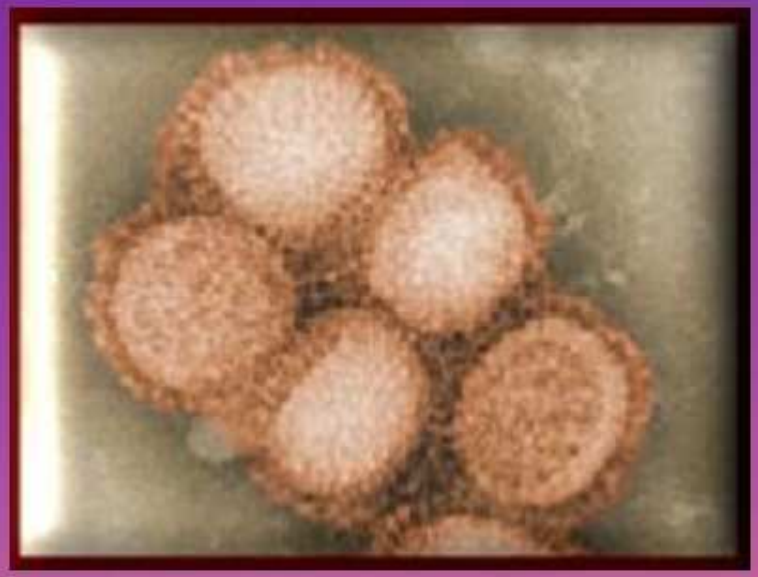

H1N1 2009 Pandemic
Human Swine Influenza
What the government can do ?
未有流感疫苗前
香港可以怎麼辦

Human Swine Influenza



Dr. Lai Kang Yiu

Intensive Care Unit

Queen Elizabeth Hospital

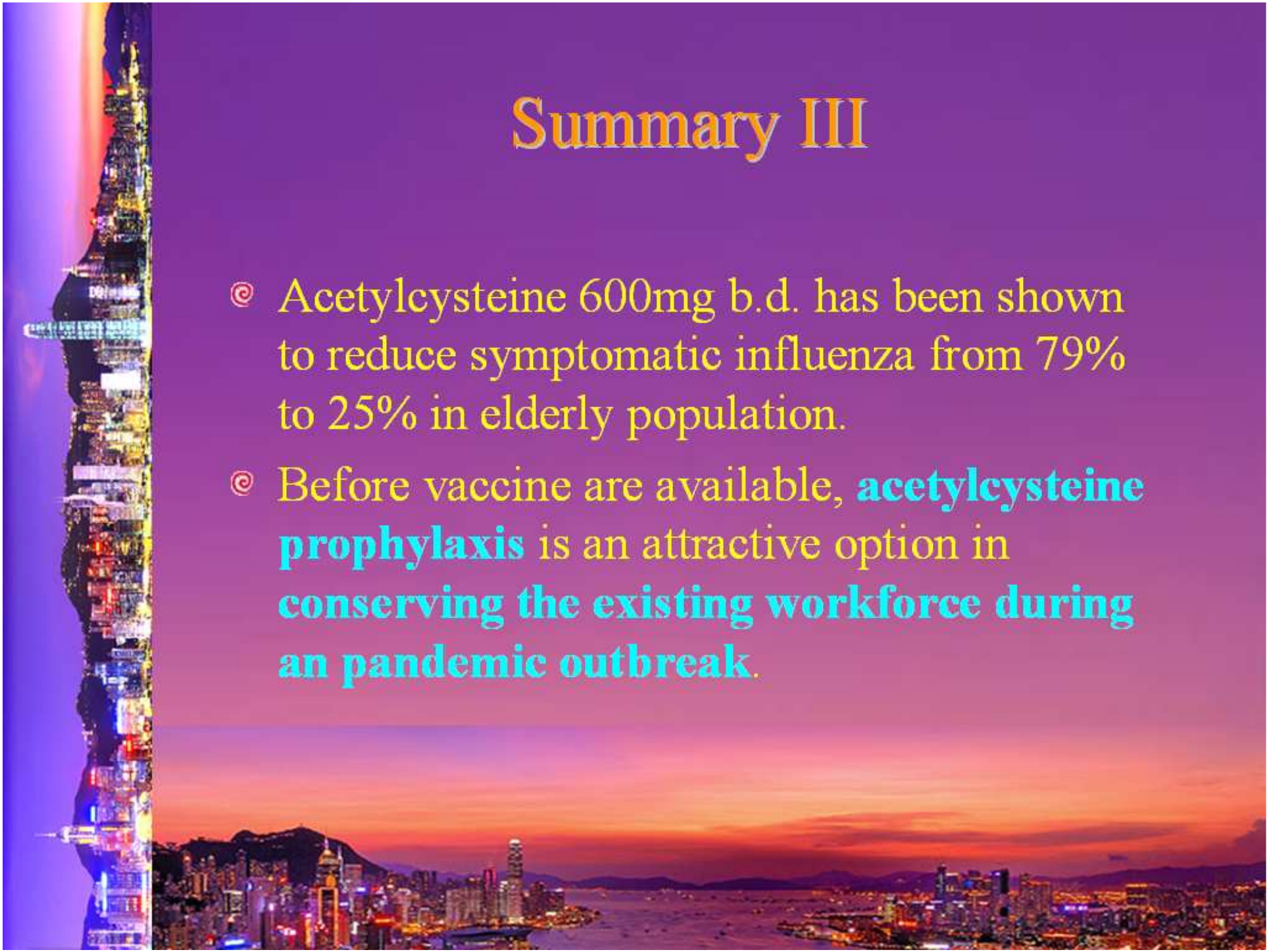
Summary I

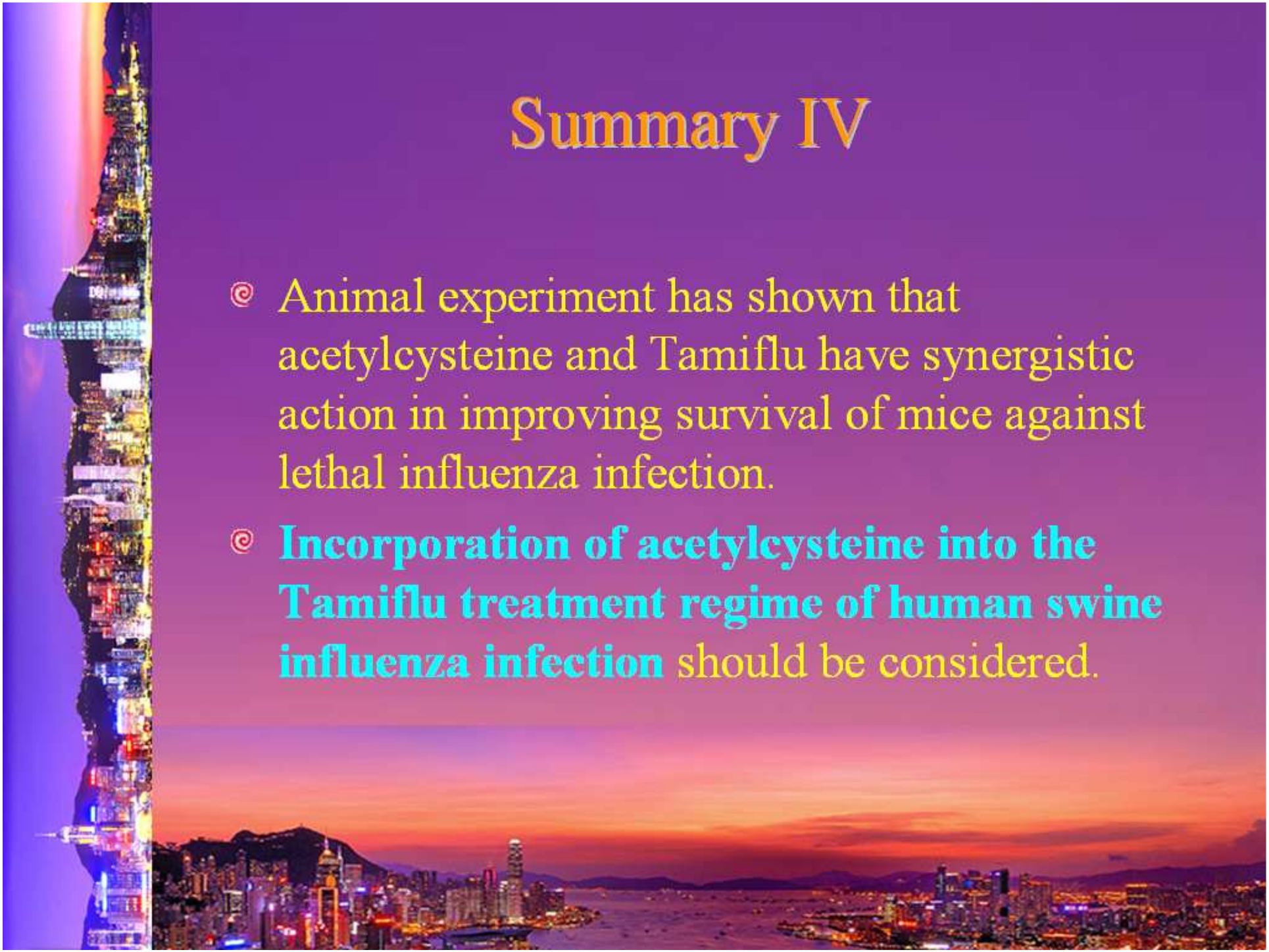
- The 2009 H1N1 Human Swine Influenza has a high attack rate among children.
- The mortality rate would increase 10x in the present of bacterial co-infection.
- 30-80% of the co-infection are related to pneumococcus and Haemophilus influenza which are vaccine preventable.
- **The government should prevent 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.
- Hong Kong pneumococcal population has high rate of penicillin resistance.
- **The government should prepare the above at risk population against pneumococcal co-infection by vaccination before pandemic.**


Summary III
Acetylcysteine 600mg b.d. has been shown to reduce symptomatic influenza from 79% to 25% in elderly population.
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.

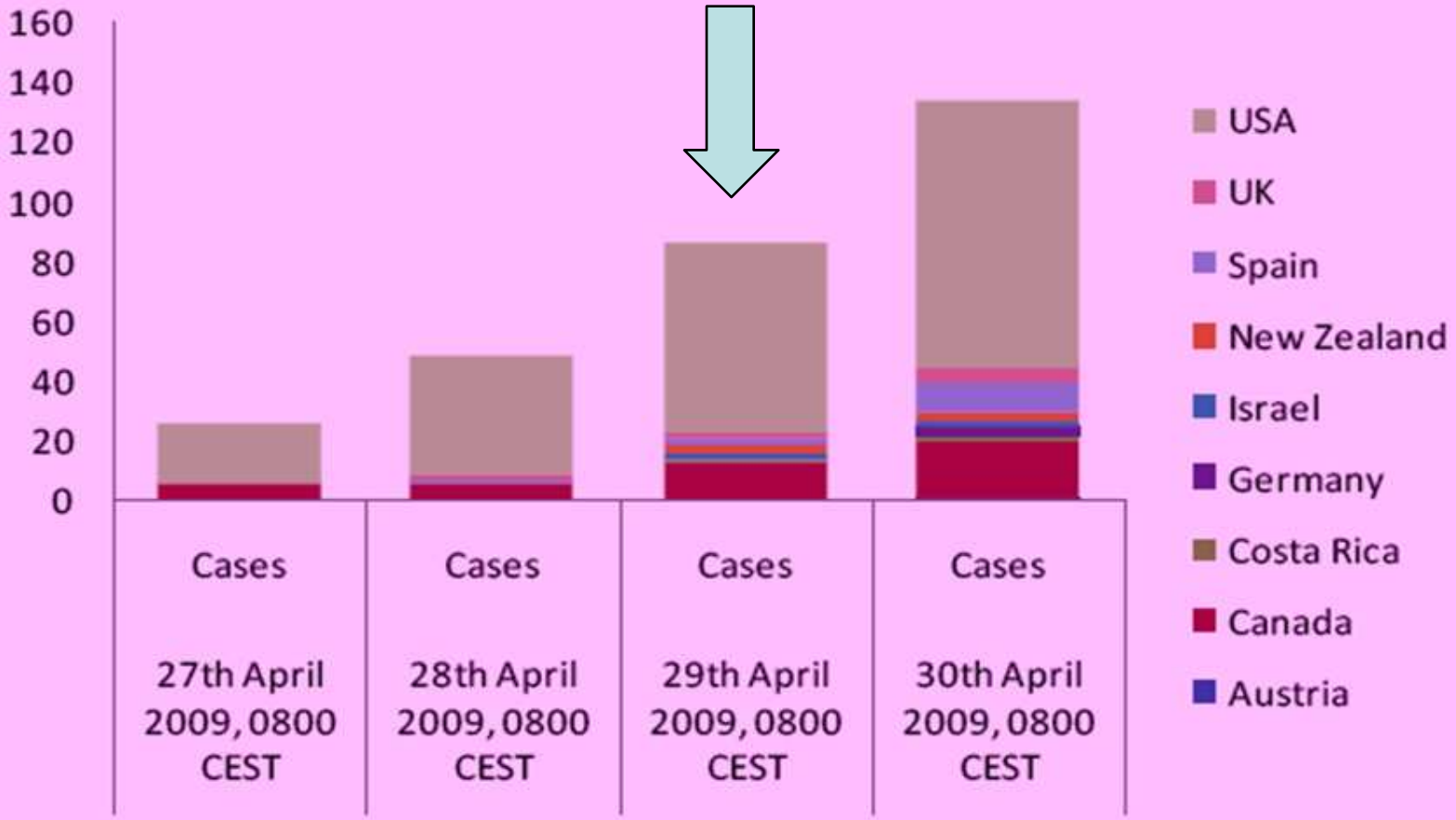
Mexican Flu, Swine Flu, H1N1 Pandemic Pandemonium Origin

- 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

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.

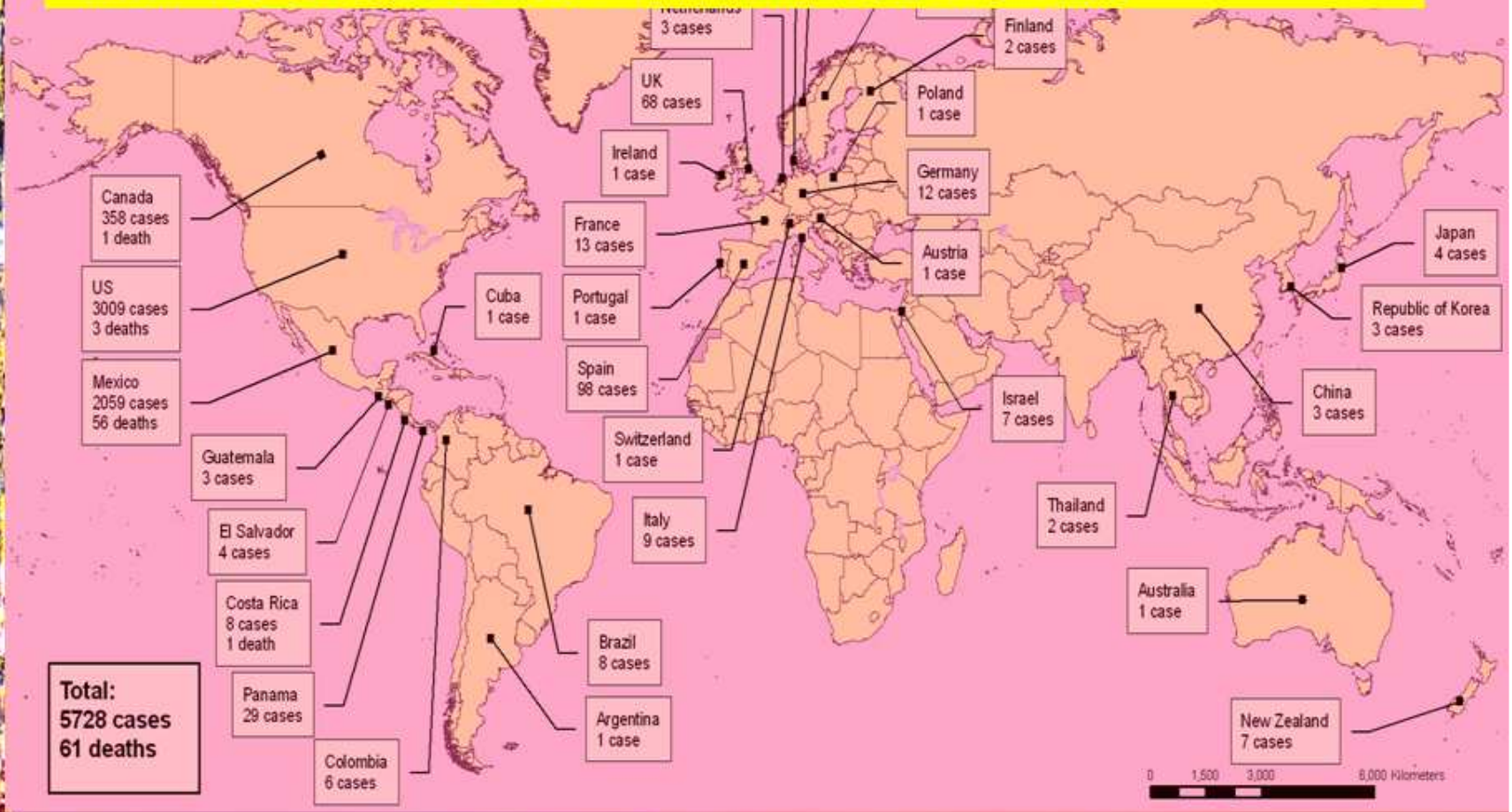
香港政府的應變系統及 醫管局應變系統

	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)

- 死亡率爲 0.4%
- 平均傳染機率爲 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爲 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歲以下小童染病率爲 61%， 15歲以上爲 29%

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

Symptom	Frequency (%)
Cough	456 (82.0%)
Fever	378 (68.0%)
Hyaline rhinorrea	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

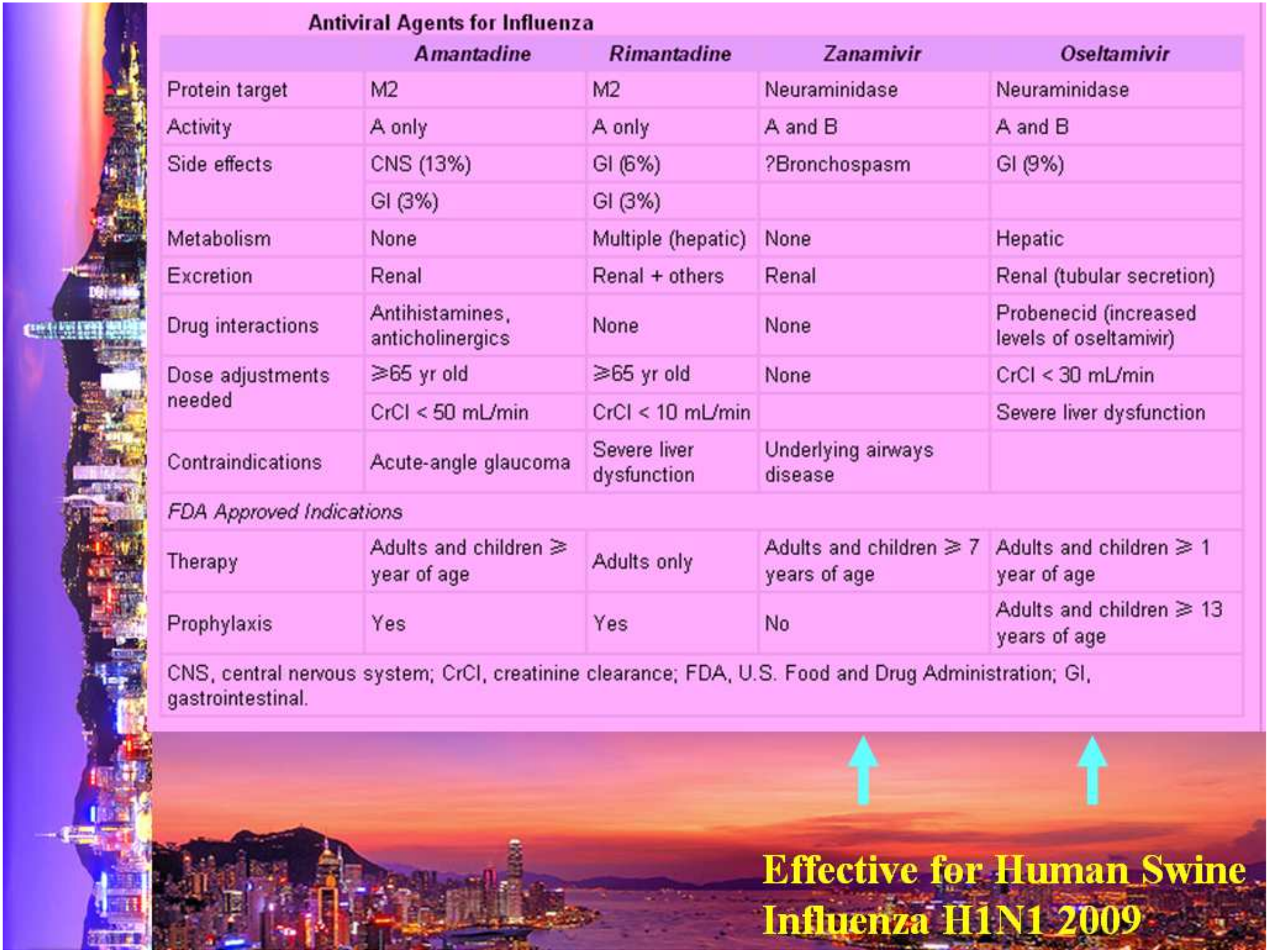
(Pandemic Potential of a Strain of Influenza A (H1N1) : Early Findings Christophe FRASER Science 10.1126 science.1176062 2009)

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

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*?	*YES*	No
Vaccine Exists?	No	*YES*
Human Immunity?	No	*YES*
Human Infections known prior to 2009	No	*YES*
Hemagglutinin (H1) origin	Swine influenza virus	Human Influenza virus



Antiviral Agents for Influenza

	Amantadine	*Rimantadine*	*Zanamivir*	*Oseltamivir*
Protein target	M2	M2	Neuraminidase	Neuraminidase
Activity	A only	A only	A and B	A and B
Side effects	CNS (13%)	GI (6%)	?Bronchospasm	GI (9%)
	GI (3%)	GI (3%)		
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	≥65 yr old	None	CrCl < 30 mL/min
	CrCl < 50 mL/min	CrCl < 10 mL/min		Severe liver dysfunction
Contraindications	Acute-angle glaucoma	Severe liver dysfunction	Underlying airways disease	
FDA Approved Indications				
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.

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

Asian Influenza H2

Russian Influenza H1

Hong Kong Influenza H3

Avian Influenza H9 H7 H5 H5

1918 1957 1968 1977 1997 2003 1998/9

1918 Spanish Influenza H1N1

1957 Asian Influenza H2N2

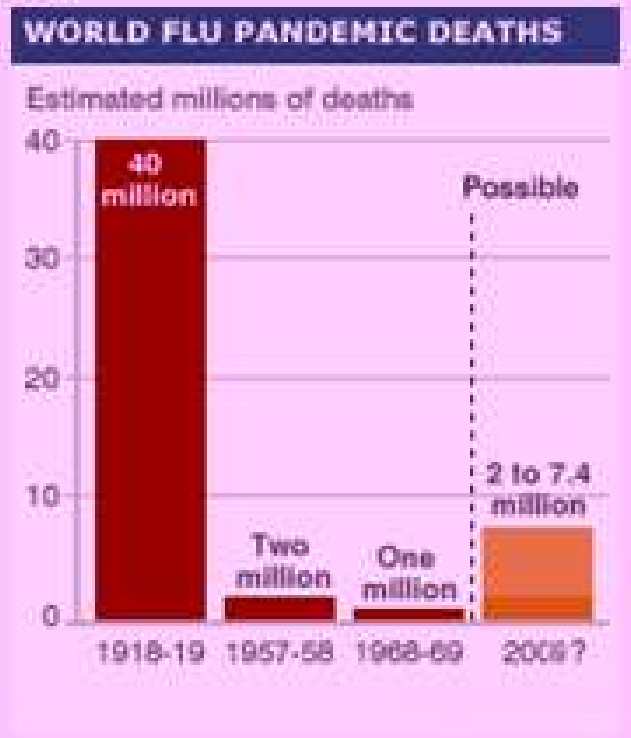
1968 Hong Kong Influenza H3N2

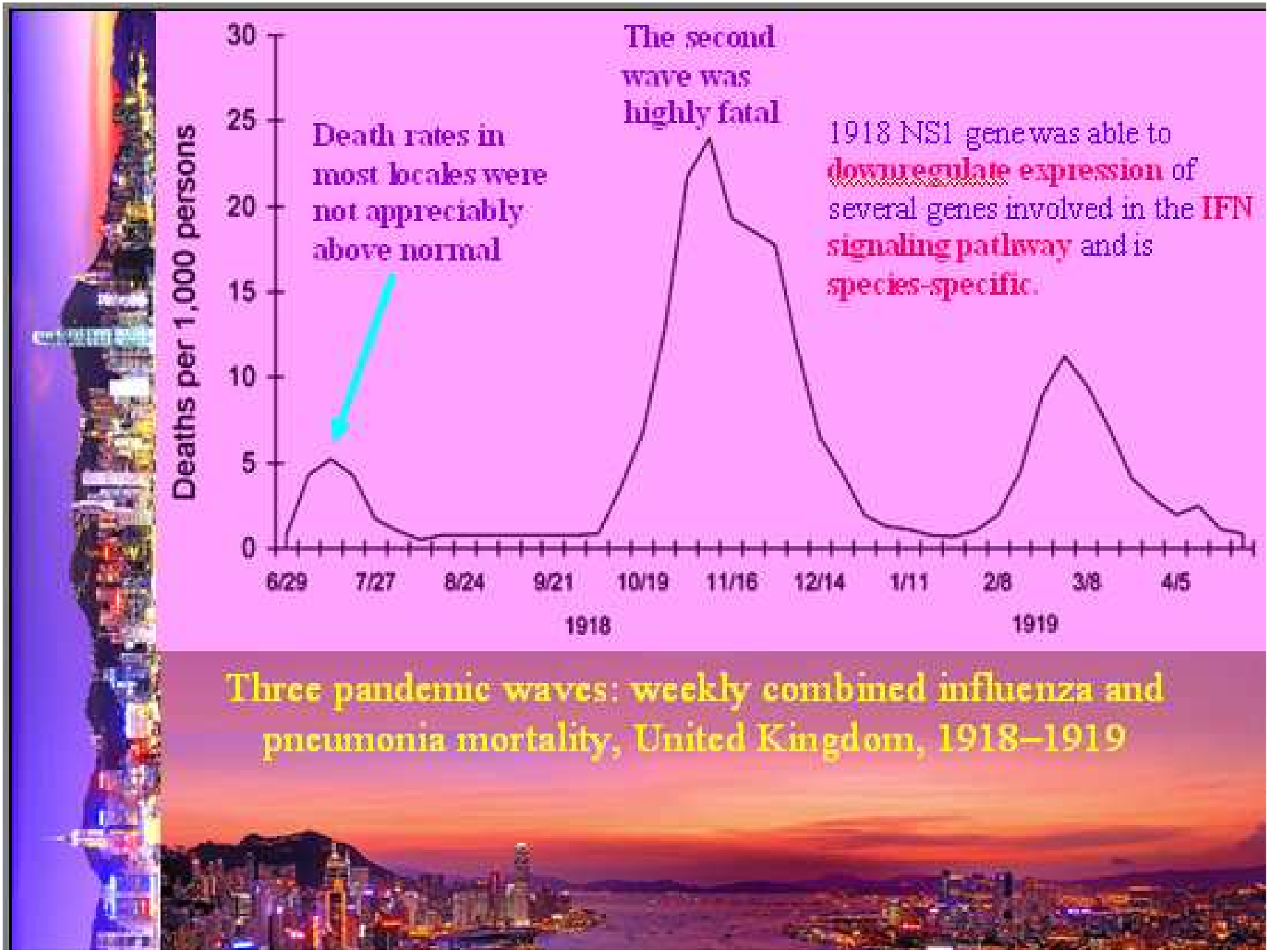
Pandemic in the past

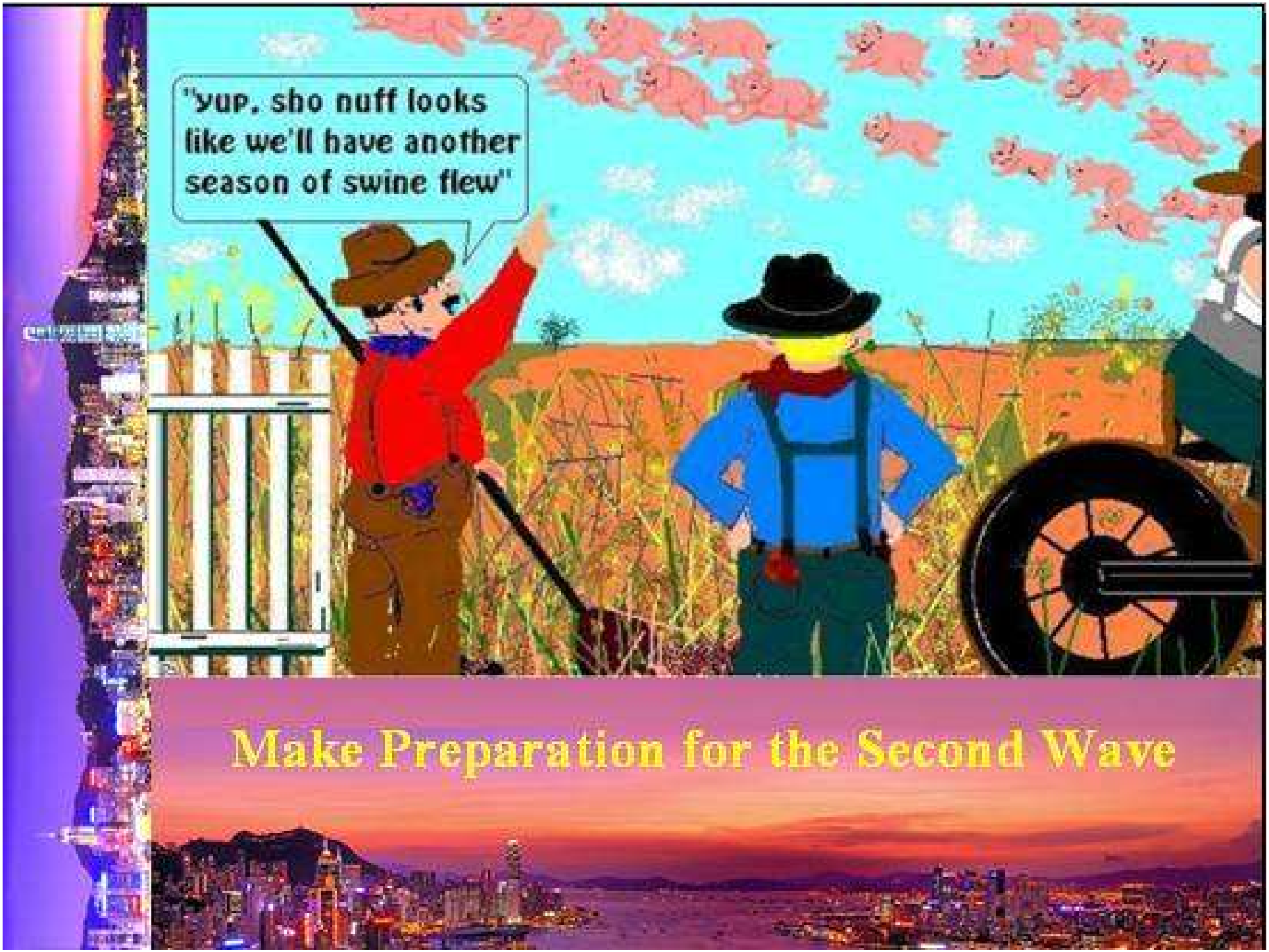
Pandemic Severity Index

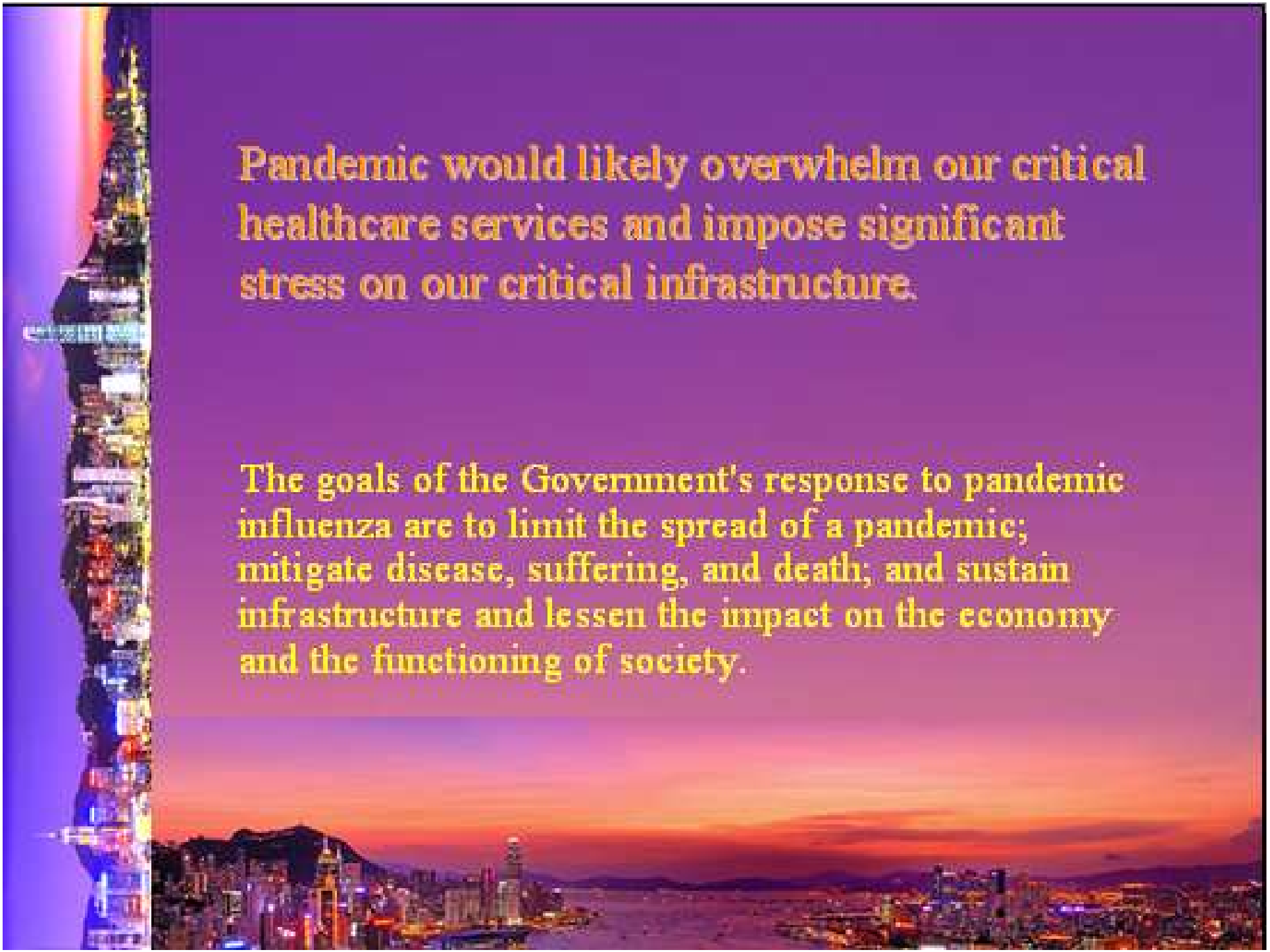
Case Fatality Ratio		Projected Number of Deaths* Population of HKSAR 7 million
		30% population = 2.1 million
≥2.0%	Category 5	>42,000
1.0 - <2.0%	Category 4	21,000 - <42,000
0.5 - <1.0%	Category 3	10,500 – <21,000
0.1% - <0.5%	Category 2	2,100 – <10,500
<0.1%	Category 1	<2,100 → Much more death than SARS

