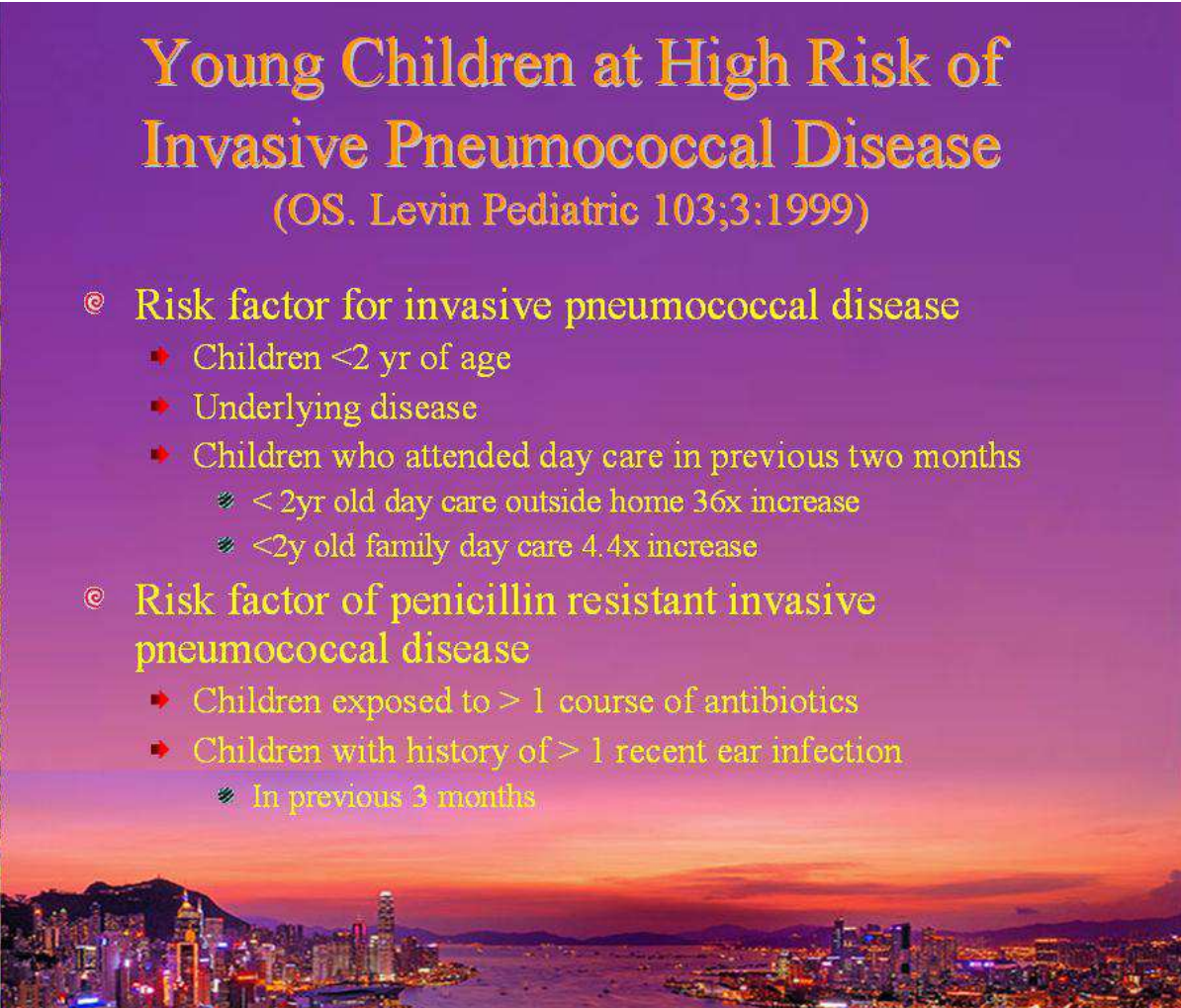
Age	Per 100 000
6-11 months	235
< 12 months	205
< 23 months	165
Ethnicity	
African American	>400
Native American, Native Alaskan	557 – 2400
Australian Aborigine	170
Splenic Dysfunction	600-6500
HIV Infection	587-11300





Young Children at High Risk of Invasive Pneumococcal Disease

(OS. Levin Pediatric 103;3:1999)

- © Risk factor for invasive pneumococcal disease
 - ◆ Children <2 yr of age
 - ◆ Underlying disease
 - ◆ Children who attended day care in previous two months
 - ◆ <2yr old day care outside home 36x increase
 - ◆ <2y old family day care 4.4x increase
 - © Risk factor of penicillin resistant invasive pneumococcal disease
 - ◆ Children exposed to > 1 course of antibiotics
 - ◆ Children with history of > 1 recent ear infection
 - ◆ In previous 3 months
- 



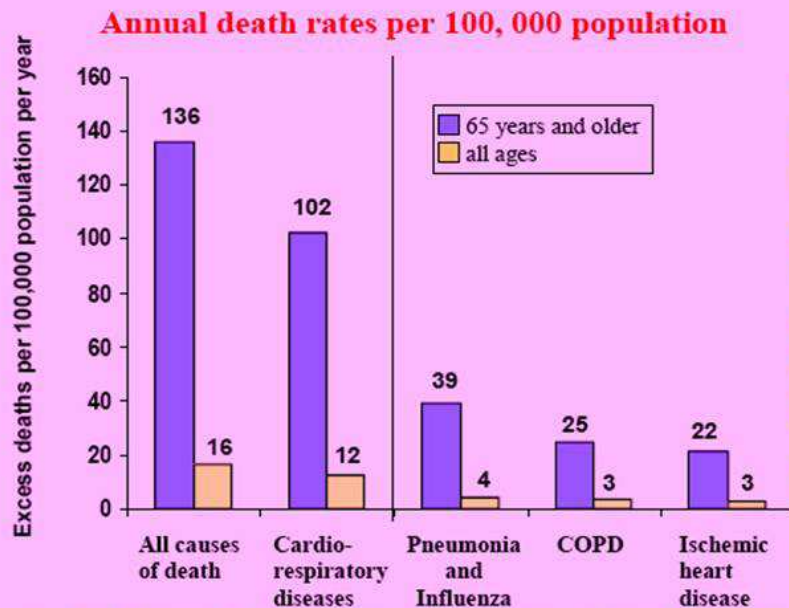
How many excess deaths from influenza per year in Hong Kong during 1996-1999?

	≥ 65 years	< 65 years
All causes	933	140
Cardiorespiratory	699	114
Pneumonia	270	2
Chronic Obstructive Pulmonary Disease (COPD)	169	35
Ischaemic heart disease	147	53

Deaths Caused by Influenza in Hong Kong: The First Report from a Tropical Region 1 December 2004 Chit-Ming Wong



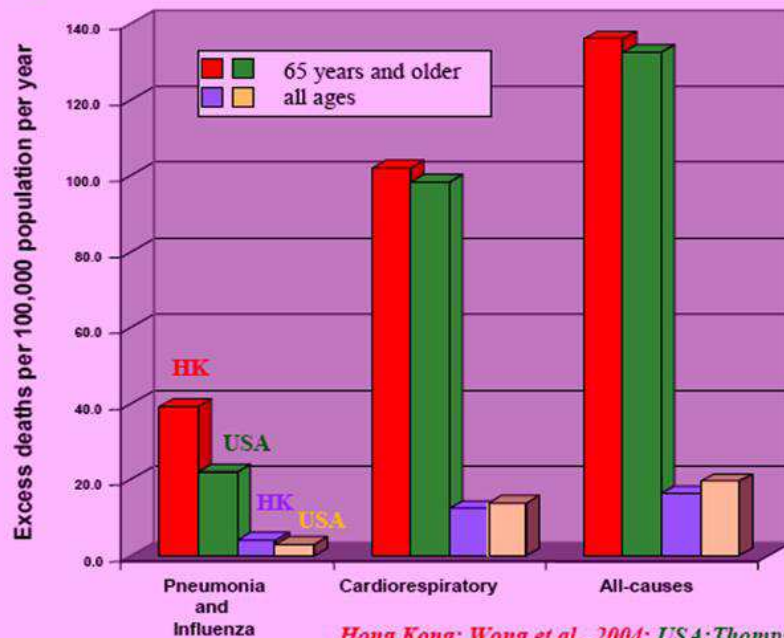
Influenza-associated death rates in Hong Kong (1996-1999)



Older people have higher risk of death due to influenza compared to the average across all age groups

Deaths Caused by Influenza in Hong Kong: The First Report from a Tropical Region 1 December 2004 Chit-Ming Wong

Influenza-associated death rates in Hong Kong are no less than in “cold-climates”

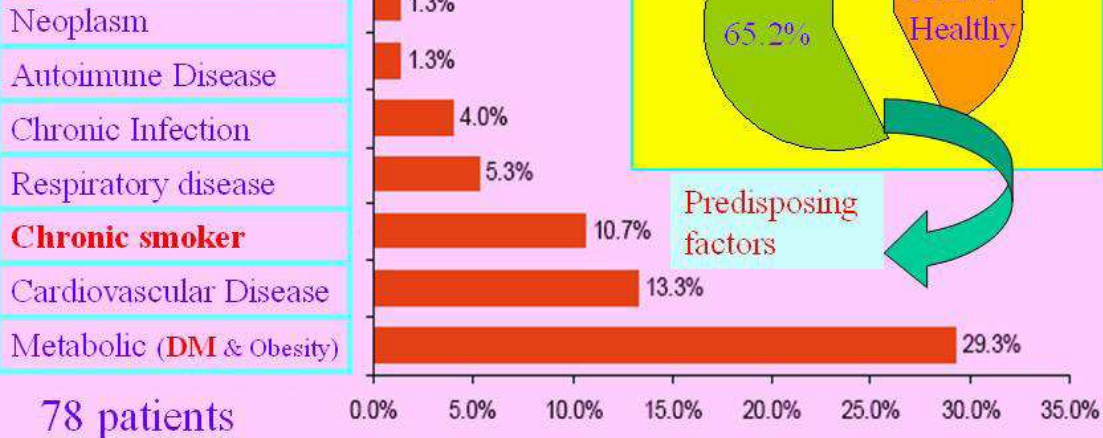


Deaths Caused by Influenza in Hong Kong: The First Report from a Tropical Region 1/12/2004
Chit-Ming Wong

Hong Kong: Wong et al., 2004; USA: Thompson et al., 2003

Antecedentes Patológicos

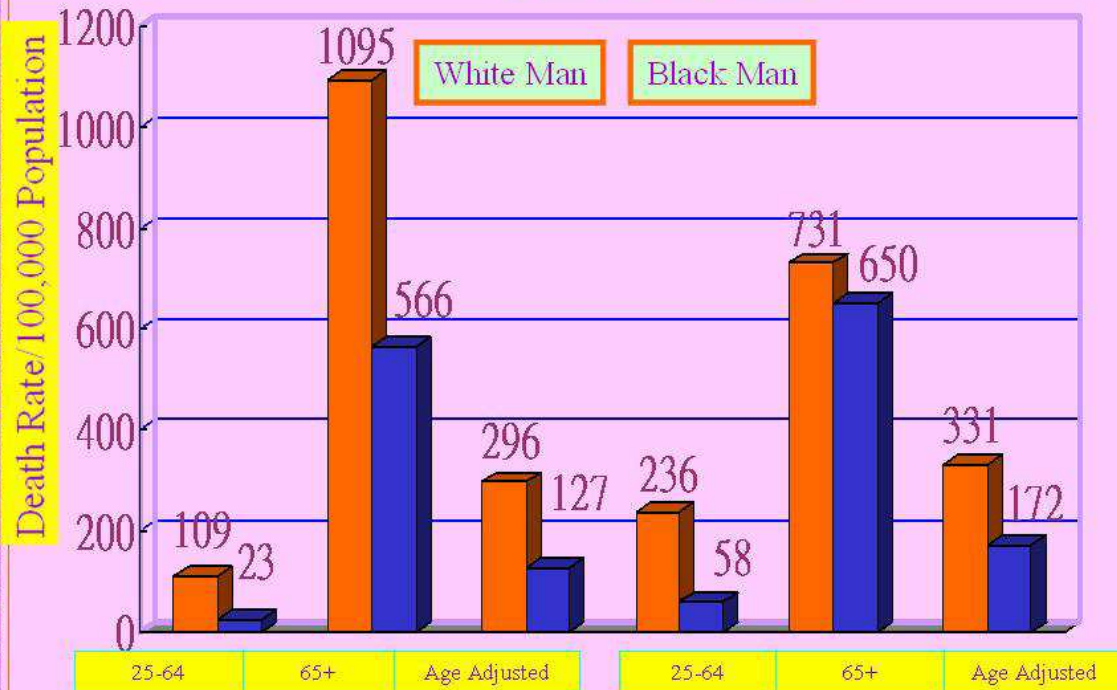
Mexico



Chronic smokers and diabetic patients have increased risk of death from HSI H1N1 2009

Impact of diabetes mellitus on mortality associated with pneumonia and influenza

among non-Hispanic black and white US adults. R Valdez American Journal of Public Health, Vol. 89, Issue 11 1715-1721 1999



Risk Difference

529

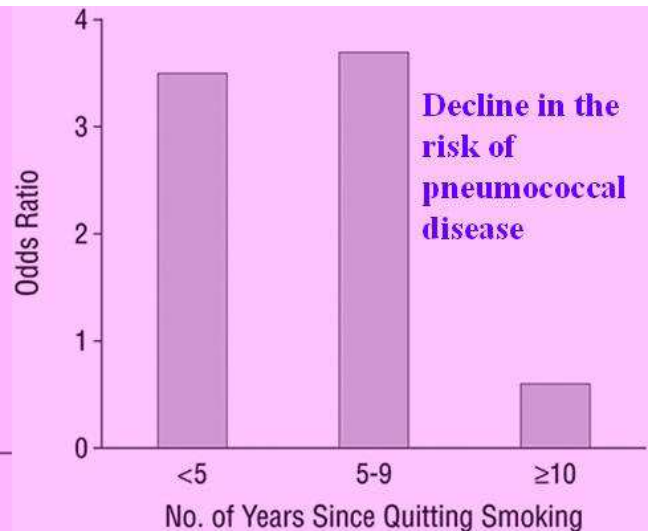
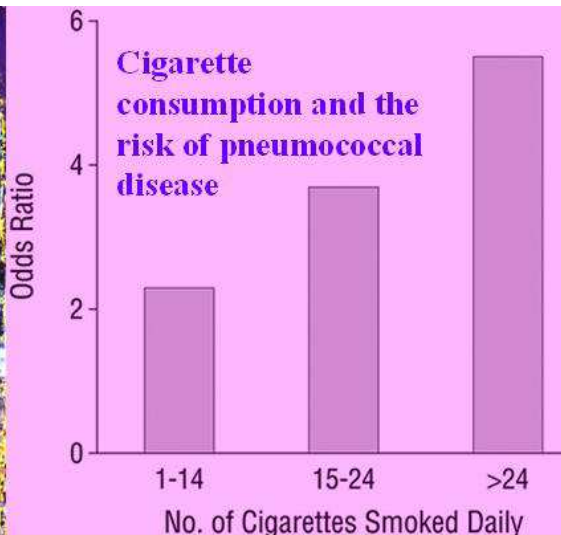
86

171

178

81

159



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.

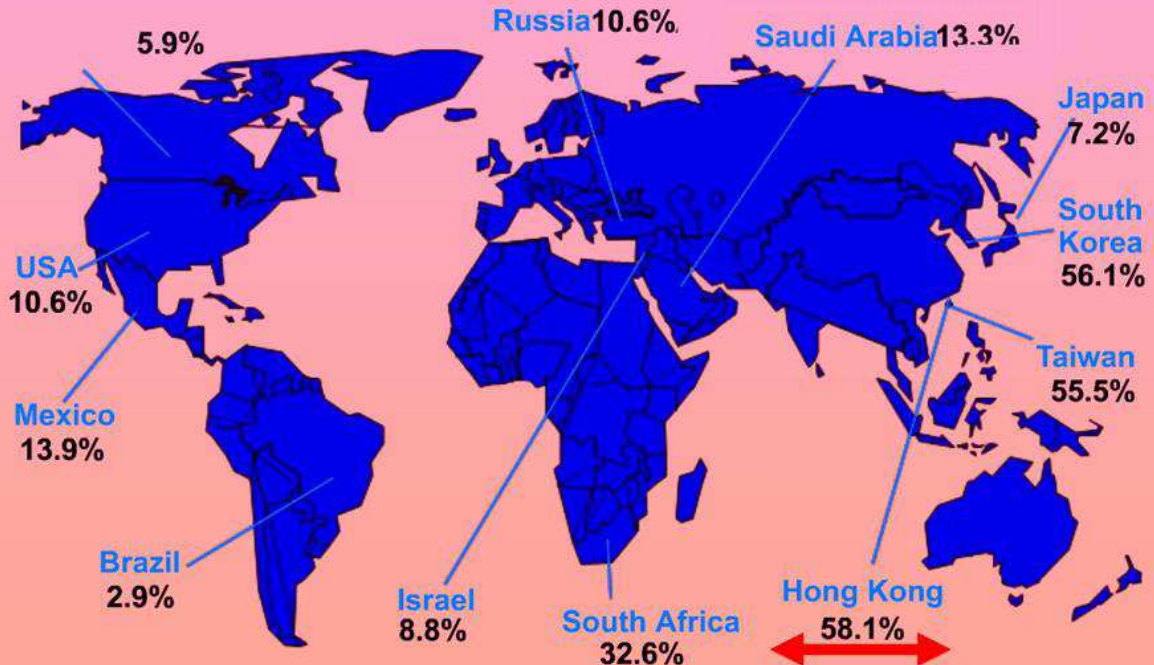
Cigarette smoking cause activation of platelet-activating factor facilitating attachment and invasion of cells by pneumococcal strains. This may contribute to the increased incidence of bacterial superinfection in people who develop influenza.



Updated ACIP Recommendations for Use of Pneumococcal Vaccines October 22, 2008

- © *Persons aged 19 through 64 years who smoke cigarettes should receive a single dose of PPSV23 and smoking cessation counseling.*
 - © *Persons aged 19 through 64 years who have asthma should receive a single dose of PPSV23.*
 - © *A second dose of PPSV23 is recommended 5 years after the first dose of PPSV23 for persons aged ≥ 2 years who are immunocompromised, have sickle cell disease, or functional or anatomic asplenia*
- 

Multi-drug resistant *S. pneumoniae*



Problem facing HKSAR over stockpiling antibiotic for bacterial co-infection in preparation for pandemic influenza



The use of PncCV in children and 23-valent PPV in adults against *Streptococcus pneumoniae* as part of a pandemic influenza strategy would be consistent with recommendations resulting from current published data.

**Bacterial Pneumonia and Pandemic
Influenza Planning
Emerging Infectious Disease
Volume 14, Number 8–August 2008**





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 !