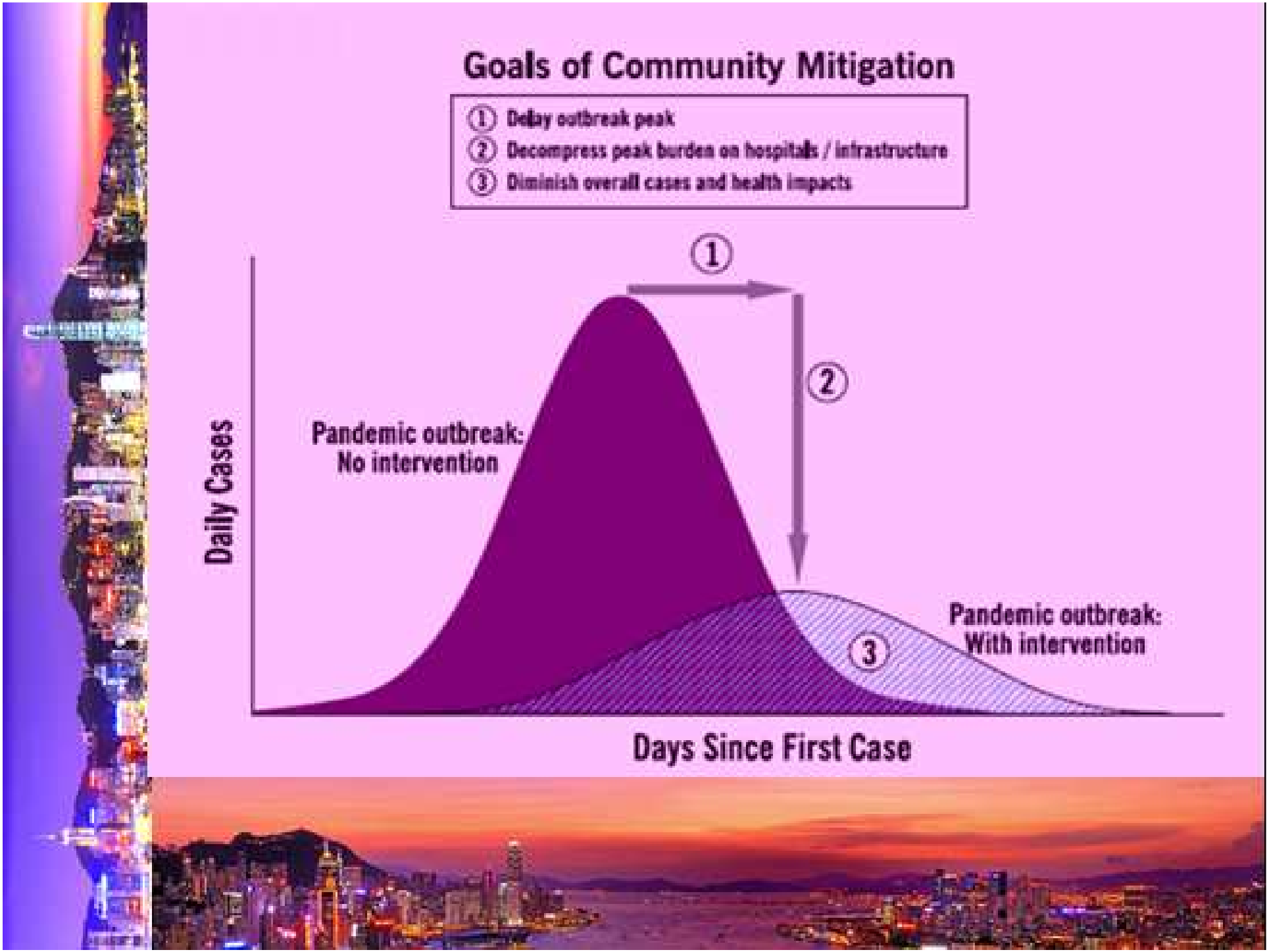
*Assumes 30% Illness Rate and Unmitigated Pandemic Without Interventions

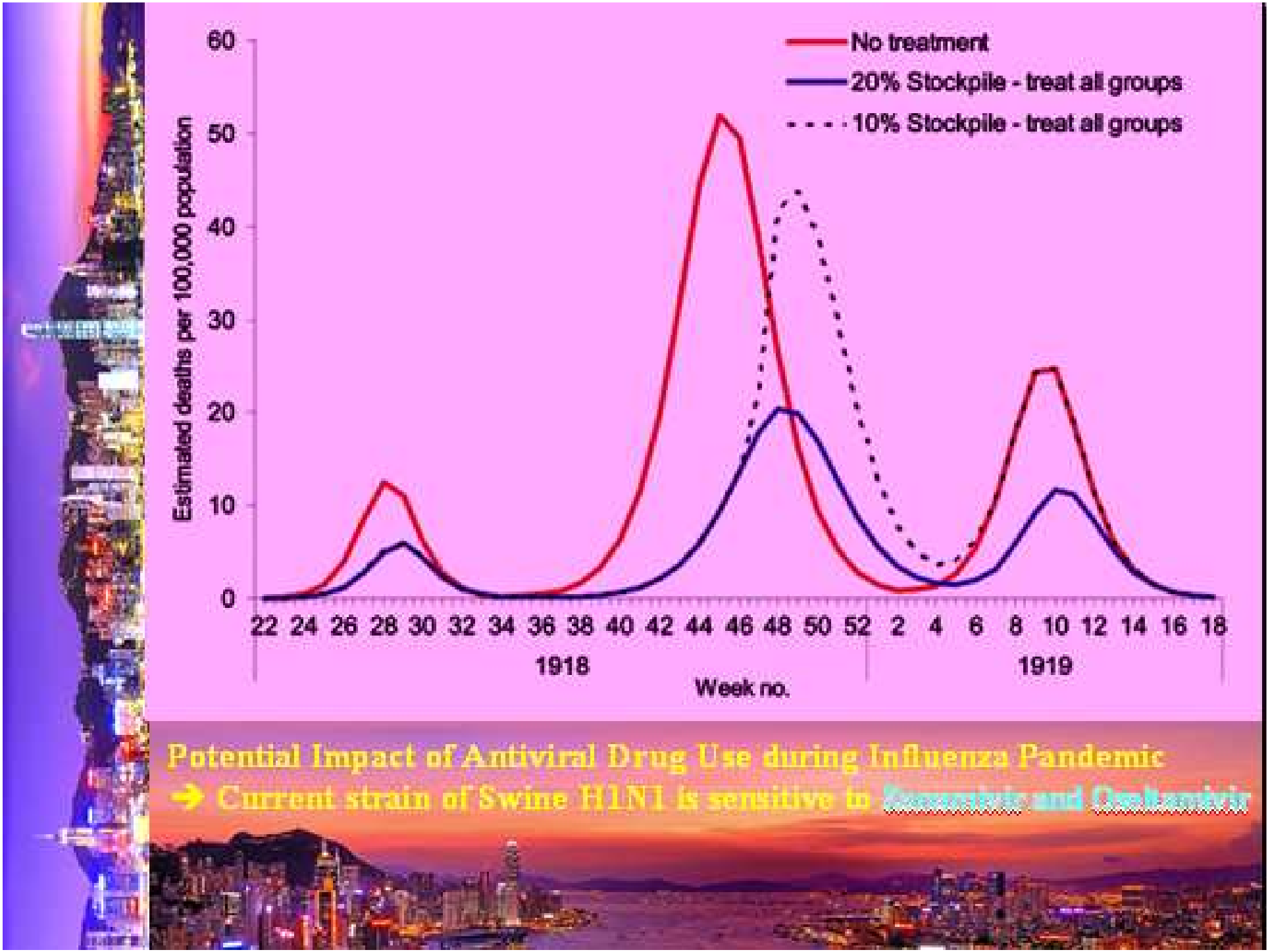


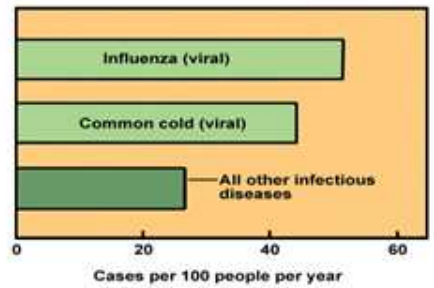

30
25
20
15
10
5
0
Deaths per 1,000 persons
Death rates in most locales were not appreciably above normal
The second wave was highly fatal
1918 NS1 gene was able to downregulate expression of several genes involved in the IFN signaling pathway and is species-specific.
6/29
7/27
8/24
9/21
10/19
11/16
12/14
1/11
2/8
3/8
4/5
1918
1919
Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919

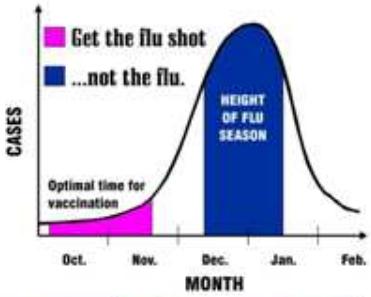

"Yup, sho nuff looks like we'll have another season of swine flew"
Make Preparation for the Second Wave


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
1
2
Pandemic outbreak:
No intervention
Daily Cases
Pandemic outbreak:
With intervention
3
Days Since First Case


No treatment
20% Stockpile - treat all groups
10% Stockpile - treat all groups
Estimated deaths per 100,000 population
60
50
40
30
20
10
0
22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 2 4 6 8 10 12 14 16 18
1918
1919
Week no.
Potential Impact of Antiviral Drug Use during Influenza Pandemic
➔ Current strain of Swine H1N1 is sensitive to Zanamivir and Oseltamivir





FLU SHOTS ARE AVAILABLE

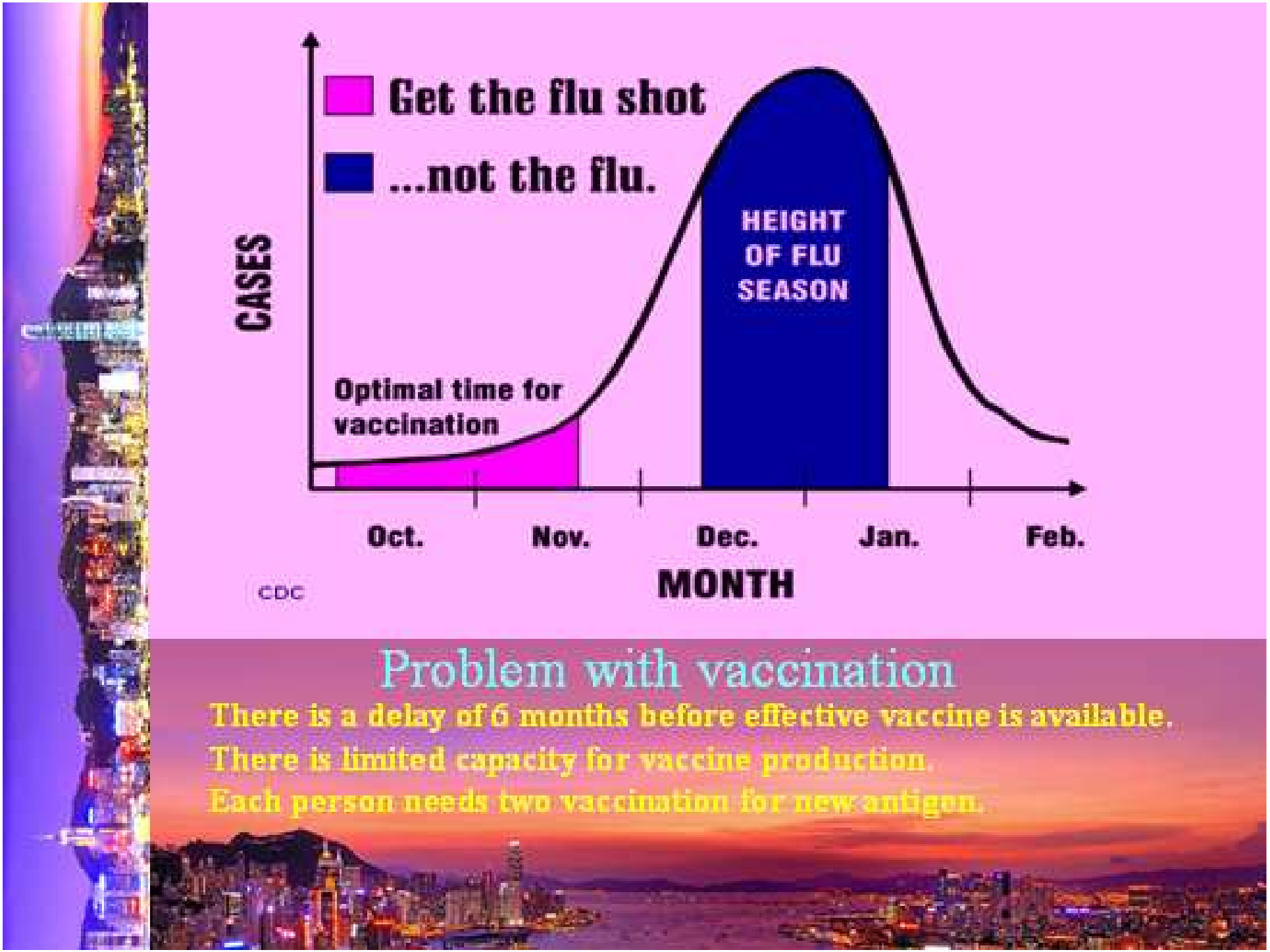
STUDENTS: $5.
STAFF: $10.

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

Vaccination

Don't get the

The most important measure to protect population at large from pandemic influenza if mutation cannot be prevented by public measures

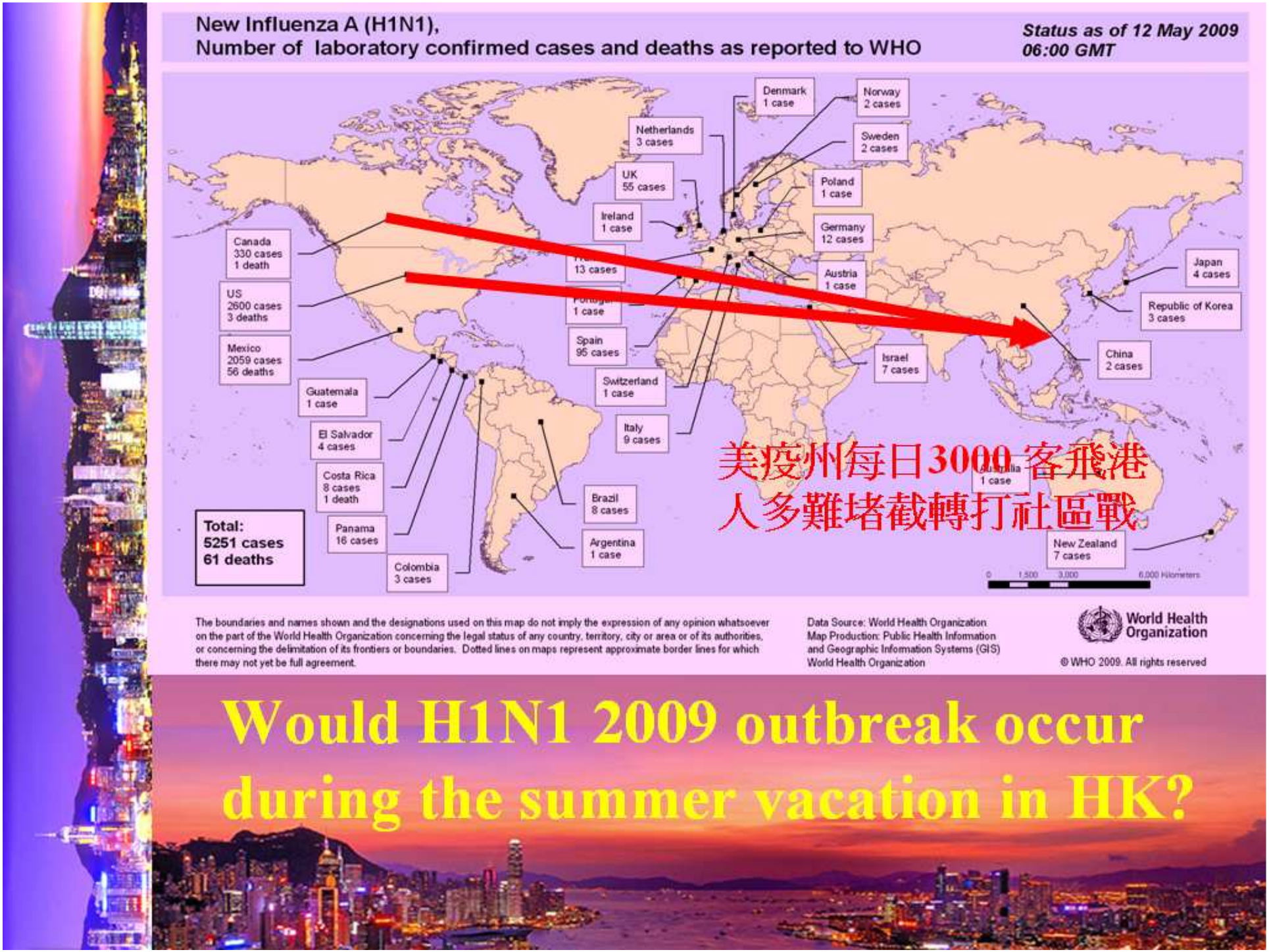


Problem with vaccination

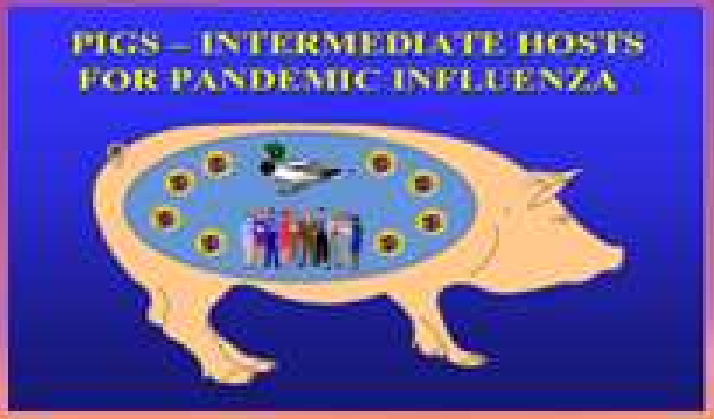
There is a delay of 6 months before effective vaccine is available.

There is limited capacity for vaccine production.

Each person needs two vaccination for new antigen.


New Influenza A (H1N1),
Number of laboratory confirmed cases and deaths as reported to WHO
Status as of 12 May 2009
06:00 GMT
Denmark
1 case
Norway
2 cases
Netherlands
3 cases
Sweden
2 cases
UK
55 cases
Poland
1 case
Ireland
1 case
Germany
12 cases
Canada
330 cases
1 death
13 cases
Austria
1 case
Japan
4 cases
US
2600 cases
3 deaths
1 case
Republic of Korea
3 cases
Mexico
2059 cases
56 deaths
Spain
95 cases
Israel
7 cases
China
2 cases
Switzerland
1 case
Guatemala
1 case
Italy
9 cases
El Salvador
4 cases
Costa Rica
8 cases
1 death
1 case
Brazil
8 cases
Total:
5251 cases
61 deaths
Panama
16 cases
Argentina
1 case
New Zealand
7 cases
Colombia
3 cases
0 1,500 3,000 6,000 Kilometers
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
© WHO 2009. All rights reserved
Would H1N1 2009 outbreak occur during the summer vacation in HK?

The Worst Scenario !!!!!!



- 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

Avian viruses:
$HA226_{gln}$

Alpha-(2,3) sialic acid

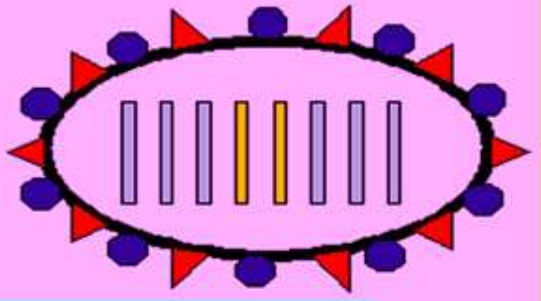
H5N1

Human viruses:
$HA226_{leu}$

Alpha-(2,6) sialic acid

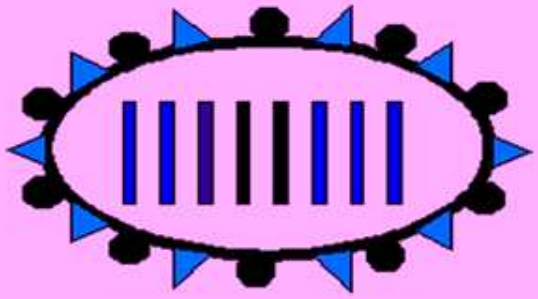
Human Swine H1N1
HumanH1N1

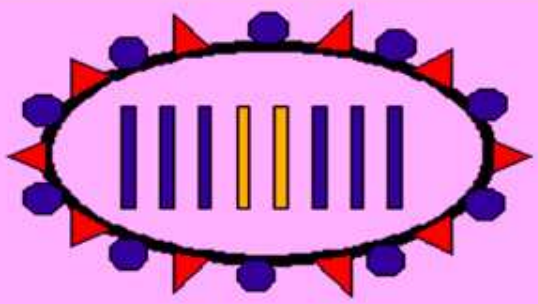
If the swine influenza H1N1 2009 virus has acquired the highly lethal NS gene of H5N1 and the neuraminidase inhibitor resistant NA gene of existing H1N1 virus after reassortment, a high transmissible and lethal (60-70% mortality) influenza virus with pandemic potential but resistant to all existing anti-viral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



H5N1 → NS gene

H1N1 → NA gene

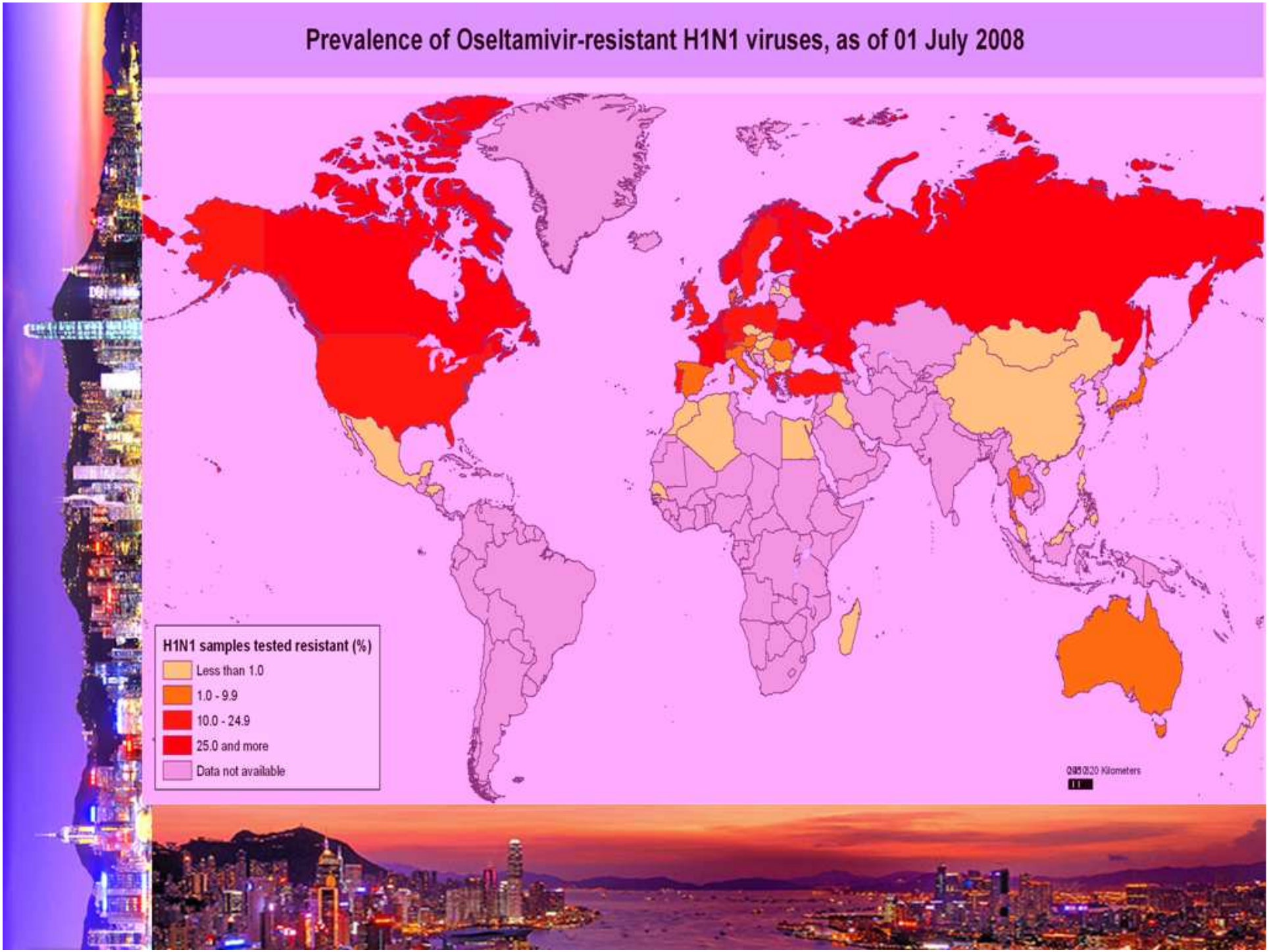




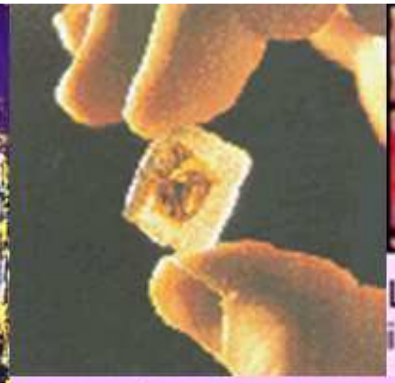
Swine Influenza H1N1 2009

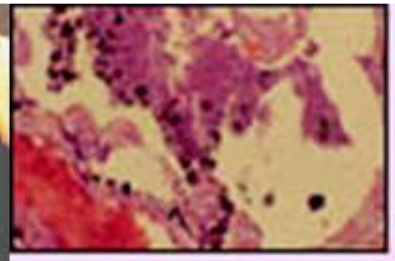
Worst Case Scenario

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




BIRD FLU OUTBREAKS AROUND THE WORLD
EUROPE (Detailed map below)
RUSSIA
KAZAKHSTAN
MONGOLIA
AFGHANISTAN
CHINA
JAPAN
ISRAEL
GAZA
JORDAN
IRAN
PAKISTAN
BURMA
SOUTH KOREA
BURKINA FASO
NIGER
EGYPT
IRAQ
KUWAIT
INDIA
LAOS
SAUDI ARABIA
BANGLADESH
THAILAND
CAMBODIA
VIETNAM
SUDAN
NIGERIA
DJIBOUTI
MALAYSIA
CAMEROON
TOGO
GHANA
IVORY COAST
Indian Ocean
INDONESIA
Countries with outbreaks
Countries with outbreaks including human cases
SOURCE: FAO/WHO

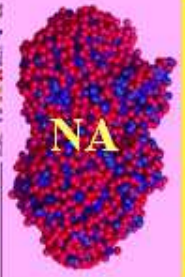




Lung tissue from 1918 influenza victim.

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.

NS1 Protein



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

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

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

6/18 = 33% mortality

F103 and M106 Increase mortality to 70%

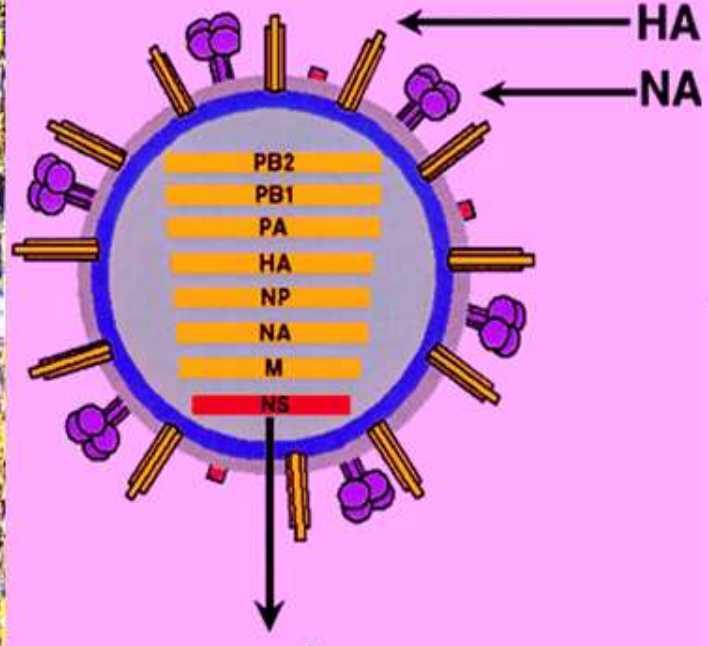
BIRD-FLU SCARE SWEEPS HONG KONG!

MILLION CHICKEN MASSACRE

流行性感冒病毒

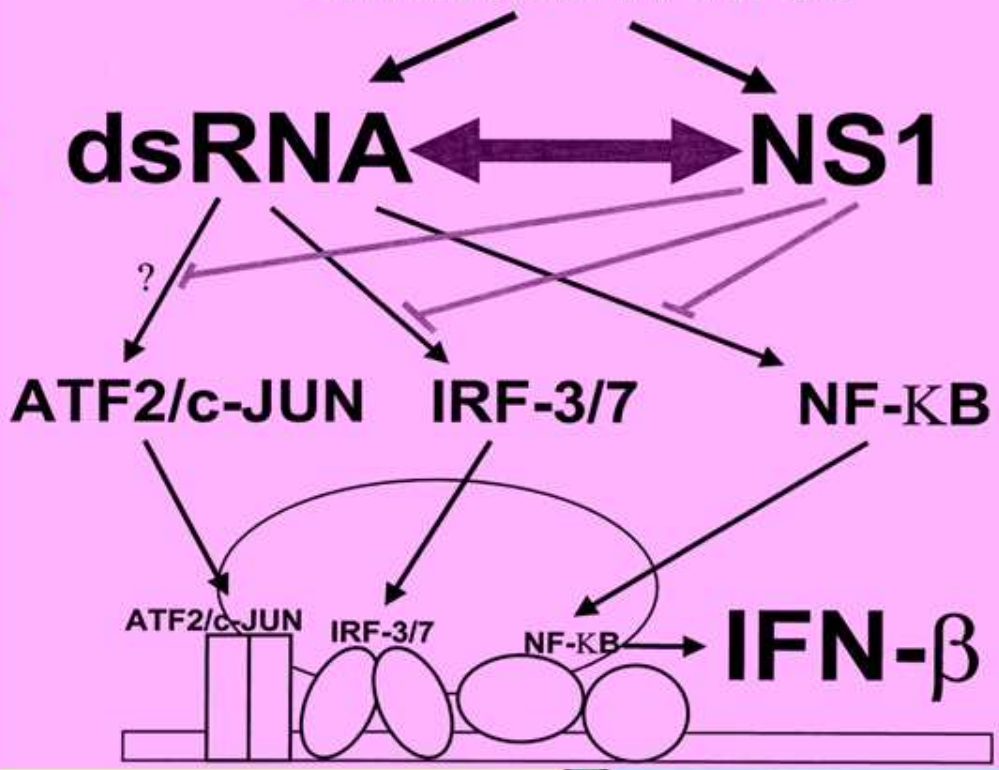
March 1997

INFLUENZA VIRUS

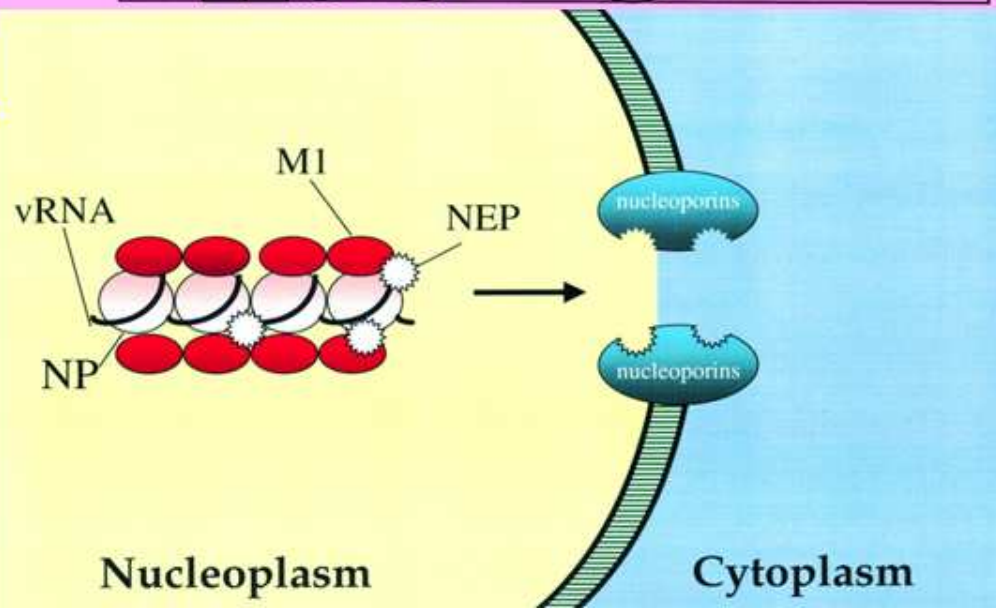


encodes
NS1 and NEP

Influenza A virus



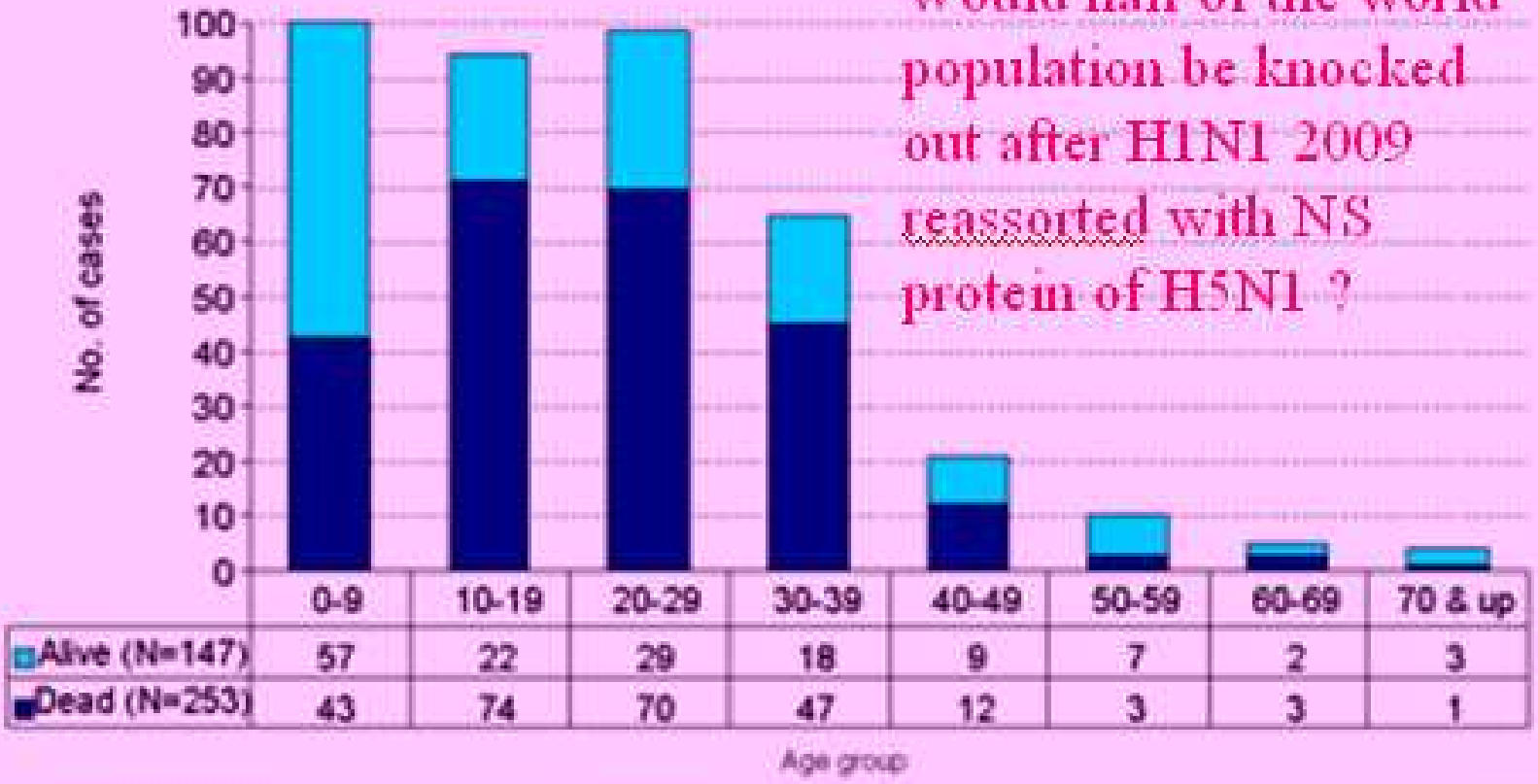
- The NS1 is an antagonist of the cellular type I interferon system, and the nuclear export protein (NEP) functions in viral assembly.



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)

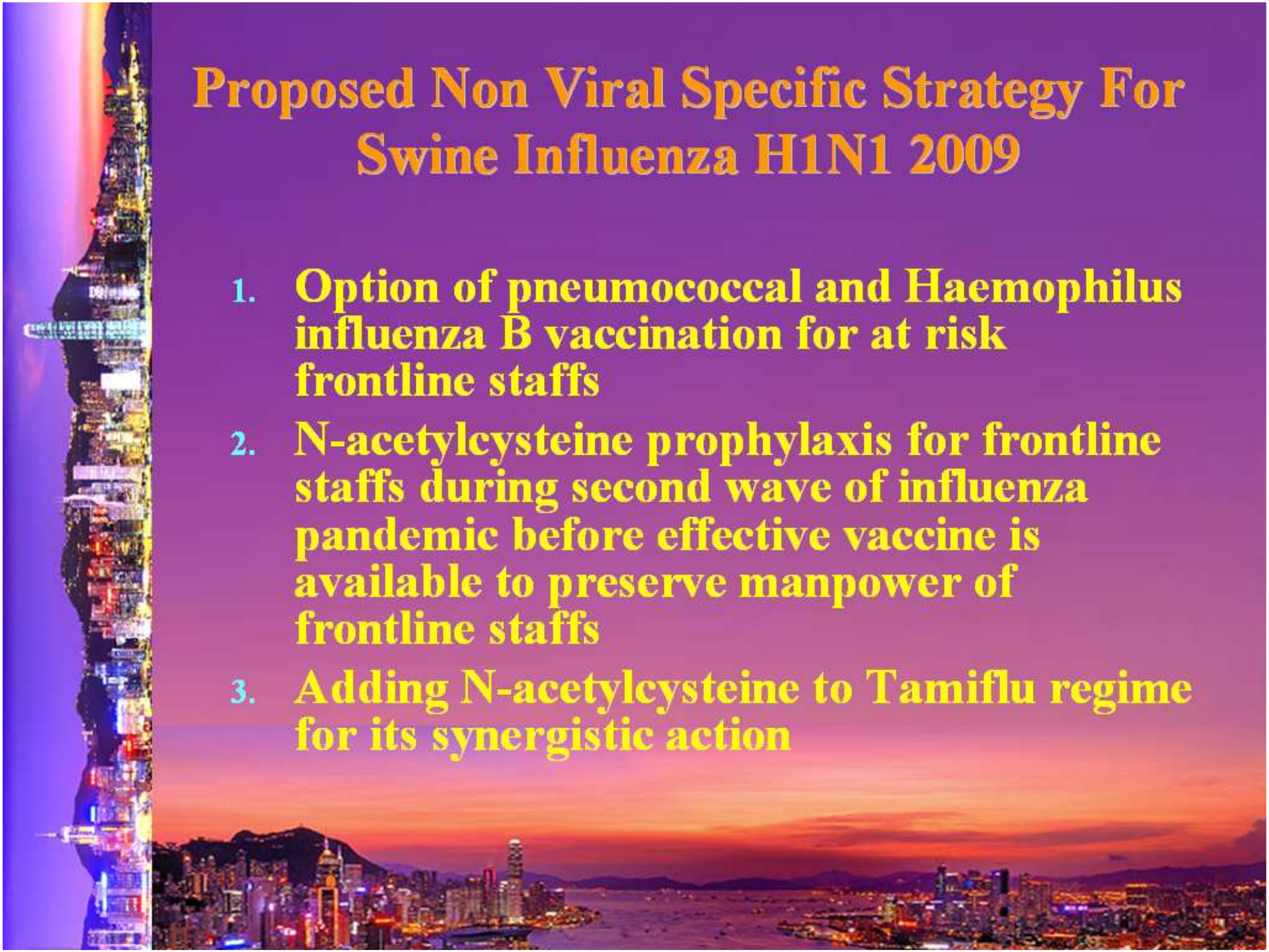


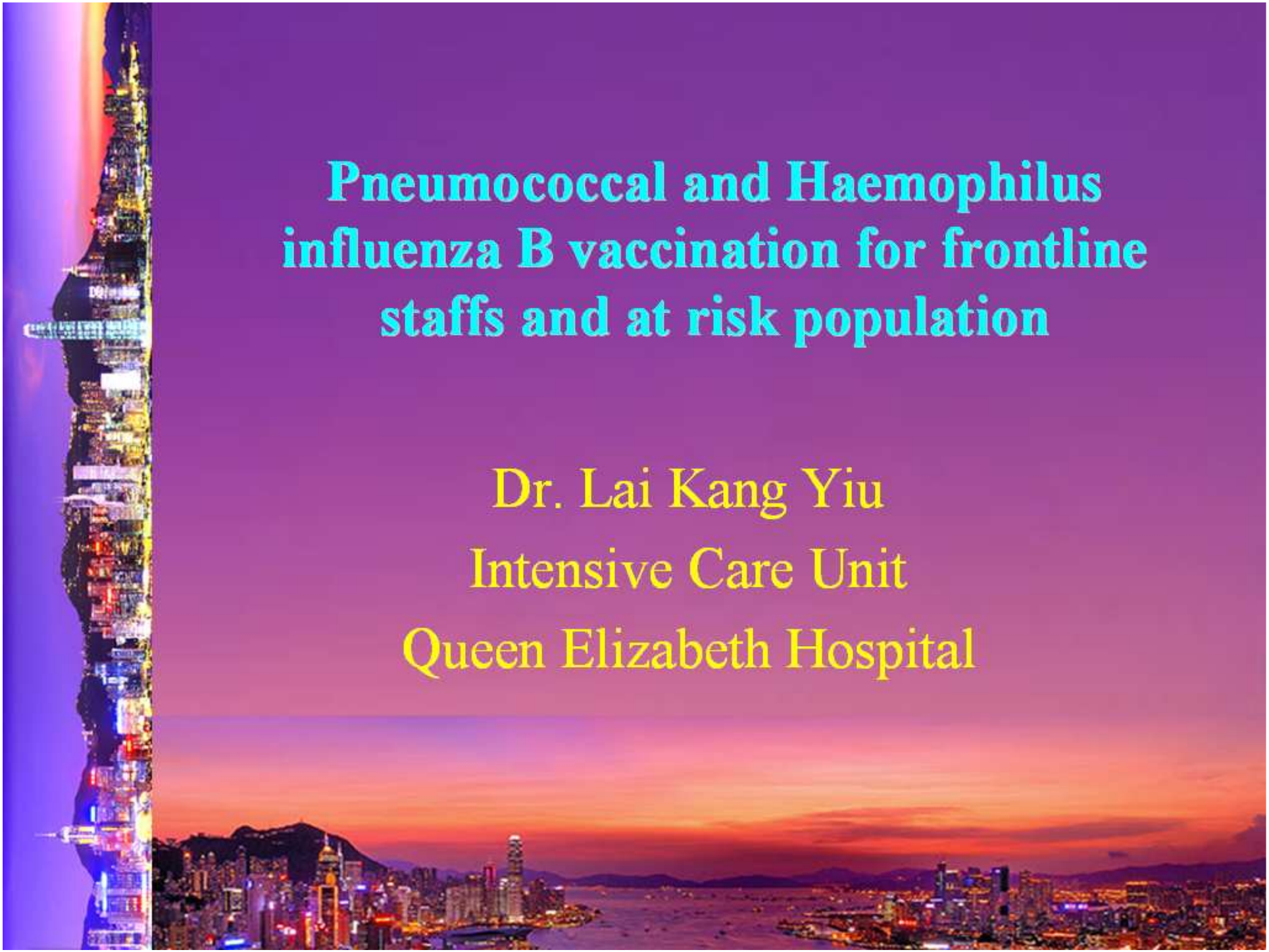
	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70 & up
Alive (N=147)	57	22	29	18	9	7	2	3
Dead (N=253)	43	74	70	47	12	3	3	1

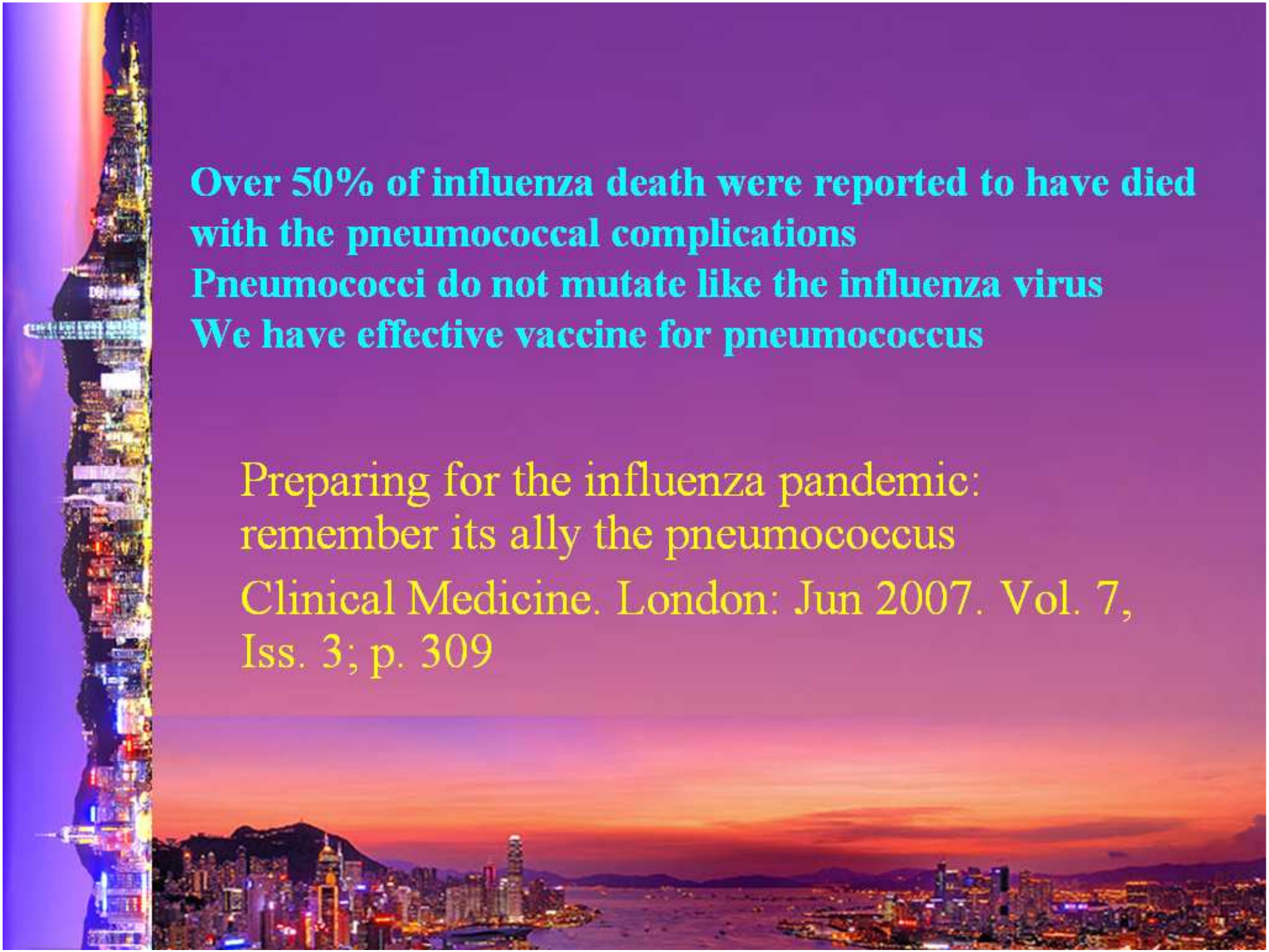
Would half of the world population be knocked out after H1N1 2009 reassorted with NS protein of H5N1 ?

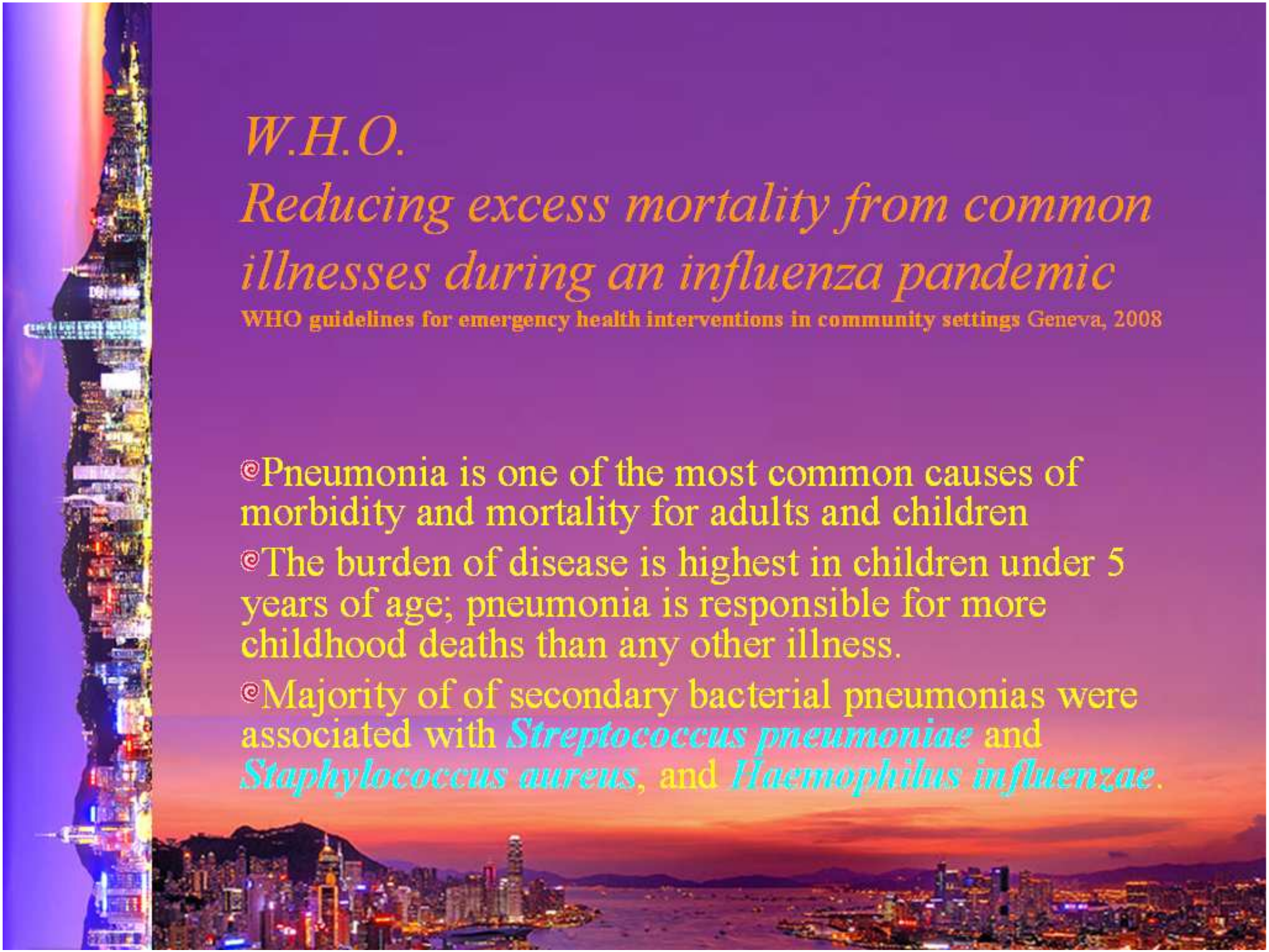
Worst Scenario Estimation after Swine H1N1 2009 spread to SEA and China and mix with H5N1.

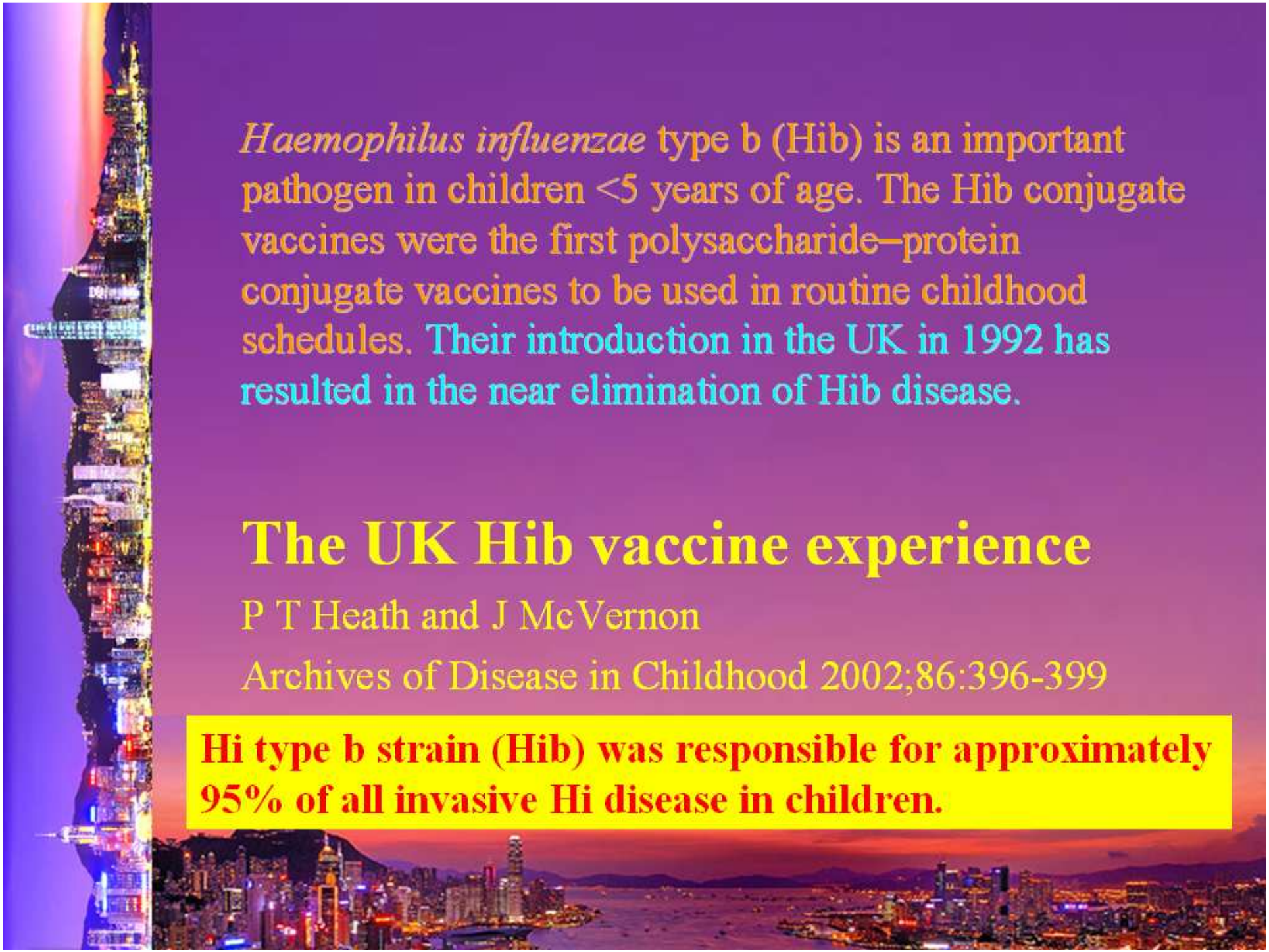

What should be our strategy before effective vaccine is available and Swine H1N1 has mutated to a malignant strain with high mortality rate and show some degree of resistant to oseltamivir ?
Non Viral Specific Strategy For Swine Influenza H1N1 2009
Dr. Lai Kang Yiu
Intensive Care Unit
Queem Elizabeth Hospital


Proposed Non Viral Specific Strategy For Swine Influenza H1N1 2009
1. Option of pneumococcal and Haemophilus influenza B vaccination for at risk frontline staffs
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


Pneumococcal and Haemophilus influenza B vaccination for frontline staffs and at risk population
Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital


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.


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.

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

The UK Hib vaccine experience

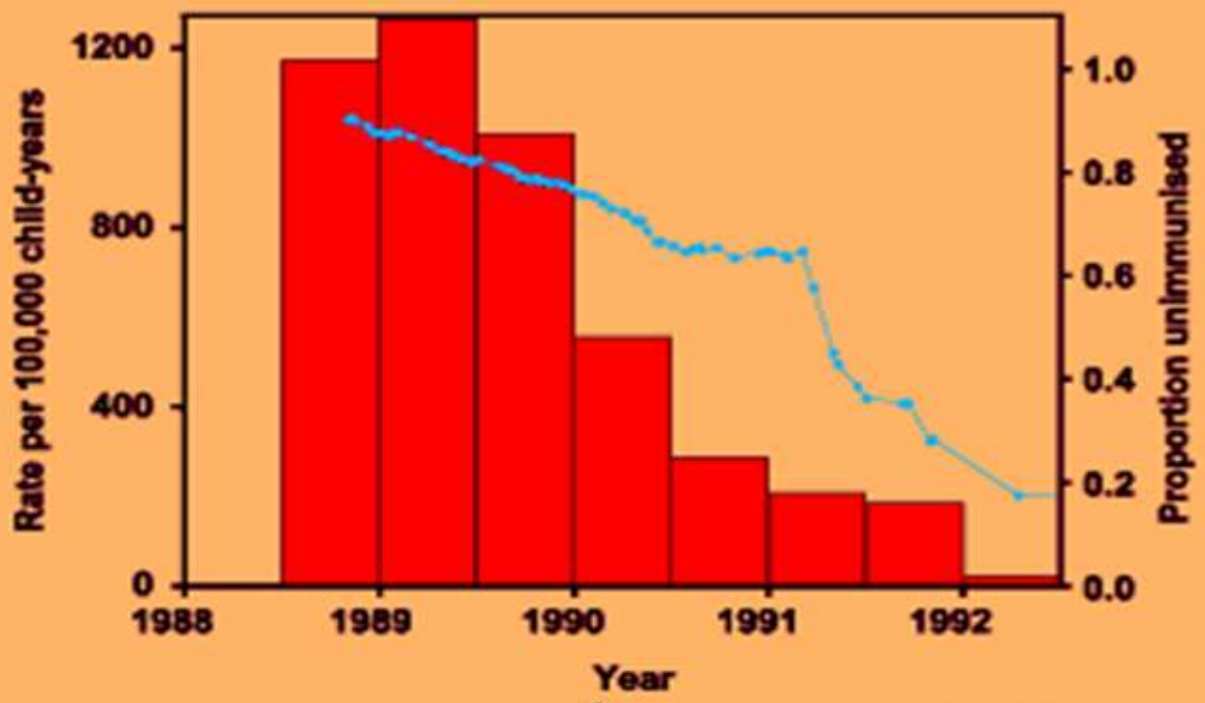
P T Heath and J McVernon Archives of Disease in Childhood 2002;86:396-399

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.

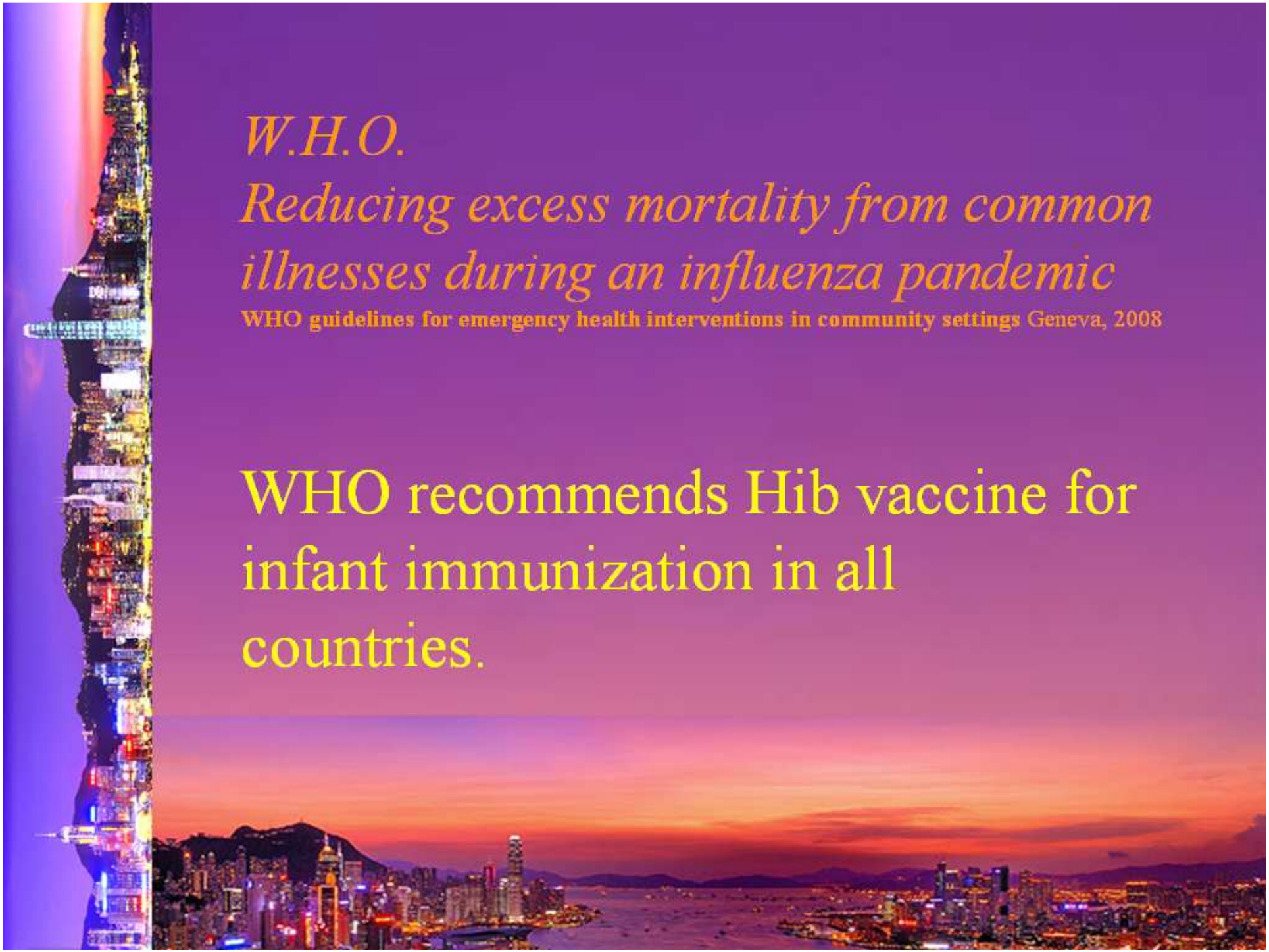
Age	Vaccine
Two months	DTaP/IPV/Hib + pneumococcal (PCV)
Three months	DTaP/IPV/Hib + MenC
Four months	DTaP/IPV/Hib + MenC and PCV
12 months	Hib/MenC
13 months	MMR + PCV

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.

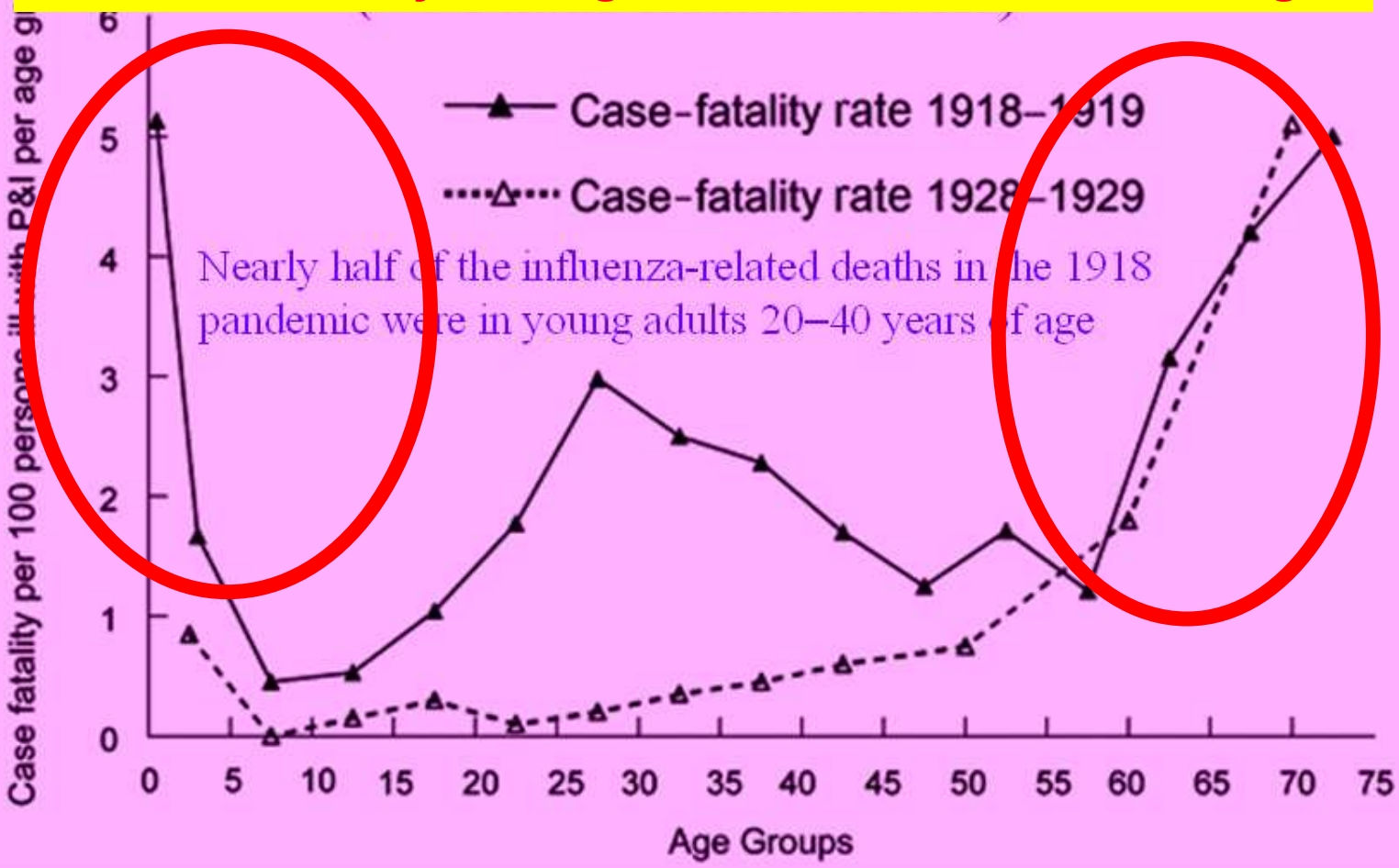
Estimated number of persons affected by pandemic influenza per 1000 population for resource-poor settings (W.H.O.)

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)	30–50% (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 infuenza co infection to reduce this potential volume load?

Case Fatality is highest at extremes of age



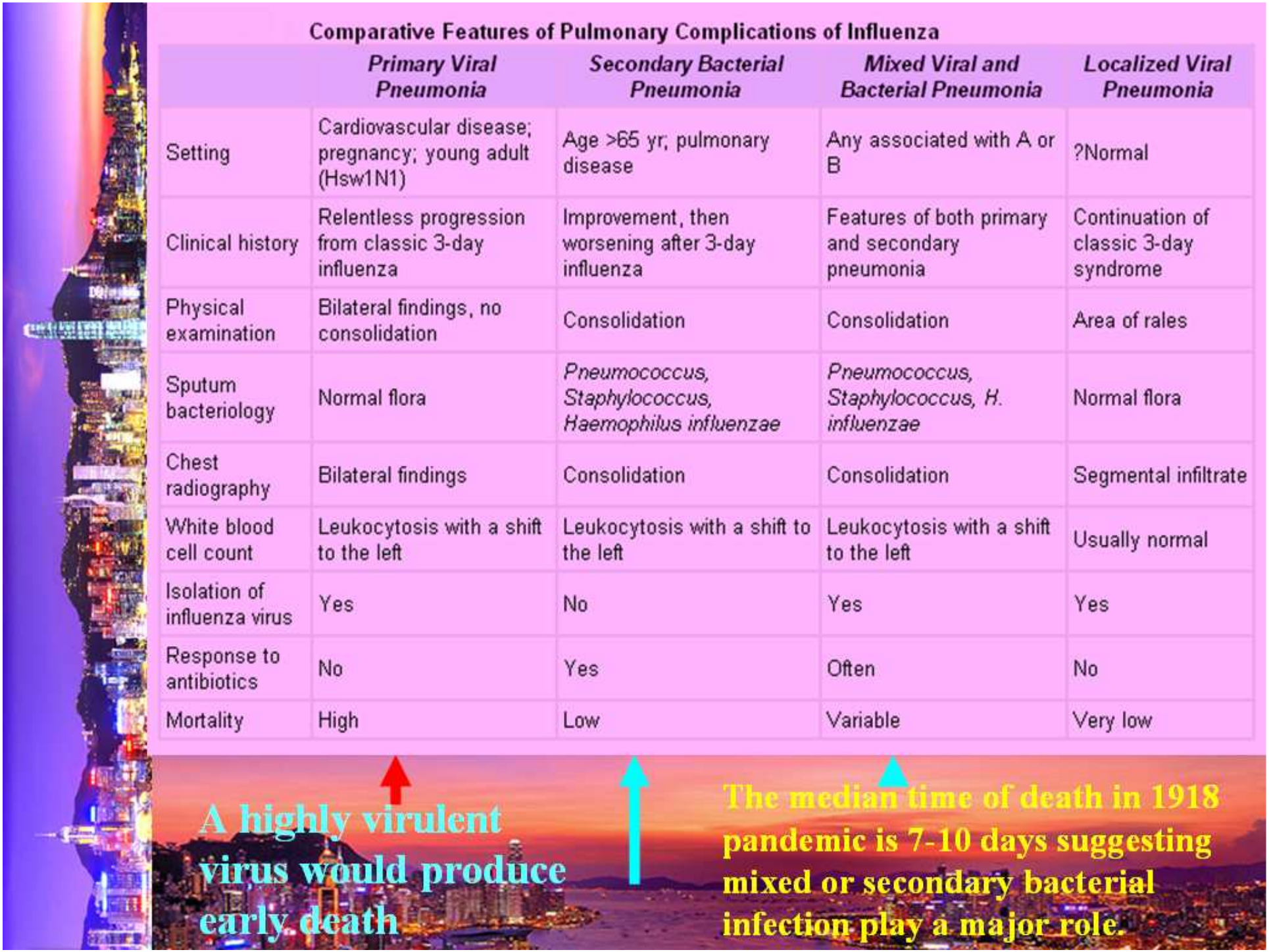
How can we reduce this mortality ?

Bacterial co-infection ➔

(a) NA facilitate bacterial adhesion and invasion.