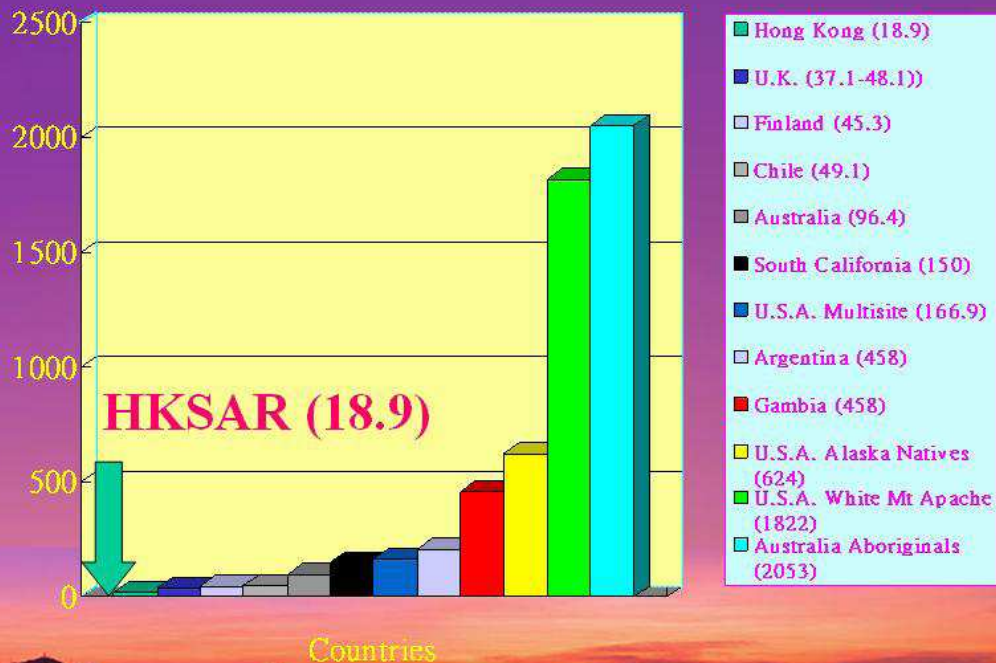
世事有得有失 香港以身証之

The incidence of invasive
pneumococcal disease and
penicillin resistant pneumococcus



Incidence, cases per one hundred thousand population

Incidence of Invasive Pneumococcal Disease in children <2 years old

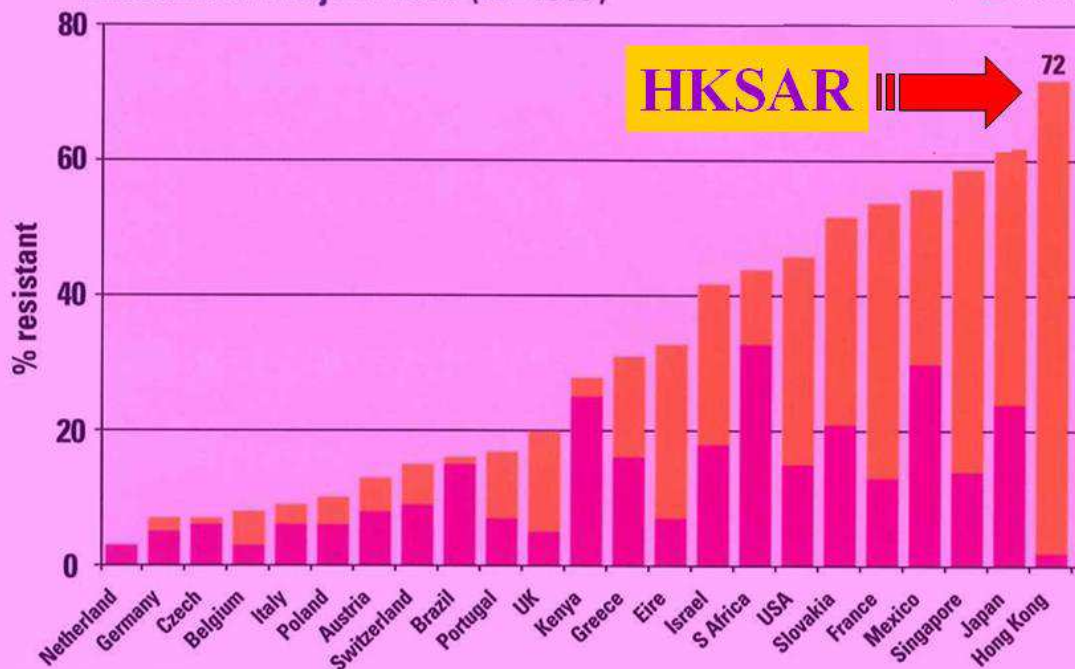


Cortesell M *Arch Intern Med* 1992; Eskola J *JAMA* 1992; Davidson M *JID* 1994; Torzillo PF *Med J Austr* 1995; O'Dempsey TJ *PIDJ* 1996; Levine MM *PIDJ* 1998; Robinson KA *JAMA* 2001; Berkley NE *JM* 2005; P. L. Ho, et al, The Paediatric Infection Disease Journal, Vol 25 (5) 454-455 May 2006

Penicillin resistance - *S. pneumoniae*
Alexander Project 1998 (N=4017)

(Jacobs ICAAC
1999 Poster #1044)

Pen R
Pen I



肺炎鏈球菌疫苗預防接種



◎為什麼要施打肺炎鏈球菌疫苗？

肺炎鏈球菌的感染常造成許多的疾病發生，由於潛伏在人類鼻腔內，一旦感冒或是免疫力降低，肺炎鏈球菌就可能從呼吸道或血液入侵，輕微的引起中耳炎、鼻竇炎等，嚴重則會造成肺炎、敗血症、腦膜炎，危及生命。由於台灣之肺炎鏈球菌抗藥性問題日益嚴重，使得肺炎鏈球菌感染的治療更加困難。臨床上亦顯示由於嬰幼兒免疫功能不成熟以及老年人免疫力低下、慢性疾病患者居多，常常合併肺炎鏈球菌及其他細菌感染症，增加醫療困難性及合併症產生。因此，藉由防疫接種來預防此疾病，就顯得格外重要。

◎每個人都需要施打肺炎鏈球菌疫苗嗎？

肺炎鏈球菌是導致肺炎的主要元凶之一，有些人患此病的風險比較大，這包括65歲以上的老人、嬰幼兒及有特別健康問題，例如：慢性心血管疾病、慢性肺病、糖尿病、酗酒、腎臟功能衰退、愛滋病毒感染、或有某種癌症的病人。世界衛生組織（WHO）及美國預防接種諮詢委員會（ACIP）皆建議運用施打疫苗的策略避免感染肺炎鏈球菌性肺炎，凡是65歲以上（含）的老年人或2-64歲之高危險群（例如：患有慢性心血管疾病、糖尿病、慢性肺病、慢性肝病或免疫功能不全者）皆應施打肺炎鏈球菌疫苗（23價型）。由於兒童肺炎鏈球菌疫苗（7價型）已經上市，而世界衛生組織及加拿大、英國、澳洲、紐西蘭、比利時、德國及美國等皆已建議注射兒童肺炎鏈球菌疫苗，在美國及澳洲則是全面免費接種。

◎施打肺炎鏈球菌疫苗後是否就一定不會被肺炎鏈球菌感染？

與其他任何疫苗一樣，都是預防性作用，並不能保證100%保護接種者。

◎為什麼小於兩歲的嬰幼兒不建議施打23價型疫苗？

一般而言，小於兩歲的兒童對23價型肺炎鏈球菌疫苗內所含英藜多醣體所產生的免疫反應不佳，且小於兩歲的嬰幼兒其對23價肺炎鏈球菌疫苗的安全性及有效性尚未建立，因此不建議用於此年齡層的小孩。



◎7價及23價的肺炎鏈球菌疫苗有什麼不同？

目前分有兩種不同型態的肺炎球菌疫苗，兩者比較如下表：

疫苗商品名稱	中文名	建議注射對象	注射時間	疫苗單價																				
Pneumovax [®] 23	紐賓斯 [®] 多糖糖 肺炎鏈球菌疫苗	1. > 65 歲以上老年人 2. 2-64 歲高危險群 3. 因缺乏安全疫苗故不建議注射第三劑。	1. 通常接種一劑即可。 2. 是否追加第二劑需由醫師評估，但至少需隔 3-5 年。 3. 因缺乏安全疫苗故不建議注射第三劑。	約 1200 元/每劑 0.5 毫升																				
Prevenar [®] 7	沛兒 [®] 肺炎球菌 七價結合型疫苗-針筒或注射劑	小於兩歲以下嬰幼兒	<table border="1"> <tr> <th>接種年齡</th><th>2-6 個月大</th><th>7-11 個月大</th><th>12-23 個月大</th><th>2-5 歲孩童</th></tr> <tr> <td>應施打劑數</td><td>4</td><td>3</td><td>2</td><td>1</td></tr> <tr> <td>每劑施打間隔</td><td colspan="4">至少一個月</td></tr> <tr> <td>備註</td><td colspan="4">第四劑建議於年滿一歲後施打 第三劑建議於年滿一歲後施打</td></tr> </table>	接種年齡	2-6 個月大	7-11 個月大	12-23 個月大	2-5 歲孩童	應施打劑數	4	3	2	1	每劑施打間隔	至少一個月				備註	第四劑建議於年滿一歲後施打 第三劑建議於年滿一歲後施打				約 3200 元/每劑 0.5 毫升
接種年齡	2-6 個月大	7-11 個月大	12-23 個月大	2-5 歲孩童																				
應施打劑數	4	3	2	1																				
每劑施打間隔	至少一個月																							
備註	第四劑建議於年滿一歲後施打 第三劑建議於年滿一歲後施打																							



7價



23價

◎施打肺炎鏈球菌疫苗有什麼副作用？

通常可能出現一些局部反應（注射部位的紅、腫、熱、癢和硬塊）及發燒（低於38.9℃）的情形。接種肺炎鏈球菌疫苗的人約有半數會出現輕度的局部反應（這些反應通常不會持續超過48小時）。出現嚴重過敏反應的報告佔極少數。



S. pneumoniae polysaccharide vaccine (Pneumovax 23)

- © Purified pneumococcal polysaccharide (23 types)
- © Not effective in children <2 years
- © 60-70% effective against invasive disease
- © Less effective against pneumonia
- © U.S.:
 - adults 65 years and older
 - children >2 years at high risk (HIV, sickle cell, asplenia)

Pneumococcal capsular type in Pneumovax 23

1 2 3 4 5 6B** 7F 8 9N 9V** 10A 11A 12F 14** 15B 17F 18C 19F** 19A** 20 22F 23F** 33F

**These serotype most frequently cause drug-resistant pneumococcal infections.





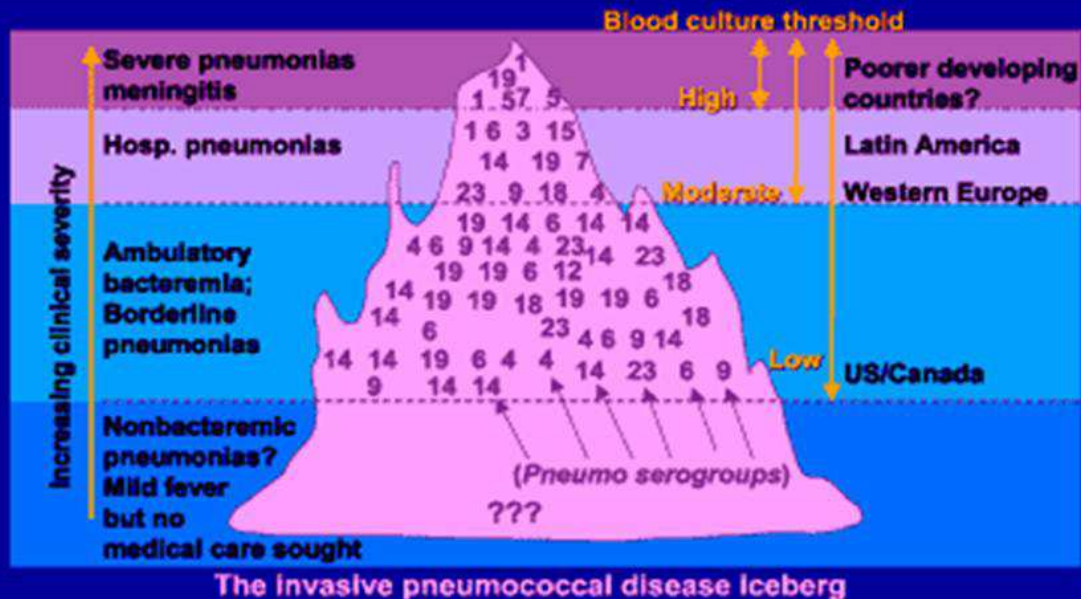
S. pneumoniae conjugate vaccine (7-valent conjugate vaccine) (Prevenar)

- ⊙ Purified pneumococcal polysaccharide (7 types) conjugated to CRM197 diphtheria toxoid
- ⊙ Highly immunogenic in infants and young children
- ⊙ >90% effective against invasive disease
- ⊙ Less effective against pneumonia, otitis media
- ⊙ U.S.:
 - all children at 2, 4, 6, 15 months some older children at high risk
 - (HIV, sickle cell, asplenia)

4, 6B, 9V, 14, 18C, 19F, and 23F

1 2 3 4 5 6B** 7F 8 9N 9V** 10A 11A 12F 14** 15B 17F 18C 19F** 19A** 20 22F 23F** 33F

Which Pneumococcal Serogroups Are Most Responsible for Invasive Disease? It May Depend on How Intensively You Look...





Disease burden in Hong Kong

- Incidence of Invasive Pneumococcal Disease per 100 000 children < 5 yr*
 - Meningitis: 1 case
 - Bacteraemia: 20 cases
 - Pneumonia: 100 cases

- The most common serotype:
- 14, 6B, 19F, 23F#

(Licensed PCV7 contains:

4, 6B, 9V, 14, 18C, 19F and 23F)

*Hong Kong Journal of Pediatric (New Series) 2001: 6: 127 – 132

#Dr. PL Ho *et al.* Vaccine 22 (2004), 3334-3339





Coverage by PCV7 in Hong Kong

	Coverage by PCV7
Invasive	89.7%
Nasopharyngeal Carriage	66.1%
Invasive (resistance)*	87.5%
Nasopharyngeal Carriage (resistance)*	82.8%

- Serotype: 14, 6B, 19F, 23F#
(Licensed PCV7 contains:
4, 6B, 9V, 14, 18C, 19F and 23F)

Dr. PL Ho *et al.* Vaccine 22 (2004), 3334-3339

* resistance to penicillin, erythromycin and cefotaxime





Advisory Committee on Immunization (ACIP)

- Recommend use of PCV7 for:
- Universal vaccination of all infants ≤ 23 months of age
- Vaccination of all children, 24-59 months of age, with the following conditions:
 - Sick cell anaemia
 - Splenic dysfunction
 - HIV / AIDS
 - Chronic disease
 - Immunocompromising condition

MMWR 2000; 49(No.RR-9):1-38

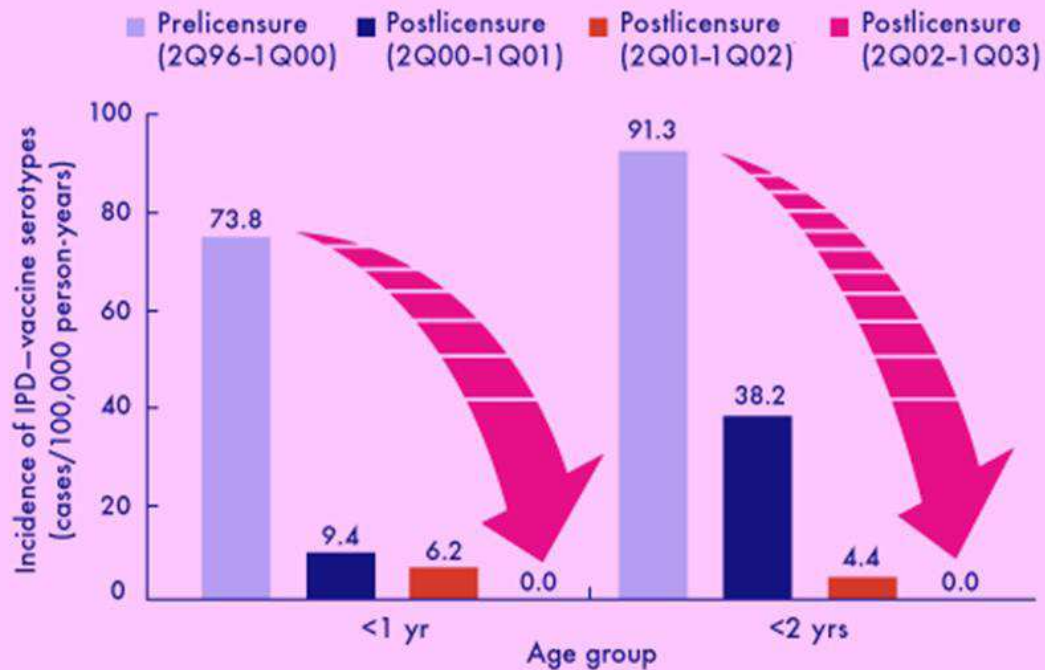




PCV7 schedule in children less than 5 years

AGE range	No of PCV7 doses
• 0 to 6 month	✓ 4
• 7 to 11 month	✓ 3
• 12 to 23 month	✓ 2
• 24 to 59 month	✓ 1





Black: Pediatr Infect Dis J, Volume 23(6).June 2004.485-489



Updated Recommendations from the ACIP 2008

CDC , MMWR

April 4, 2008 / 57(13);343-344

In October 2007, the ACIP approved the following revised recommendation for use of PCV7 in children aged 24--59 months[†]:

- For all **healthy children** aged 24--59 months who have not completed any recommended schedule for PCV7, administer 1 dose of PCV7
 - For all children **with underlying medical conditions** aged 24--59 months who have received **3 doses**, administer 1 dose of PCV7
 - For all children **with underlying medical conditions** aged 24--59 months who have received **<3 doses**, administer 2 doses of PCV7 at least 8 weeks apart
- 



Impact of Conjugate Vaccine on Pneumococcal Epidemiology

summary

- Large decline in invasive disease rates in young children
- Reduction in **Nasal Carriage**
- **Herd benefit** in unvaccinated children and adults
- **Indirect benefit** in older children and adults
- **Fewer antibiotic resistant infections**



Decline in PID - Population based study in US 1998 - 2001

Per 100 000 population	1998/1999	2001	Rate of reduction
Rate of IPD (overall)	24.3	17.3	
< 2 yr	188	59	69% p<0.001
Vaccine / vaccine related serotype			78% p<0.001 50% p<0.001
20-39	11.2	7.6	32% p<0.001
40-64	21.5	19.7	8% p=0.03
≥ 65	60.1	49.5	18% p<0.001
Disease Pen resistant	6.3	4.1	35% p<0.001

Active Bacterial Core Surveillance of the Emerging Infections Program Network. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine.

Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. N Engl J Med. 2003;348:1737-46.

**Rates of Invasive Pneumococcal Infection per 100,000 among
Children $\leq$ 23 Months of Age According to Year and Serotype***



* Data from CASPER Surveillance 1998–2004. Reprinted from Kellner JD, Church DL, MacDonald J et al. *Progress in the prevention of pneumococcal infection*, Canadian Medical Association Journal 2005;173:1149–1151 by permission of the publisher. © 2005 CMA Media Inc.

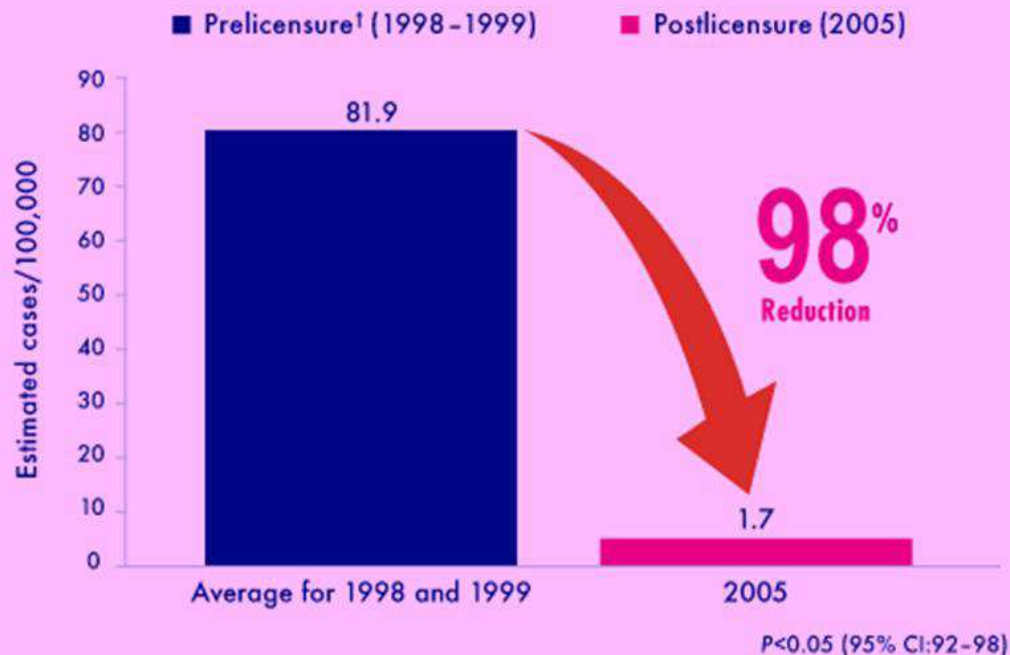


In the context of pneumococcal disease not specifically associated with influenza, use of PPV has protected against invasive pneumococcal disease but not against pneumococcal pneumonia in the absence of bacteremia.

Efficacy of polysaccharide pneumococcal vaccine in adults in more developed countries: the state of the evidence.

Mangtani P, Cutts F, Hall AJ. Lancet Infect Dis. 2003;3:71-8

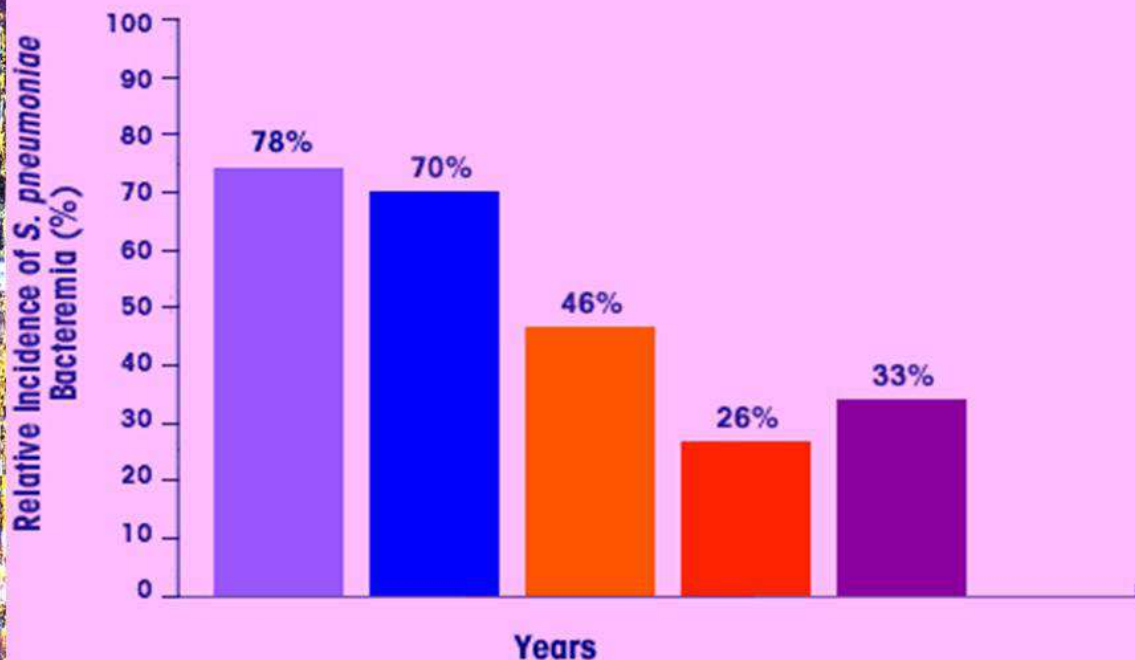




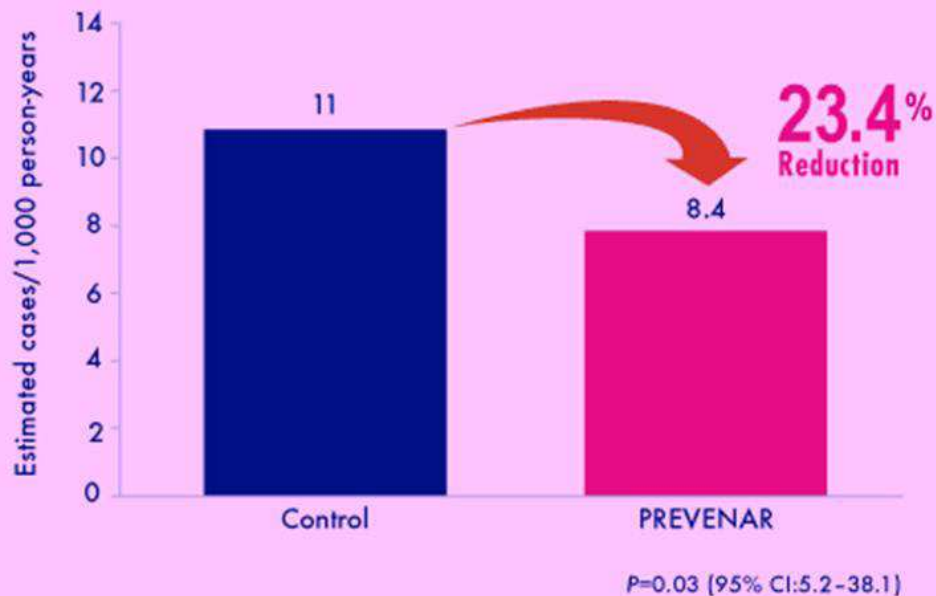
CDC data

Estimated IPD rates due to vaccine serotypes among children <5 years of age. Active Bacterial Core Surveillance of the Emerging Infections Program Network¹¹

Prelicensure[†] (1998-1999) Postlicensure[†] (1999-2000) Postlicensure[†] (2000-2001) Postlicensure[†] (2001-2002) Postlicensure[†] (2002-2003)



Relative Incidence of *S. pneumoniae* Bacteremia: Prelicensure of PREVENAR vs. Postlicensure⁵⁶



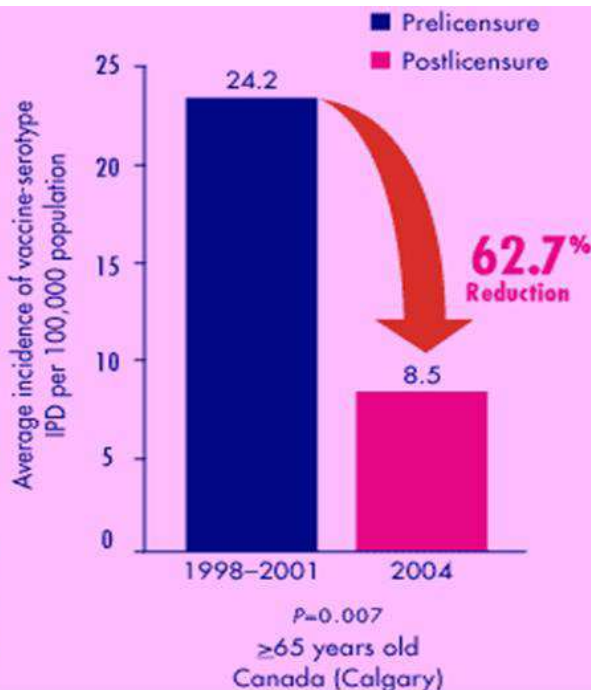
**Reported incidence of first x-ray confirmed pneumonia episodes
among children <2 years of age⁵⁰**

Northern California Kaiser Permanente randomized efficacy trial

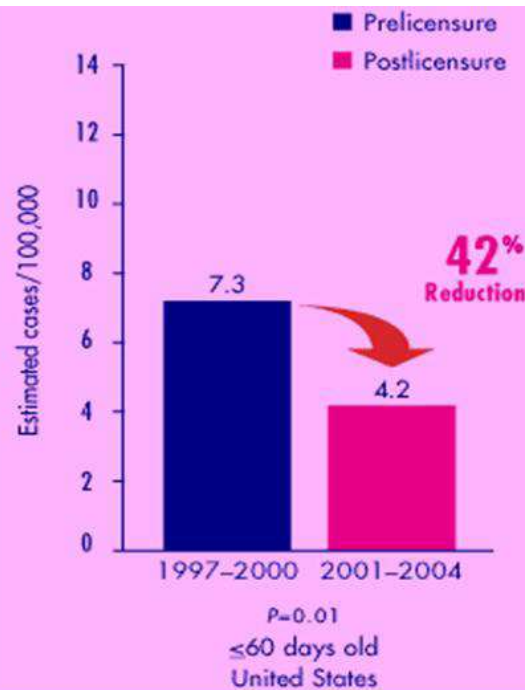


Vaccine Trialist Group. A role for *Streptococcus pneumoniae* in virus-associated pneumonia.
Madhi SA, Klugman KP, Nat Med. 2004;10:811–3.

- © PncCV greatly reduced the incidence of pneumonia in children when a virus was isolated. This effect was more pronounced when influenza A was isolated; protective efficacy was 41% (95% confidence interval 13%–60%).
- © The study provided indirect evidence of the frequency of pneumococcal superinfection of viral pneumonias in children in this setting.
- © **If similar results could be achieved through vaccination before an influenza pandemic, the benefits of preventing pneumococcal complications could be substantial.**



ADULTS—Reductions in IPD due to vaccine serotypes³¹

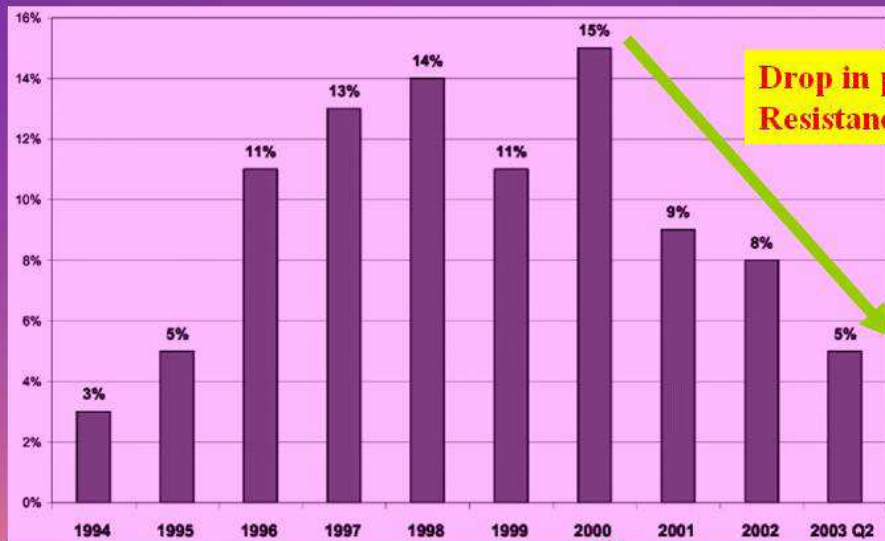


INFANTS—Reductions in IPD due to vaccine serotypes among infants ≤ 60 days of age⁴⁰

Indirect Effects

Penicillin resistance in pneumococci in Northern California Kaiser Permanente.

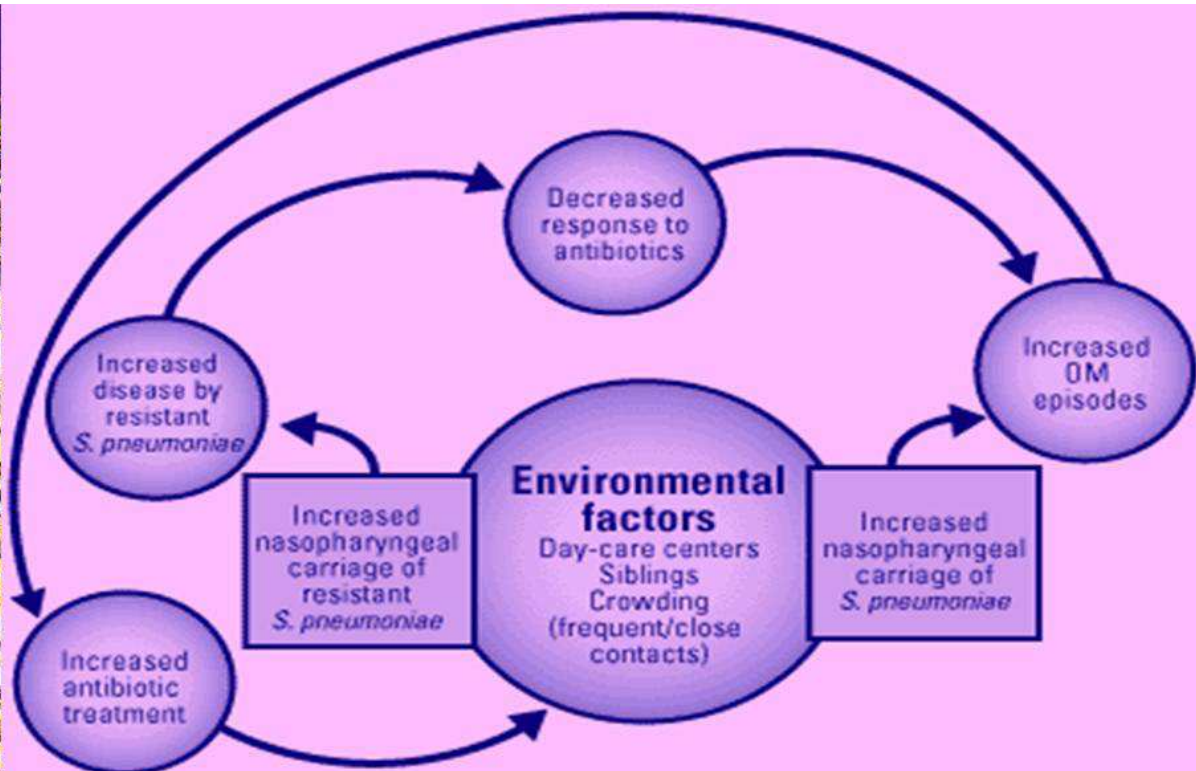
[Black: *Pediatr Infect Dis J*, Volume 23(6).June 2004.485-489]



Drop in penicillin Resistance

Heptavalent pneumococcal conjugate (PNCV7) vaccine

April 2000



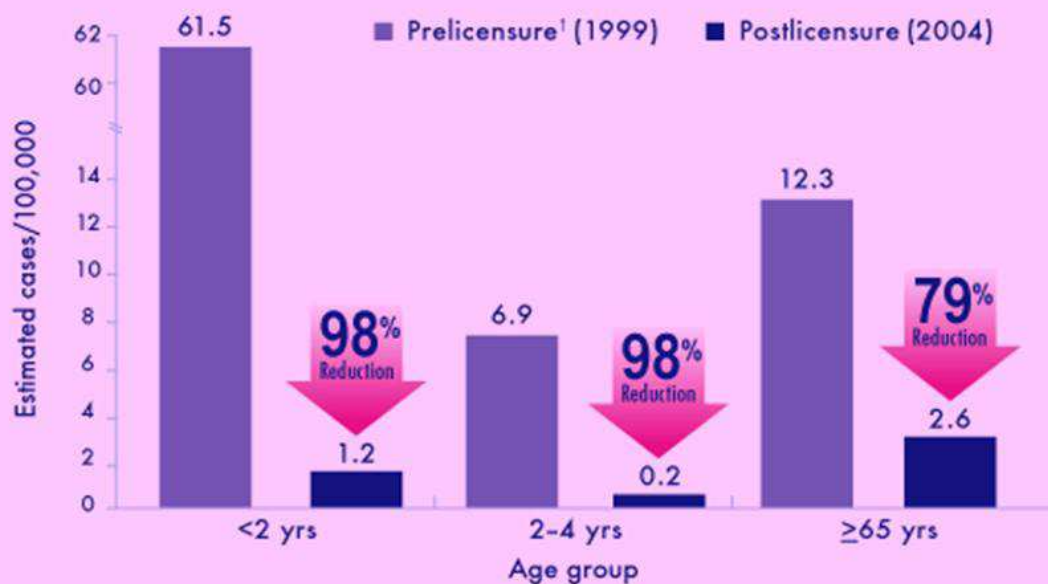
Adapted from: Dagan R, et al. *Pediatr Infect Dis J* 1997;16:1060-1064



Kaiser Permanente Vaccine Study – Postlicensure surveillance study

- Compare year 1998-1999 to 2001-2002
 - Penicillin: 28.9% to 19.5%
 - Erythromycin: 29.5% to 15.0%
 - Tetracycline: 39.3% to 13.9%
- p value all<0.001

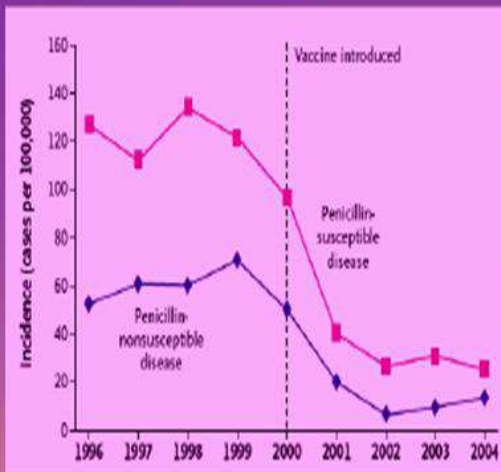
- *Black S, Shinefield H, Baxter R, et al. Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in Northern California Kaiser Permanente. Pediatr Infect Dis J. 2004;23:485-489*
- 



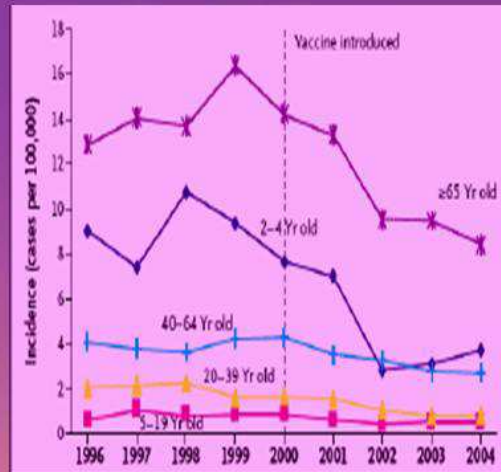
CDC data

Decline in incidence of penicillin-nonsusceptible IPD due to vaccine serotypes. Active Bacterial Core Surveillance of the Emerging Infections Program Network²³

Vaccination and resistance (NEJM 2006 351:14 April 6 2006)



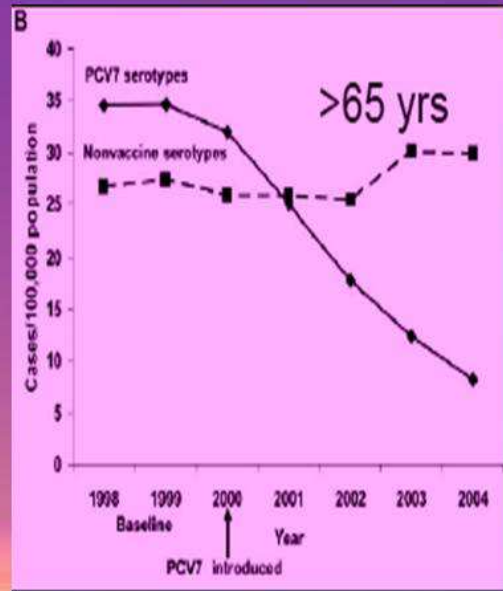
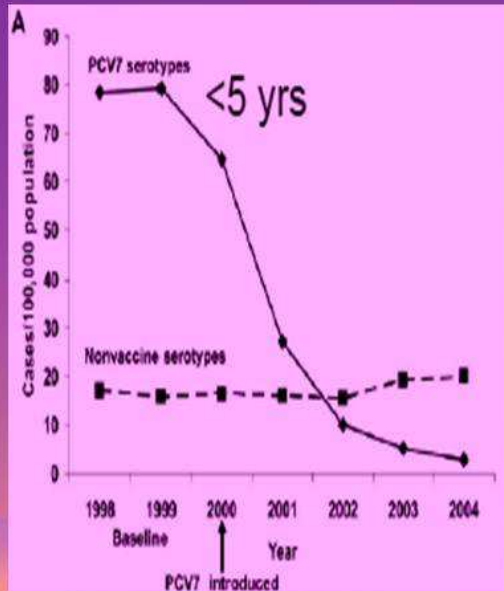
Annual Incidence of Invasive Disease Caused by Penicillin-Susceptible and Penicillin-Nonsusceptible Pneumococci among Children under Two Years of Age, 1996 to 2004.



Annual Incidence of Invasive Disease Caused by Penicillin-Nonsusceptible Pneumococci in Persons Two Years of Age or Older, 1996 to 2004.

Vaccination and serotype replacement

Increase in non-vaccine serotypes, especially serotype 19A, since introduction of PCV-7.



7-valent pneumococcal conjugate vaccine reduce *S. pneumoniae* colonisation → ? Effect on serotype replacement

Countries with Universal Vaccination with Conjugate Pneumococcal Vaccine

- US (Feb 2000),
- Canada, France (March 2002),
- [Kuwait](#), Luxembourg, Netherlands, Switzerland, UK (Sept 2006), Norway, Australia, [Qatar](#), Germany, Greece, Belgium, Italy and Mexico.
- **Planned:** [New Zealand](#) June 2008, [Costa Rica](#), [Ireland](#), [Denmark](#), [United Arab Emirates of Dubai and Abu Dhabi](#), [Cyprus](#) and [Panama](#).





Recommendation from the Strategic Advisory Group of Experts (SAGE) on Immunization

- “..... WHO considers that it should be a priority to include this vaccine in national immunization programmes,

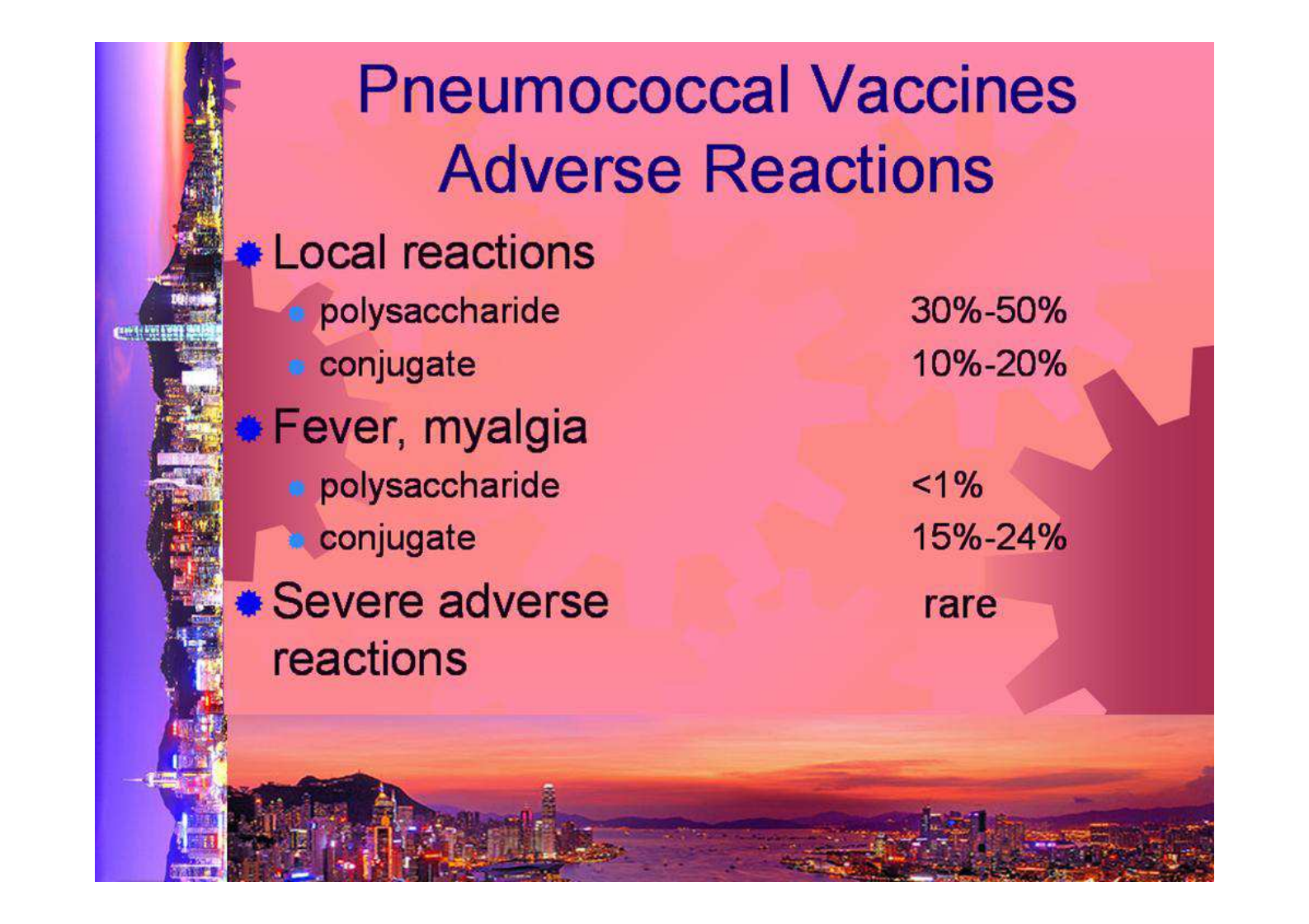
WHO Weekly Epidemiological Record, 23 Mar 2007

Pneumococcal Conjugate Vaccine for childhood immunization – WHO position paper.

23 March 2007, 82nd year. No. 12, 2007, 82, 93-104.

<http://www.who.int/wer>





Pneumococcal Vaccines Adverse Reactions

• Local reactions

- polysaccharide 30%-50%
- conjugate 10%-20%

• Fever, myalgia

- polysaccharide <1%
- conjugate 15%-24%

• Severe adverse reactions

rare



The use of PncCV in children and 23-valent PPV in adults against *Streptococcus pneumoniae* as part of a pandemic influenza strategy would be consistent with recommendations resulting from current published data.