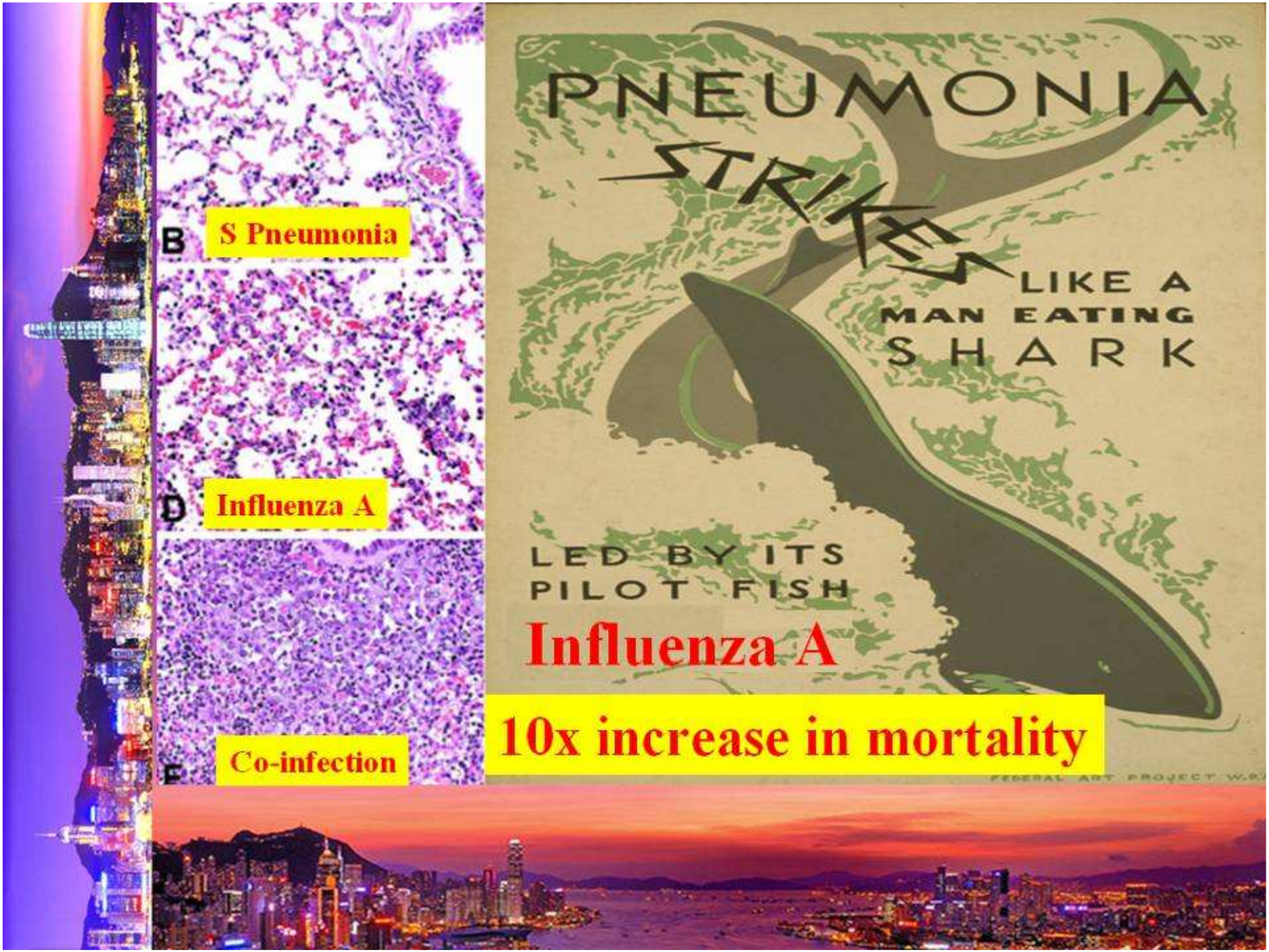
(b) Cleavage activation of HA by bacteria amplify virus replication

Cytokine storm ➔ NS protein suppress IFN production



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	*Pneumococcus, Staphylococcus, Haemophilus influenzae*	*Pneumococcus, Staphylococcus, H. influenzae*	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


B
S Pneumonia
D
Influenza A
F
Co-infection
PNEUMONIA
STRIKES
LIKE A
MAN EATING
SHARK
LED BY ITS
PILOT FISH
Influenza A
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

Influenza virus

Neuraminidase facilitate bacterial adhesion and invasion

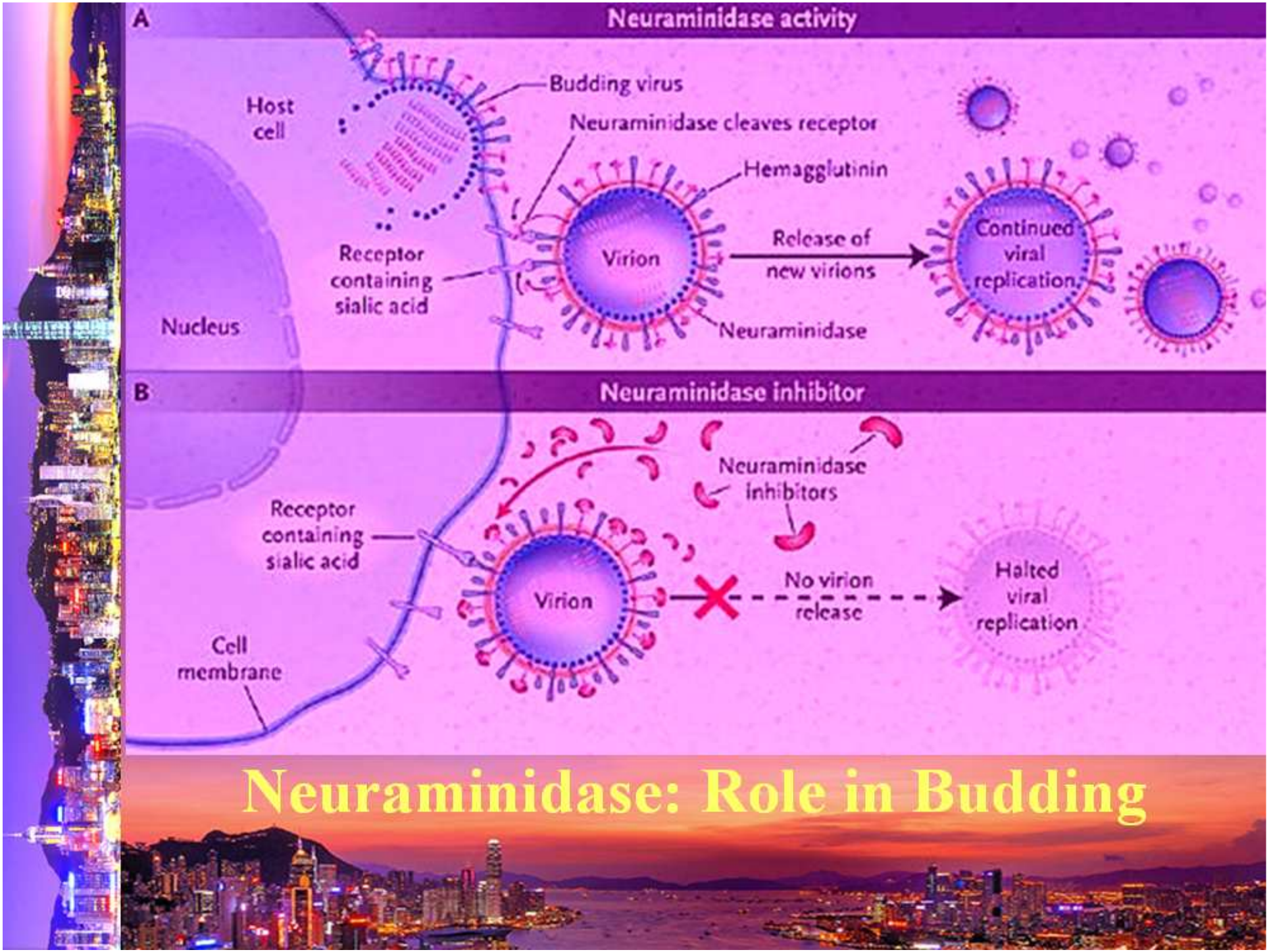
NS1 protein of H1N1 1918 & H5N1

Epithelial damage

Upregulation of PAFr
Fibrin and fibrinogen deposition facilitate adhesion

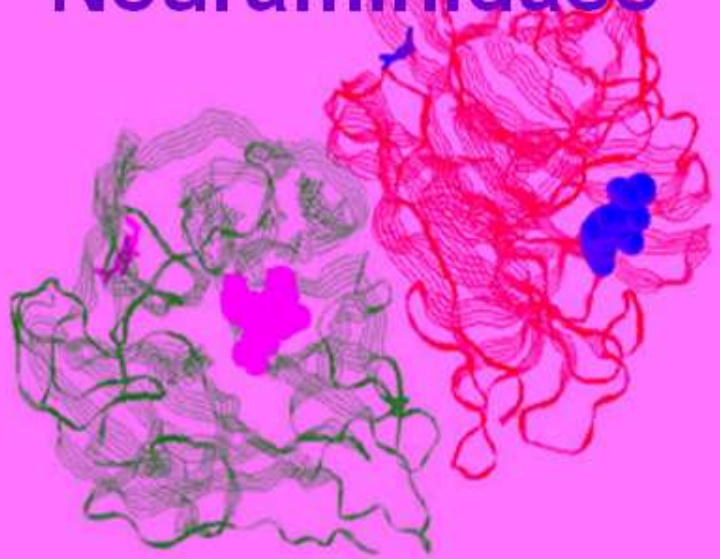
Cleavage activation of Haemagglutinin amplify viral proliferation

Pneumococcus

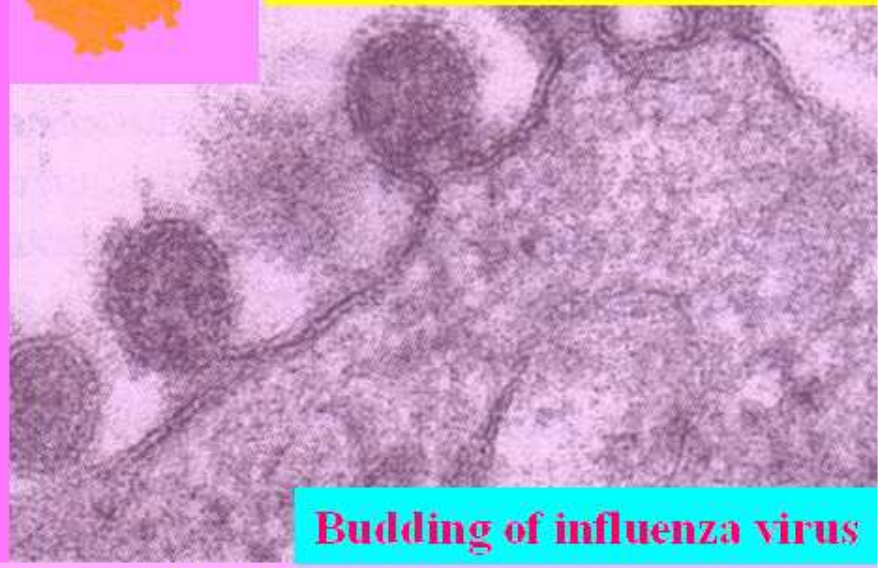


Neuraminidase: Role in Budding

Neuraminidase



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



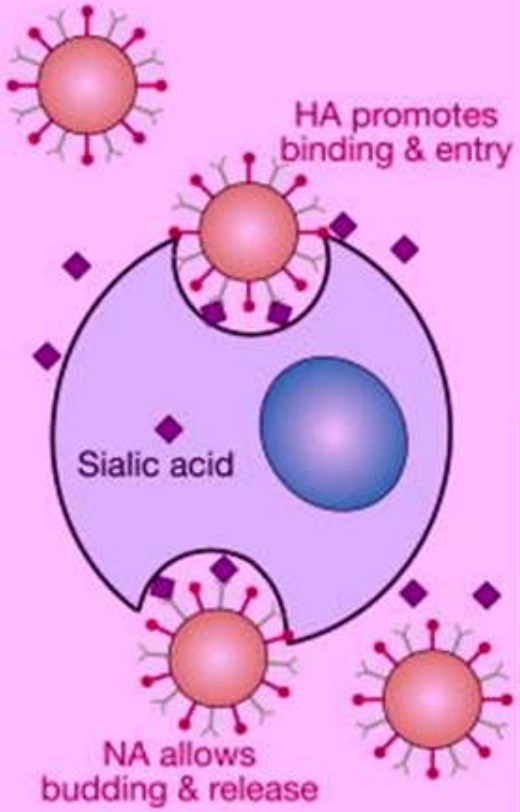
Budding of influenza virus

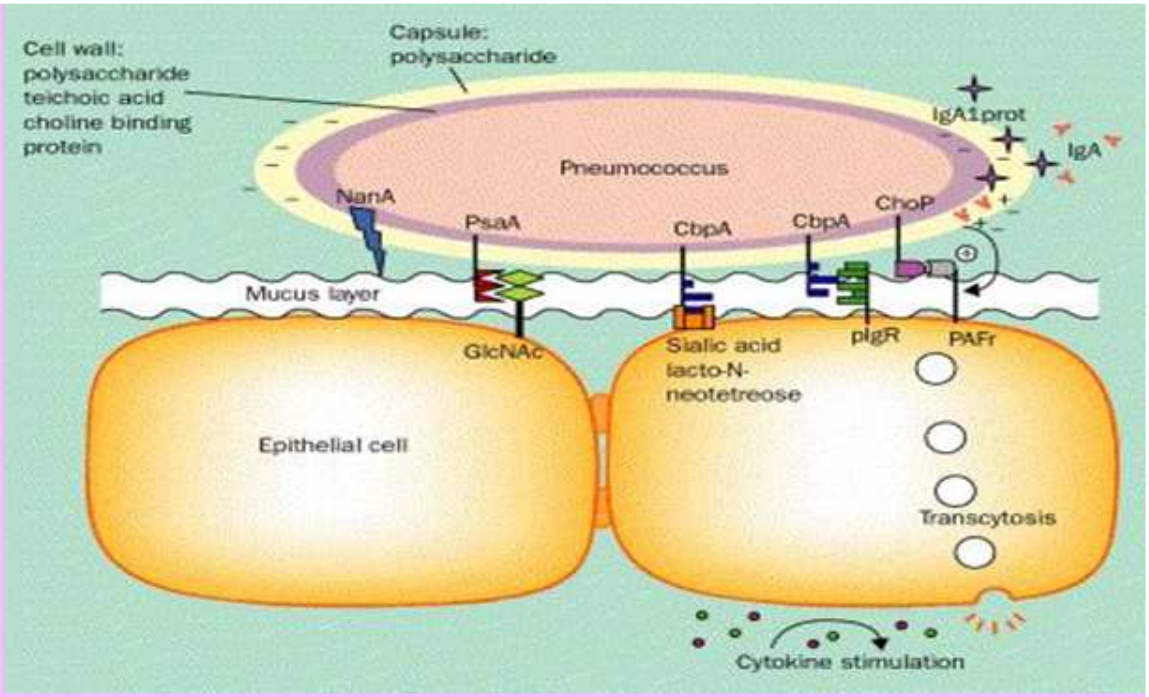
Ville The Journal of Infectious Diseases 2005;192:249–257

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



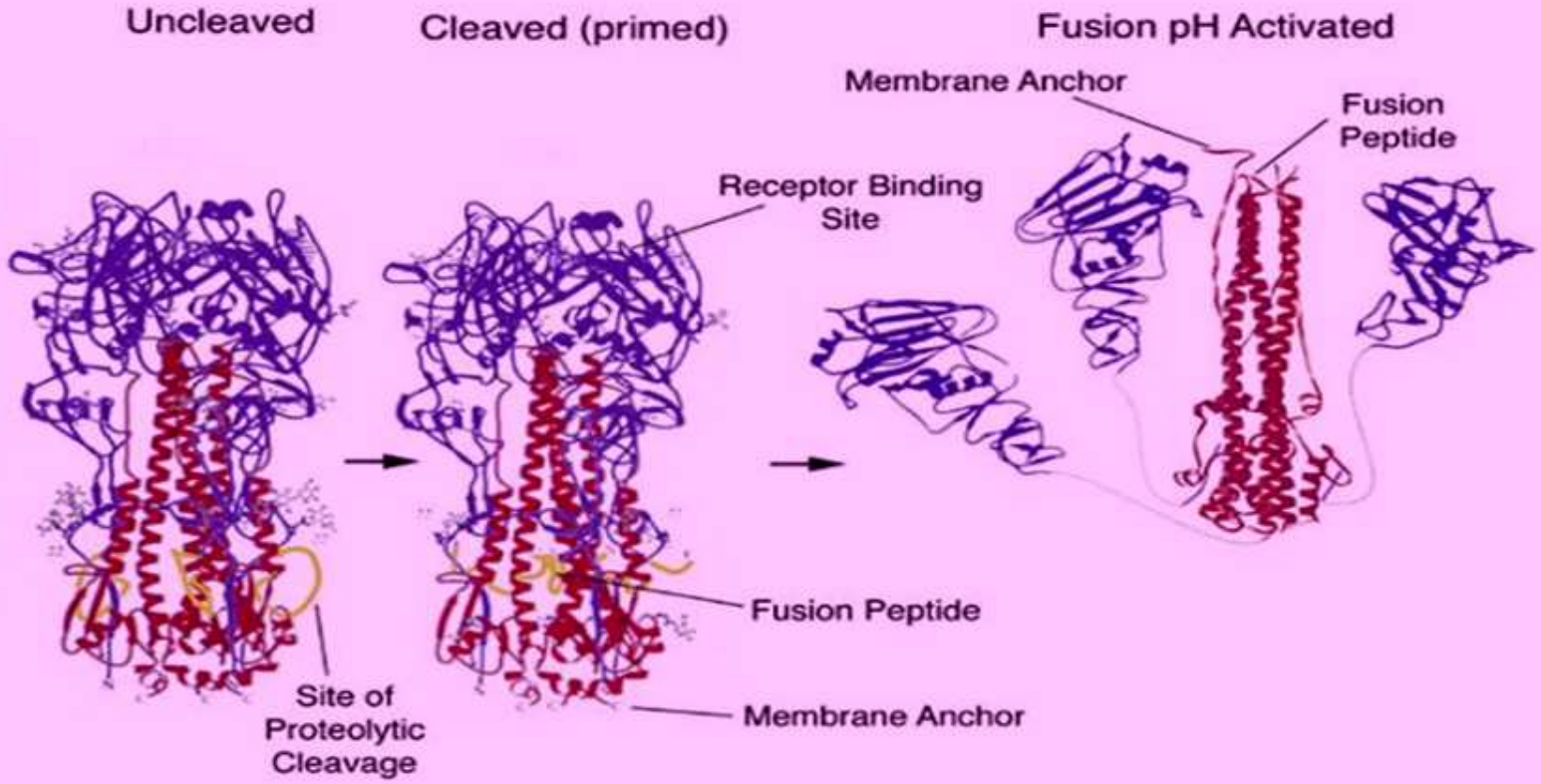


Interaction between *S pneumoniae* and epithelial cells. Neuraminidase (NanA) decreases the viscosity of the mucus and exposes the N-acetyl-glycosamine (GlcNAc) receptors on the epithelial cells, which can interact with pneumococcal surface-associated proteins such as PsaA. In response to cytokine stimulation, 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-neotreatose, 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.

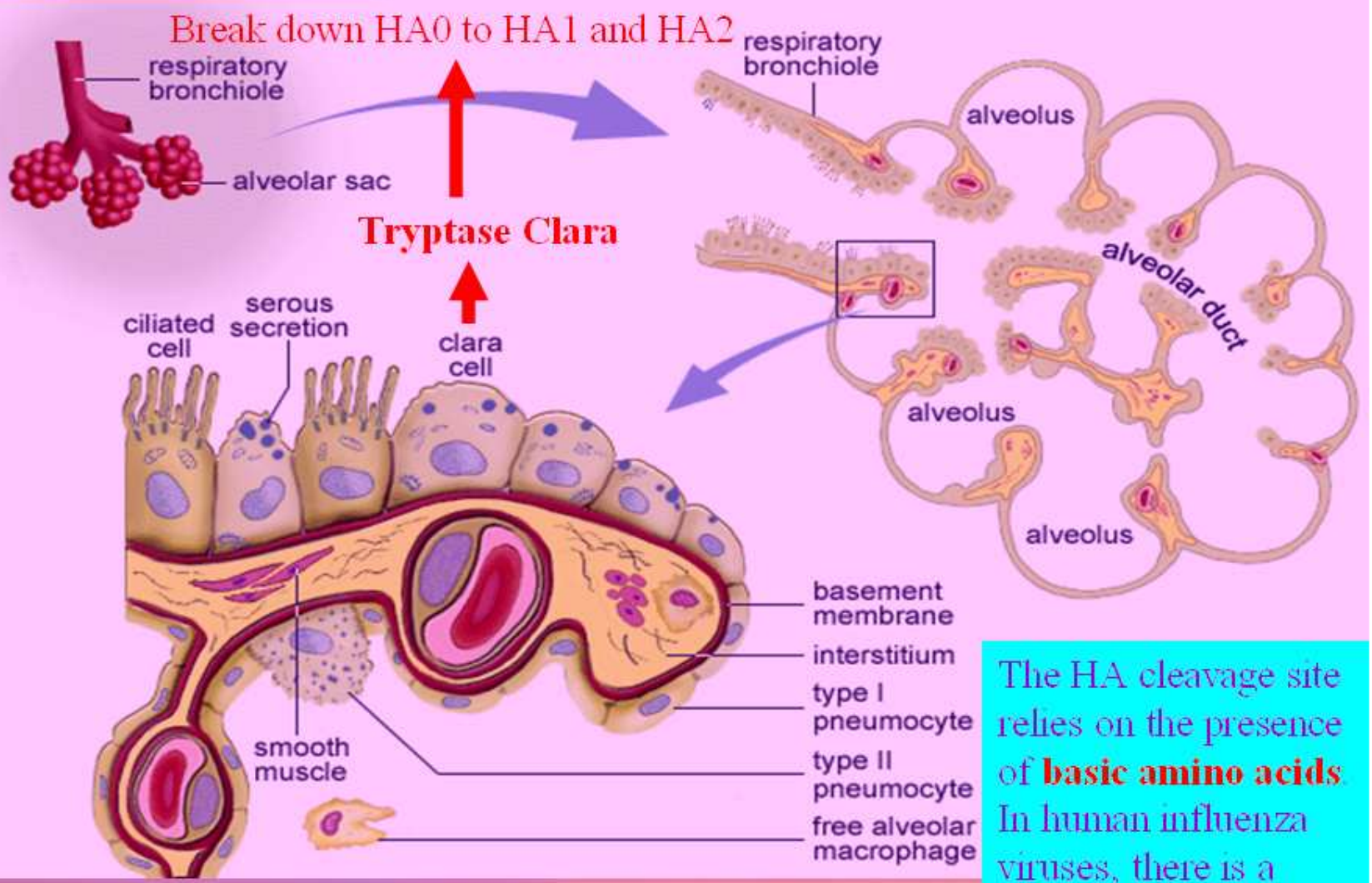
Oseltamivir treatment prevents secondary bacterial pneumonia **even if administered late** during the course of the influenza infection.

The Conformations of the Haemagglutinin



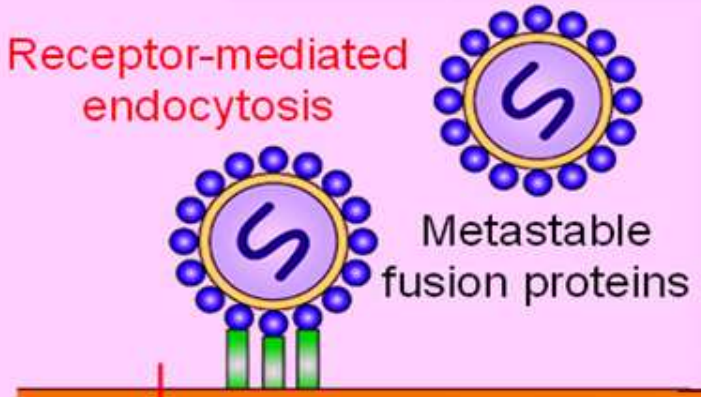
Influenza virus hemagglutinin HA0 required cleavage into HA1, HA2 during activation. Cleavage of HA0 is vital for the subsequent infection of new cells. Without proteolysis, the acid-triggered conformational change in HA to expose the fusion peptide cannot occur, and therefore the virus is essentially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

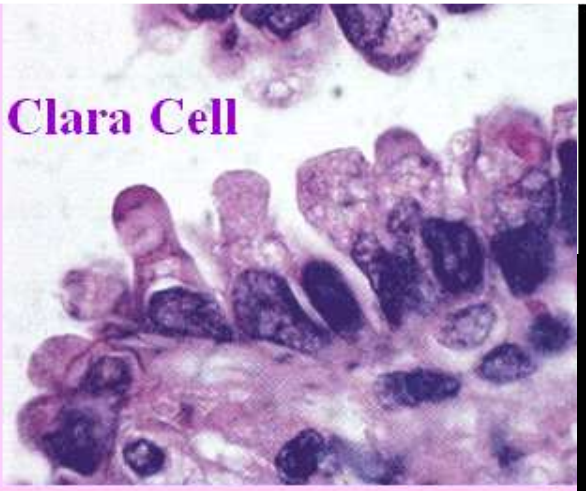
Respiratory Bronchiole

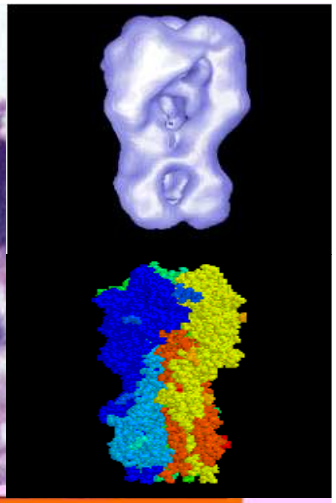


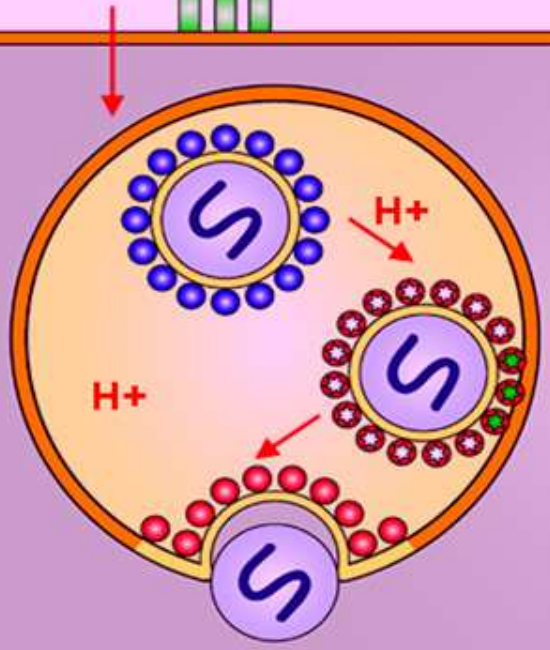
The cleavage site is specific and the protease has limited tissue distribution. Both of these features mean that influenza infections are generally limited to the upper respiratory tract.

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).





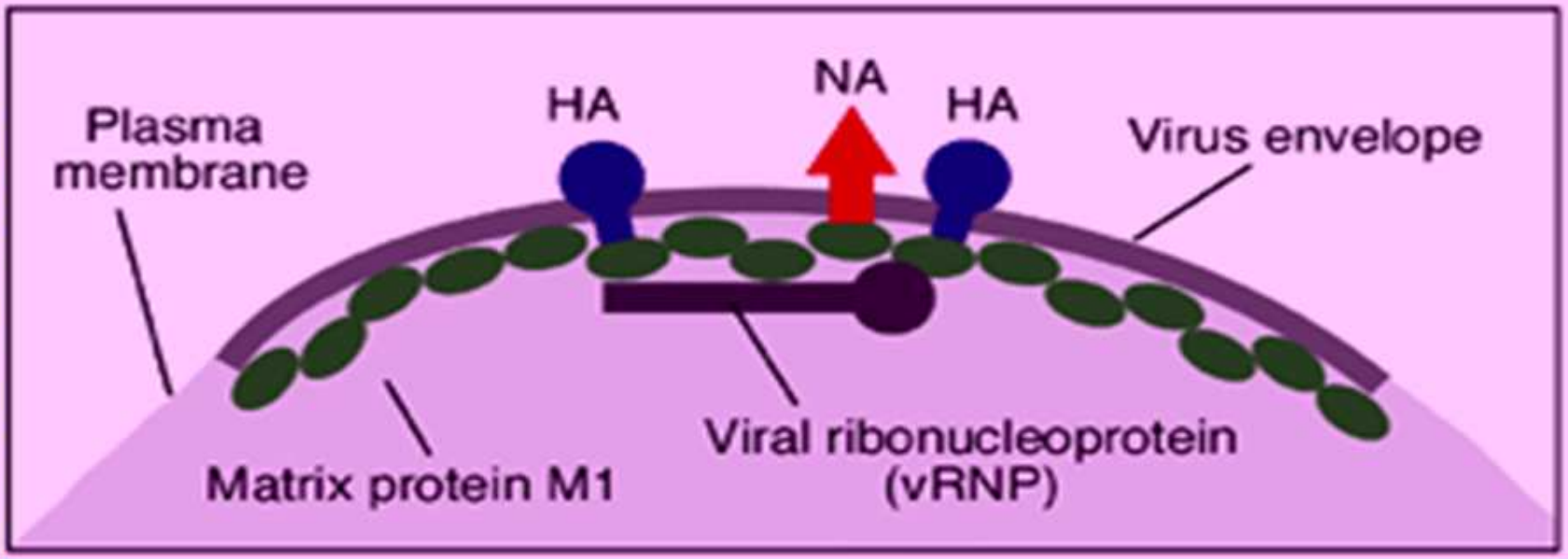




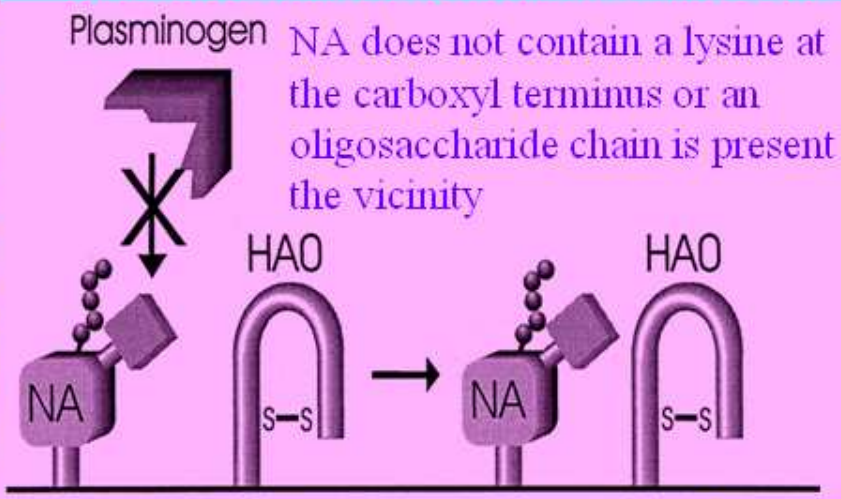
- Bacteria such as *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and various Gram-negative bacilli often produce *extracellular proteases* that can cleave monobasic cleavage sites on HA, **enhancing virus spread.**

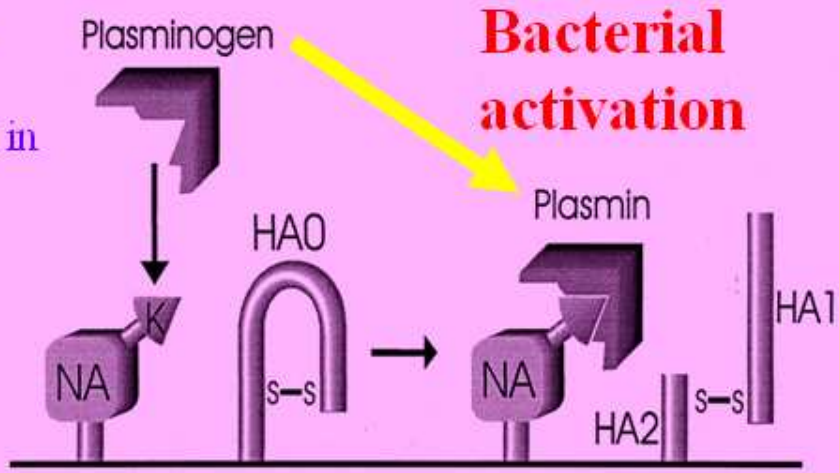
Role of Secondary Bacterial Infection in HA0 Cleavage

[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]



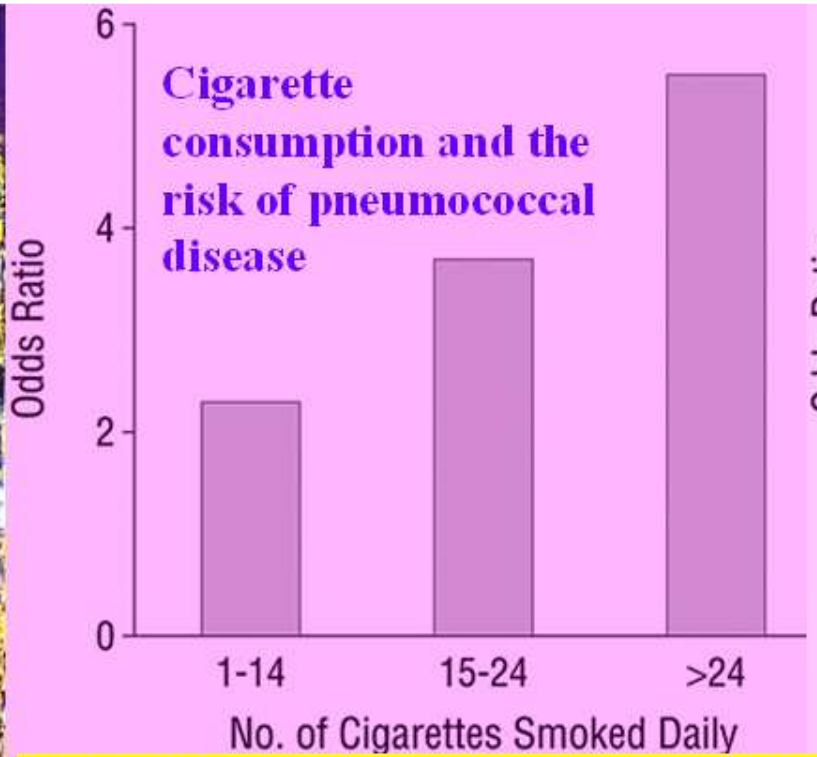
Lysine at the carboxyl terminus of NA can lead to ubiquitous HA cleavage by plasmin

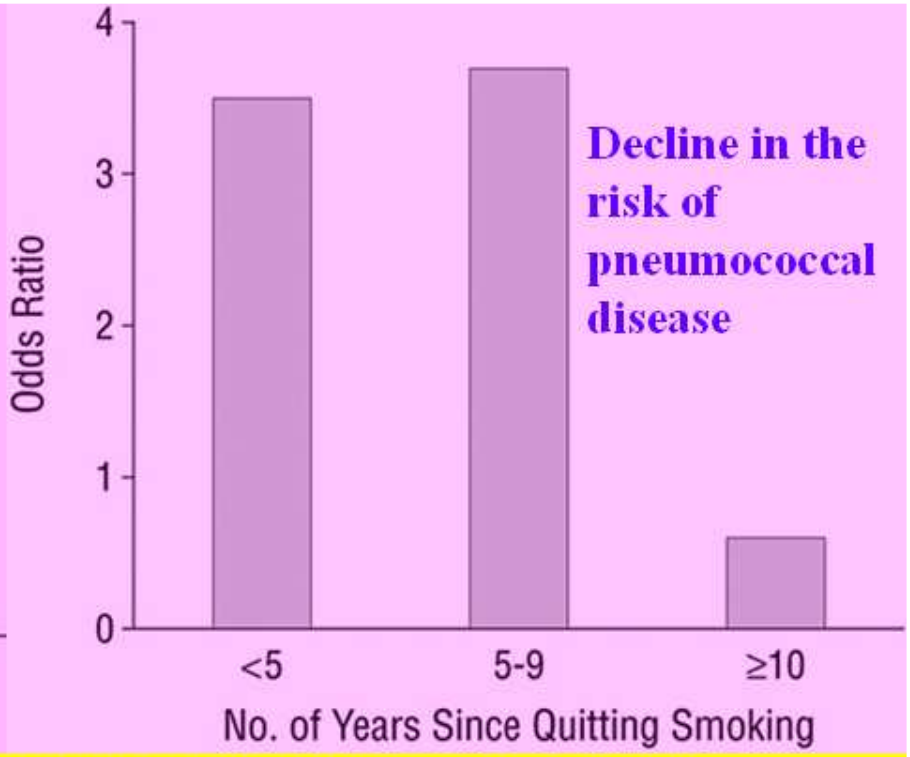




Lysine at the carboxyl terminus of NA

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

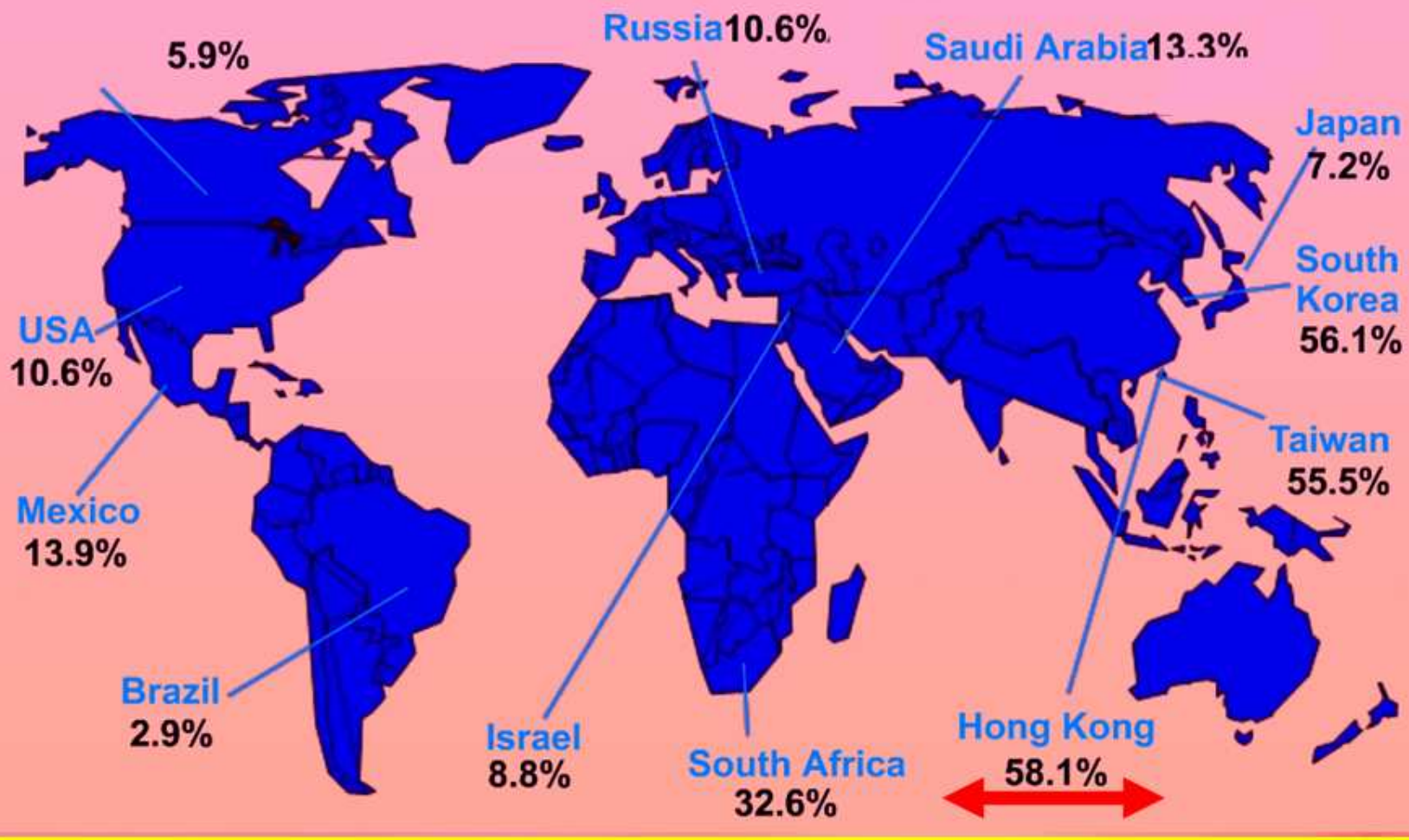




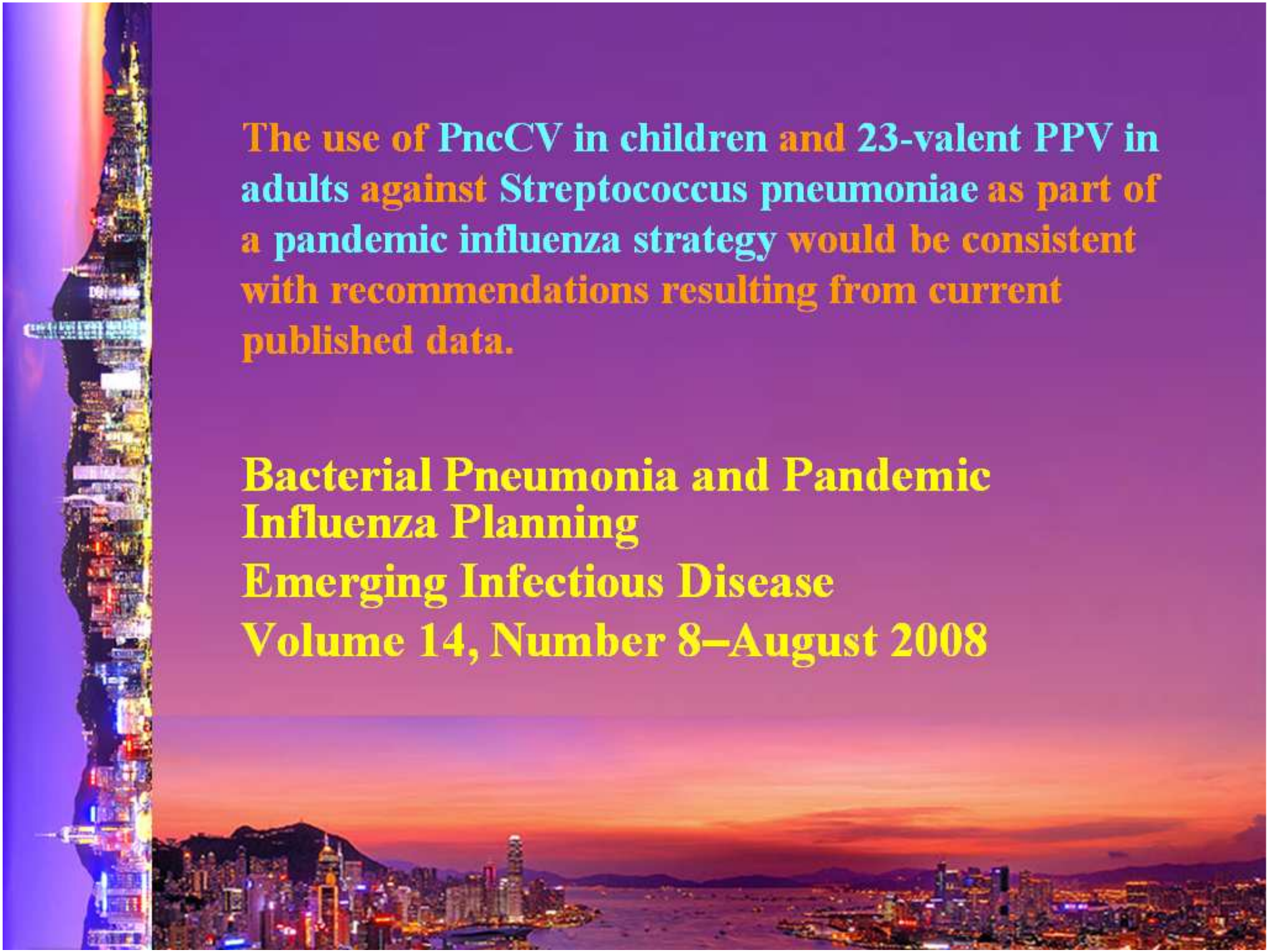
Nuorti JP, Butler JC, Farley MM, et al, Active Bacterial Core Surveillance Team. Cigarette smoking and invasive pneumococcal disease. N Engl J Med 2000;342:681–689.