**Bacterial Pneumonia and Pandemic
Influenza Planning
Emerging Infectious Disease
Volume 14, Number 8–August 2008**



Use of Pneumococcal Vaccines for Influenza Pandemic Preparedness

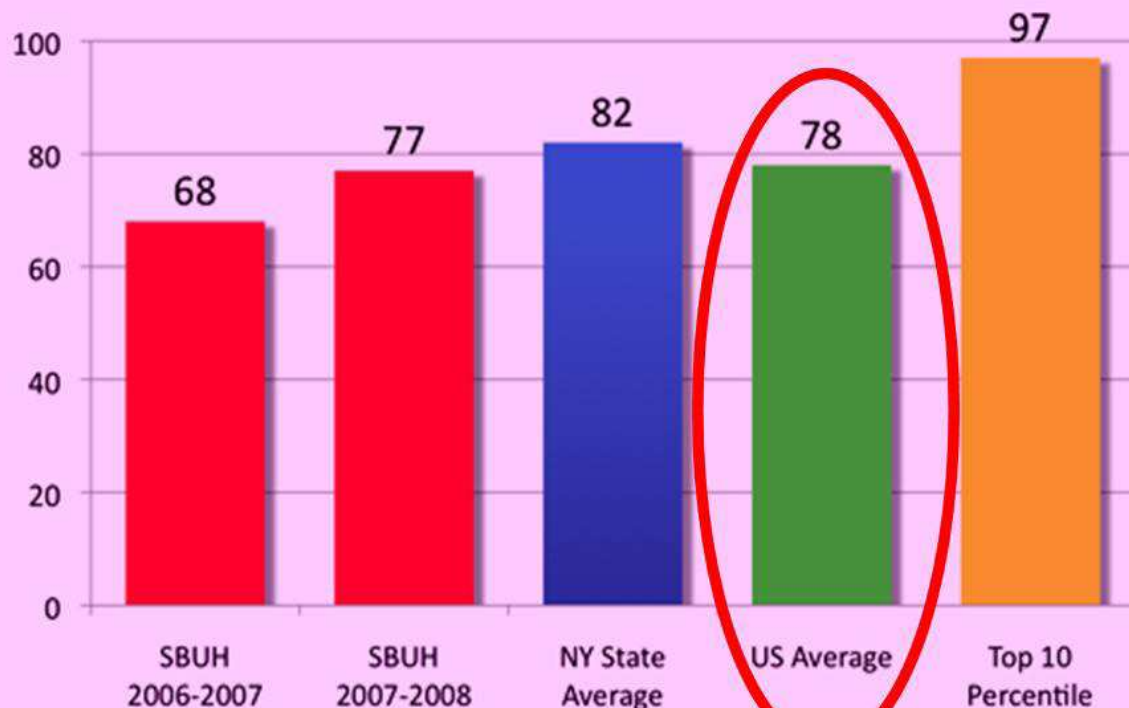
U.S. recommendations for use of pneumococcal vaccines

	Pneumococcal polysaccharide vaccine	Pneumococcal conjugate vaccine
Universal vaccination	Persons 65 years and older	Children <2 years of age
Medical Indications	Persons 2-64 years with - chronic cardiovascular disease (congestive heart failure and cardiomyopathies) - chronic pulmonary disease including chronic obstructive pulmonary disease and emphysema but excluding asthma - diabetes mellitus - alcoholism - chronic liver disease, including cirrhosis - cerebrospinal fluid leaks - functional or anatomic asplenia including sickle cell disease and splenectomy - living situations in special environments or social situations including Alaska Natives and certain American Indian populations - immuno-compromised conditions including HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome; or those receiving immunosuppressive chemotherapy (including corticosteroids); and those who have received an organ or bone marrow transplant	Children 24-59 months with - chronic cardiac disease, particularly cyanotic congenital heart disease and cardiac failure - chronic pulmonary disease, excluding asthma unless on high dose corticosteroid therapy - diabetes mellitus - cerebrospinal fluid leaks - sickle cell disease and other hemoglobinopathies - congenital or acquired asplenia or splenic dysfunction - renal failure and nephrotic syndrome - immunocompromising conditions, including HIV; congenital B- (humoral) or T-lymphocyte immunodeficiencies; complement (c1, c2, c3, and c4) deficiencies; phagocytic disorders, excluding chronic granulomatous disease - diseases associated with immunosuppressive therapy or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin's disease, or solid organ transplantation
Consider use of vaccine in:		All children 24-59 months with priority given to children aged 24-35 months, children of Alaska Native or American Indian descent, children of African-American descent, and children who attend day care centers

Advisory Committee on Immunization Practices

→ ensuring that all persons with pneumococcal vaccine indications have been vaccinated before a pandemic occurs may be the best way to prevent pneumococcal disease during a pandemic

Pneumococcal screen / vaccination (%)



Majority of elderly and at risk population is protected by pneumococcus vaccination in U.S.A. by 2008



La Gloria clinical attack rates by age and gender

Age Group	Male (%)	Female(%)	Total(%)
<1	91.2	73.7	83.9
1-4	66.2	66.1	58.1
5-14	49.7	66.3	57.7
15-24	25.6	28.2	27.0
25-44	22.8	39.4	31.6
45-64	18.4	42.7	29.6
65+	17.5	25.7	22.0
Total	33.5	44.6	39.1





Budget Requirement for Vaccination is HUGE

Vaccine	Unit price
Pneumovax 23 vaccine	HK\$105.7
7 polyvalent conjugate vaccine	HK\$534.8
Haemophilus influenza B vaccine	HK\$137





天心莫測 劫隨心轉

- ◎ 物競天擇，適者生存。
- ◎ 物極必反，道窮則變！

IDDM after Haemophilus Influenza B
Vaccination.

CA-MRSA after PCV-7 vaccination.



Pittsburgh: Diabetes 0-4 Year Olds

1975-1984

6

Diabetes Care

16:1606-1611, 1993;

21:1278-1281, 1998

1985-1994

+ HiB Vaccine

13

Incidence of Type I diabetes/ 100,000

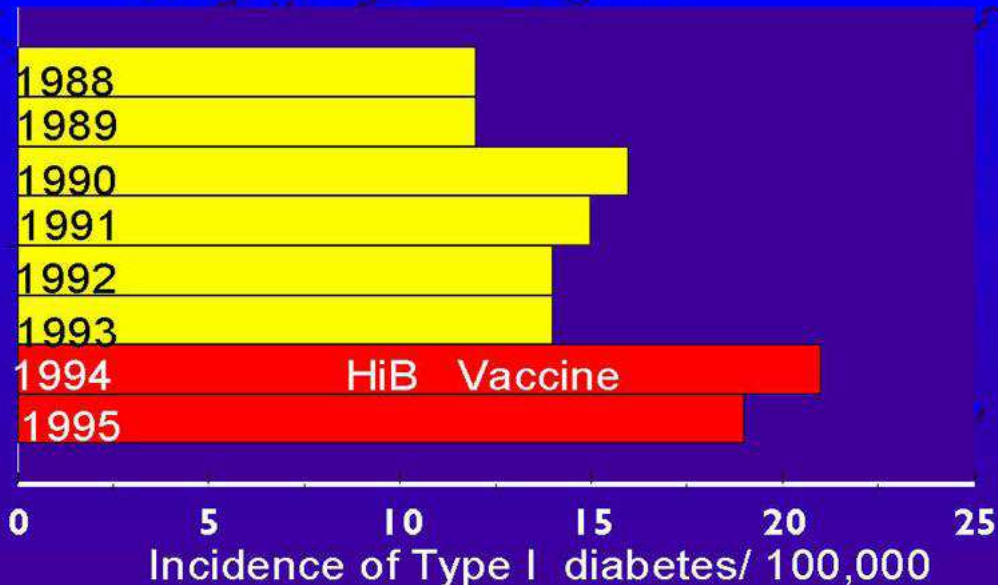
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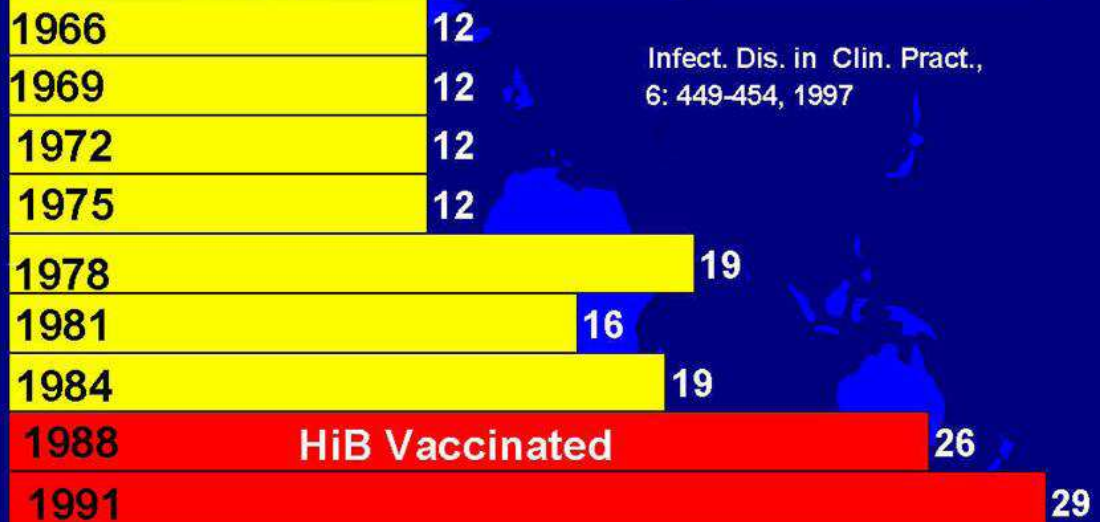
The graph below shows that the annual incidence of diabetes rose drastically after hemophilus immunization began in Pittsburgh.

England: Diabetes 0-4 Year Olds



The graph below shows that the annual incidence of diabetes rose in England after the hemophilus vaccine became widely utilized in the UK (Reference British Medical Journal 315:713-716 1997). The hemophilus vaccine was started in October of 1992 in most regions however large studies were conducted in some regions about 2 years earlier

Diabetes in Finland rises abruptly after Hemophilus immunization begins



Infect. Dis. in Clin. Pract.,
6: 449-454, 1997

Incidence of Type I diabetes/ 100,000 (age 0-4)

0 5 10 15 20 25 30



Impact of Conjugate Vaccine on Pneumococcal Epidemiology

summary

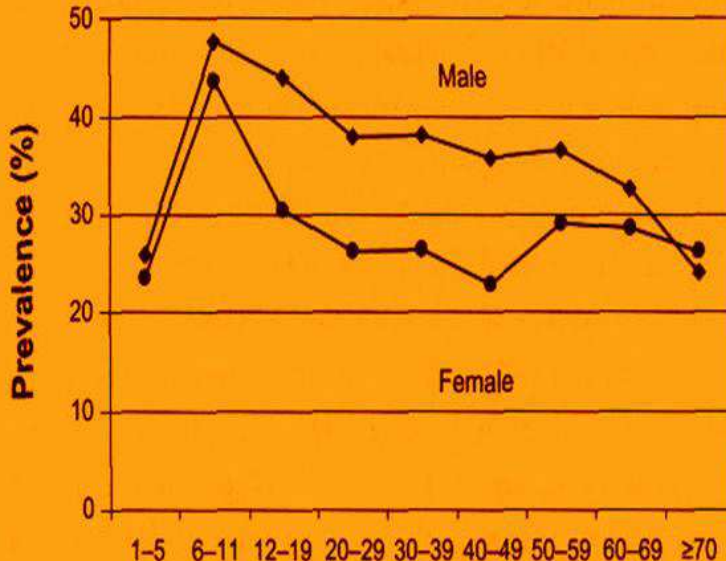
- Large decline in invasive disease rates in young children
- Reduction in **Nasal Carriage**
- **Herd benefit** in unvaccinated children and adults
- **Indirect benefit** in older children and adults
- **Fewer antibiotic resistant infections**



Prevalence of Staphylococcus aureus nasal colonization, by age and sex

National Health and Nutrition Examination Survey, 2001-2002.

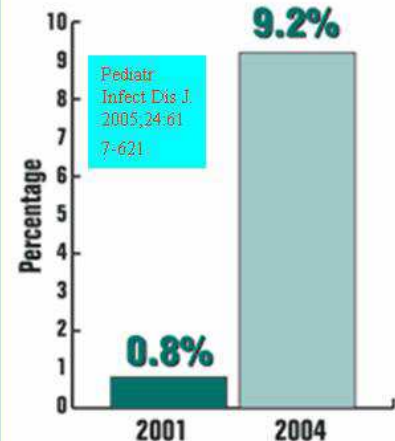
75/10000 (0.8% of the total) harbored MRSA



Resistant to desiccation 7m Age (years)

DM, chronic skin conditions, IV addict and dialysis patients

Nasal Carriage of MRSA in Nashville

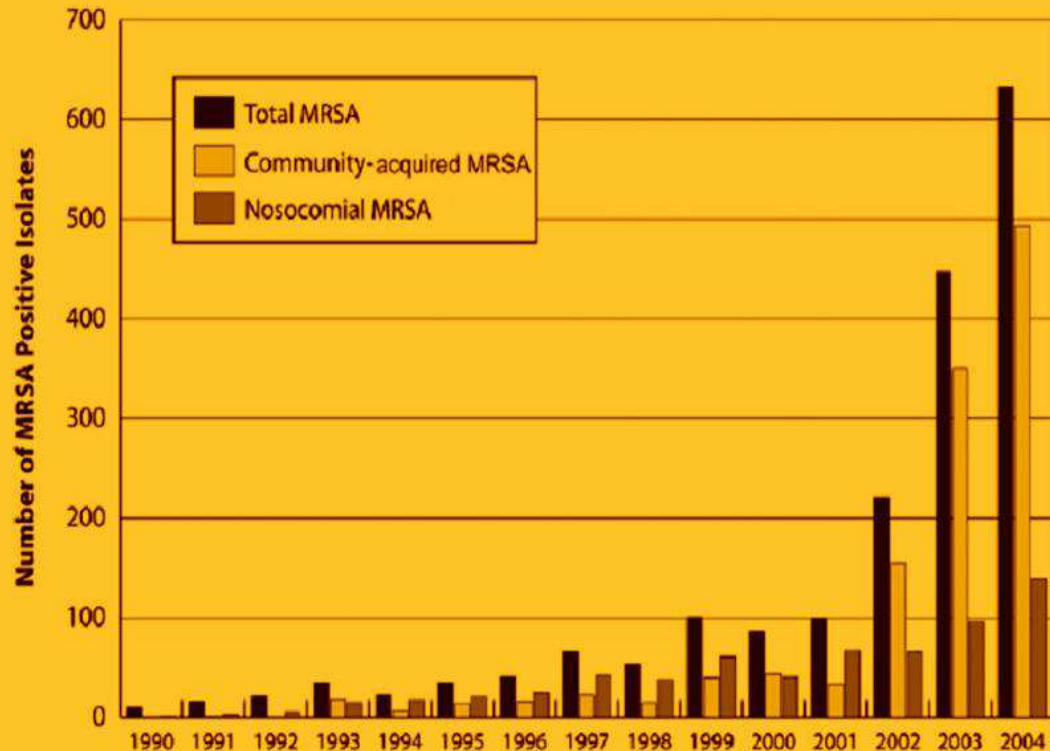


In the 2001 study, the researchers demonstrated that the nasal carriage rate of MRSA in children in Nashville was 0.8%. The follow-up study conducted three years later found that the pediatric carriage rate of MRSA in Nashville to be 9.2%, a tenfold increase since 2001.



Changing Epidemiology of MRSA /

Crum et al. Am. J. Med 2006



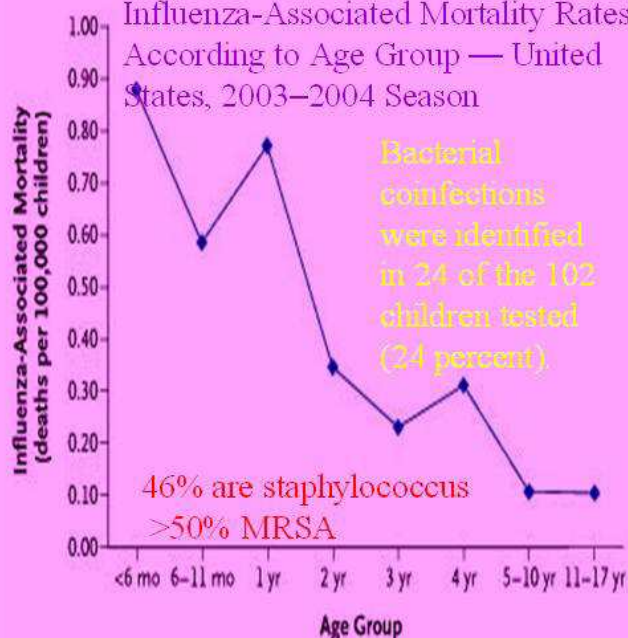


A controversial, hypothesis to explain the increase in CA-MRSA is the decreased nasal colonization by competing *Streptococcus pneumoniae* due to the pneumococcal Prevnar™ vaccine.

The rate of nasopharyngeal colonization by *S. aureus* is inversely proportional to that of pneumococcal serotypes targeted by the vaccine, suggesting a competitive interaction in the nasopharynx whereby elimination of one pathogen opens a niche for others.

Bogaert D, van Belkum A, Sluijter M, *et al.* Colonisation by *Streptococcus pneumoniae* and *Staphylococcus aureus* in healthy children. **Lancet** 2004;**363**:1871–1872.

Influenza-Associated Mortality Rates According to Age Group — United States, 2003–2004 Season



Bacterial Coinfections in 24 Children with Fatal Influenza — United States, 2003–2004 Season.*

Bacterial Agent	No. of Children
<i>Staphylococcus aureus</i>	11
Methicillin-resistant	6
Methicillin-susceptible	1
Unknown sensitivity	4
<i>Staphylococcus</i> , species not specified	1
<i>Streptococcus pneumoniae</i> †	2
Group A streptococcus	3
<i>Bordetella pertussis</i> ‡	1
<i>Haemophilus influenzae</i>	4
Nontypeable	2
Type a	1
Type b	1
<i>Pseudomonas aeruginosa</i>	1
<i>Enterococcus faecalis</i>	1
<i>Neisseria meningitidis</i>	1
<i>Mycoplasma pneumoniae</i> §	1

Niranjan Bhat NEJM Volume 353:2559-2567 December 15, 2005 Number 24

**“Influenza-Associated Pediatric Mortality in the United States:
Increase of *Staphylococcus aureus* co-infection”**

L Finelli *et al. Pediatrics* October 2008

- © **From 2004, there was an increase in the proportion of children with influenza and bacterial co-infection. with *S. aureus* 2004-2005: 1/47 deaths (2%) were associated with *S. aureus* co-infection**
 - **2005-2006: 3/46 deaths (6%) were associated with *S. aureus* co-infection**
 - **2006-2007: 22/73 deaths (30%) were associated with *S. aureus* co-infection**
- © **Of all 26 *S. aureus* co-infections identified**
 - **15/26 methicillin-resistant *S. aureus* (MRSA) (58%)**
 - **6/26 MSSA**
 - **5/26 methicillin susceptibility unknown**

**“Influenza-Associated Pediatric Mortality in the United States:
Increase of *Staphylococcus aureus* co-infection”**

L Finelli *et al. Pediatrics* October 2008

- © **Death was often rapidly fatal, with almost half of children dying 3 to 4 days after onset of symptoms**
 - © **Almost half of the children died at home or in the emergency department**
 - © **Many deaths occurred in children without a health condition or age-based recommendation for vaccination at the time the study was done.**
- 



Staphylococcus aureus

Penicillin G introduced
in the 1940s.

Acquisition of a **plasmid gene** carrying the
enzyme **penicillinase** which hydrolyses and
destroys Penicillin G.

Methicillin (1959) Sensitive *Staphylococcus aureus*

Introduction of cloxacillin in
1960s

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**.

Methicillin Resistance *Staphylococcus aureus*

(1961 U.K. 1968 U.S.A.)

Acquisition of **staphylococcal
cassette chromosomal mobile
gene SCC *mecA* in type I-III** that
encodes a **transpeptidase PBP2a**
(role in bacterial cell wall
synthesis) with poor affinity for
all beta-lactam antibiotics
including methicillin or cloxacillin.

1993 Aborigines of
Western Australia
USA 1997
Europe 1999
HKSAR 2004

HA-MRSA

(30% MRSA
rate in HA
Hospitals)

CA-MRSA

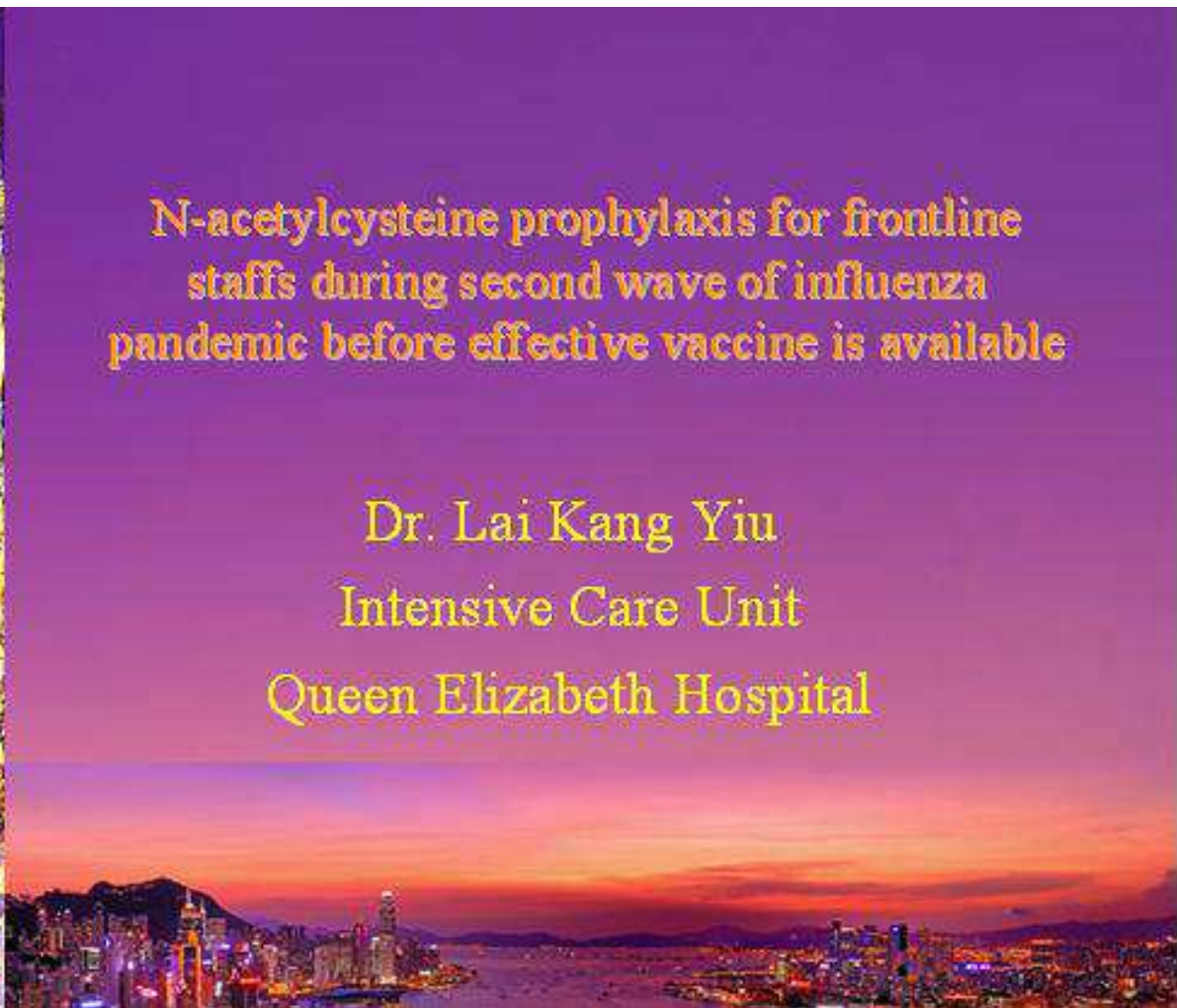
Genes carrying a virulent factor called
Panton Valentine Leukocidin (PVL)
and the gene cassettes called **SCC*mec*
type IV and type V7**.

Vancomycin (1958)

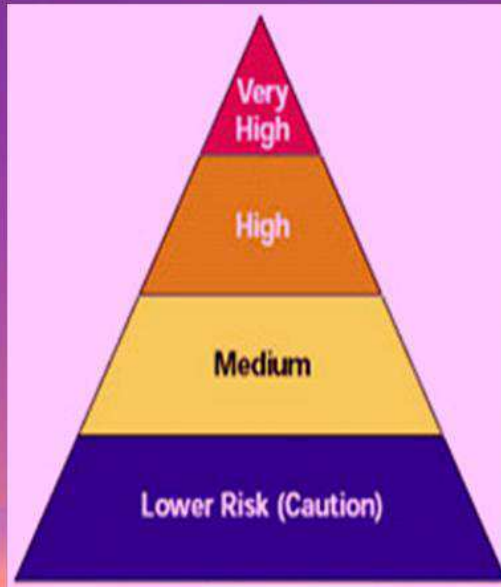
Vancomycin Resistance *Staphylococcus aureus* (2002)

**N-acetylcysteine prophylaxis for frontline
staffs during second wave of influenza
pandemic before effective vaccine is available**

**Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital**



Occupational Risk Pyramid for Pandemic Influenza



- © Very High Exposure Risk:
 - Healthcare employees (for example, doctors, nurses, paramedics, or dentists) performing aerosol-generating procedures on known or suspected pandemic patients (for example, cough induction procedures, tracheal intubations, bronchoscopies, some dental procedures, or invasive specimen collection).
 - Healthcare or laboratory personnel collecting respiratory tract specimens from known or suspected pandemic patients.



Influenza A ? Role of N-acetylcysteine

Dr. Lai Kang Yiu
Consultant Intensive Care Unit
Queen Elizabeth Hospital





Protective effect of n-acetylcysteine in a model of influenza infection in mice.

[Ungheri D, Pisani C, Sanson G, Bertani A, Schioppacassi G, Delgado R, Sironi M, Ghezzi P Int J Immunopathol Pharmacol. 2000 Sep;13(3):123-128.]

- # Reactive oxygen intermediates (ROI) and cytokines, particularly tumor necrosis factor (TNF) have been implicated in the pathogenesis of influenza. Using a murine model of influenza, the levels of TNF, interleukin 6 (IL-6) and of superoxide-generating xanthine oxidase (XO) is monitored.
 - # Mice infected intranasally with influenza virus APR/8 had high levels of XO, TNF and IL-6 in the bronchoalveolar lavage, as early as 3 d after infection. XO was elevated also in serum and lung tissue.
 - # Administration of the antioxidant N-acetylcysteine (NAC, 1 g/kg per day, orally) significantly decreased the mortality in infected mice, indicating a role for ROI in the lethality associated with influenza infection.
- 

**Attenuation of influenza-like
symptomatology and improvement of
cell-mediated immunity with long-term
N-acetylcysteine treatment**

S. De Flora, C. Grassi, L. Carati
Eur Respir J 1997; 10: 1535–1541





Recruitment and Protocol

- # A total of 262 subjects of both sexes (78% ≥ 65 yrs, and 62% suffering from non-respiratory chronic degenerative diseases) were enrolled in a randomized, double blind trial involving 20 Italian Centers.
 - # They were randomized to receive either placebo or NAC tablets (600 mg) twice daily for 6 months.
 - # Patients suffering from chronic respiratory diseases were not eligible, to avoid possible confounding by an effect of NAC on respiratory symptoms.
- 



Result

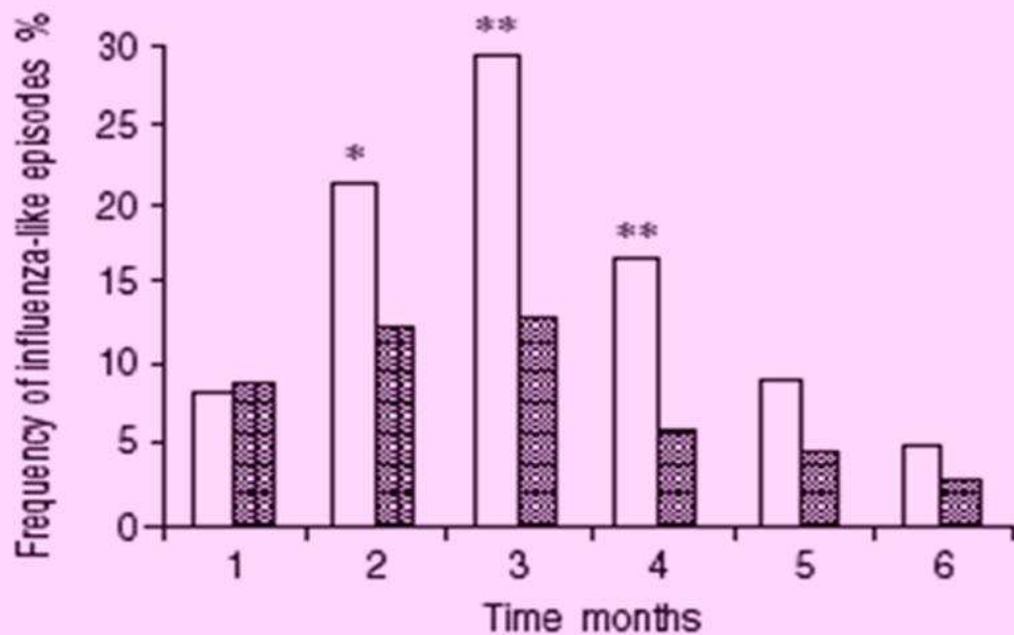
- # NAC treatment was well tolerated and resulted in a significant decrease in the frequency of influenza-like episodes, severity, and length of time confined to bed.
- # Both local and systemic symptoms were sharply and significantly reduced in the NAC group. Frequency of seroconversion towards A/H1N1 Singapore 6/86 influenza virus was similar in the two groups, but **only 25% of virus-infected subjects under NAC treatment developed a symptomatic form, versus 79% in the placebo group.**
- # **Evaluation of cell-mediated immunity showed a progressive, significant shift from anergy to normoergy following NAC treatment.**



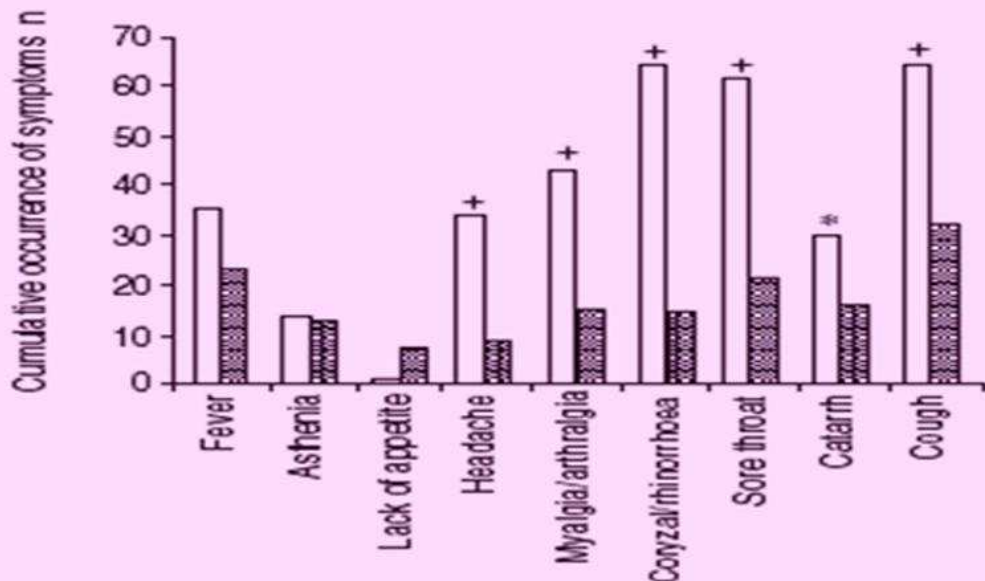
Compliance with treatment, adverse effects, and frequency of influenza-like episodes as related to treatments

Variable	Treatment	
	Placebo	NAC
Compliance with treatment* n	120 (93)	125 (94)
Adverse events n		
Total	7 (5)	12 (9)
Dysuria	0	2 (2)
Epigastralgia	3 (2)	4 (3)
Nausea/vomiting	1 (1)	1 (1)
Constipation	0	1 (1)
Diarrhoea	3 (2)	2 (2)
Flushing	0	2 (2)
Nonevaluable patients n		
Adverse events before first control	1 (1)	1 (1)
Lost to follow-up	6 (5)	6 (5)
Patients evaluable for efficacy n	122 (95)	126 (95)
Duration of treatment days	167±34 (32–199)	166±35 (33–206)
Treatment ≥5 months n	116 (90)	108 (81)
Influenza-like symptomatic cases n		
Total cases	62 (51)	37 (29) [†]
Patients suffering from 1 episode	36 (30)	24 (19)
Patients suffering from 2–3 episodes	18 (15)	11 (9)
Patients suffering from ≥4 episodes	8 (7)	2 (2)

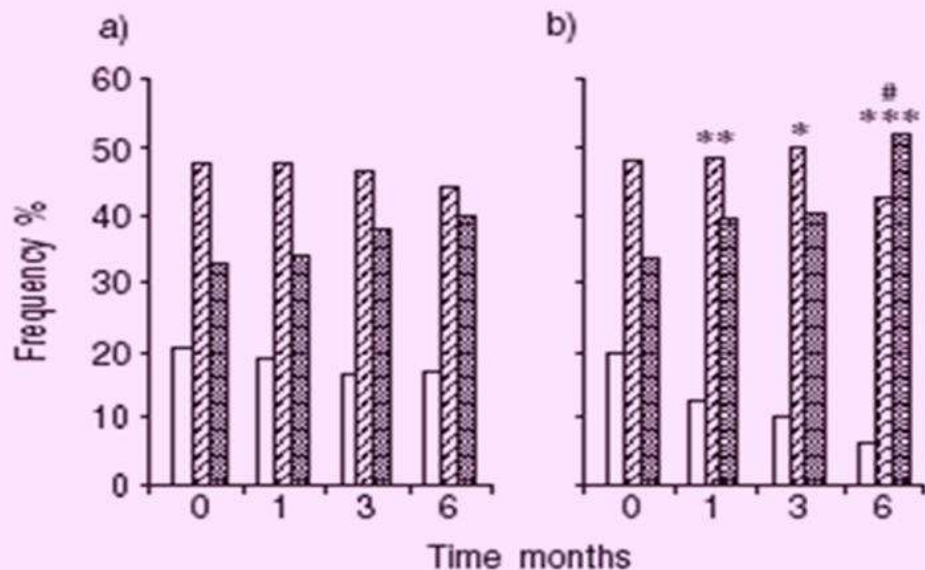
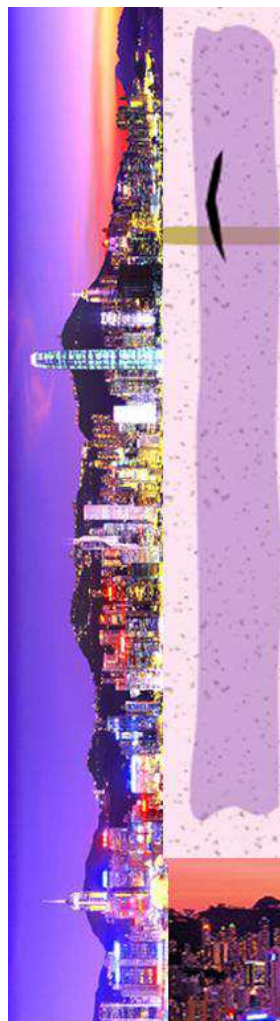
Data are presented as mean±SD and range in parenthesis, or as absolute value and percentage in parenthesis. *: drug or placebo intake ≥80%. NAC: N-acetylcysteine. †: significantly lower than in the placebo group (p=0.0006), as assessed by Chi-squared analysis.



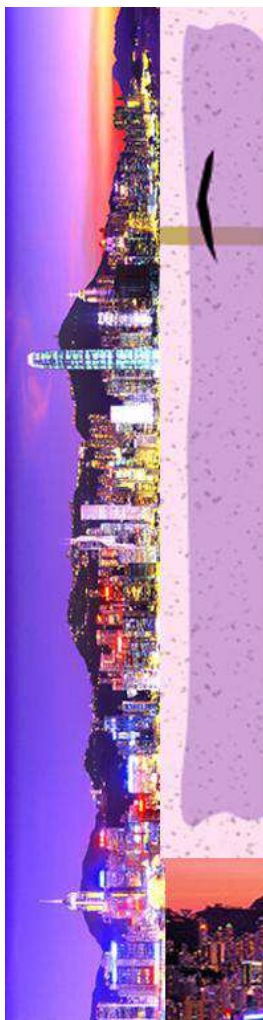
Effect of N-acetylcysteine (NAC) treatment on the frequency of influenza-like episodes during the 6 months of treatment.
□ : placebo; ▨ : NAC. *: $p < 0.05$; **: $p < 0.01$, significance of difference between the frequency of episodes occurring in the NAC group and in the placebo group, as assessed by Chi-squared analysis.



Effect of N-acetylcysteine (NAC) treatment on the cumulative occurrence of individual influenza-like signs and symptoms throughout the duration of the study. : placebo; : NAC. *: $p < 0.05$; +: $p < 0.0001$, significance of difference between the frequency of symptoms in the NAC group and the placebo group, as assessed by Chi-squared analysis. Note that the data reported in this figure also include isolated signs and/or symptoms whereas, as indicated in "Materials and methods", episodes are assessed based on the presence of at least two signs and/or symptoms.



– Effect of N-acetylcysteine (NAC) treatment on cell-mediated immunity. a) Placebo group; b) NAC-treated group. : anergy; : hypoergy; : normoergy. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$, significance of difference in the frequency of anergy, within the NAC group, after 1, 3 and 6 months, compared to the start of the study (time 0); #: $p < 0.05$, significance of difference in the frequency of anergy between the NAC group and the placebo group, as assessed by Chi-squared analysis.



– Distribution of subjects as related to seroconversion towards A/H₁N₁ Singapore 6/86 influenza virus and to the presence or absence of symptomatology

Subjects	Treatment			
	Placebo		NAC	
	n	%	n	%
Seroconversion	29/122	(24)	36/126	(29)
Symptomatic episodes	23/29	(79)	9/36	(25)+
No symptomatic episodes	6/29	(21)	27/36	(75)+
No seroconversion	93/122	(76)	90/126	(71)
Symptomatic episodes	39/93	(42)	28/90	(31)
No symptomatic episodes	54/93	(58)	62/90	(69)

NAC: N-acetylcysteine. +: significantly different from the placebo group ($p < 0.0001$), as assessed by Chi-squared analysis.





Conclusion

- # Administration of N-acetylcysteine during the winter, thus, appears to provide a significant attenuation of influenza and influenza-like episodes, especially in elderly high-risk individuals.
 - # N-acetylcysteine did not prevent A/H1N1 virus influenza infection but significantly **reduced the incidence of clinically apparent disease**.
 - # There is progressive **improvement in cell-mediated immunity** (significant shift from anergy to normoergy) following NAC treatment.
- 

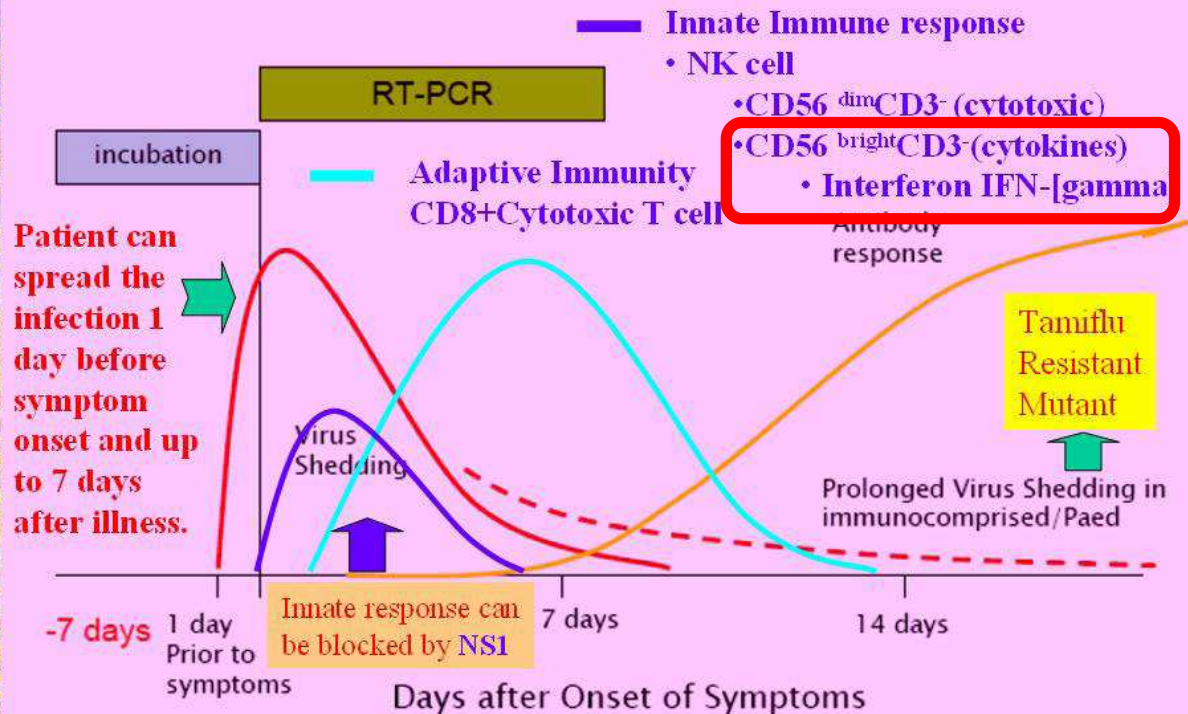


Nuclear factor-kappa B

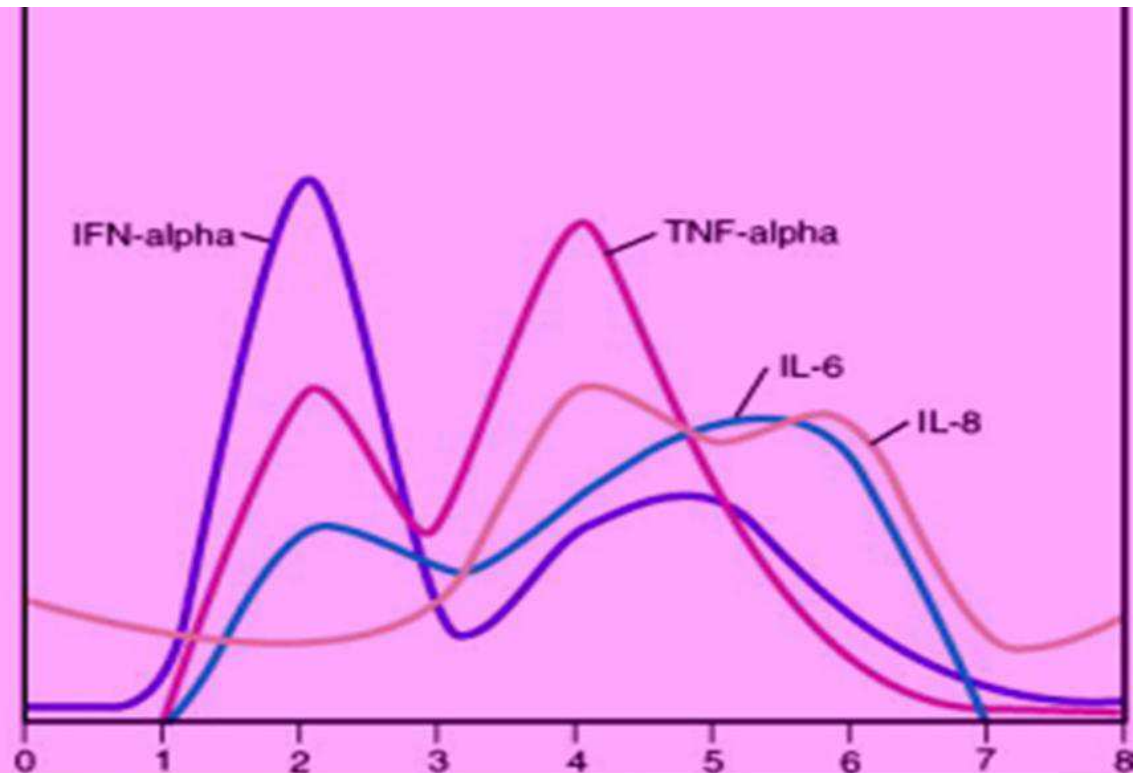
Role in cytokine storm
Role in Influenza Infection
Inhibition by NAC



Virological Profile of Influenza



Depletion of NK cells abrogated fluA-specific CD8+ T cell responses both in vitro and in vivo. At an early stage of recurrent viral infection, NK-mediated innate immunity to the virus is enhanced by IL-2 production from preexisting virus-specific T cells



Time course of cytokine responses of healthy adults after experimental inoculation with wild-type A/Texas/36/91 virus by nasal drops.