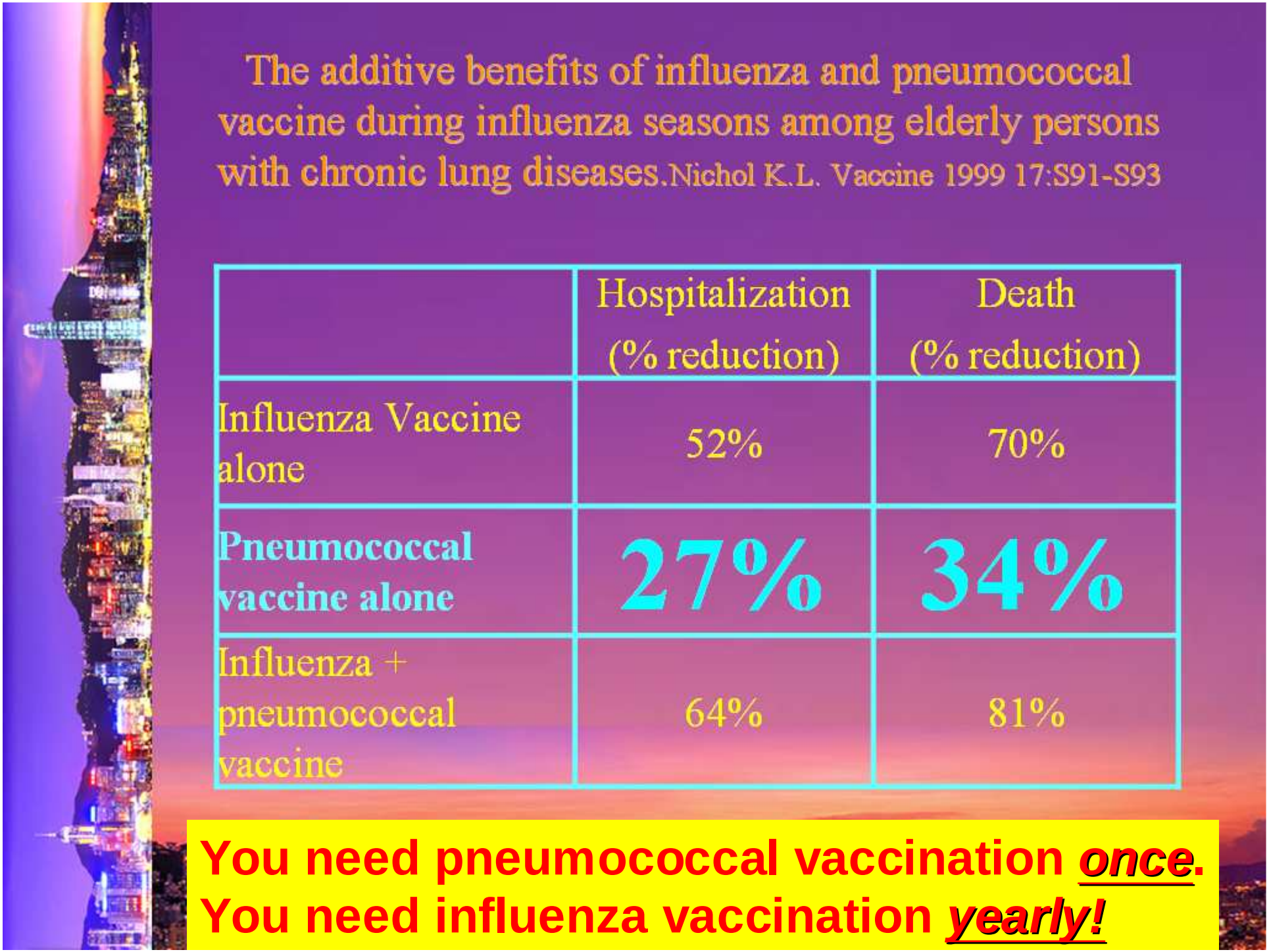
Cigarette smoking cause activation of platelet-activating factor facilitating attachment and invasion of cells by pneumococcal strains. This may contribute to the increased incidence of bacterial superinfection in people who develop influenza.

Multi-drug resistant *S. pneumoniae*

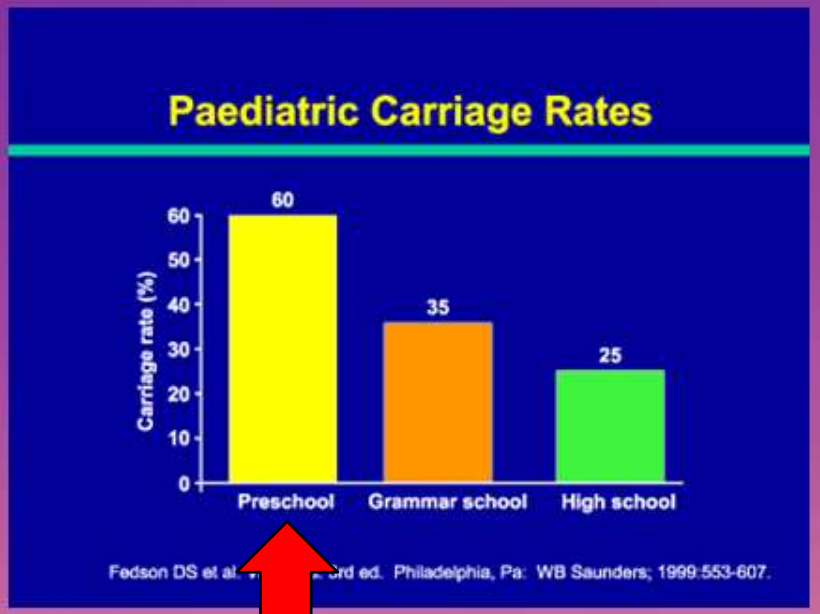


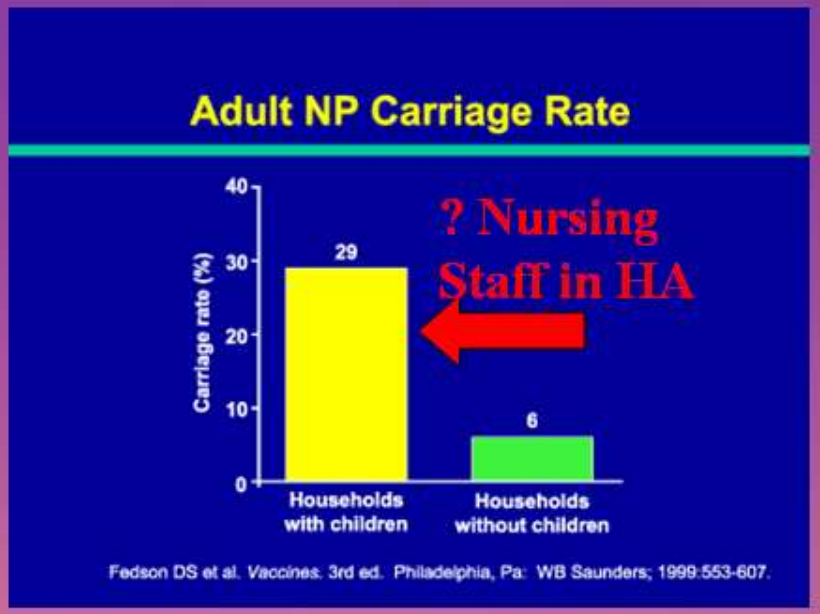
Problem facing HKSAR over stockpilling antibiotic for bacterial co-infection in preparation for pandemic influenza


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

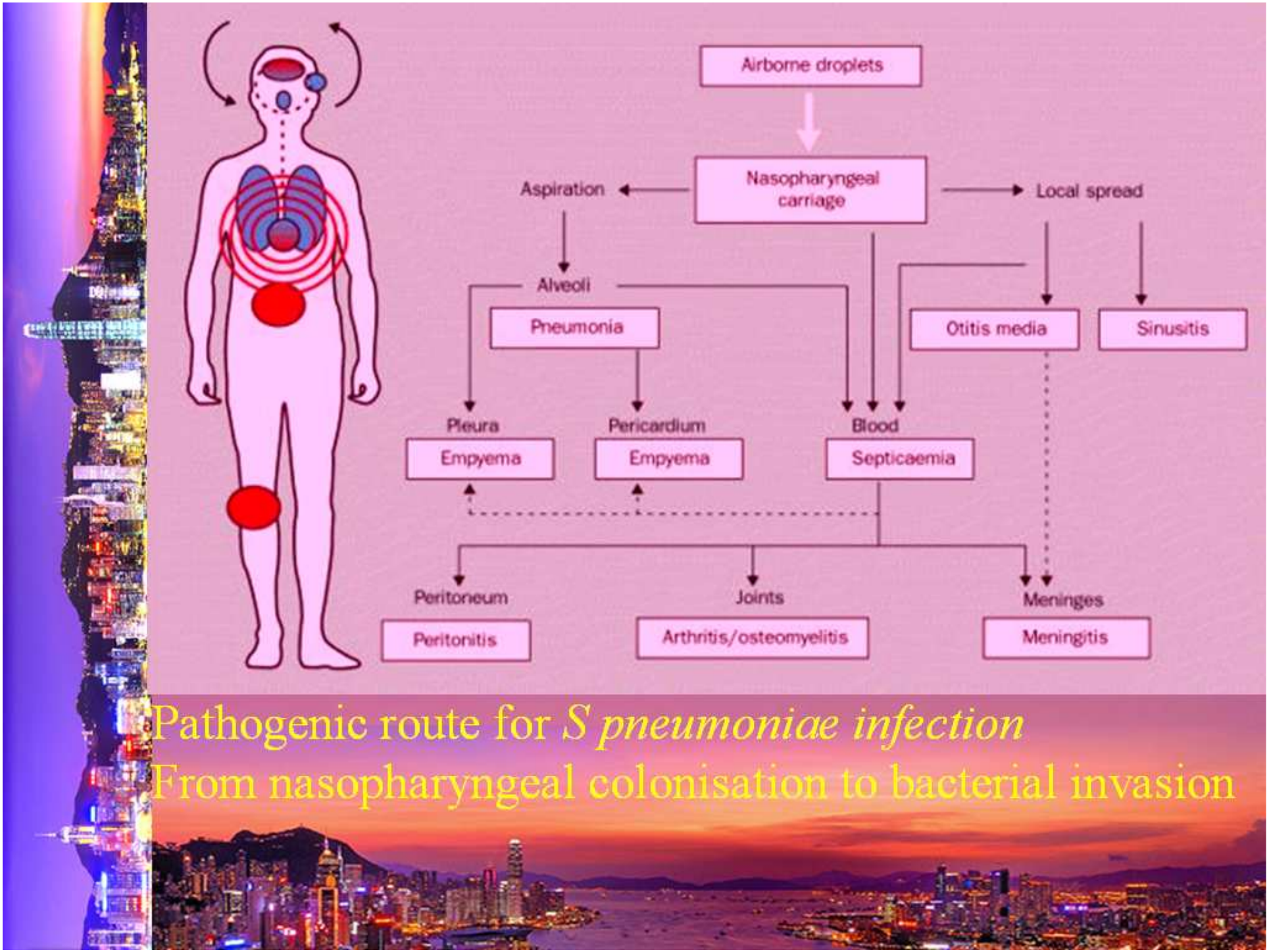

The additive benefits of influenza and pneumococcal vaccine during influenza seasons among elderly persons with chronic lung diseases. Nichol K.L. Vaccine 1999 17:S91-S93
Hospitalization (% reduction)
Death (% reduction)
Influenza Vaccine alone
52%
70%
Pneumococcal vaccine alone
27%
34%
Influenza + pneumococcal vaccine
64%
81%
You need pneumococcal vaccination once.
You need influenza vaccination yearly!

Nasopharyngeal carriage of pneumococcus

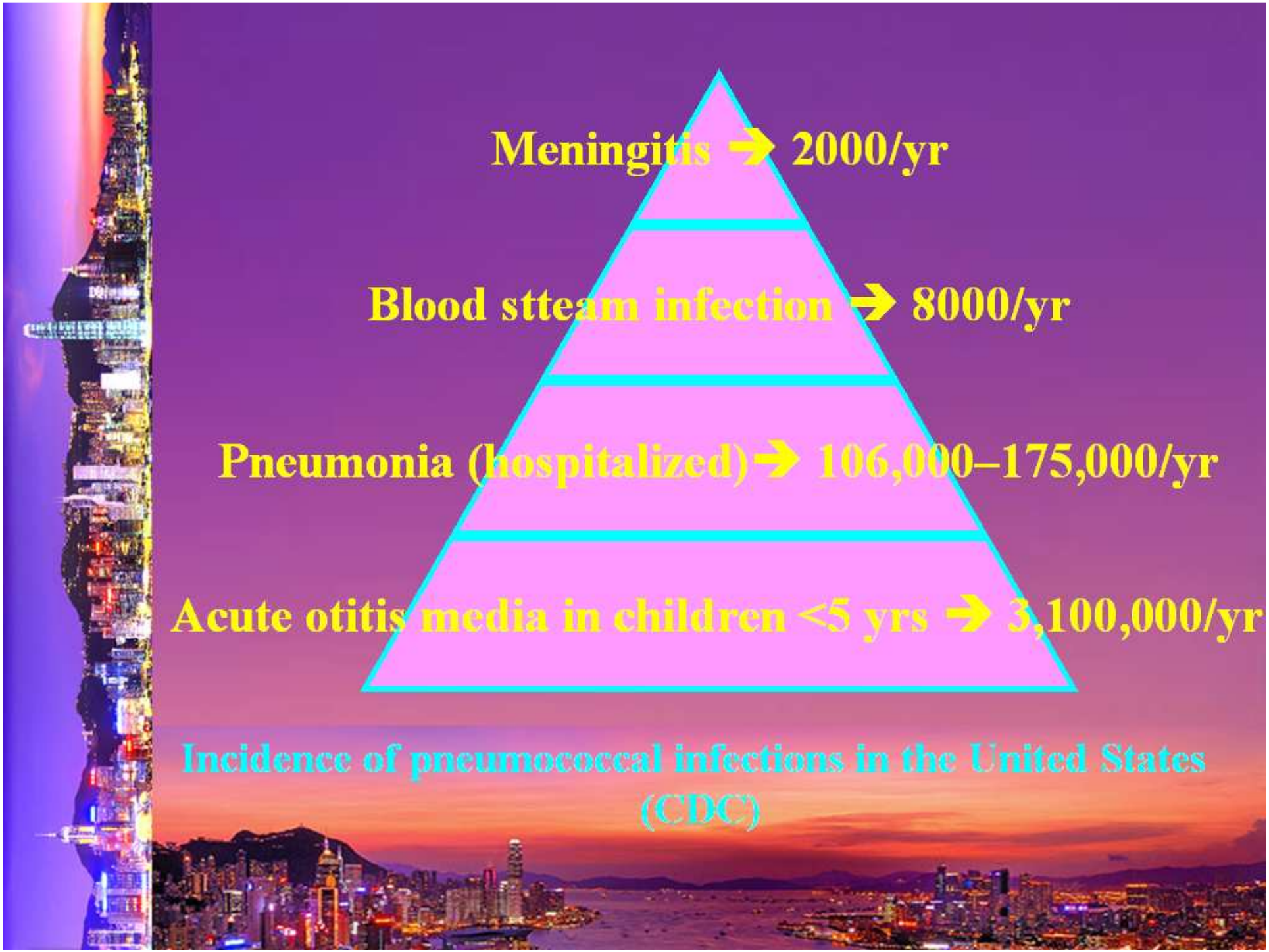




Patients with high risk of co-infection during pandemic influenza

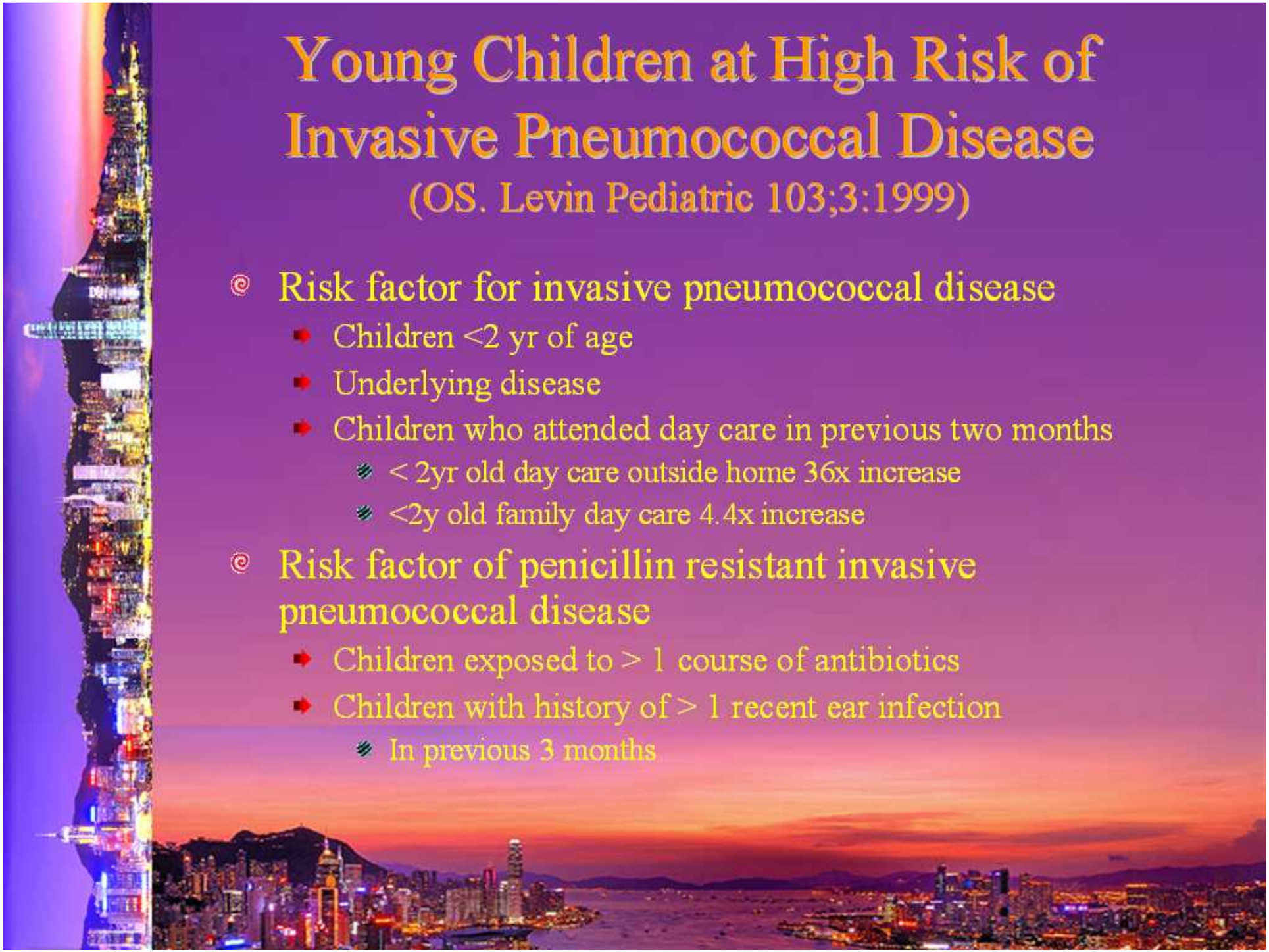


Pathogenic route for *S pneumoniae infection*
From nasopharyngeal colonisation to bacterial invasion


Meningitis → 2000/yr
Blood stteam 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)

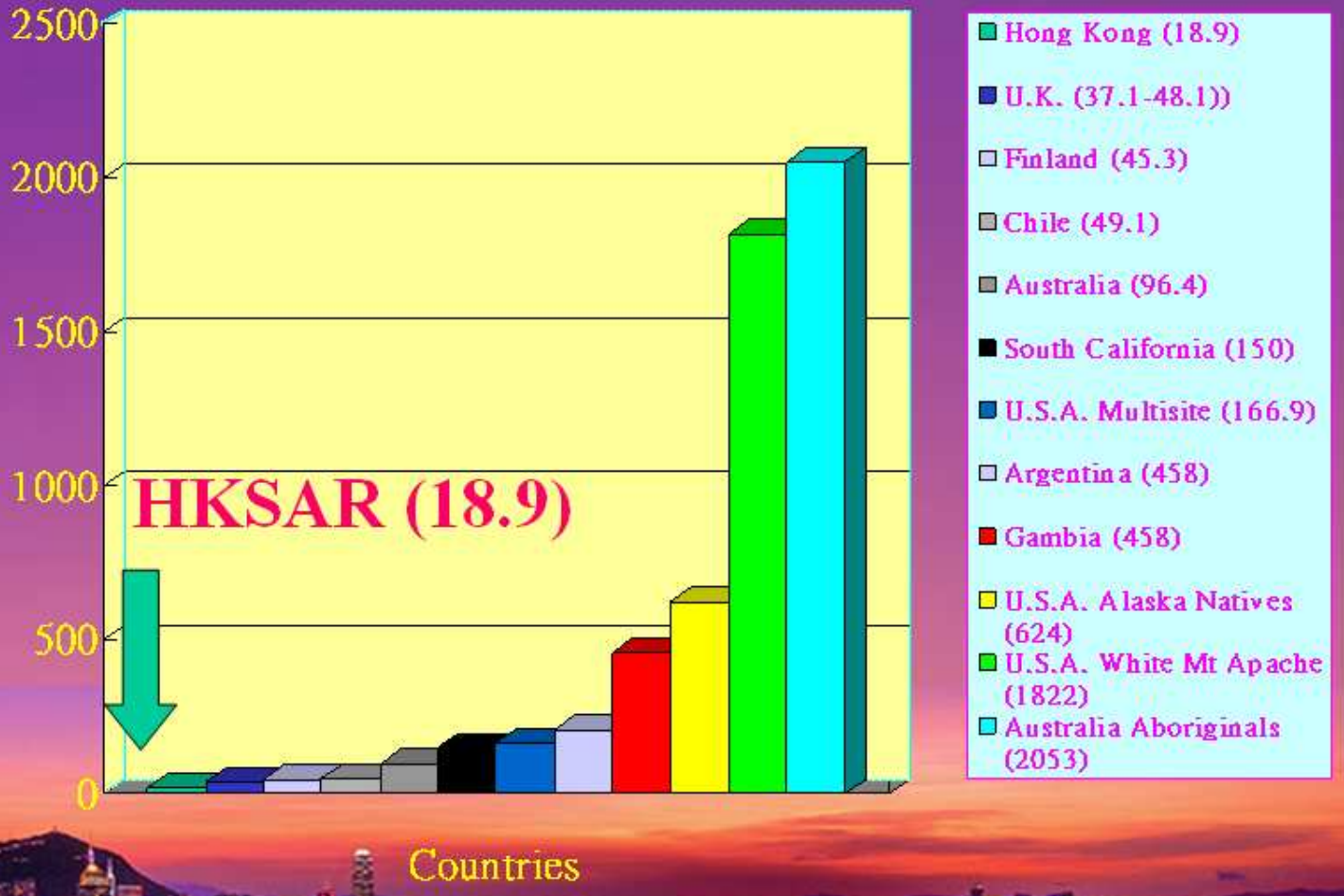
Risk for IPD

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

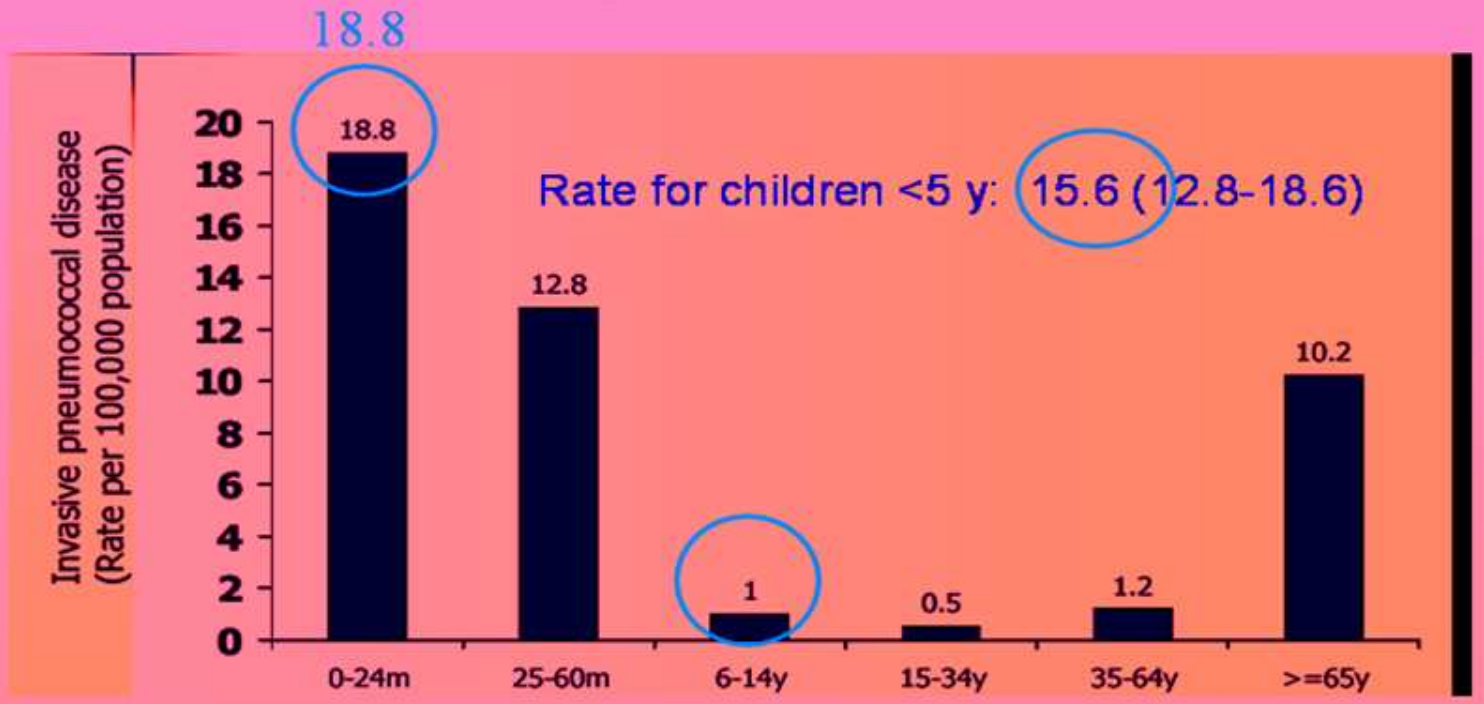

Young Children at High Risk of Invasive Pneumococcal Disease
(OS. Levin Pediatric 103;3:1999)
Risk factor for invasive pneumococcal disease
Children <2 yr of age
Underlying disease
Children who attended day care in previous two months
< 2yr old day care outside home 36x increase
<2y old family day care 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


世事有得有失
香港以身証之
The incidence of invasive
pneumococcal disease and
penicillin resistant pneumococcus

Incidence of Invasive Pneumococcal Disease in children <2 years old



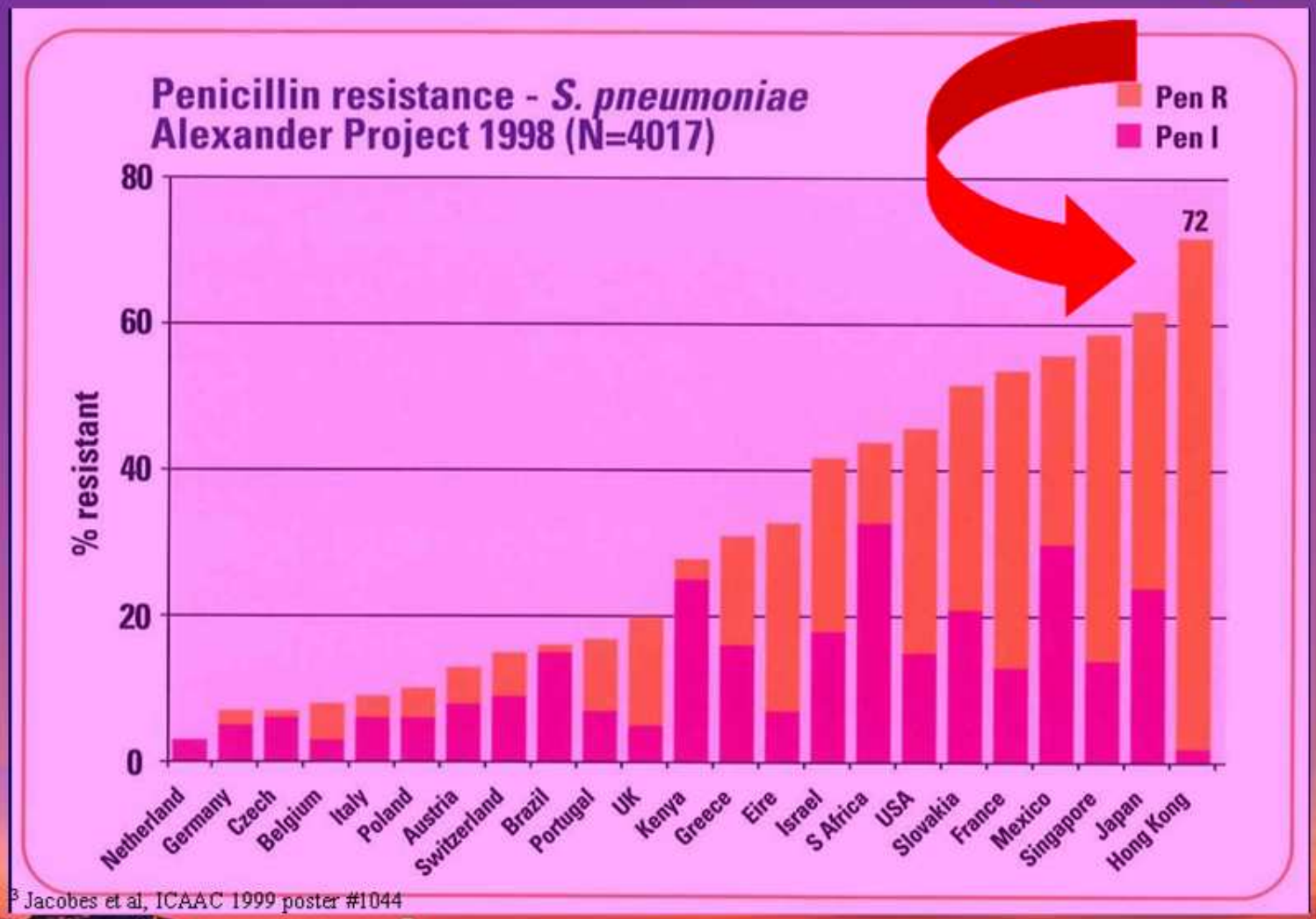
Annual incidence of culture-confirmed IPD, Hong Kong Island, by age, 1995-2004.



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.