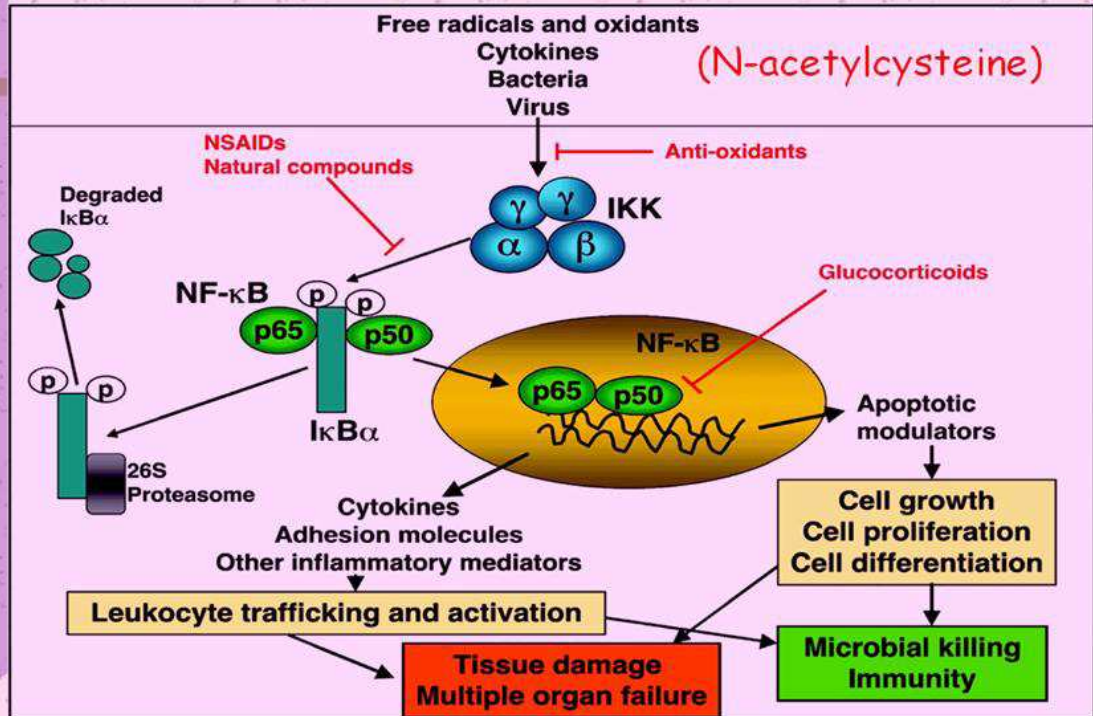


NF- κ B is known to induce the transcription of several genes coding for the inflammatory cytokines TNF- α , IL-1 β , IL-6, and IL-8. On the other hand, NF- κ B has been shown to be activated in response to mediators implicated in the inflammatory response, including LPS, TNF- α , and IL-1 β , and oxidative stress

TNF-[α]-induced activation of NF- κ B activity was suppressed by N-acetylcysteine. N-acetylcysteine along with vitamin E suppressed NF- κ B activation by oxidant stress



NK- κ B's Role in cytokine storm





Active NF-kappaB signalling is a prerequisite for influenza virus infection.

[Nimmerjahn F, Dudziak D, Dirmeier U, Hobom G, Riedel A, Schlee M, Staudt LM, Rosenwald A, Behrendts U, Bornkamm GW, Mautner J. *Journal of General Virology*. 85(Pt 8):2347-56, 2004 Aug.]

Cells with low NF- B activity were resistant to influenza virus infection, but became susceptible upon activation of NF- B. In addition, blocking of NF- B activation severely impaired influenza virus infection of otherwise highly susceptible cells





Oxidants are involved in influenza virus-induced activation of NF-kappa B, in the expression of IL-8 and MnSOD, and in virus-induced cell death. Pretreatment of A549 cells with N-acetyl-L-cysteine attenuated virus-induced NF-kappa B activation and interleukin (IL)-8 mRNA induction but did not block induction of MnSOD mRNA.

Role of oxidants in influenza virus-induced gene expression.

Knobil K, Choi AM, Weigand GW,
Jacoby DB Am J Physiol. 1998
Jan;274(1 Pt 1):L134-42.





Influenza virus infection activates NF- κ B leading to IL-8 expression and **antioxidants inhibit influenza virus infection-induced NF- κ B activation**

[Kujime K. Hashimoto S. Gon Y. Shimizu K. Horie T. p38 mitogen-activated protein kinase and c-jun-NH2-terminal kinase regulate RANTES production by influenza virus-infected human bronchial epithelial cells. *Journal of Immunology*. 164(6):3222-8, 2000 Mar 15.]

NAC did not affect influenza virus infection-induced increases in p38 MAP kinase and JNK phosphorylation, whereas NAC attenuated RANTES production by 18.2%. Collectively, these results indicated that **ROS generated by influenza virus infection might act as a second messenger leading to the induction of RANTES production** via p38 MAP kinase- and JNK-independent pathway.



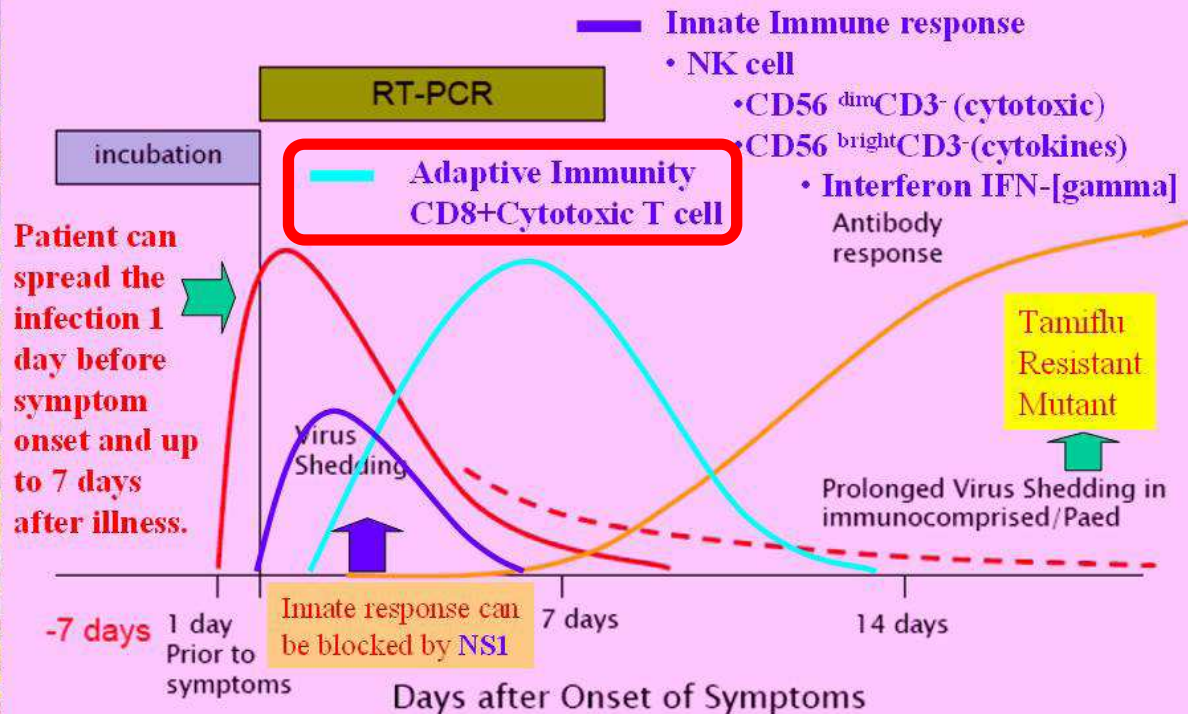


Immune Response to Influenza infection

Role of N-acetylcysteine on T
cell function



Virological Profile of Influenza



Depletion of NK cells abrogated fluA-specific CD8+ T cell responses both in vitro and in vivo. At an early stage of recurrent viral infection, NK-mediated innate immunity to the virus is enhanced by IL-2 production from preexisting virus-specific T cells

B & T cell response to Influenza Virus

Host immune response to influenza virus

- B cell produce antibodies to the hemagglutinin and neuraminidase glycoproteins
 - Hemagglutinin-specific antibodies prevent virus penetration of the host cells.
 - Neuraminidase-specific antibodies prevent spread of infectious viruses from cell to cell.
- T cell immune response to internal or membrane proteins.
 - Influenzavirus-specific T cells participate both in the early inflammatory reaction and in the recovery from viral infection.
 - Protective antihemagglutinin antibodies production requires the presence of T cells.
 - In humans, the level of influenza-specific Cytotoxic T lymphocytes correlates with the rate of viral clearance but not with susceptibility to infection or subsequent illness → major role in enhancing recovery from recent infection.



Role of N-acetylcysteine in Influenza Infection

Reduce cytokine storm →
decrease symptomatology
Enhance T cell response to
influenza infection → more
rapid recovery





? Prophylactic role for frontline
staffs before vaccination is
available

The potential workforce that can be
preserved would be huge.

The estimated number of staff
falling sick due to influenza virus
infection would drop 68%

Calculation basing on formula $79\% \rightarrow 25\% = (79-25)/79 = 68.35\%$



Price of 200mg acetylcysteine = \$0.3166
Daily dose 600mg b.d = \$1.8996/staff/day
Market price = \$12-14/staff/day

Assumming HA has 50,000 staffs
Budget Required Per Month

Staff Treated	HA Price	Market Price
10%	\$285,000	\$1,950,000
20%	\$570,000	\$3,900,000
30%	\$855,000	\$5,850,000
40%	\$1,140,000	\$7,800,000
50%	\$1,425,000	\$9,750,000
60%	\$1,710,000	\$11,700,000
70%	\$1,995,000	\$13,650,000
80%	\$2,280,000	\$15,600,000
90%	\$2,565,000	\$17,550,000
100%	\$2,850,000	\$19,500,000

扶正湯水



流感初現



Not all staff would opt for acetylcysteine

病發偏方



白醋消毒法



薑、蒜頭



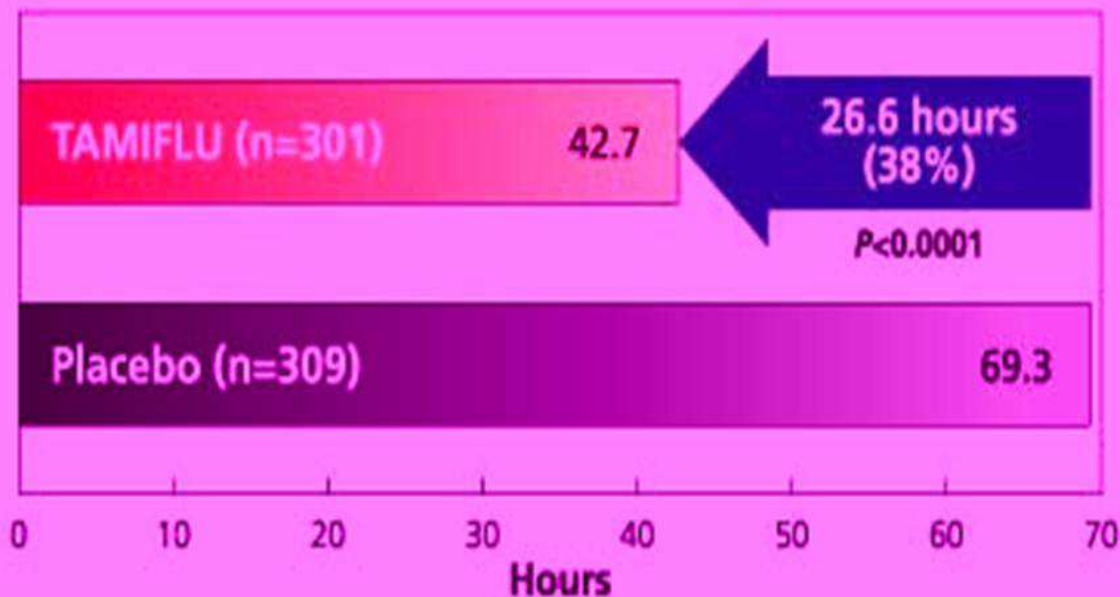


This drug has a long history
of safety profile and can be
taken on prolonged period

This treatment need the
financial commitment of
the HKSAR government
< \$2/staff/day



Reduction in fever duration
(median time to become afebrile)



What is the money spend on Tamiflu by the Hospital Authority ?



Adding N-acetylcysteine to Oseltamivir for treatment of Swine Influenza H1N1 2009

Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital





N-acetylcysteine synergizes with oseltamivir in protecting mice from lethal influenza infection.

[Garozzo A. Tempera G. Ungheri D. Timpanaro R. Castro A.

International Journal of Immunopathology & Pharmacology. 20(2):349-54, 2007 Apr-Jun.]

- # NAC was given as a single daily dose of 1000 mg/kg starting from 4 h before infection and until day 4 after infection; Oseltamivir was given twice daily at dose of 1 mg/kg/die for 5 days, starting from 4 h before infection.
- # 21-days survival.
 - **NAC alone 20%.**
 - **Oseltamivir alone 60%**
 - **Oseltamivir and NAC in combination 100%**
- # Since NAC alone does not show any antiviral action, the present findings suggest that antioxidant therapy increase survival by an improvement in host defense mechanisms, and/or by a direct antioxidant effect against oxidative stress associated with viral infection.





Synergistic combination of N-acetylcysteine and ribavirin to protect from lethal influenza viral infection in a mouse model.

[Ghezzi P. Ungheri D. International Journal of Immunopathology & Pharmacology. 17(1):99-102, 2004 Jan-Apr.]

- # Mice (12 per group) infected intranasally with a lethal dose of influenza A virus APR/8. NAC was given as a single daily dose of 1000 mg/kg starting from 4 h after infection and until day 4 after infection, in association with ribavirin (100 mg/kg, i.p.).
- # 14-day survival
 - **No Rx 17%**
 - **NAC alone 25%**
 - **Ribavirin 58%**
 - **Ribavirin + NAC 92%**
- # This suggest that antioxidant therapy can increase survival by either improving the defenses against virus or by protecting from the pathogenesis of lung inflammation.



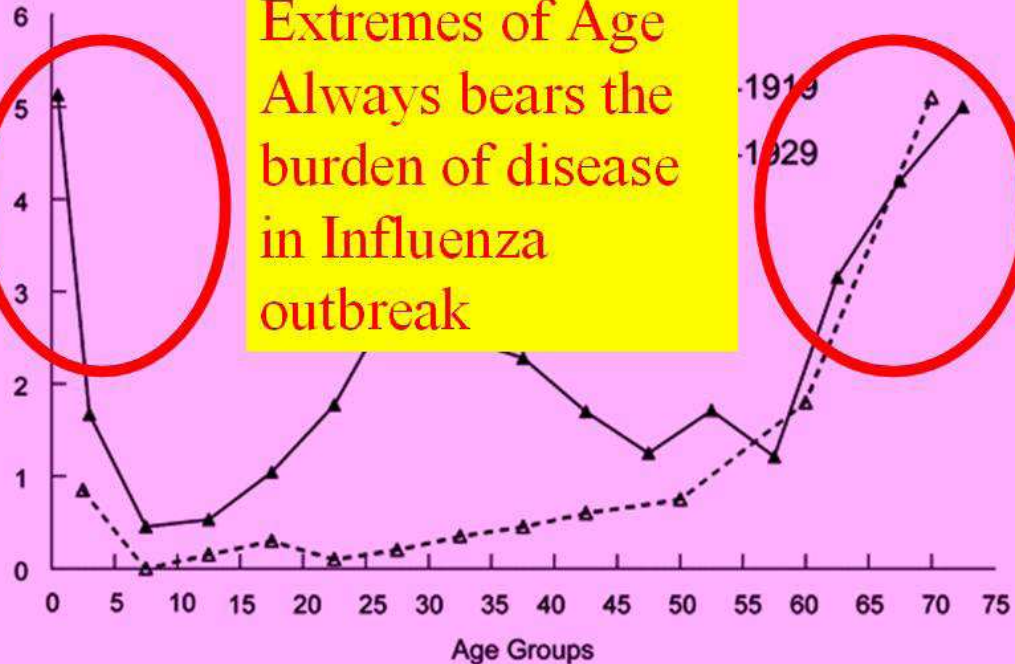
H1N1 2009 Pandemic Human Swine Influenza

What the government **can** do ?

未有流感疫苗前
香港可以怎麼辦



Case fatality per 100 persons ill with P&I per age group



Extremes of Age
Always bears the
burden of disease
in Influenza
outbreak

How can we reduce this mortality in the absence of influenza vaccine ?
PncCV in children and 23-valent PPV in adults against *Streptococcus pneumoniae*
Haemophilus Influenza B vaccination in children

Implication to Hong Kong Children

Age	Clinical attack rates	Population	Total Number (000)	Number (000) affected
0-4	<1 =83.9% 1-4= 58.1%	3.3%	229.2	181.2
5-9	57.7	3.9%	271.0	156.4
10-14	57.7	5.6%	393.1	226.8
Total population affected				564.4
1/10 may become ill and 25% of which has bacterial co-infection that may require antibiotic and have potential for clinical admission				14.11 Potential admission
0.1% mortality rate = 564 paediatric death				

Antecedentes Patológicos

Mexico



Other at Risk Populations

Neoplasm

1.3%

Autoimmune Disease

1.3%

Chronic Infection

4.0%

Respiratory disease

5.3%

Chronic smoker

10.7%

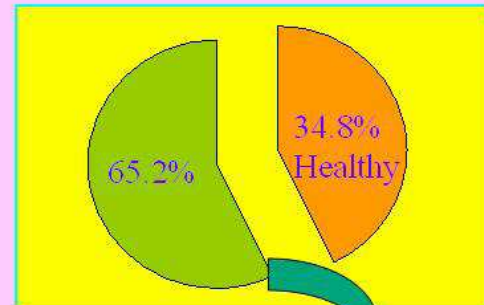
Cardiovascular Disease

13.3%

Metabolic (**DM** & Obesity)

29.3%

78 patients



Underlying Illnesses

Chronic smokers and diabetic patients have increased risk of death from HSI H1N1 2009

High Risk Group for H1N1 2009

- © Children
- © Pregnant women
- © New mothers
- © HIV-infected adults
- © Adolescents.