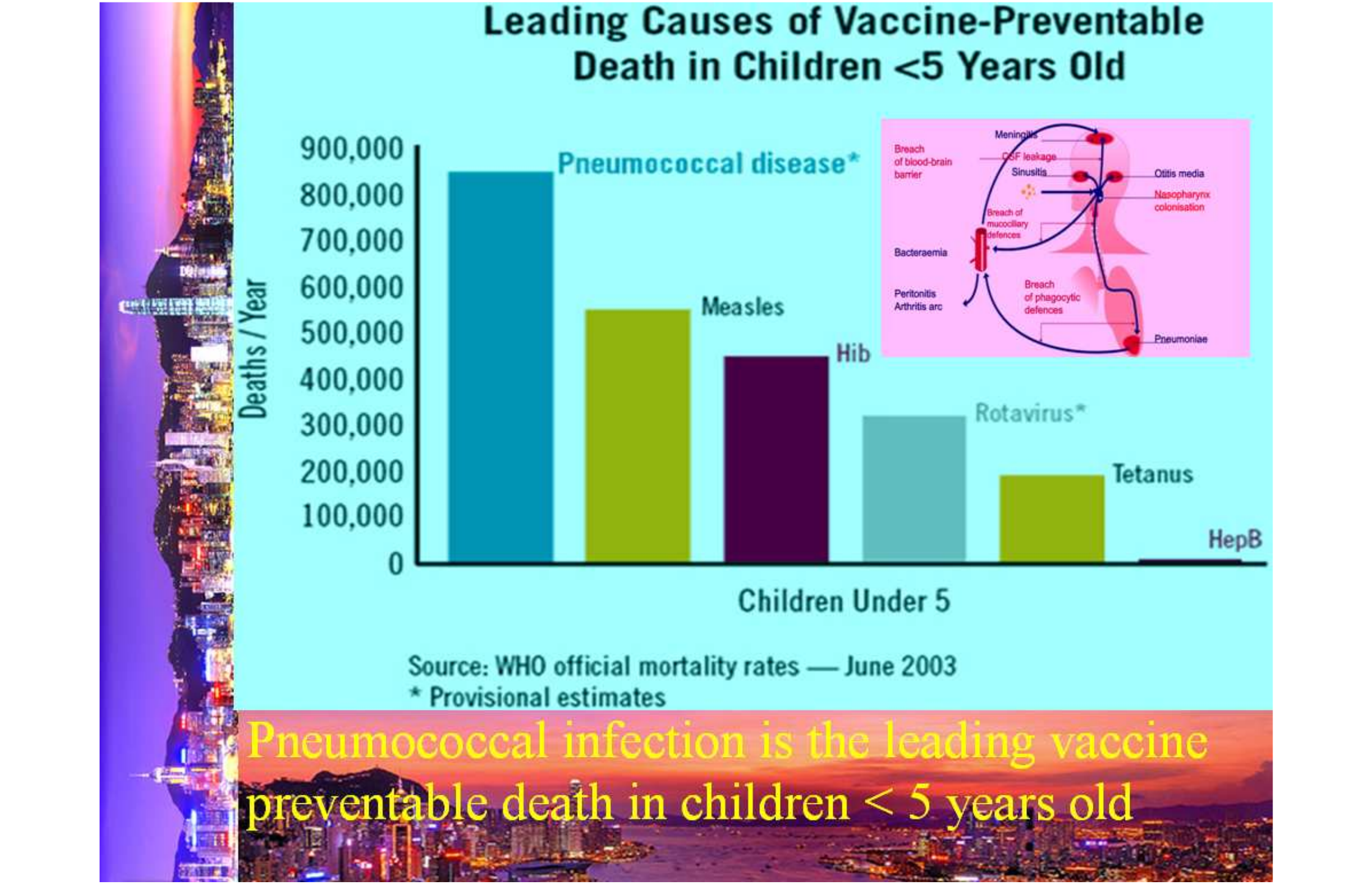
P L Ho, et al, The Paediatric Infection Disease Journal, Vol 25 (5) 454-455 May 2006

Penicillin Resistance in Hong Kong



[3] Jacobes et al, ICAAC 1999 poster #1044

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

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.**

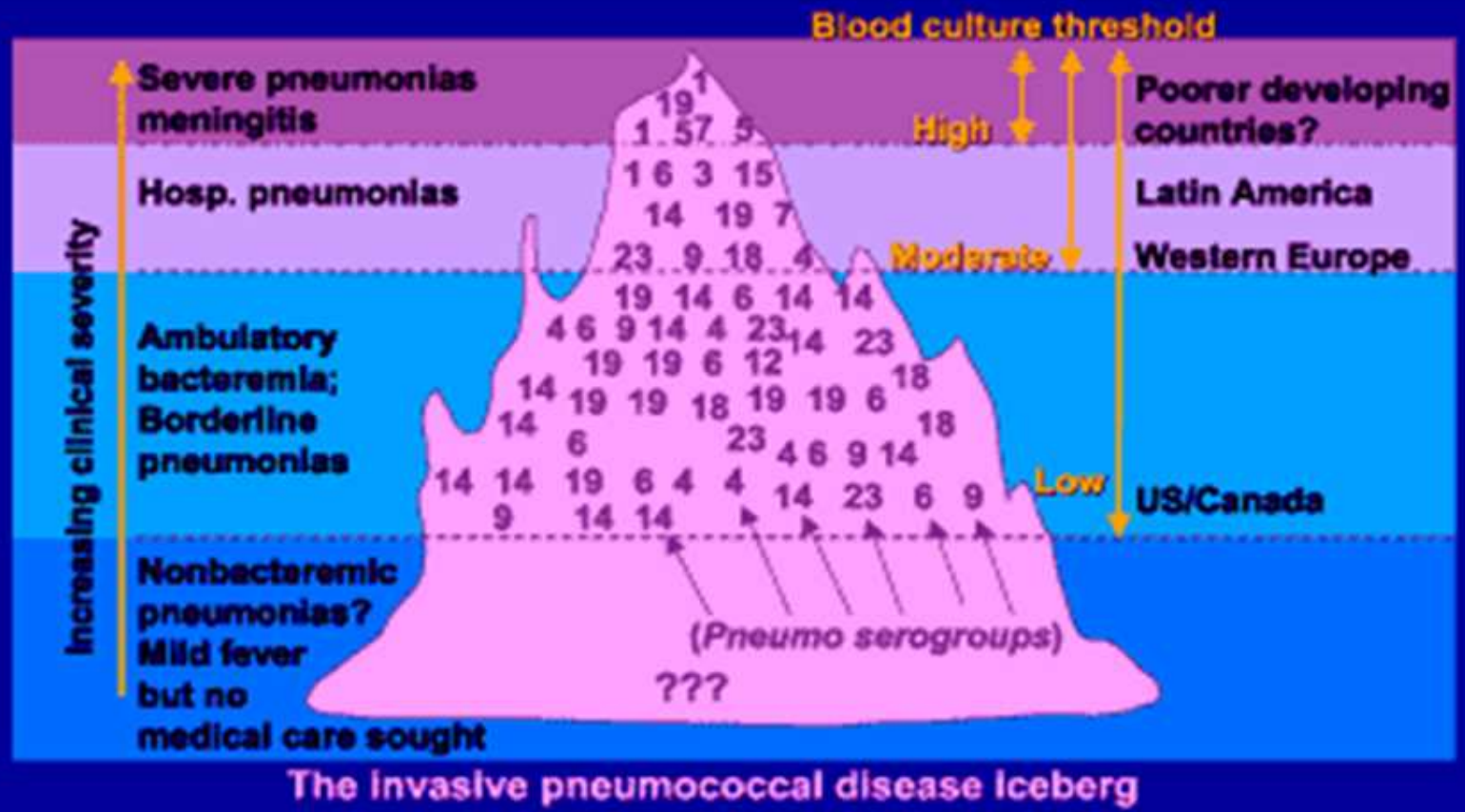
S. pneumoniae conjugate vaccine (7-valent conjugate vaccine) (Prevenar)

- 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…



The invasive pneumococcal disease iceberg

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

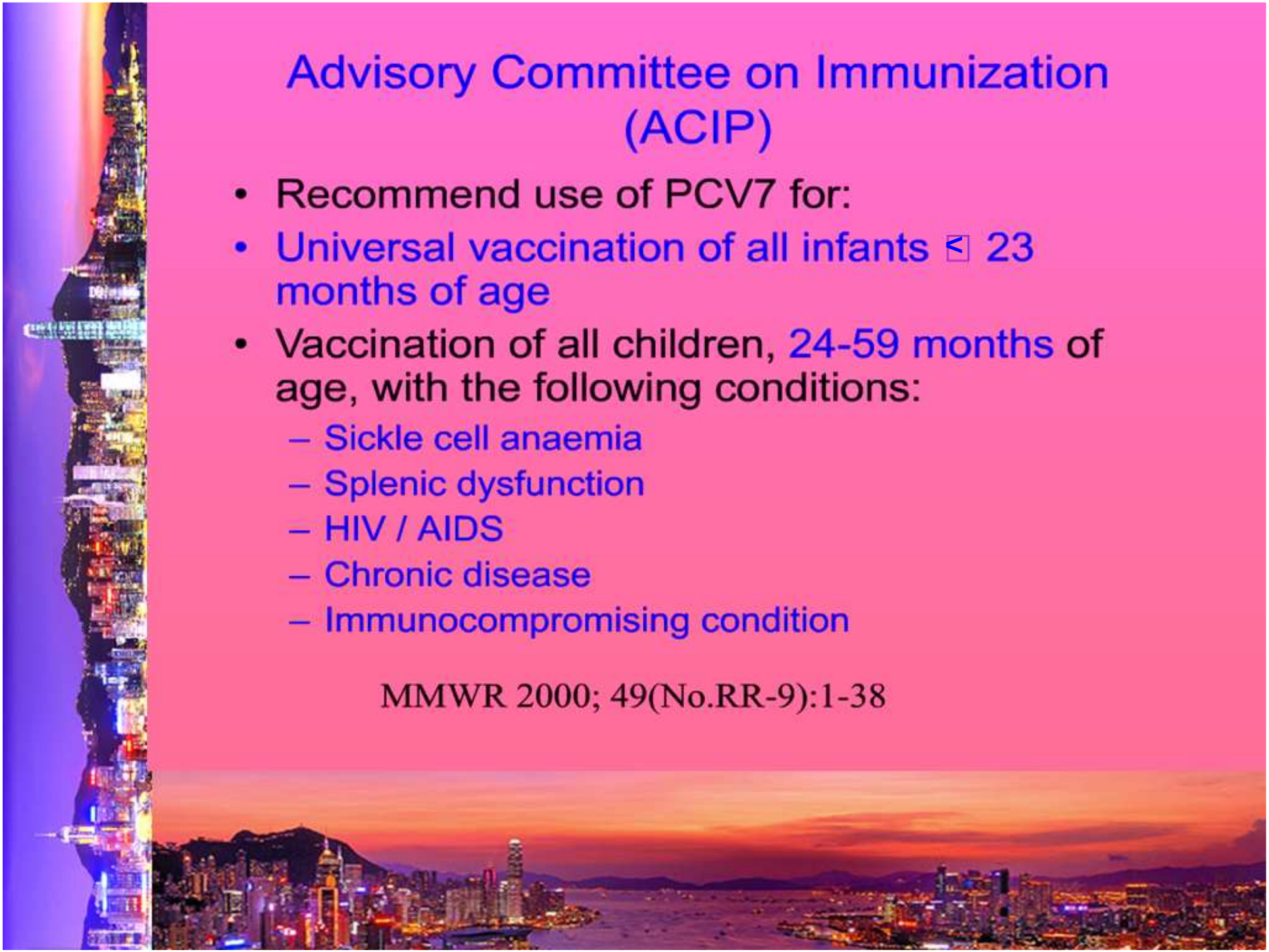
	Coverage by PCV7
Invasive	89.7%
Nasopharyngeal Carriage	66.1%
Invasive (resistance)*	87.5%
Nasopharyngeal Carriage (resistance)*	82.8%

- 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

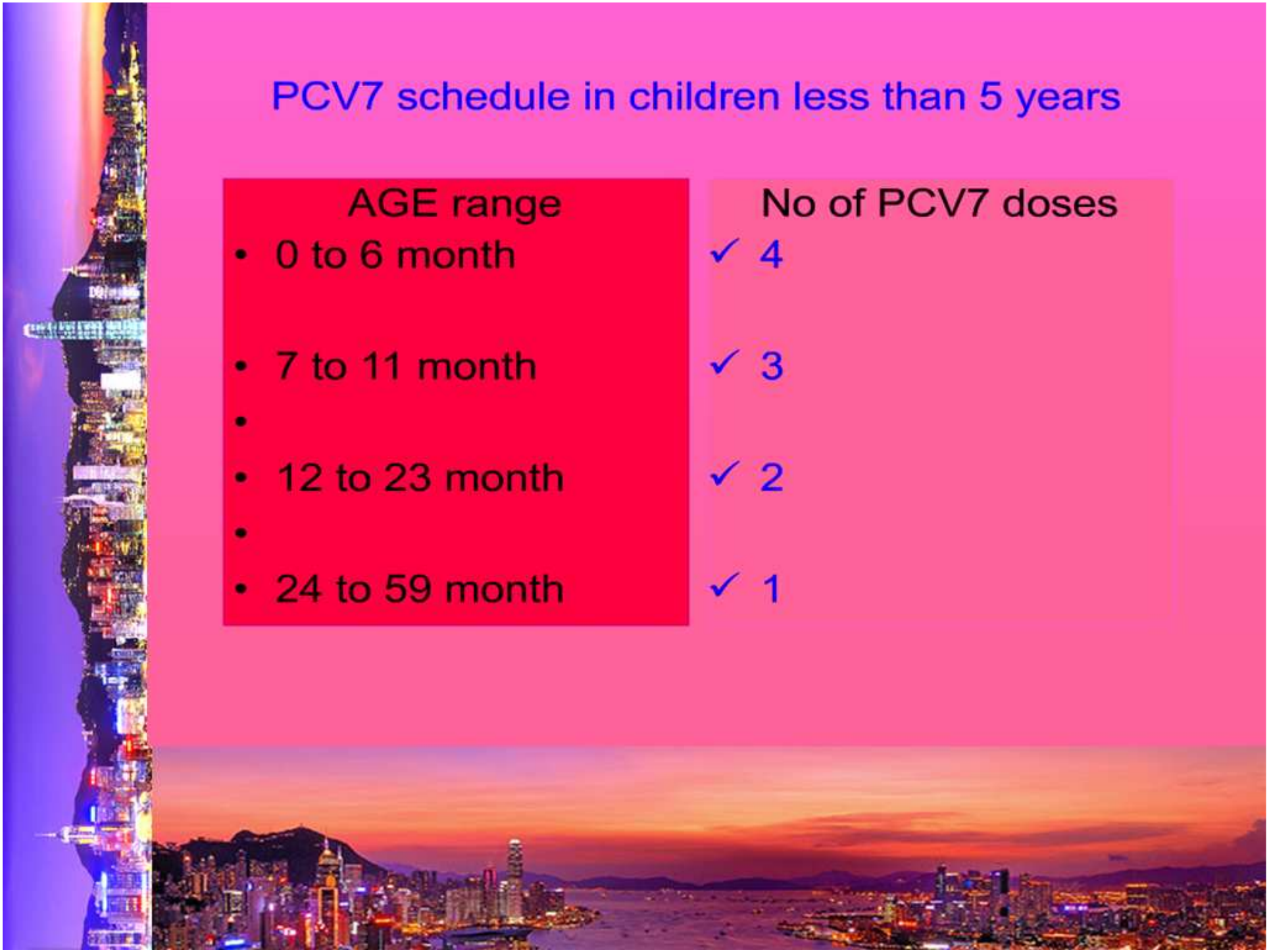
* resistance to penicillin, erythromycin and cefotaxime



Advisory Committee on Immunization (ACIP)

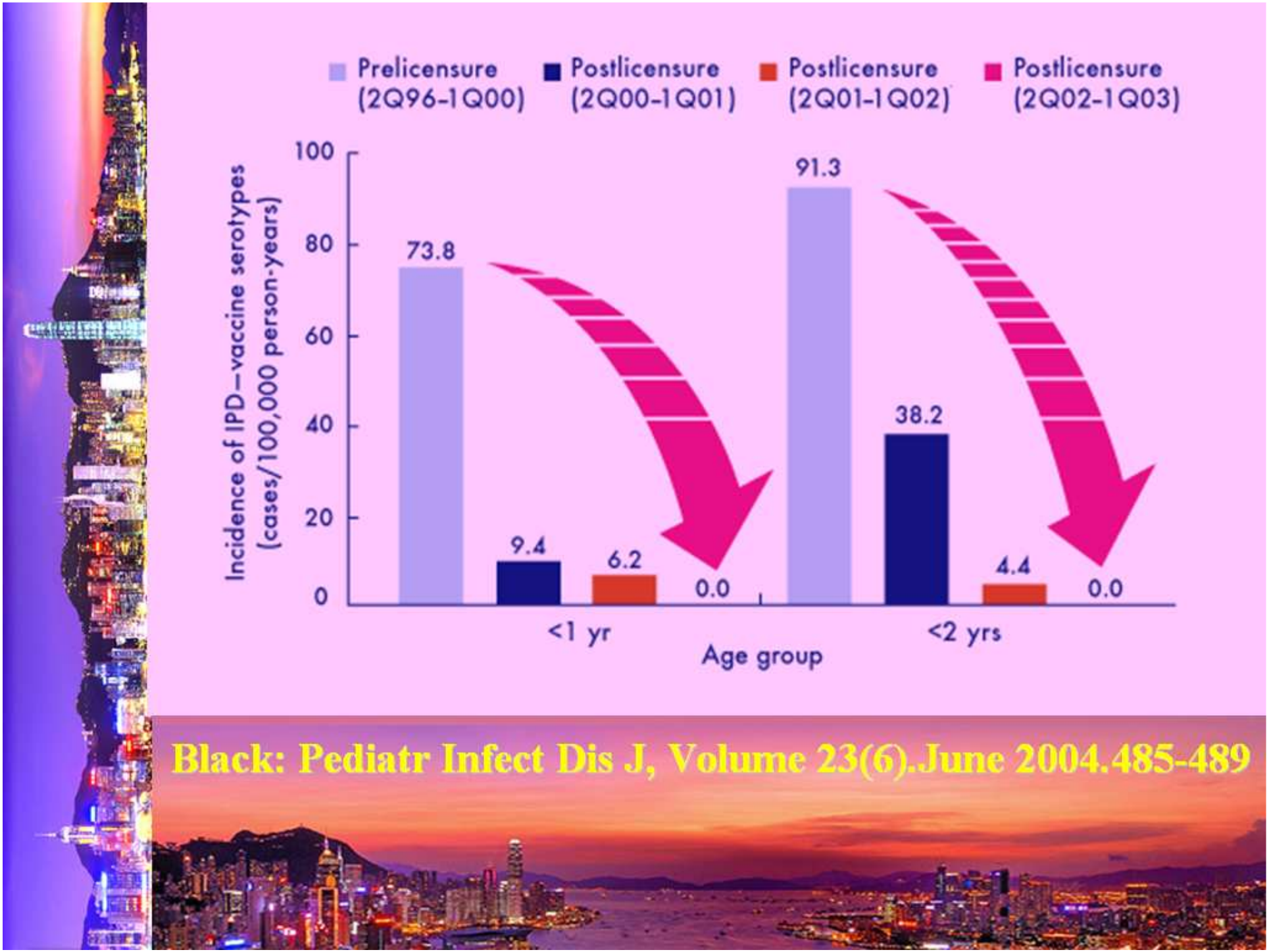
- Recommend use of PCV7 for:
- Universal vaccination of all infants < 23 months of age
- Vaccination of all children, 24-59 months of age, with the following conditions:
  - Sickle cell anaemia
  - Splenic dysfunction
  - HIV / AIDS
  - Chronic disease
  - Immunocompromising condition

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


Prelicensure (2Q96-1Q00)
Postlicensure (2Q00-1Q01)
Postlicensure (2Q01-1Q02)
Postlicensure (2Q02-1Q03)
Incidence of IPD—vaccine serotypes (cases/100,000 person-years)
100
80
60
40
20
0
73.8
9.4
6.2
0.0
91.3
38.2
4.4
0.0
<1 yr
<2 yrs
Age group
Black: Pediatr Infect Dis J, Volume 23(6).June 2004.485-489

Updated Recommendations from the ACIP 2008

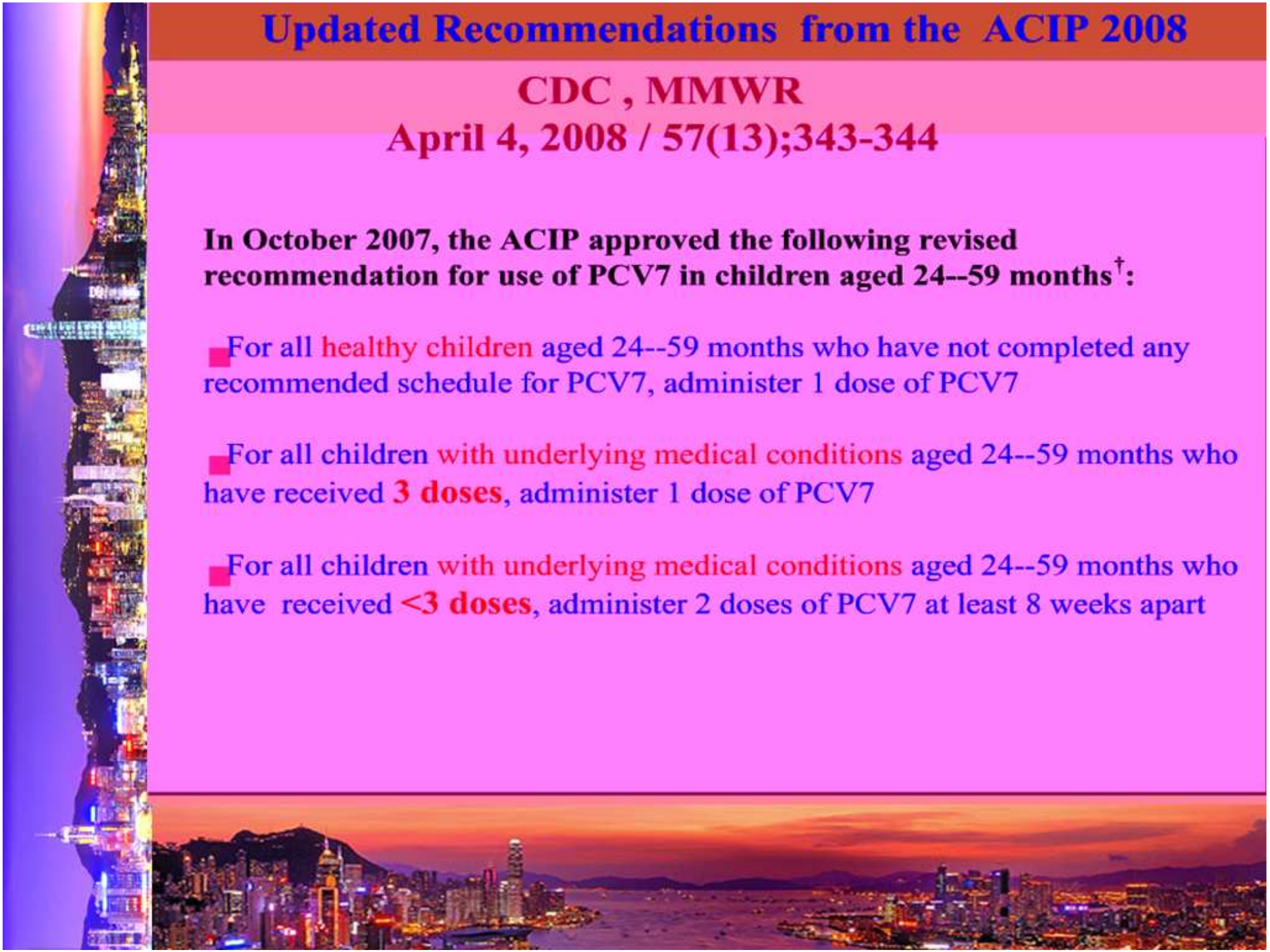
CDC , MMWR
April 4, 2008 / 57(13);343-344

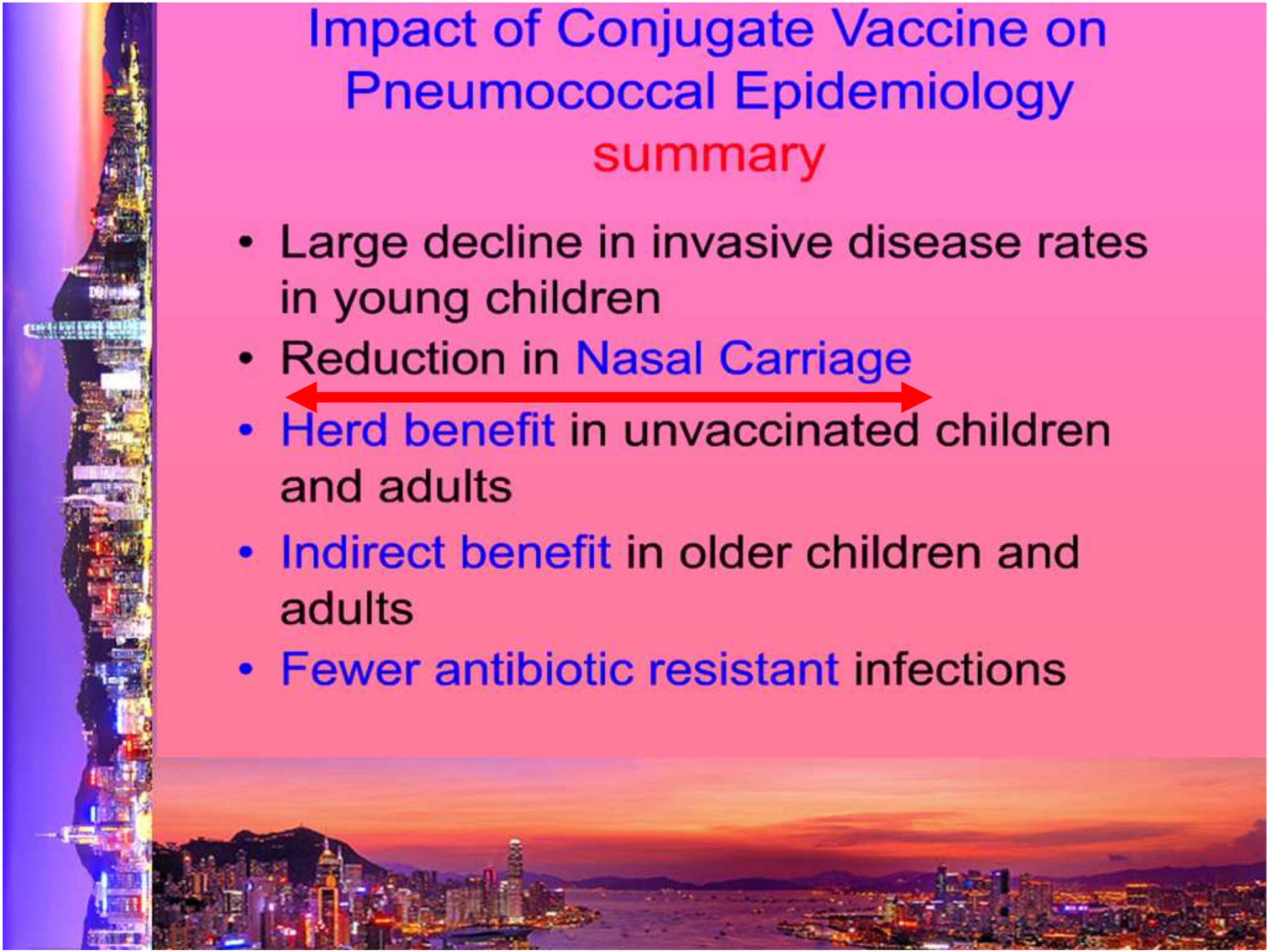
In October 2007, the ACIP approved the following revised recommendation for use of PCV7 in children aged 24--59 months[†]:

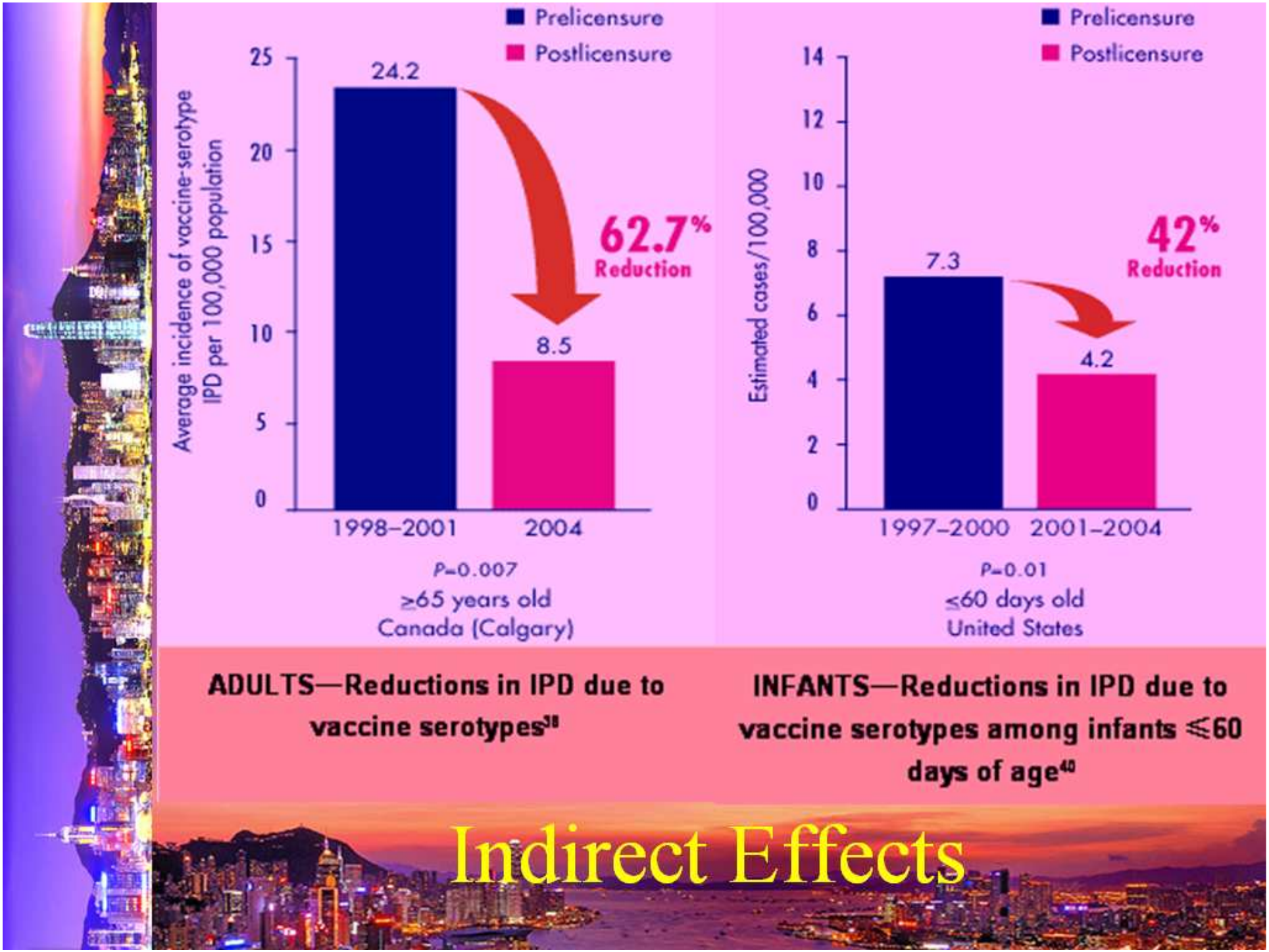
- For all healthy children aged 24--59 months who have not completed any recommended schedule for PCV7, administer 1 dose of PCV7

- 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



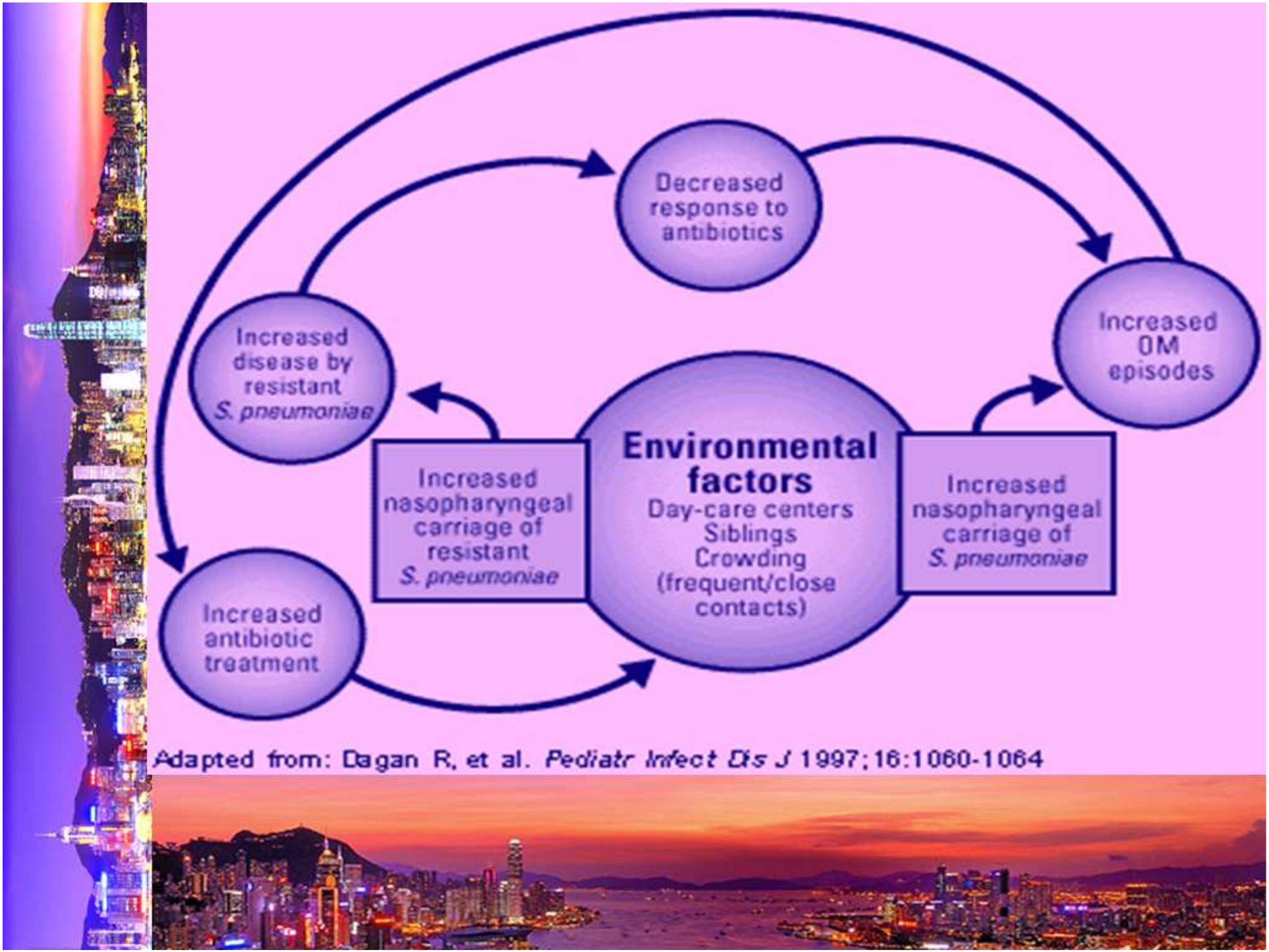

Impact of Conjugate Vaccine on Pneumococcal Epidemiology
summary
• Large decline in invasive disease rates in young children
• Reduction in Nasal Carriage
• Herd benefit in unvaccinated children and adults
• Indirect benefit in older children and adults
• Fewer antibiotic resistant infections


Prelicensure
Postlicensure
Average incidence of vaccine-serotype IPD per 100,000 population
25
20
15
10
5
0
24.2
8.5
62.7%
Reduction
1998–2001
2004
P=0.007
≥65 years old
Canada (Calgary)
Prelicensure
Postlicensure
Estimated cases/100,000
14
12
10
8
6
4
2
0
7.3
4.2
42%
Reduction
1997–2000
2001–2004
P=0.01
≤60 days old
United States
ADULTS—Reductions in IPD due to vaccine serotypes[38]
INFANTS—Reductions in IPD due to vaccine serotypes among infants ≤60 days of age[40]
Indirect Effects

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

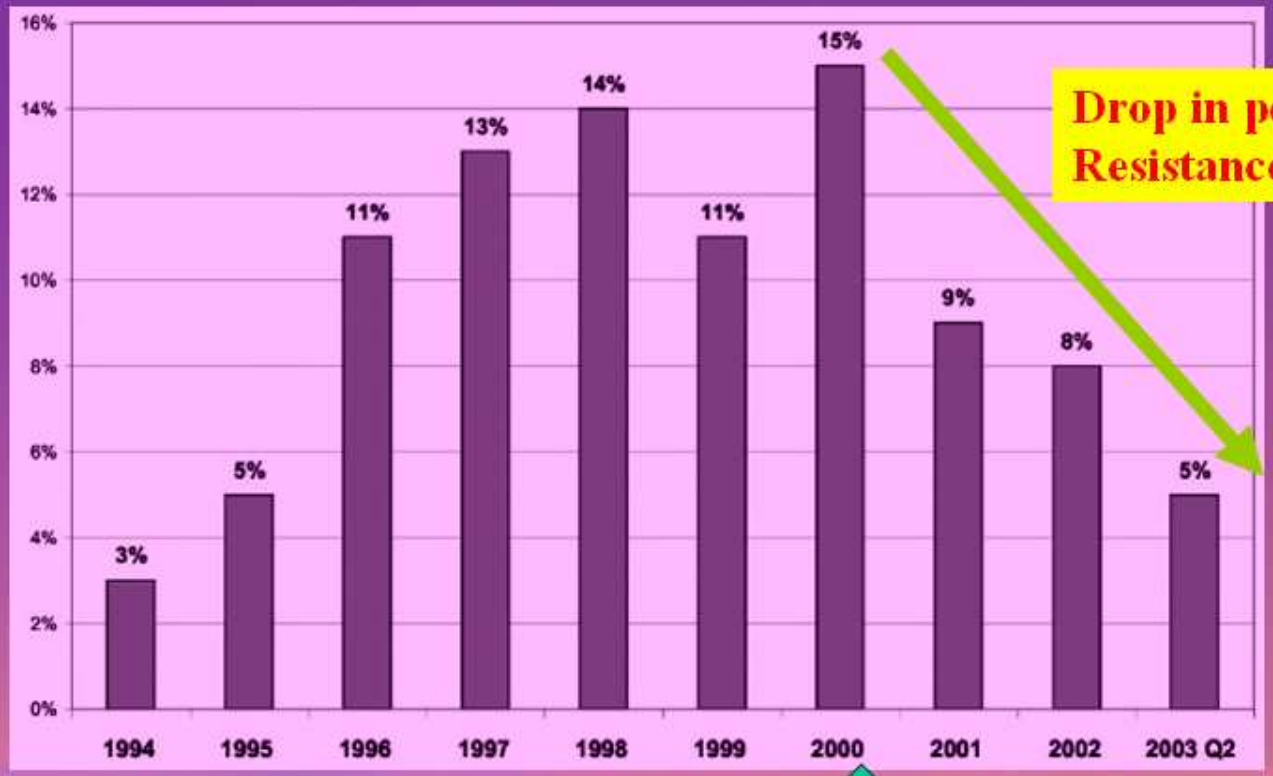
Active Bacterial Core Surveillance of the Emerging Infections Program Network. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine.
Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. N Engl J Med. 2003;348:1737–46.



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

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

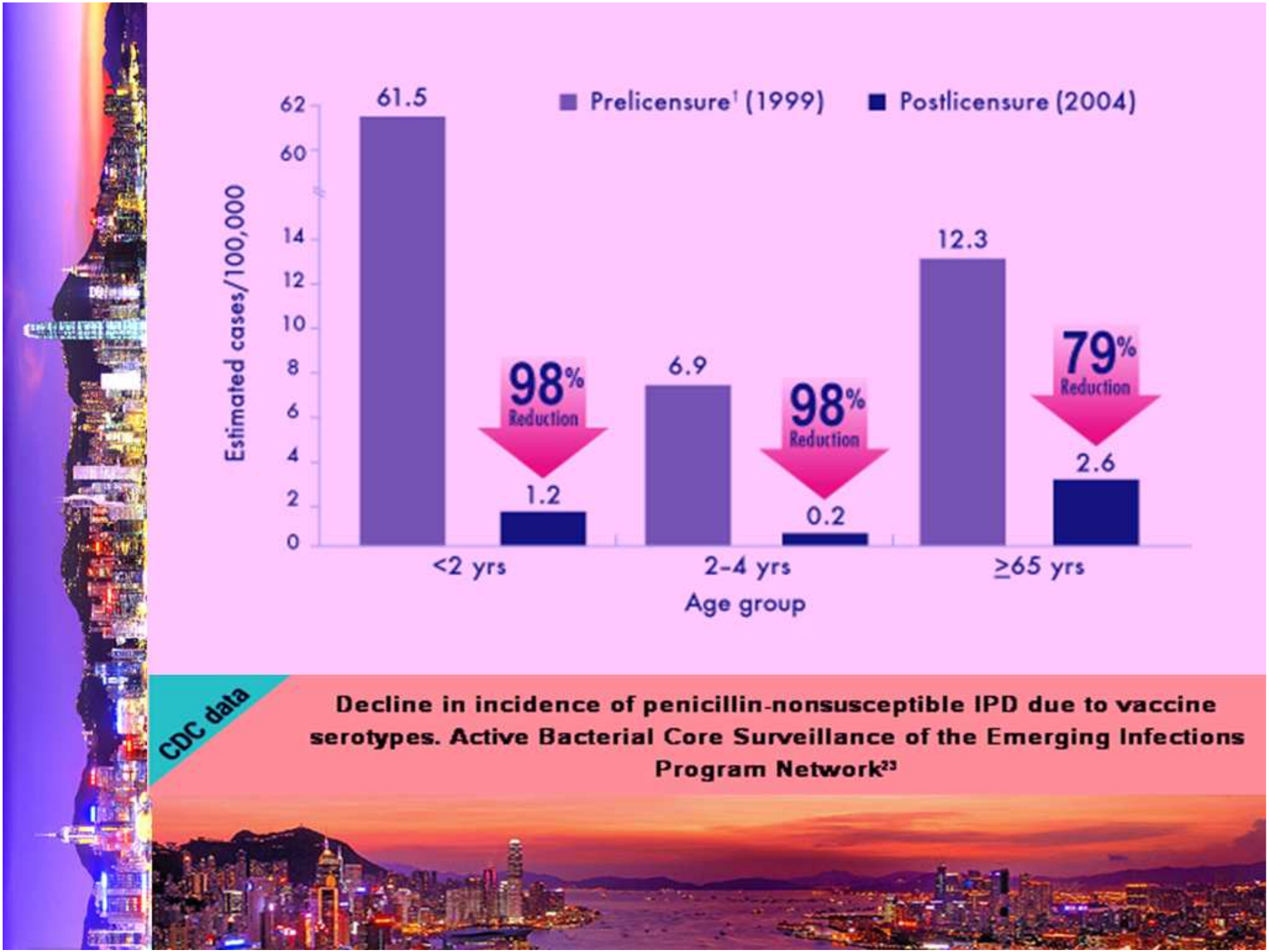
April 2000

Kaiser Permanente Vaccine Study – Postlicensure surveillance study

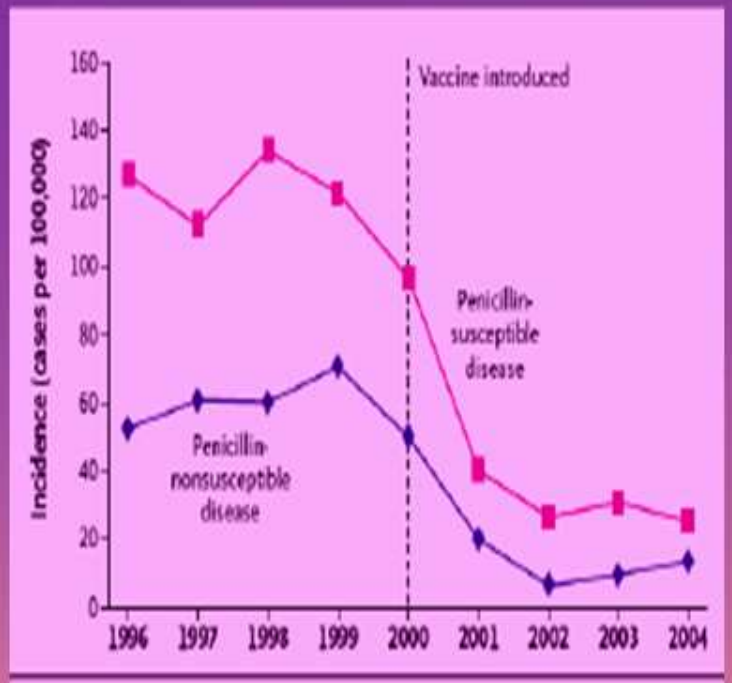
- Compare year 1998-1999 to 2001-2002
- Penicillin: 28.9% to 19.5%
- Erythromycin: 29.5% to 15.0%
- Tetracycline: 39.3% to 13.9%

  p value all<0.001

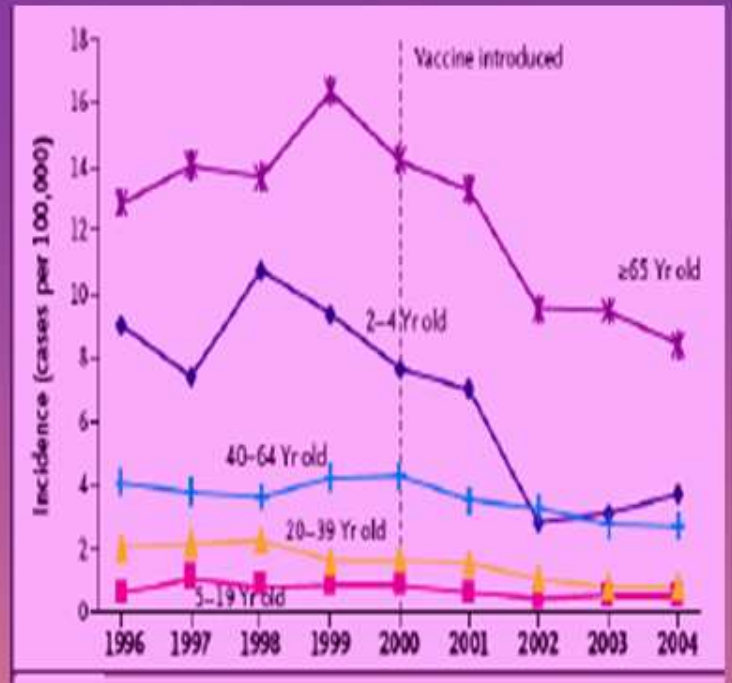
- *Black S, Shinefield H, Baxter R, et al. Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in Northern California Kaiser Permanente.*
  Pediatr Infect Dis J. 2004;23:485-489


Prelicensure[1] (1999)
Postlicensure (2004)
Estimated cases/100,000
62
60
14
12
10
8
6
4
2
0
61.5
1.2
6.9
0.2
12.3
2.6
98% Reduction
98% Reduction
79% Reduction
<2 yrs
2–4 yrs
≥65 yrs
Age group
CDC data
Decline in incidence of penicillin-nonsusceptible IPD due to vaccine serotypes. Active Bacterial Core Surveillance of the Emerging Infections Program Network[23]

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



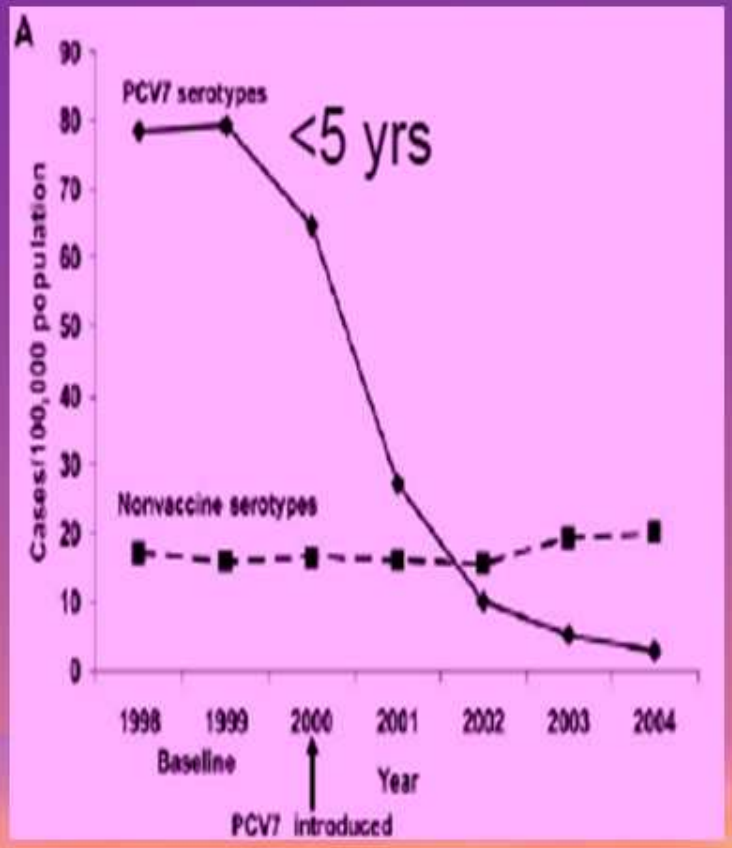
Annual Incidence of Invasive Disease Caused by Penicillin-Susceptible and Penicillin-Nonsusceptible Pneumococci among Children under Two Years of Age, 1996 to 2004.

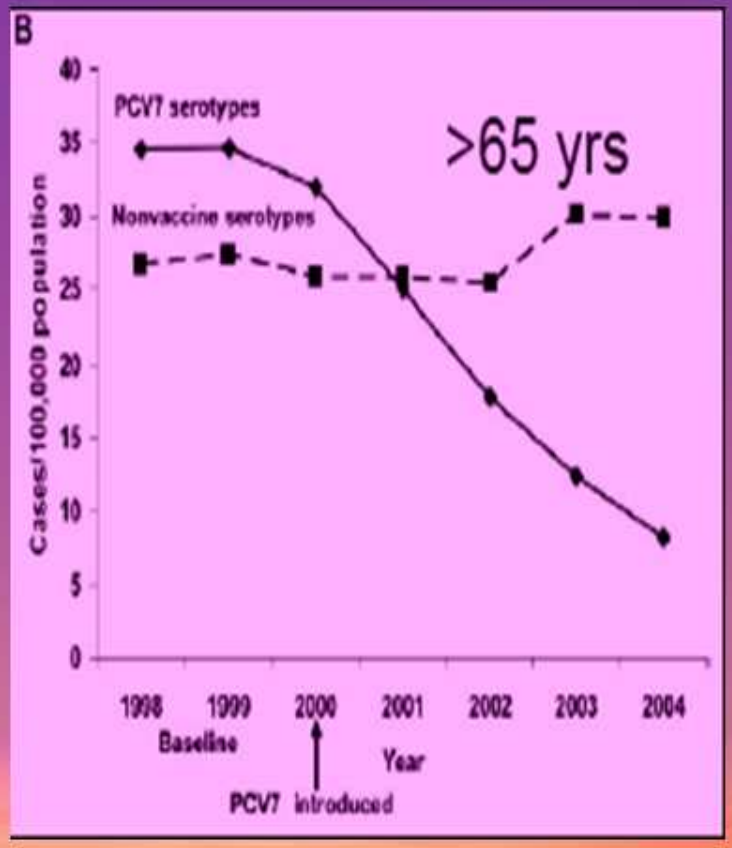


Annual Incidence of Invasive Disease Caused by Penicillin-Nonsusceptible Pneumococci in Persons Two Years of Age or Older, 1996 to 2004.

Vaccination and serotype replacement

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

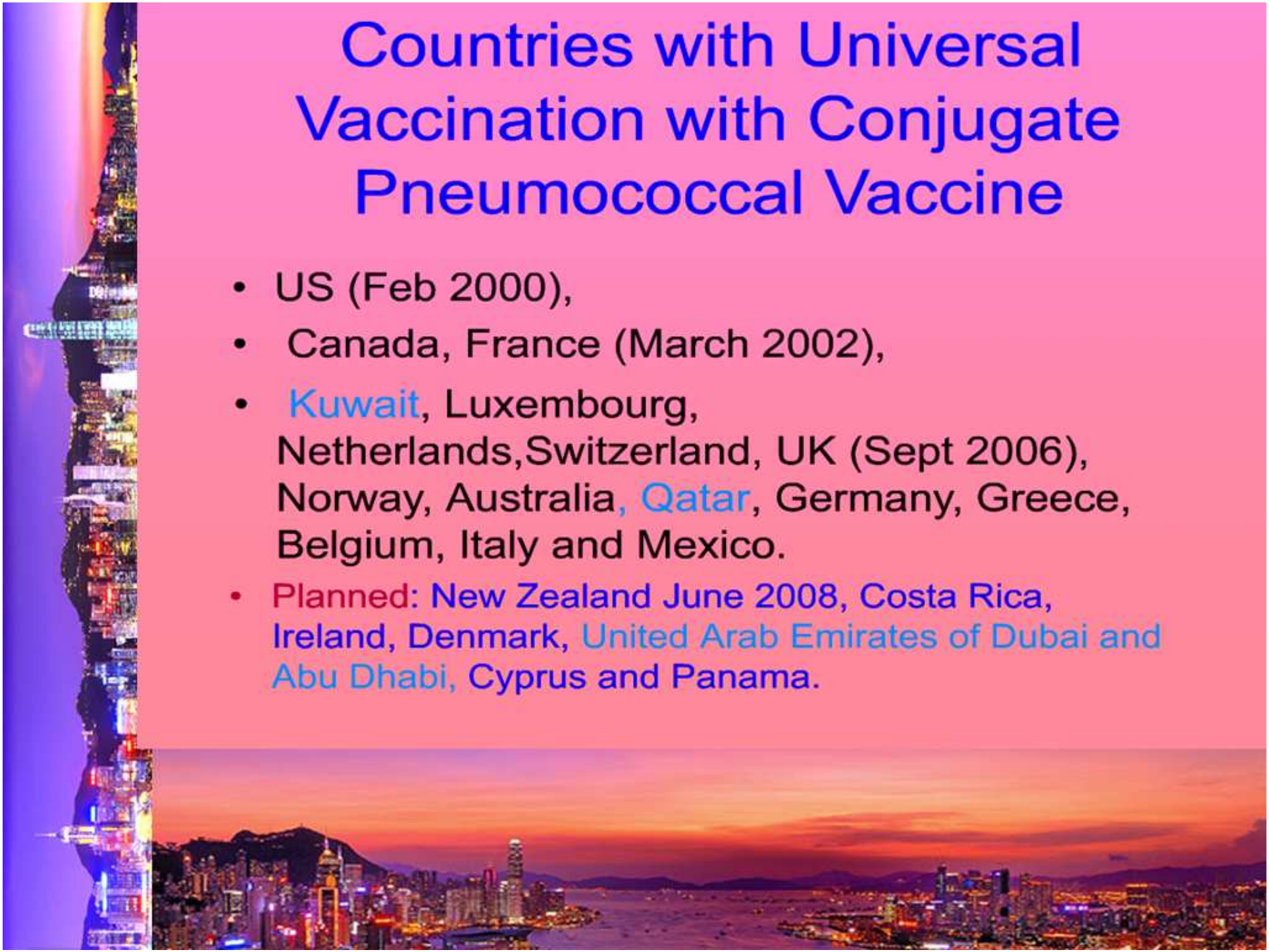


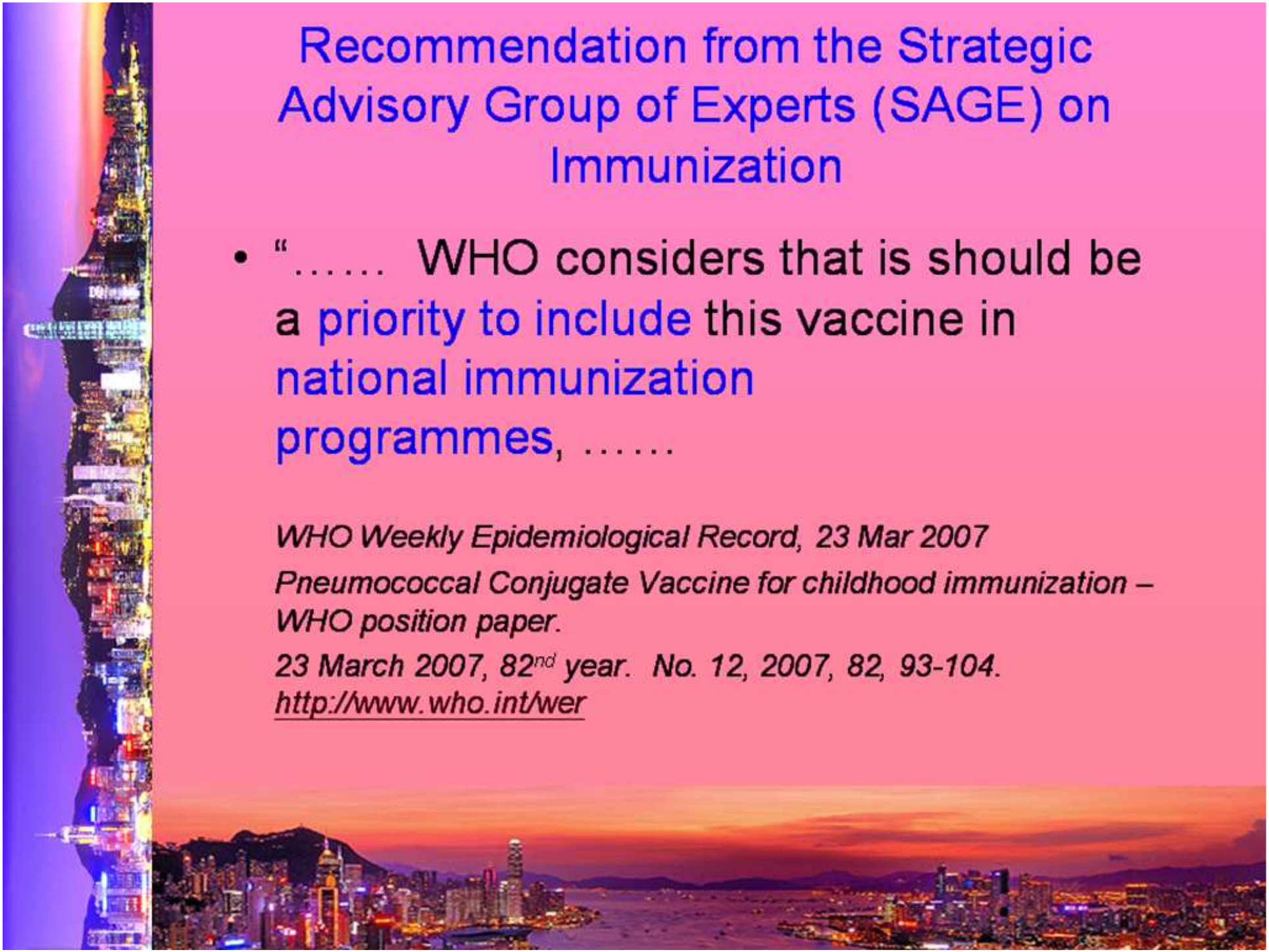


7-valent pneumococcal conjugate vaccine reduce *S. pneumoniae* colonisation ➔ ? Effect on serotype replacement

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 is should be a priority to include this vaccine in national immunization programmes, ……

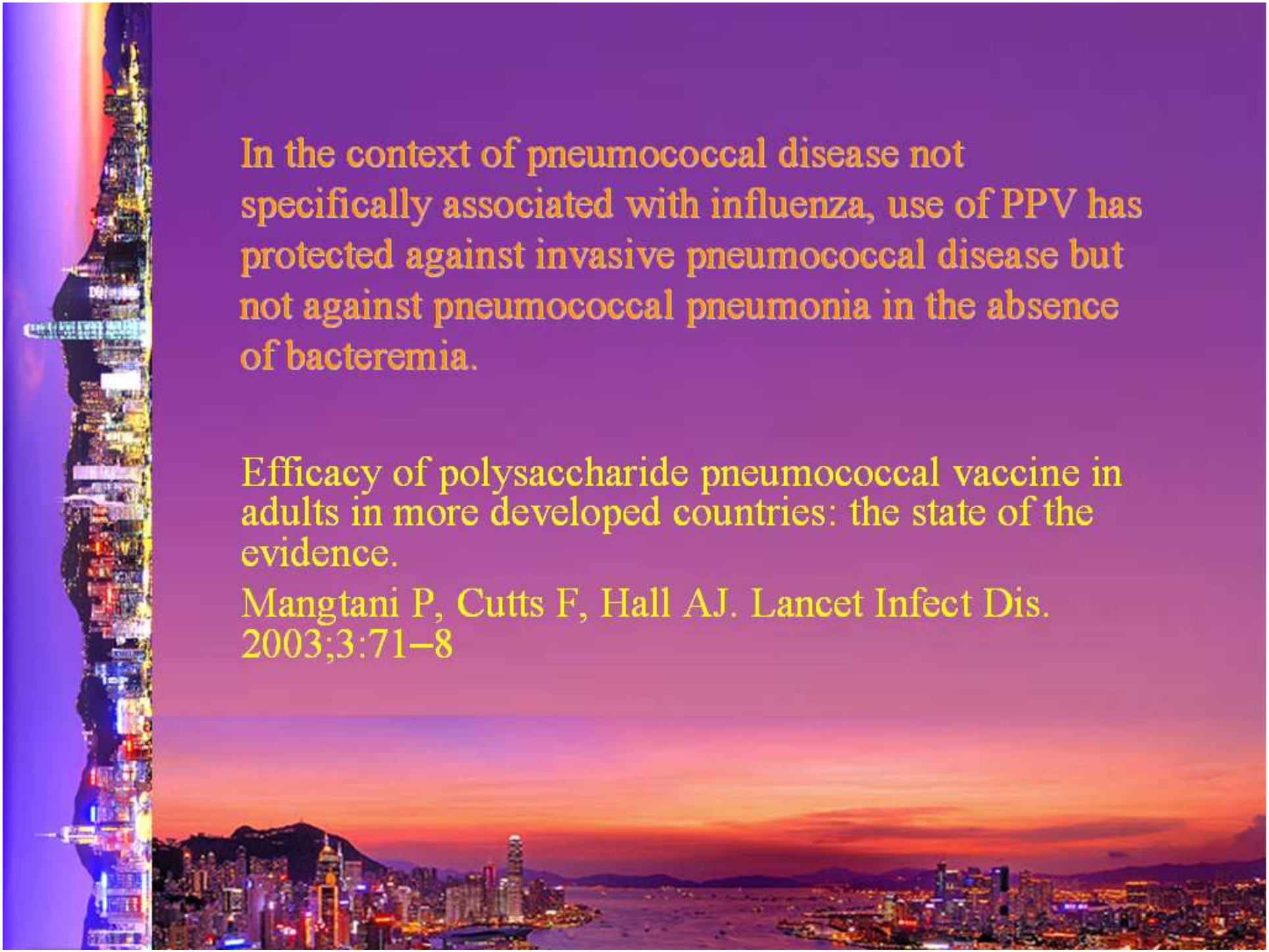
WHO Weekly Epidemiological Record, 23 Mar 2007

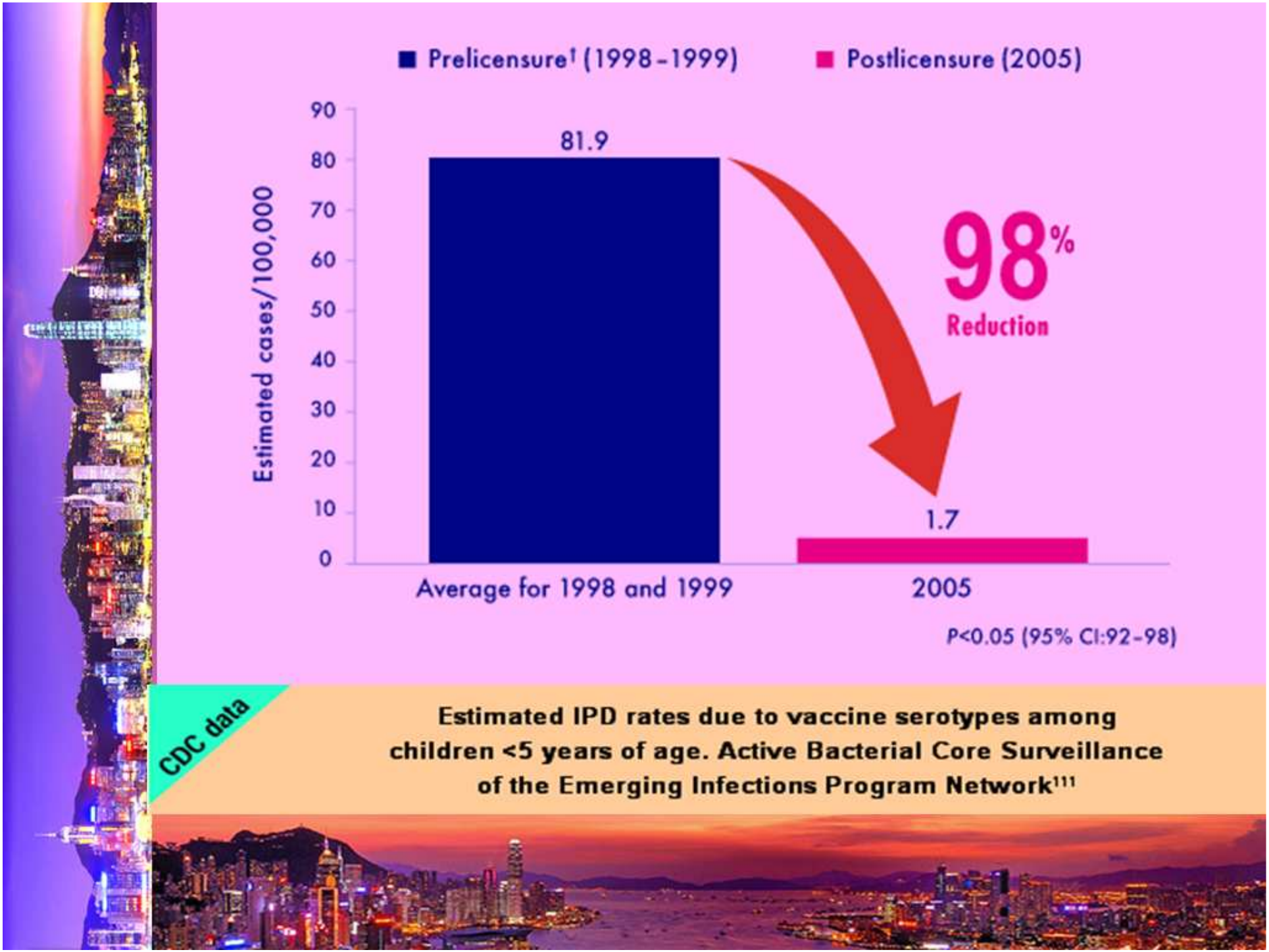
Pneumococcal Conjugate Vaccine for childhood immunization – WHO position paper.

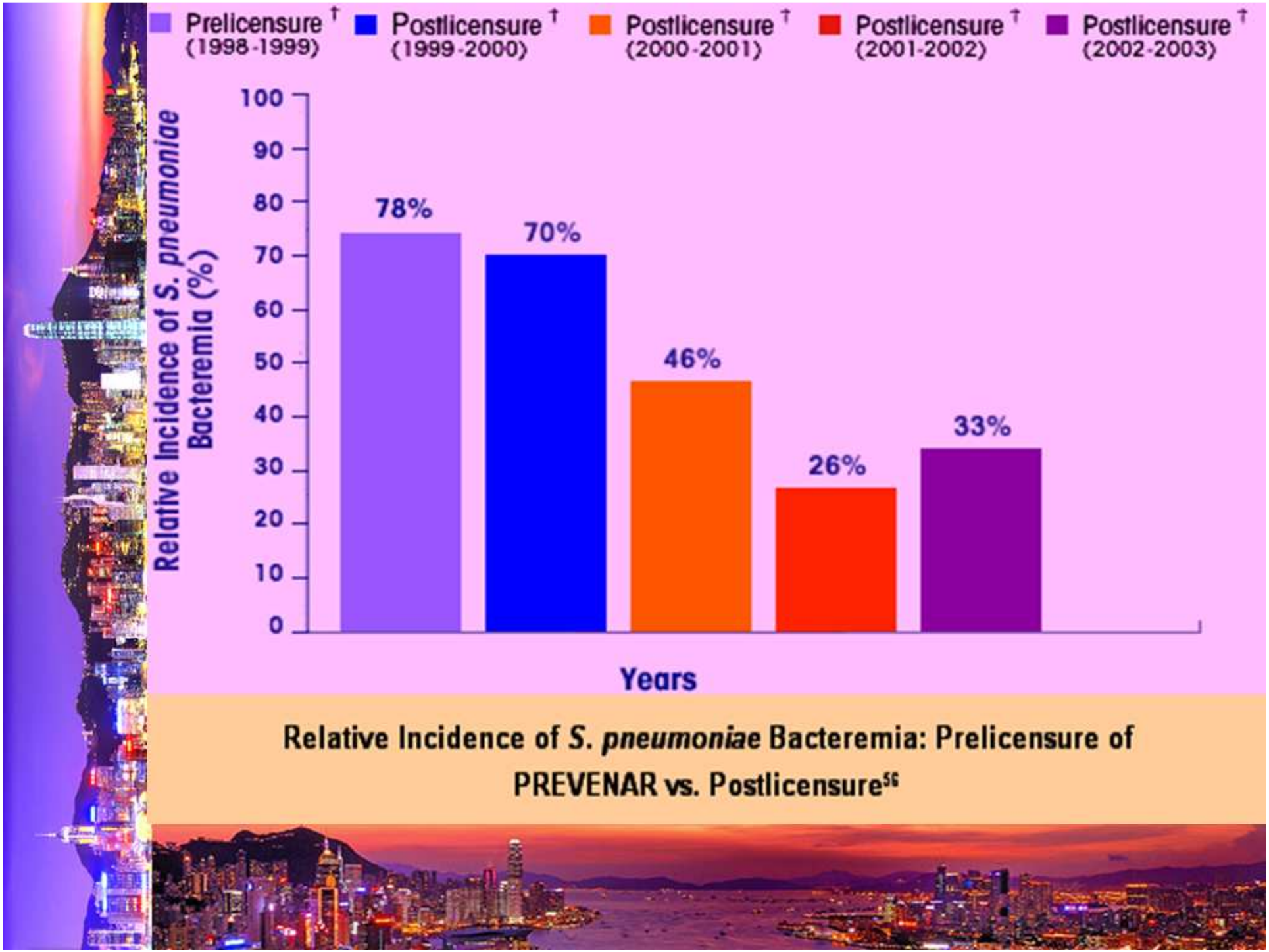
23 March 2007, 82nd year. No. 12, 2007, 82, 93-104.
http://www.who.int/wer

Pneumococcal Vaccines Adverse Reactions

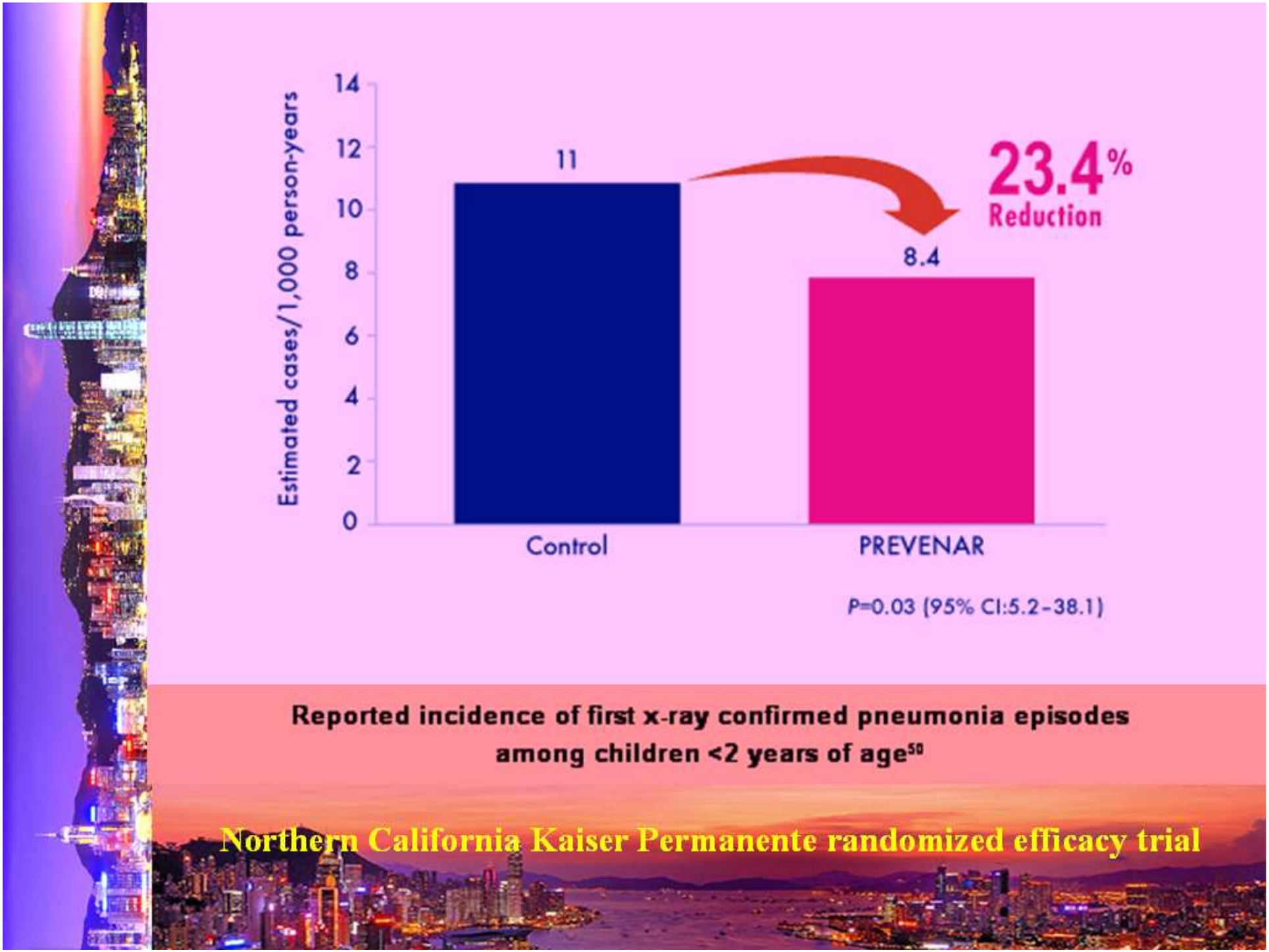
- Local reactions
  - polysaccharide 30%-50%
  - conjugate 10%-20%
- Fever, myalgia
  - polysaccharide <1%
  - conjugate 15%-24%
- Severe adverse reactions rare


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


Prelicensure[1] (1998–1999)
Postlicensure (2005)
Estimated cases/100,000
90
80
70
60
50
40
30
20
10
0
81.9
1.7
98%
Reduction
Average for 1998 and 1999
2005
P<0.05 (95% CI:92–98)
CDC data
Estimated IPD rates due to vaccine serotypes among children <5 years of age. Active Bacterial Core Surveillance of the Emerging Infections Program Network[111]