Adult NP Carriage Rate



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

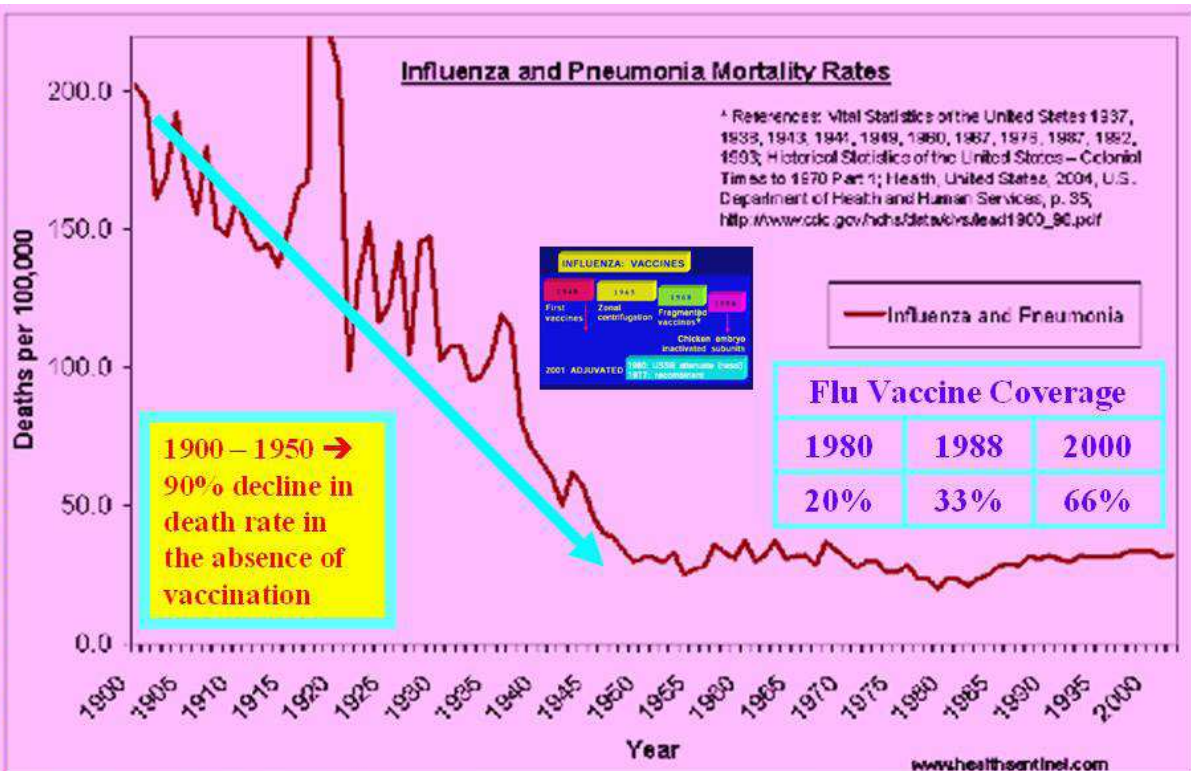
Use of Pneumococcal Vaccines for Influenza Pandemic Preparedness

U.S. recommendations for use of pneumococcal vaccines

	Pneumococcal polysaccharide vaccine	Pneumococcal conjugate vaccine
Universal vaccination	Persons 65 years and older	Children <2 years of age
Medical Indications	Persons 2-64 years with - chronic cardiovascular disease (congestive heart failure and cardiomyopathies) - chronic pulmonary disease including chronic obstructive pulmonary disease and emphysema but excluding asthma - diabetes mellitus - alcoholism - chronic liver disease, including cirrhosis - cerebrospinal fluid leaks - functional or anatomic asplenia including sickle cell disease and splenectomy - living situations in special environments or social situations including Alaska Natives and certain American Indian populations - immuno-compromised conditions including HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome; or those receiving immunosuppressive chemotherapy (including corticosteroids); and those who have received an organ or bone marrow transplant	Children 24-59 months with - chronic cardiac disease, particularly cyanotic congenital heart disease and cardiac failure - chronic pulmonary disease, excluding asthma unless on high dose corticosteroid therapy - diabetes mellitus - cerebrospinal fluid leaks - sickle cell disease and other hemoglobinopathies - congenital or acquired asplenia or splenic dysfunction - renal failure and nephrotic syndrome - immunocompromising conditions, including HIV; congenital B- (humoral) or T-lymphocyte immunodeficiencies; complement (c1, c2, c3, and c4) deficiencies; phagocytic disorders, excluding chronic granulomatous disease - diseases associated with immunosuppressive therapy or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin's disease, or solid organ transplantation
Consider use of vaccine in:		All children 24-59 months with priority given to children aged 24-35 months, children of Alaska Native or American Indian descent, children of African-American descent, and children who attend day care centers

Advisory Committee on Immunization Practices

→ ensuring that all persons with pneumococcal vaccine indications have been vaccinated before a pandemic occurs may be the best way to prevent pneumococcal disease during a pandemic



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

Last But Most Important of ALL

[illegible][illegible]

與其他任何窗簾一樣，都使輔助性作用，這不能保證100%保護隱私也。

一、引言：本论文旨在探讨中国20世纪以来文学批评的发展与现状，并分析其在当代文学创作中的影响。

◎「偵及23條的結合就等於沒有什麼不對？」

在综合判断过程中，如果判断者认为，在某一具体情况下，某一行为是符合法律规定的，那么，该行为就是合法的。反之，如果判断者认为，在某一具体情况下，某一行为是不符合法律规定的，那么，该行为就是非法的。

Two photographs of the 'Little People' series. The left photo shows a white box labeled '7' and a small white figure. The right photo shows a blue box labeled '23' and a small blue figure.

酒精与酸反应——此反应与酯化（生成酯和H₂O）

林道這片林小徑，出過劉聖清被反黨的地點也極少數。

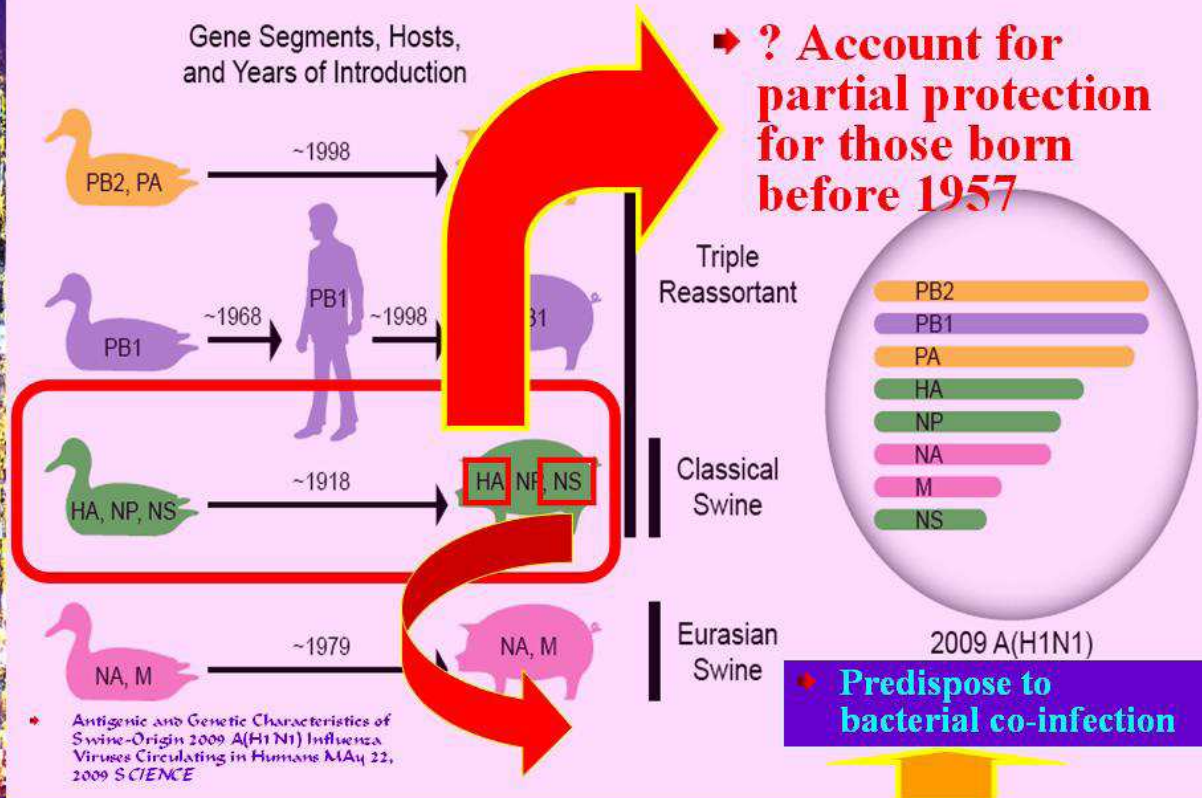


Sep.8, 2008

Sep 8, 2008

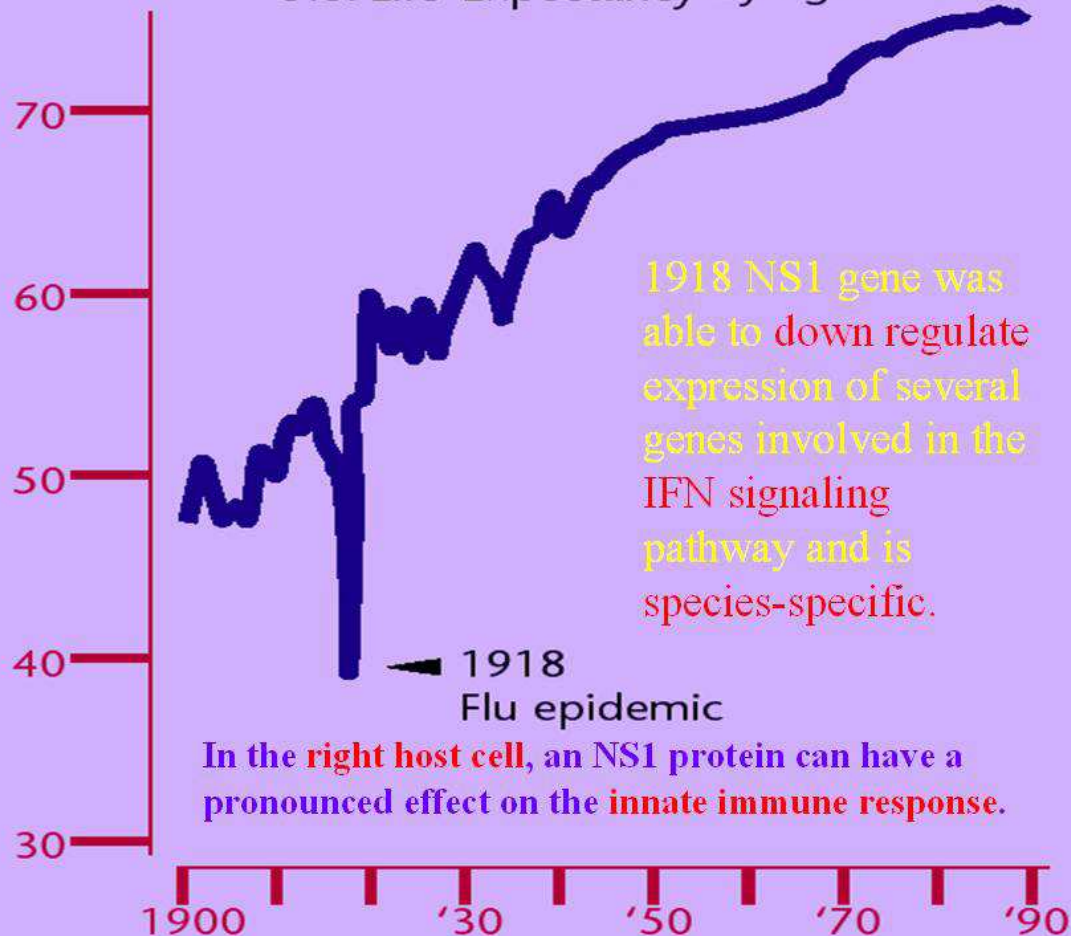
黎鏡堯醫生
伊利沙伯醫院

Gene Segments, Hosts,
and Years of Introduction



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

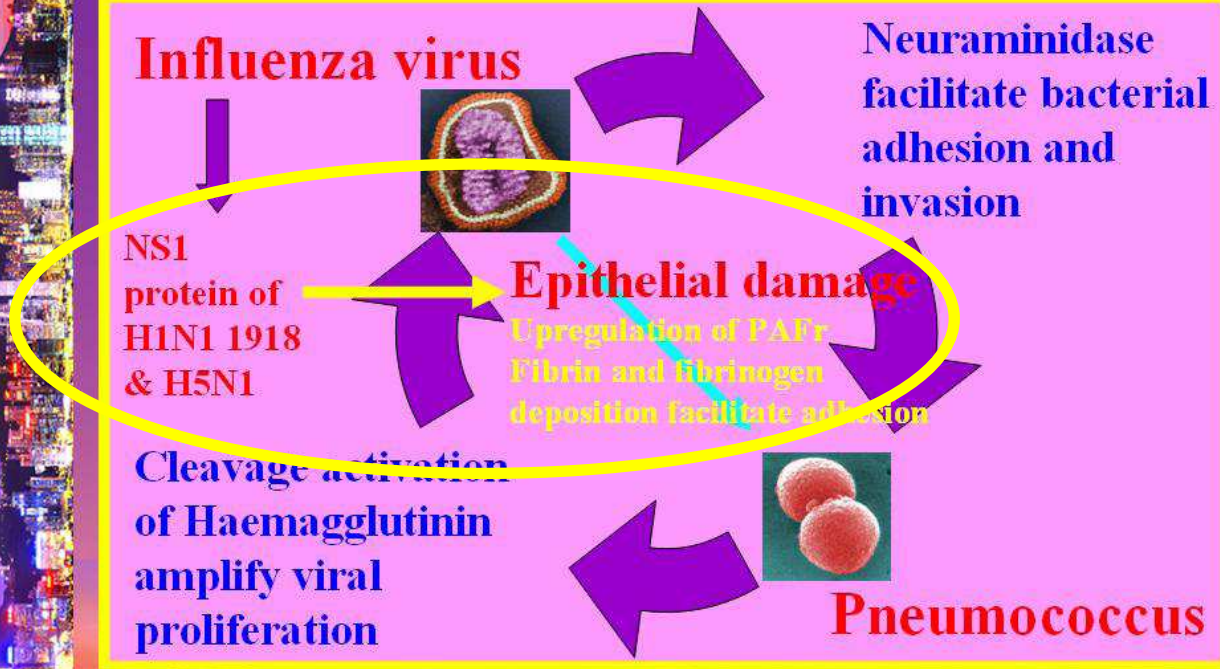
U.S. Life Expectancy By age



Current Situation of Hong Kong and China

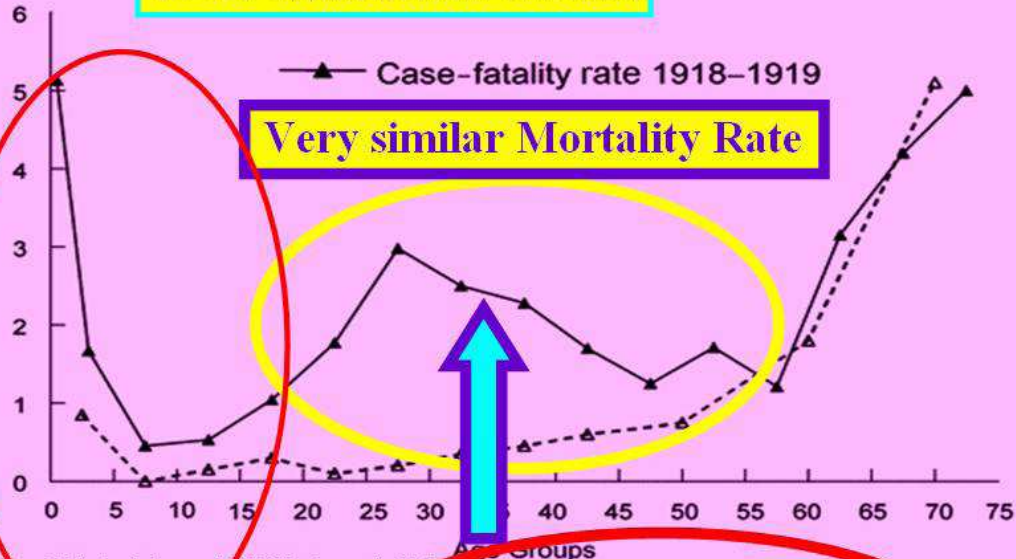
We are already in the Second Wave of 1918

We have to Act Fast !!!!!!!



1918 Influenza U.S.A.

Case fatality per 100 persons ill with P&I per age group



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

Comparative Infant Mortality of 46 Large American Cities
Year Ending September 28, 1918

Cities	Estimated Population Under 1 Year	Reported Deaths Under 1 Year	Index or Deaths per 1,000 Est. Pop. Under 1 Year
North Atlantic:			
Albany	1,688	224	132.7
Boston	14,823	2,011	135.7
Buffalo	10,365	1,547	149.3
Cambridge	2,405	251	104.4
Fall River	3,318	625	188.4
Jersey City	6,789	814	119.9
Lowell	2,435	483	198.4
Newark, N. J.	9,856	1,067	108.3
New Haven	3,527	411	116.5
New York	126,362	11,593	91.7
Philadelphia	37,546	4,748	126.5
Pittsburgh	13,601	1,915	140.8
Providence	5,428	667	122.9
Rochester	5,182	563	108.6
Syracuse	3,043	454	149.2
Worcester	3,782	432	114.2
Total	250,150	27,805	111.2

GEOGRAPHICAL AND SEASONAL VARIATIONS IN INFANT

MORTALITY IN THE UNITED STATES, 1917-1920 Frederick S.
Crum *Am J Public Health (N Y)* 1920 October; 10(10): 790-799.

**TREND OF MORTALITY RATES FROM PUERPERAL CAUSES,
EXPANDING DEATH-REGISTRATION AREA,
1900-1921.**

Year.	Deaths from puerperal causes, per 100,000 population.		
	Total	Puerperal septicemia	Other puerperal causes
1900.....	13.3	5.7	7.6
1901.....	13.7	6.0	7.7
1902.....	13.0	5.7	7.3
1903.....	14.0	6.1	7.9
1904.....	15.3	6.9	8.5
1905.....	14.9	6.8	8.1
1906.....	15.1	6.2	8.9
1907.....	15.6	6.8	8.9
1908.....	15.7	7.0	8.7
1909.....	15.3	6.7	8.6
1910.....	15.7	7.2	8.5
1911.....	16.0	7.4	8.6
1912.....	15.0	6.5	8.5
1913.....	15.8	7.2	8.7
1914.....	16.0	7.1	8.9
1915.....	15.3	6.3	9.0
1916.....	16.3	6.7	9.6
1917.....	16.7	6.9	9.8
1918.....	22.3	6.5	15.9
1919.....	17.0	5.8	11.2
1920.....	19.0	6.6	12.5
1921.....	16.9	6.8	10.1

**THE TREND OF MATERNAL-MORTALITY RATES IN THE
UNITED STATES DEATH-REGISTRATION AREA, 1900-1921**
ROBERT MORSE WOODBURY



Implication to Hong Kong & China

Age	Mexico	U.S.A.	Japan	HKSAR	China
< 15	31.3%	20.6%	14.3%	13.8%	21.4%
> 65	5.8%	12.5%	20%	12.8%	7.7%
IMR	19.01	6.3	2.8	2.93	21.16
MMR	55	8	8	2.5 (2008DHI)	55

IMR = Infant mortality rate (death per 1000 live birth) 2008

MMR = Maternal mortality rate (death per 100,000 delivery)

This may partially explained why Mexico is more affected than U.S.A. apart from immunization program. This has strong implication to China.

Immunization schedule

Vaccine Schedule

BCG	birth:
DTaPHibIPV	2, 4, 6, 18 months:
DTwP	2, 4 years:
DTwPHibHep	2, 4, 6 months:
HepB	birth, 4 months: +12 years (x3):
Influenza	6-23, 7-23, 17-23, 18-35 months: >50 years
MMR	1, 6 years:
MR	>13 years:

Mexico

Vaccine Schedule

OPV	> 6 months: < 5 Years:
Rotavirus	2, 4 months:
Td	>=12 years (x6)
Varicella	1 year: (children immunocompromised)
VitaminA	<4 years: (x2)

Hib was introduced in 1999

PCV-7 introduce in 2006

All children <2 vaccinated by 2008

Immunization schedule

Vaccine Schedule

BCG	birth:
DT	6 years:
DTaP	3, 4, 5, 18-24 months: [Part of country]
DTwP	3, 4, 5, 18-24 months:
HepA	18, 18-30 months: [Part of country]
HepB	birth: 1, 6 months:
Jap.Enc.	8 months: 2 years: [Part of country] (or 8 months (x2): 2, 6 years:)

China

Vaccine Schedule

Measles	8, 18-24 months:
MenA	6-18 months (x2): [Part of country]
MenAC	2, 6 years: [Part of country]
MMR	18-24 months: [Part of country]
MR	8 months: [Part of country]
OPV	2, 3, 4 months: 4 years:

Mexico has immunization program with Hib in 1999 and PCV-7 for all children <2yr 2008. No such program in China

**H****Haemophilus Influenza B
Immunization program****P****Pneumococcus
Immunization program**

La Gloria clinical attack rates

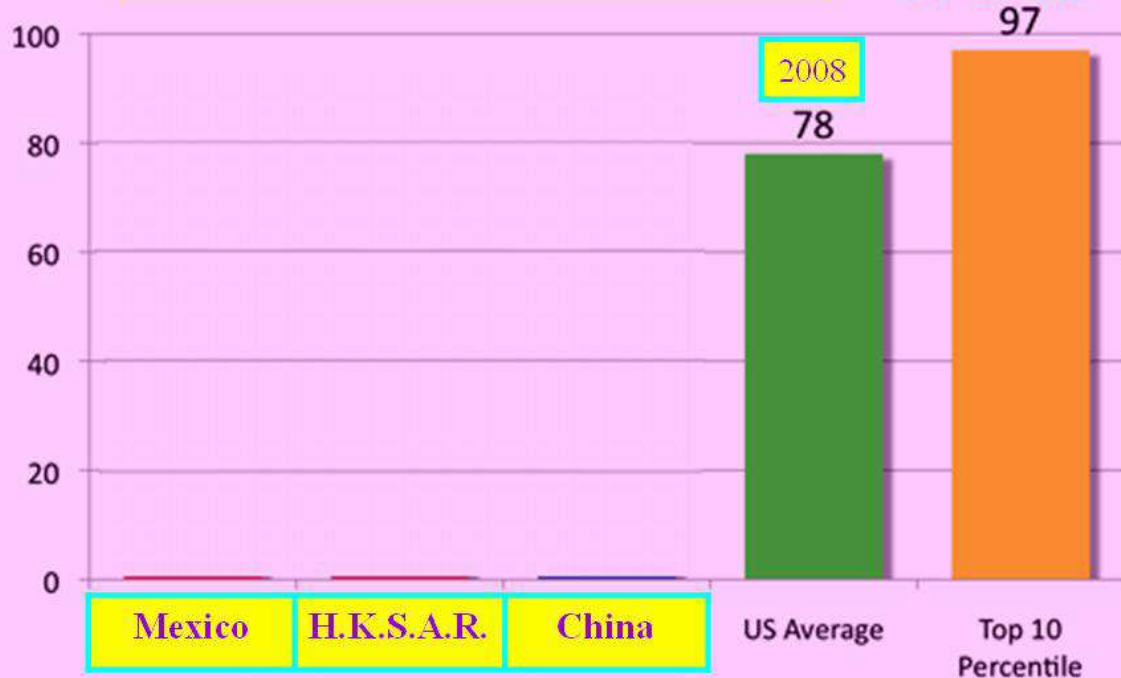


Age Group	Attack Rate	U.S.A.		Mexico		China
<1	83.9	H	P	H	P	
1-4	58.1	H	P	H	P	
5-14	57.7	H	P	H		
15-24	27.0					
25-44	31.6					
45-64	29.6					
65+	22.0		P			
Total	39.1					

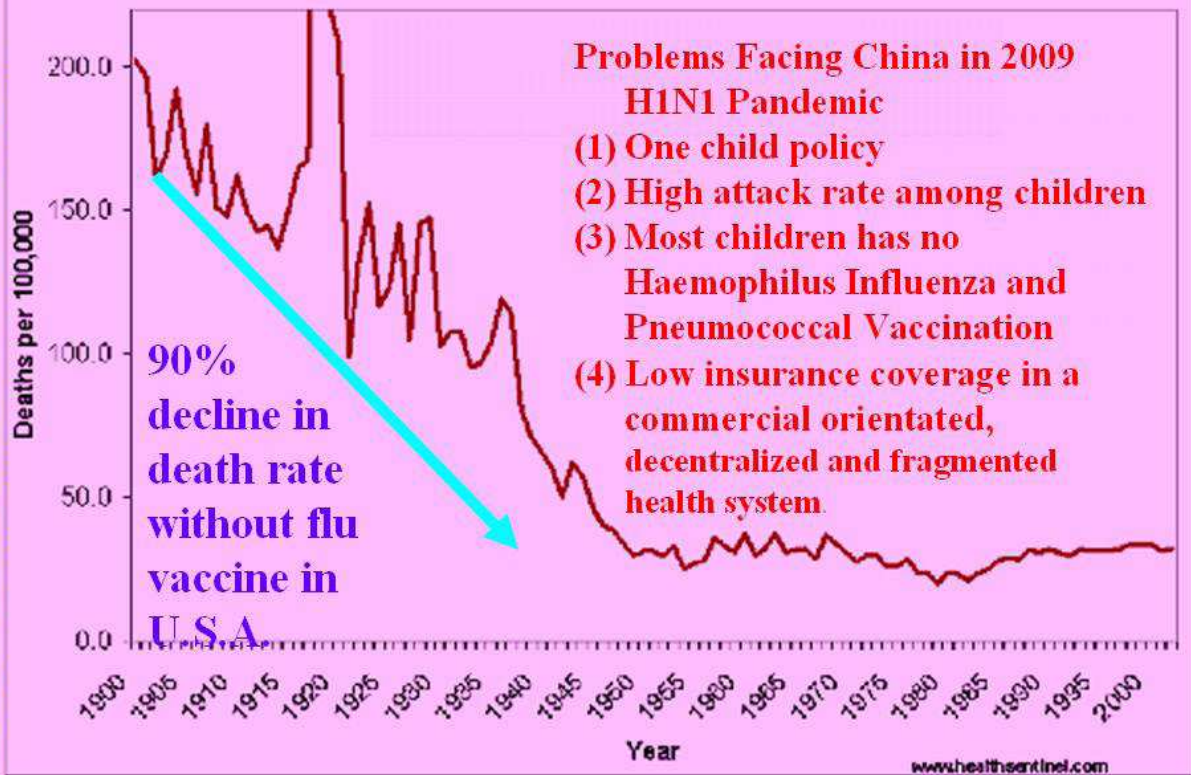
Immunization Status of U.S.A. Mexico and China

Pneumococcal Vaccination Rate

USA Health Care
Organization

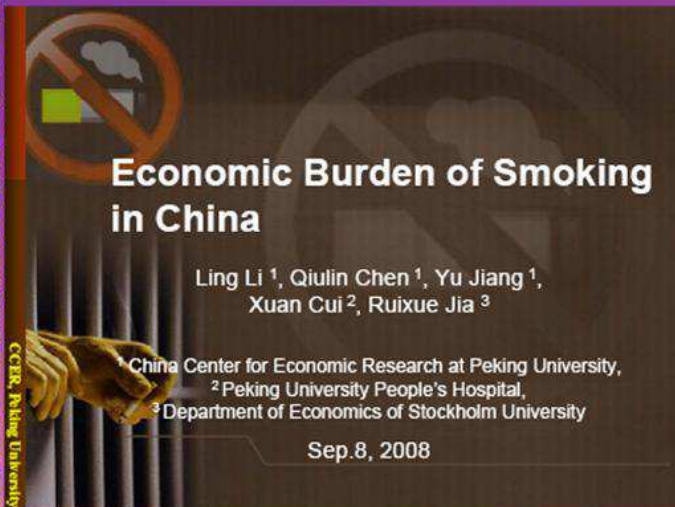


Pneumococcal Vaccination program for elderly > 65 has 78% coverage rate in U.S.A. but there is no such program in Mexico, H.K.S.A.R. and China



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

Implication of Smoker Population in China in Influenza Pandemic



©Smoker: 350 million,

♦man 320 million

♦woman 30 million

©Passive smoking: 540 million

©Death of smoking every year:

♦about 1 million

©Death of passive smoking every year: 100 thousand

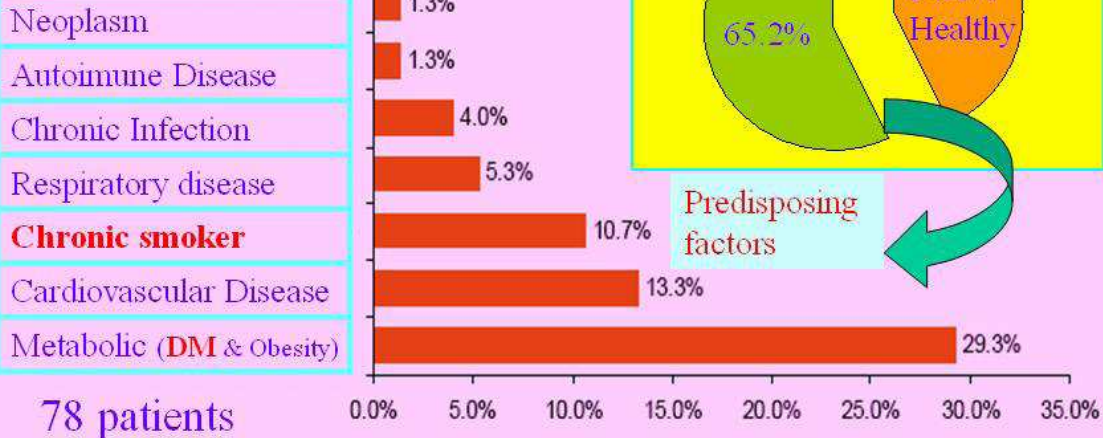
©Smoking rate of adult man: 57%

©Smoking rate of adult woman: 8%

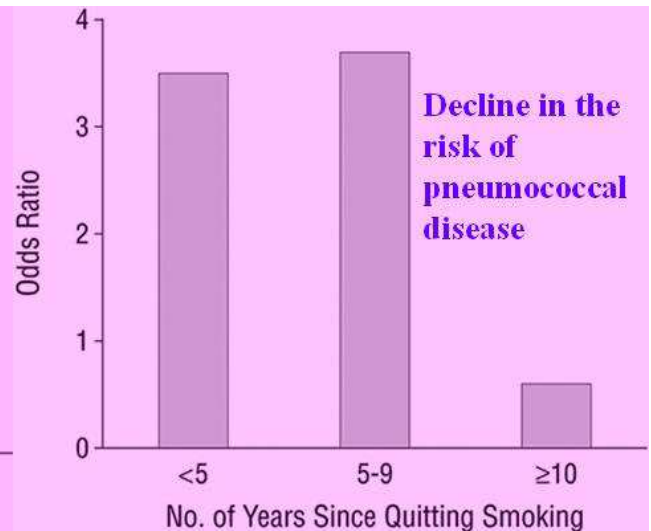
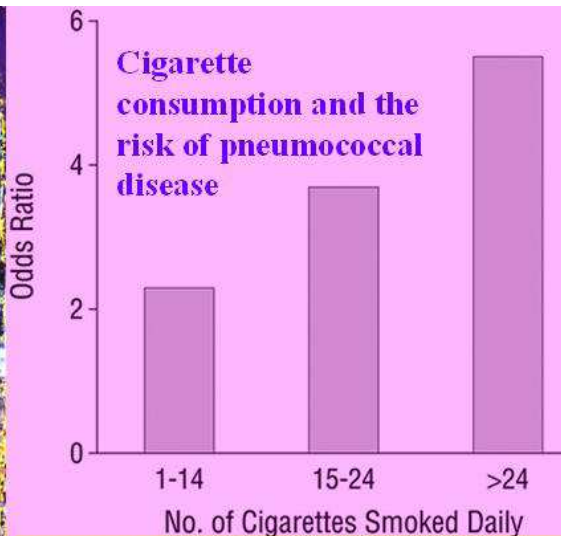
- ➔ China has the largest number of smokers in the world
- ➔ Three out of every 10 cigarettes produced globally are smoked in China.

Antecedentes Patológicos

Mexico



Chronic smokers and diabetic patients have increased risk of death from HSI H1N1 2009



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.

Comparison of Smoking Rates

Country	Male%	Female%	M:F Ratio	Period
China	66.9	3.1	21.9:1	2002(NPS)
	48.9	3.2	15.9:1	2003(NHS)
India	29.0	2.4	10.0:1	1998-1999
Algeria	43.8	6.6	6.6:1	1997-1998
Japan	47.4	11.5	4.1:1	2000
Pakistan	36.0	9.0	4.0:1	1996
Uganda	52.0	17.0	3.1:1	N/A
Kenya	66.8	31.9	2.1:1	N/A
Cuba	48.0	26.3	1.8:1	1995
Spain	39.1	24.6	1.6:1	2001
USA	25.7	21.0	1.2:1	2000
Denmark	32.0	29.0	1.1:1	2000
Norway	31.0	32.0	1.0:1	1999-2000
Sweden	17.4	20.4	0.9:1	2000-2001

Higher pneumococcal co-infection rate and mortality during influenza pandemic.

Source: Shafey O, Dolwick S, Guindon GE. Tobacco control country profiles 2003. Atlanta, GA, American Cancer Society, 2003. 1996 The Second National Prevalence Survey on Smoking in China

Economic Burden of Smoking in China

Ling Li¹, Qiulin Chen¹, Yu Jiang¹,
Xuan Cui², Ruixue Jia³

¹China Center for Economic Research at Peking University,
²Peking University People's Hospital,
³Department of Economics of Stockholm University

Sep 8, 2008

Although smoker has the same attack rate of influenza as nonsmokers but their severity of illness and incidence of pneumococcal co-infection is much higher than nonsmokers

Smoker Population Statistics

W.H.O.	Youth (13-15)		Adult (15-60)	
2008	Male	Female	Male	Female
China	7.1%	4.1%	57.4%	2.6%
HKSAR	Not Available		20.5% (2008)	3.6% (2008)
U.S.A.	20.7%	16.2%	20.6%	15.5%
Mexico	29.4%	24.8%	21.6%	6.5%



Updated ACIP Recommendations for Use of Pneumococcal Vaccines October 22, 2008

- © *Persons aged 19 through 64 years who smoke cigarettes should receive a single dose of PPSV23 and smoking cessation counseling.*
- © *Persons aged 19 through 64 years who have asthma should receive a single dose of PPSV23.*
- © *A second dose is recommended 5 years after the first dose of PPSV23 for persons aged ≥ 2 years who are immunocompromised, have sickle cell disease, or functional or*

Should pneumococcal vaccination recommended to the smoking population as an influenza pandemic strategy of the government ?



墨西哥的疫情對中國的啓示

- ◎ 從基因測試 2009 H1N1 豬流感是綜合病毒，含有四種不同的流感病毒基因，其中包括：北美洲的豬流感、歐亞型的豬流感、北美洲型的禽流感、及人類流感。其中 HA, NS1 and NP 則是於1918年傳入北美豬隻。因此我們再第一波時實已處身於1918年的第二波。
- ◎ 15歲以下小童染病率為 61%，15歲以上為 29%。但小童死亡率未有預期高。小童流感死亡率多因細菌混合感染併發症。流感的細菌混合感染三成至六成為肺炎鏈球菌及嗜血桿菌。墨西哥早於1999年已為小童提供免費 b 型嗜血桿菌疫苗。及後更於2006為兩歲以下小童免費提供肺炎鏈球菌疫苗。因此現時四歲以下小童已為疫苗保障。
- ◎ 吸煙是流感死亡高危因素之一。因吸煙會令血小板活化因數增加，增加肺炎鏈球菌感染的機會。

墨西哥的疫情對中國的啓示

中國的嬰兒死亡率與孕婦死亡率與墨西哥基本相近。墨西哥的疫情可於中國重演。但中國小童並沒b型嗜血桿菌和肺炎鏈球菌疫苗保障及中國成年人煙民數目及比例爲世界之冠。因此疫情可能比墨西哥嚴峻。



◎ 中國因此應盡速爲小童提供免費 b型嗜血桿菌和肺炎鏈球菌疫苗及呼籲成年煙民自行接種肺炎鏈球菌疫苗。

Summary I

- © The 2009 H1N1 Human Swine Influenza has a high attack rate among children.
- © The mortality rate would increase 10x in the presence of bacterial co-infection.
- © 30-80% of the co-infection are related to pneumococcus and Haemophilus influenza which are vaccine preventable.
- © **The government should prevent such complication by immunization program**

Age Group	Male (%)	Female(%)	Total(%)
<1	91.2	73.7	83.9
1-4	66.2	66.1	58.1
5-14	49.7	66.3	57.7

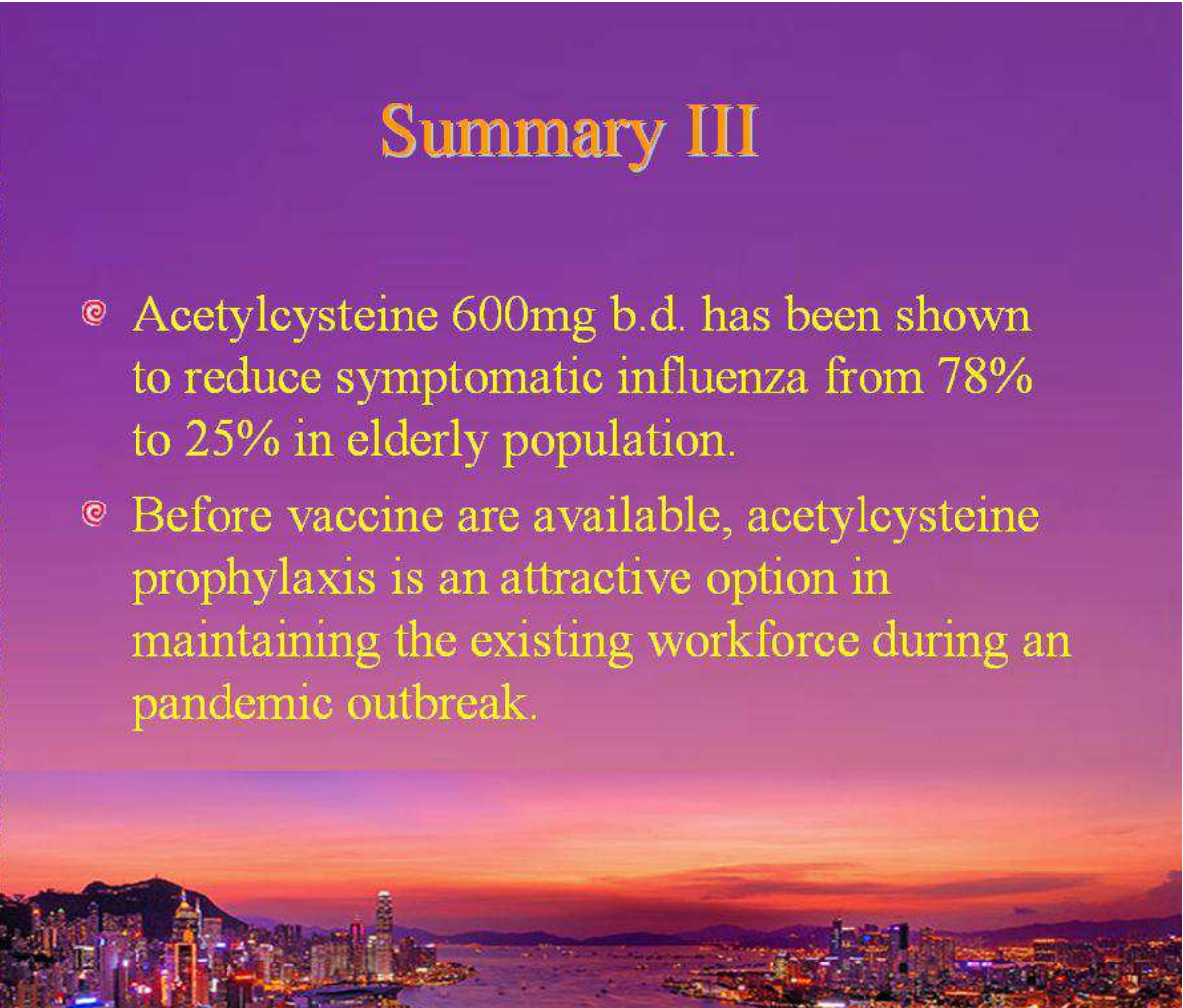


Summary II

- © Many of our frontline staffs who are working mothers and fathers have increased nasal colonization with pneumococcus
- © Elderly (age >65) has increased cardiovascular and pneumonic mortality related to pneumococcal co-infection during influenza period.
- © Chronic smokers and patient with diabetes mellitus have increased risk of pneumococcal co-infection during influenza virus infection.
- © Hong Kong pneumococcal population has high rate of penicillin resistance.
- © **The government should prepare the above at risk populations against pneumococcal co-infection by vaccination program before pandemic.**

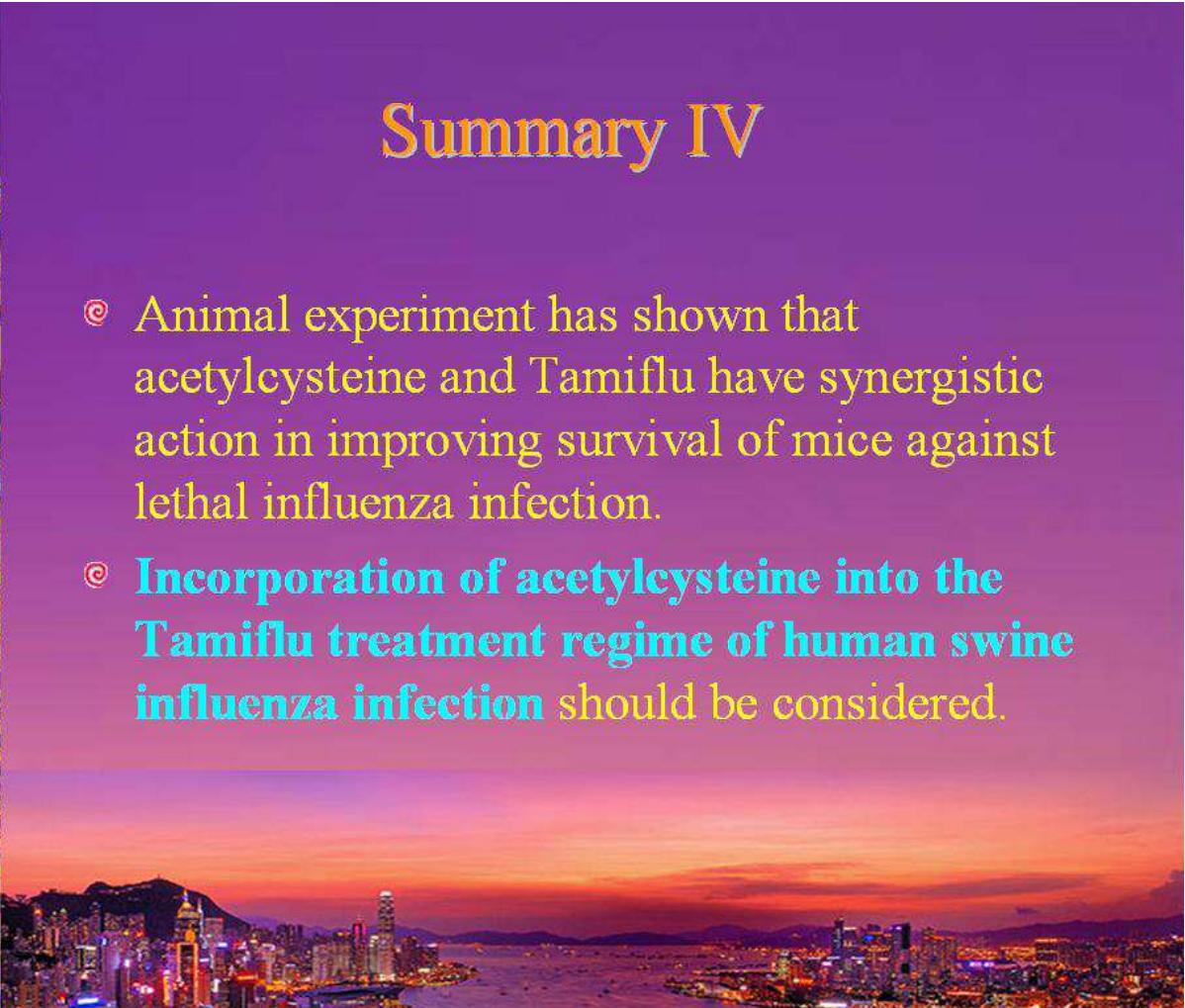


Summary III

- ② Acetylcysteine 600mg b.d. has been shown to reduce symptomatic influenza from 78% to 25% in elderly population.
 - ② Before vaccine are available, acetylcysteine prophylaxis is an attractive option in maintaining the existing workforce during an pandemic outbreak.
- 



Summary IV

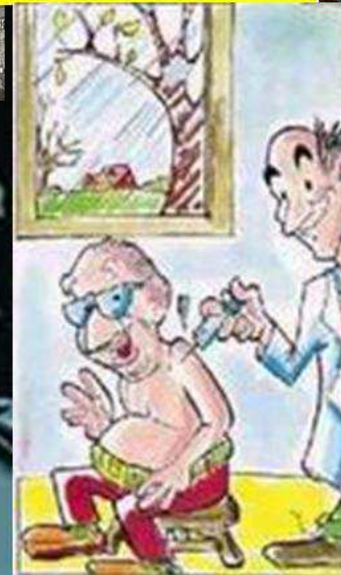
- © Animal experiment has shown that acetylcysteine and Tamiflu have synergistic action in improving survival of mice against lethal influenza infection.
 - © **Incorporation of acetylcysteine into the Tamiflu treatment regime of human swine influenza infection** should be considered.
- 



Vernon Cooper:

These days people seek knowledge, not wisdom.

Knowledge is of the past, wisdom is of the future.



“We must act now! The
future generations are
depending on us!”