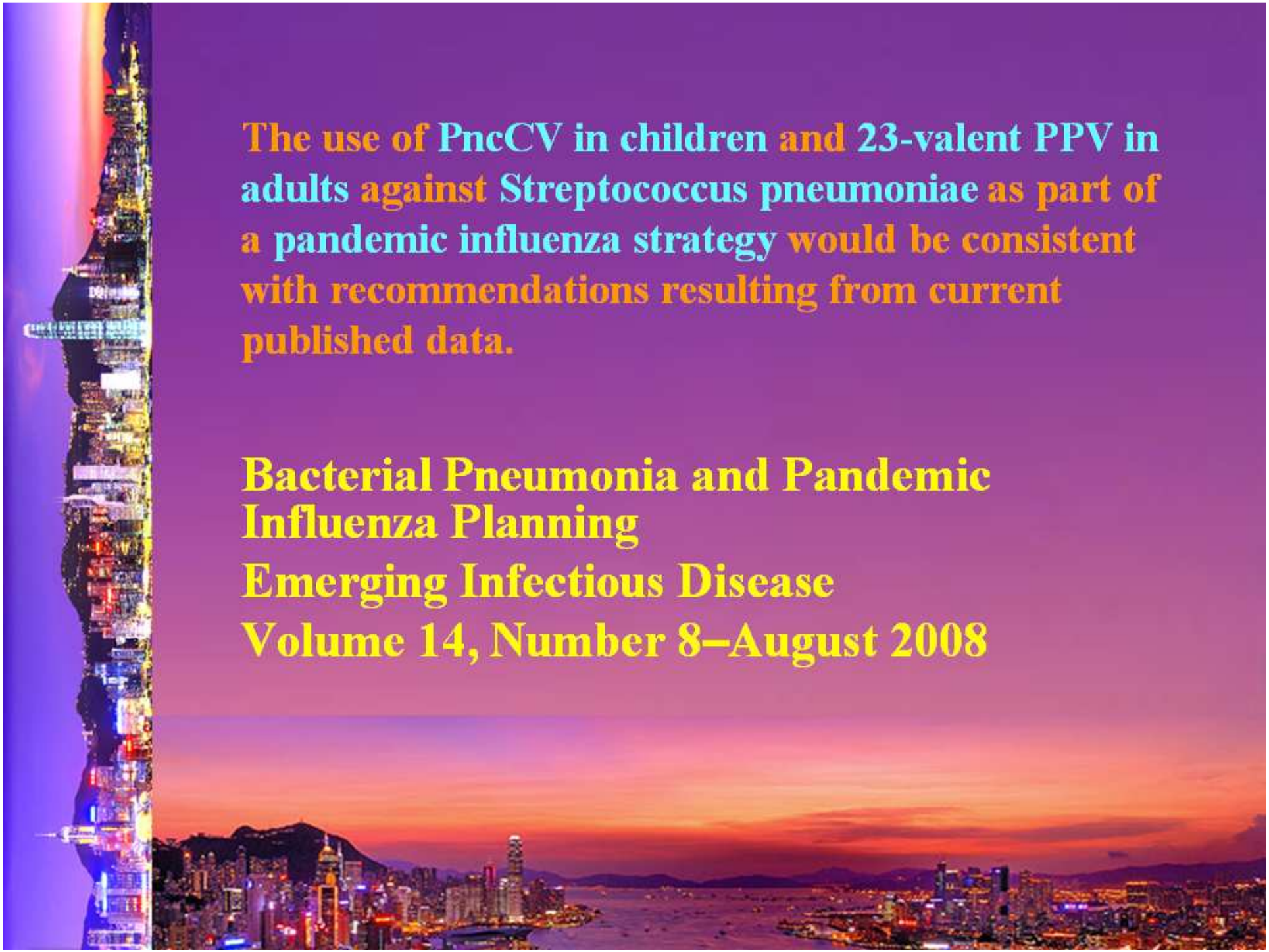


Relative Incidence of *S. pneumoniae* Bacteremia: Prelicensure of PREVENAR vs. Postlicensure[56]


Estimated cases/1,000 person-years
14
12
10
8
6
4
2
0
11
8.4
23.4%
Reduction
Control
PREVENAR
P=0.03 (95% CI:5.2–38.1)
Reported incidence of first x-ray confirmed pneumonia episodes among children <2 years of age[50]
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.**


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**	**Children 24-59 months 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	• 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 immuno-suppressive 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

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

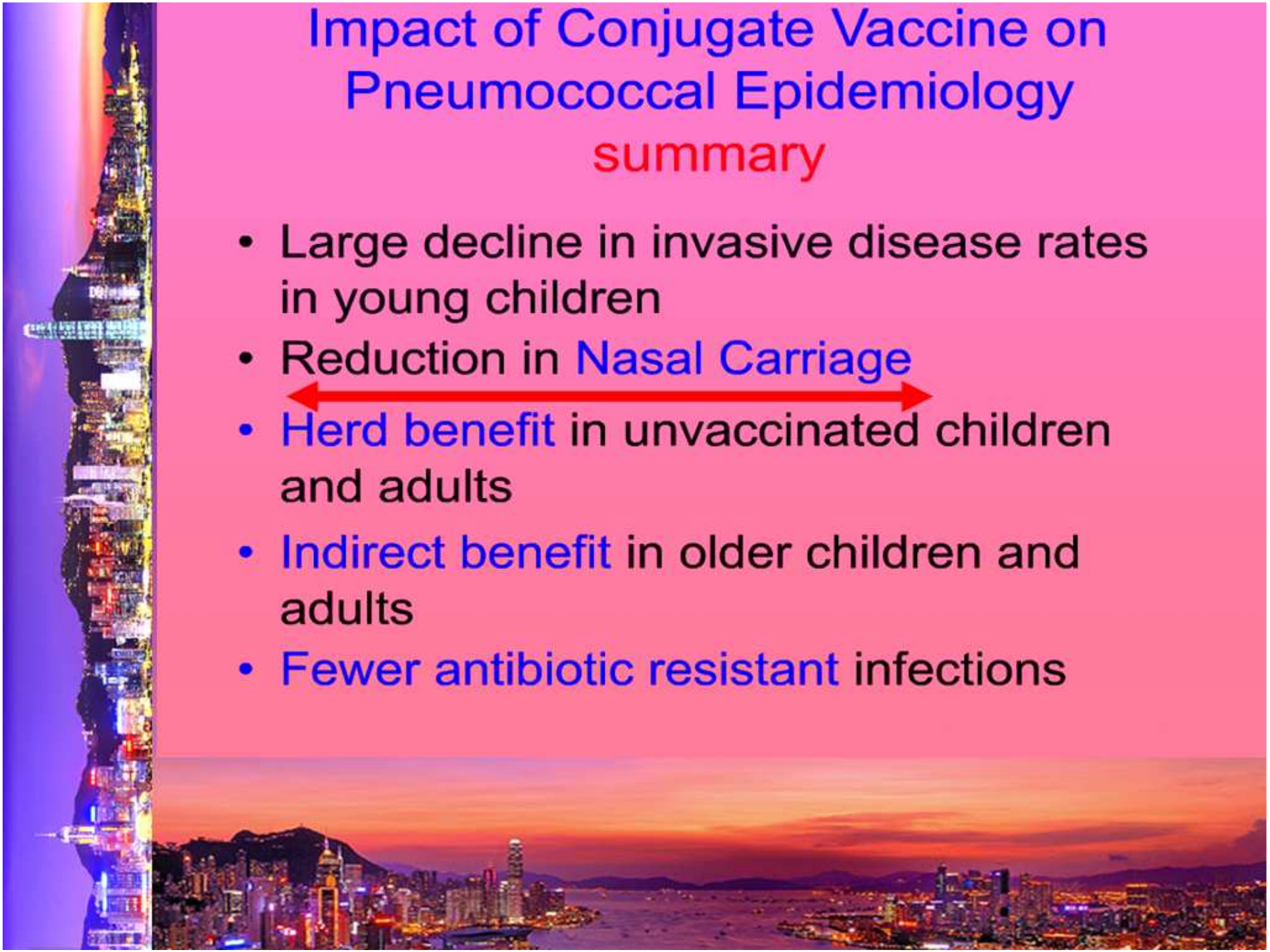
Vaccine	Unit price
Pneumovax 23 vaccine	$105.7
7 polyvalent conjugate vaccine	$534.8
Haemophilus influenza B vaccine	$137


天心莫測 劫隨心轉
物競天擇，適者生存。
物極必反，道窮則變！
What is the potential side effect of pneumococcal vaccination after 10 years in the United States ?

Impact of Conjugate Vaccine on Pneumococcal Epidemiology

summary

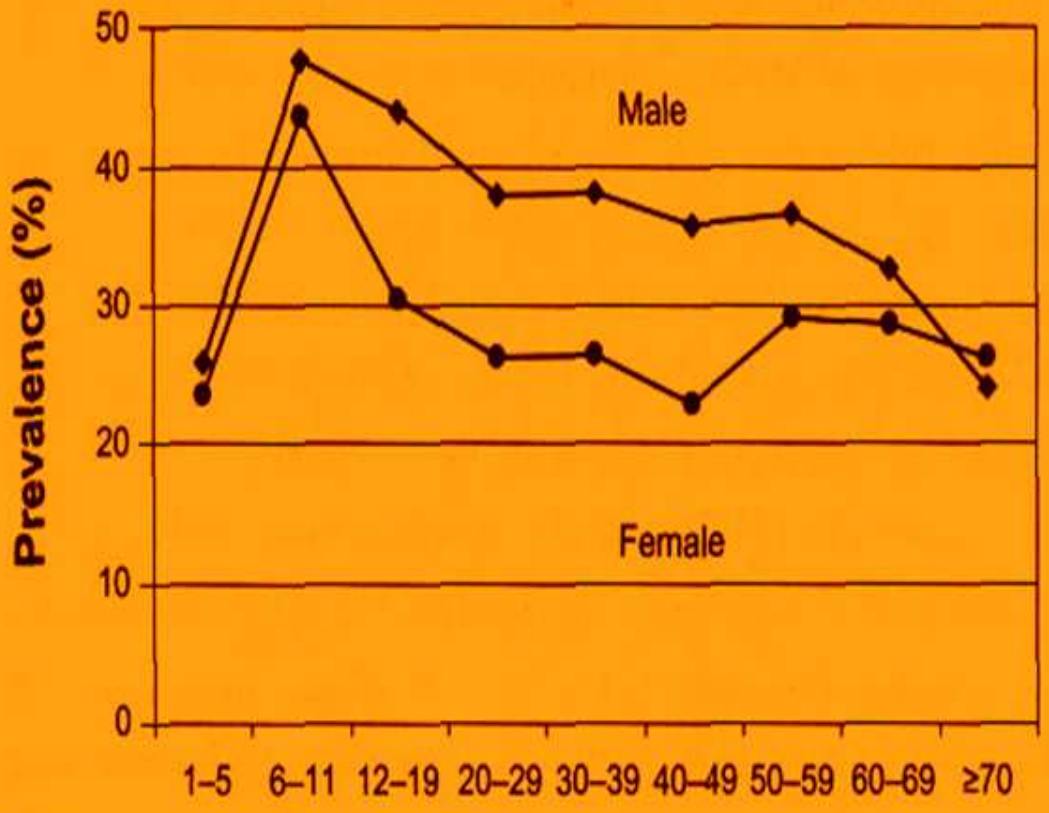
- Large decline in invasive disease rates in young children
- Reduction in Nasal Carriage
- Herd benefit in unvaccinated children and adults
- Indirect benefit in older children and adults
- Fewer antibiotic resistant infections



Prevalence of Staphylococcus aureus nasal colonization, by age and sex

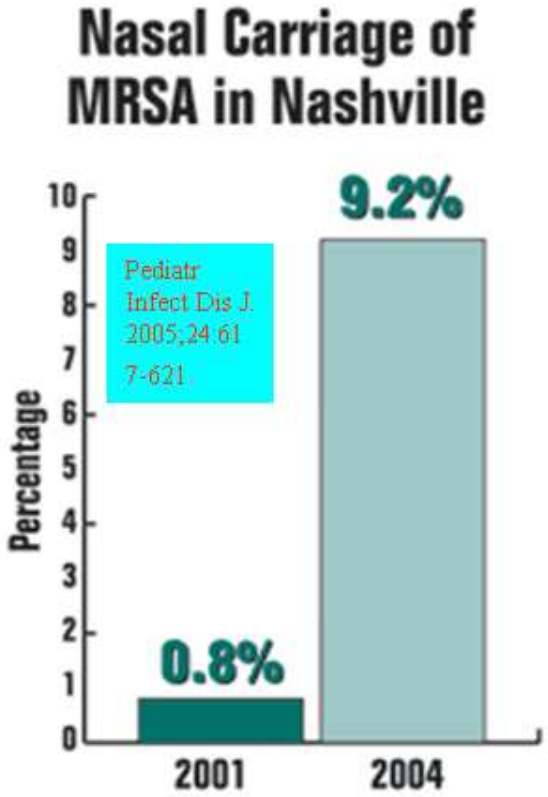
National Health and Nutrition Examination Survey, 2001-2002.

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



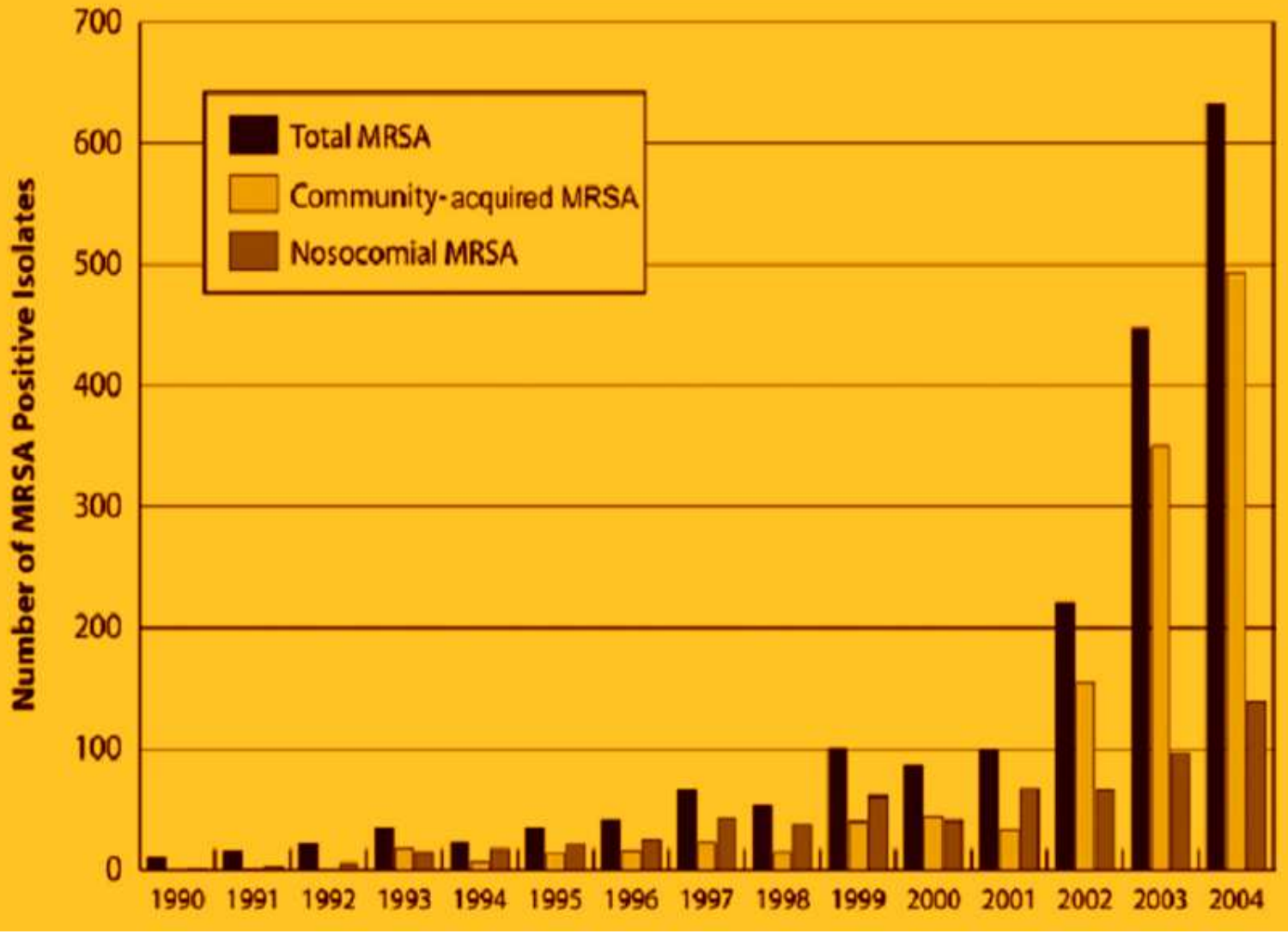
Resistant to dessication 7m

DM, chronic skin conditions, IV addict and dialysis patients



Changing Epidemiology of MRSA /

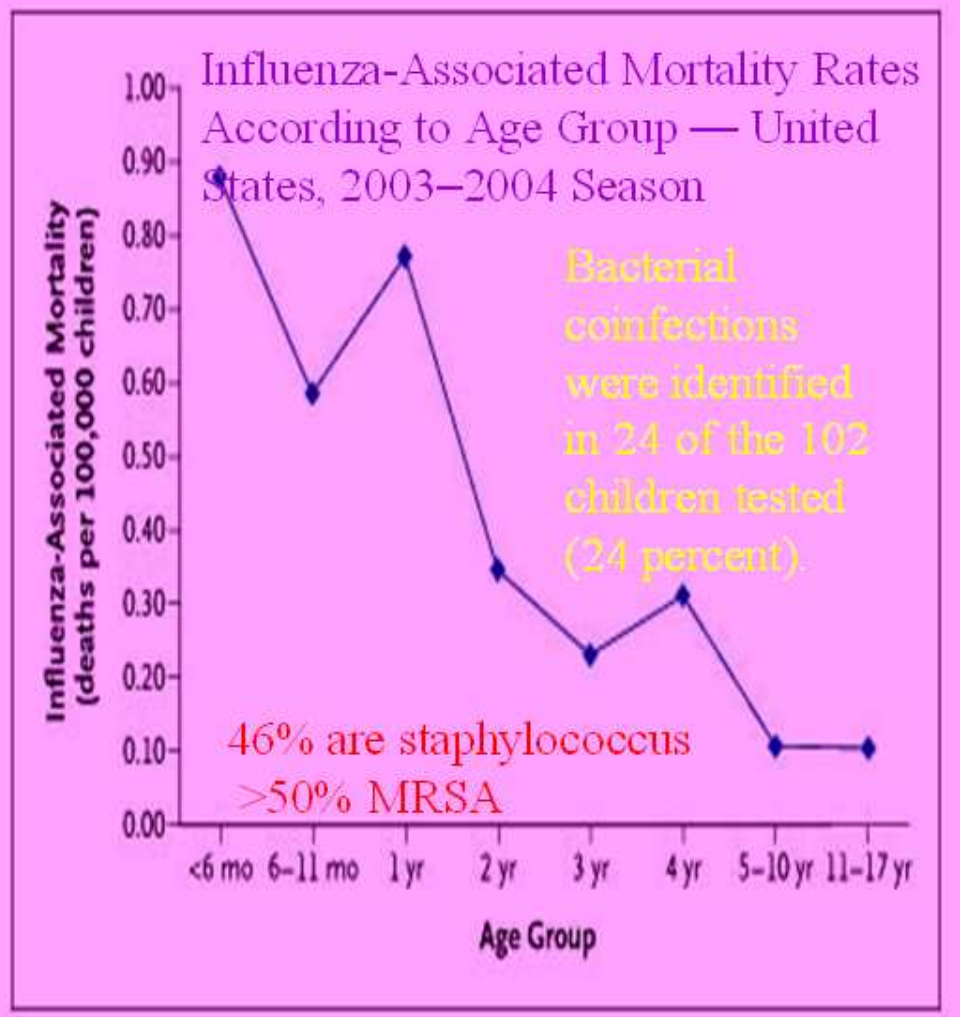
Crum et al. Am. J. Med 2006



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.

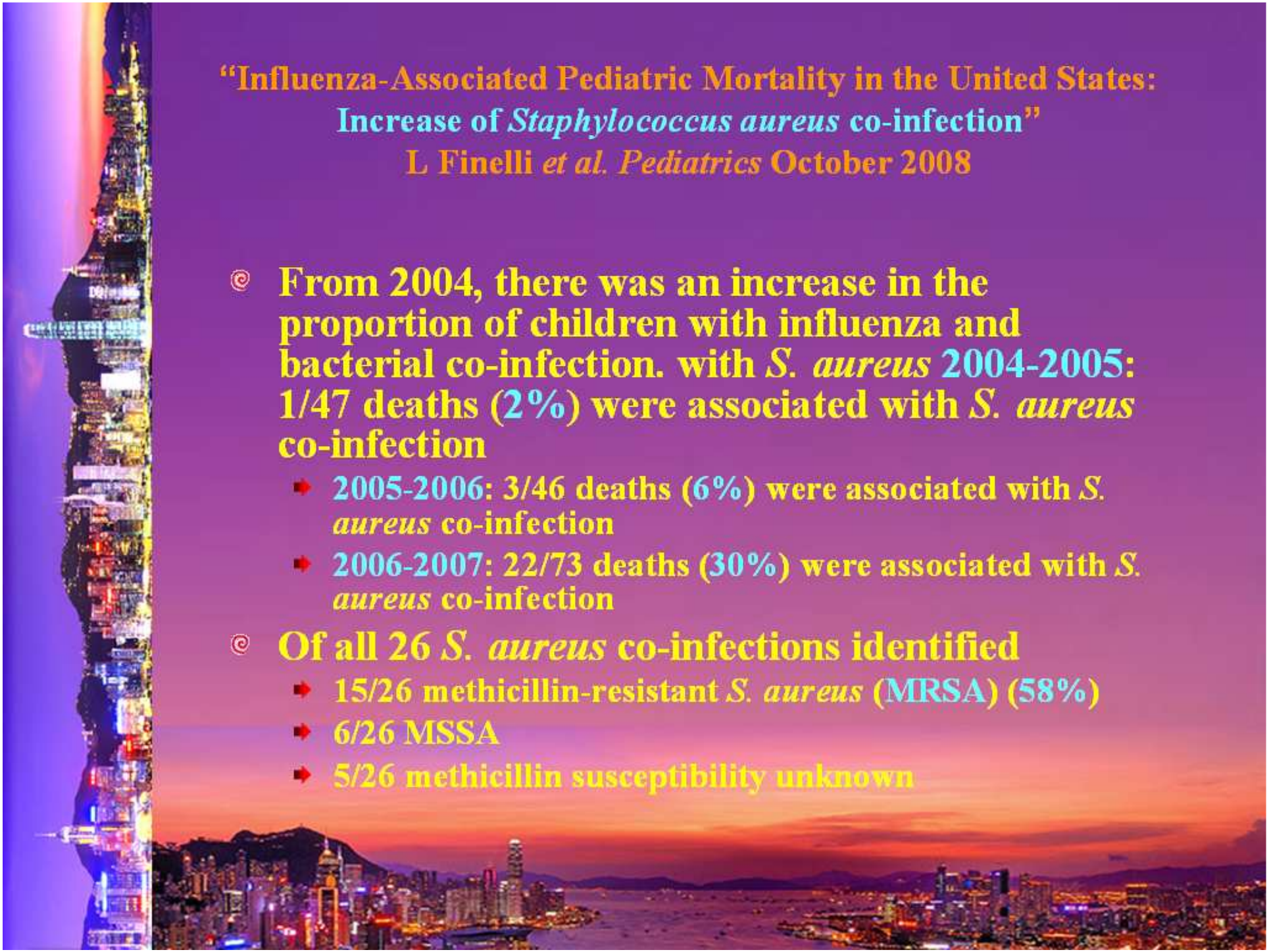
Bogaert D, van Belkum A, Sluijter M, *et al*. Colonisation by *Streptococcus pneumoniae* and *Staphylococcus aureus* in healthy children. **Lancet** 2004;**363**:1871–1872.

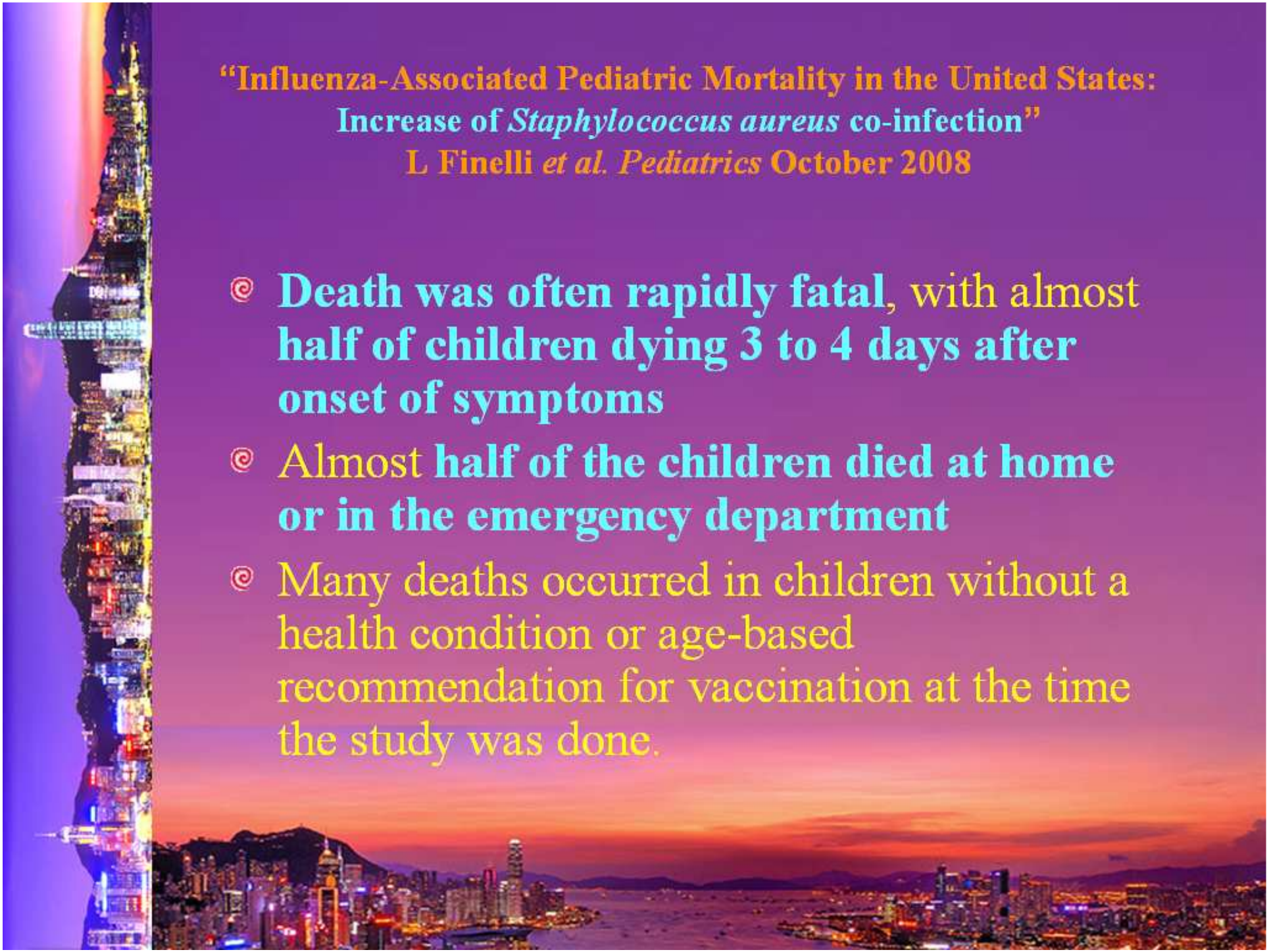


Bacterial Coinfections in 24 Children with Fatal Influenza — United States, 2003–2004 Season.*

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

Vancomycin (1958)

1993 Aborigines of Western Australia
USA 1997
Europe 1999
HKSAR 2004

HA-MRSA

(30% MRSA rate in HA Hospitals)

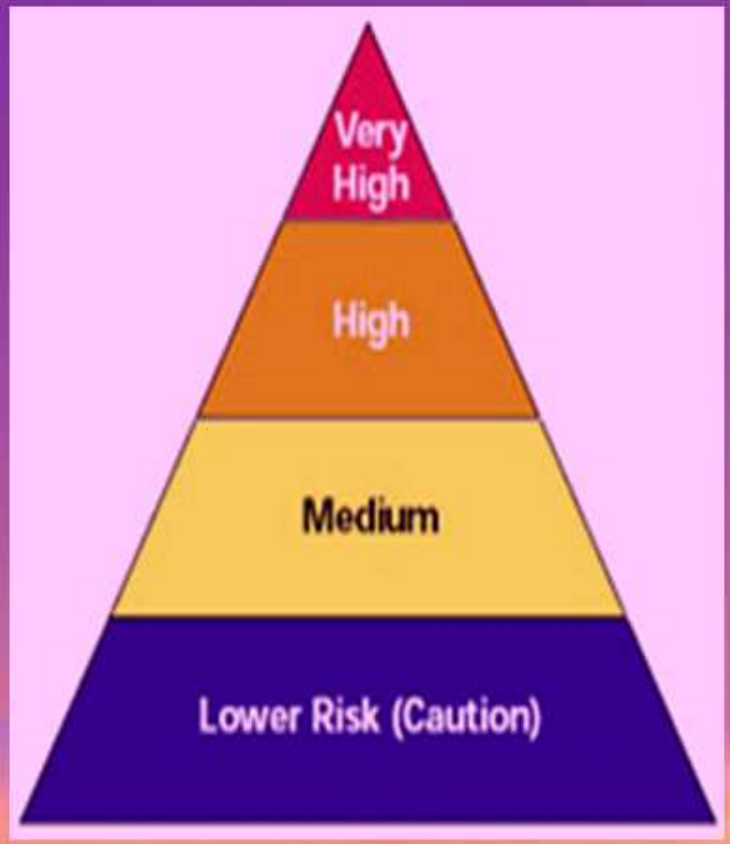
CA-MRSA

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

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 broncoalveolar 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.

Table 2. – 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.

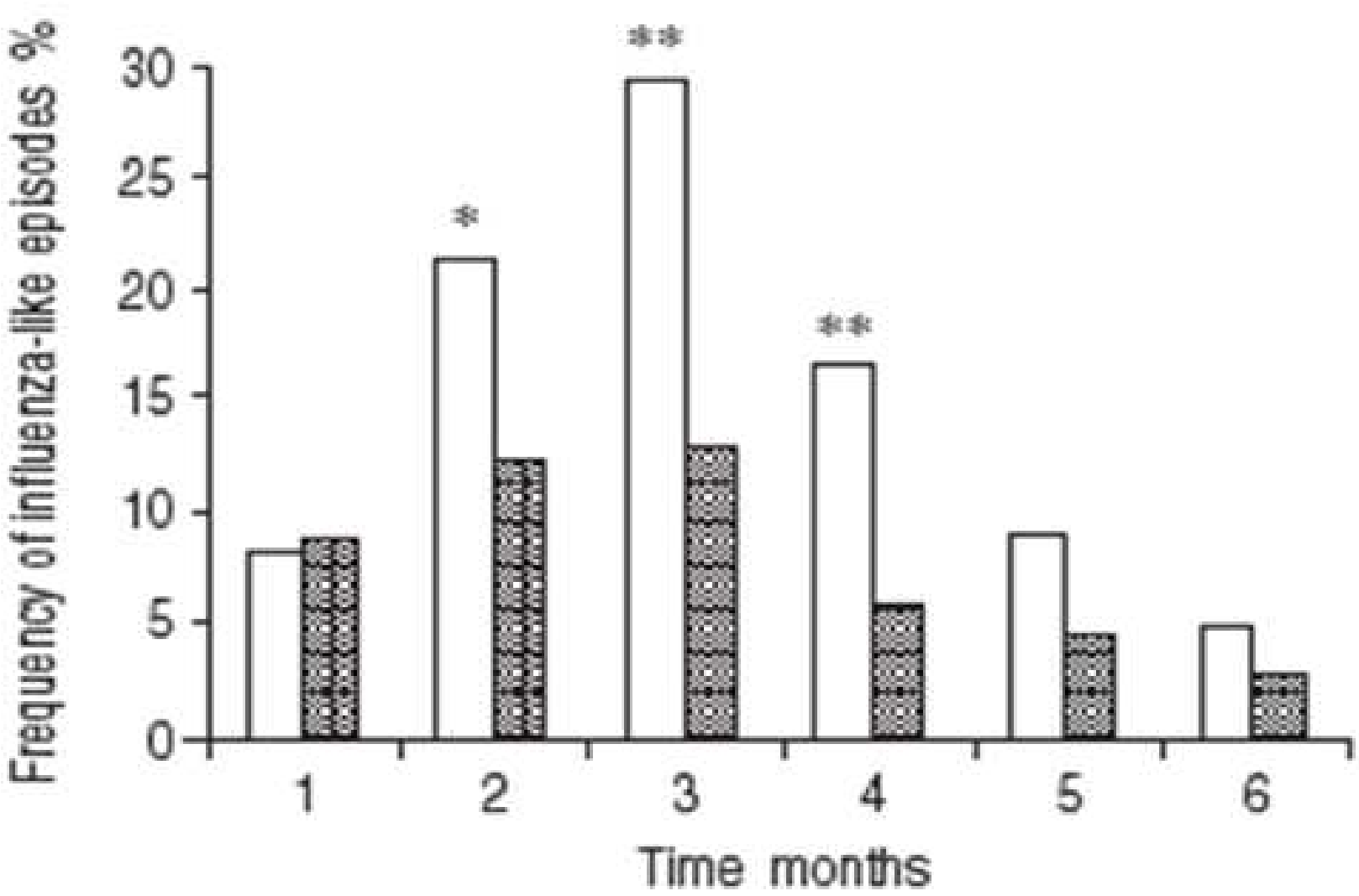


Fig. 1. — Effect of N-acetylcysteine (NAC) treatment on the frequency of influenza-like episodes during the 6 months of treatment. ☐ : placebo; ▨ : NAC. *: $p<0.05$; **: $p<0.01$, significance of difference between the frequency of episodes occurring in the NAC group and in the placebo group, as assessed by Chi-squared analysis.

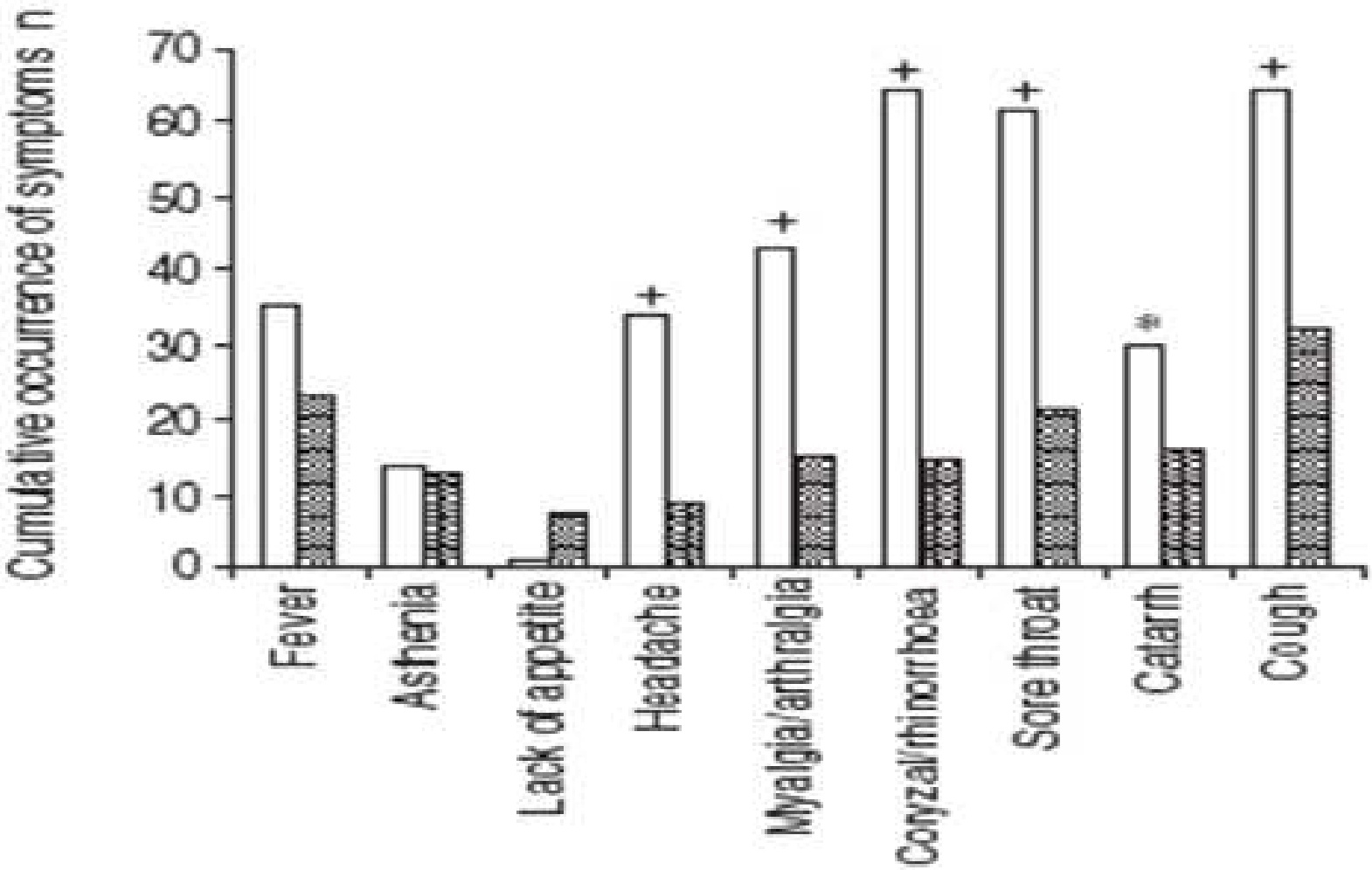


Fig. 2. — Effect of N-acetylcysteine (NAC) treatment on the cumulative occurrence of individual influenza-like signs and symptoms throughout the duration of the study. ▭ : placebo; ▨ : NAC. *: $p<0.05$; +: $p<0.0001$, significance of difference between the frequency of symptoms in the NAC group and the 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.

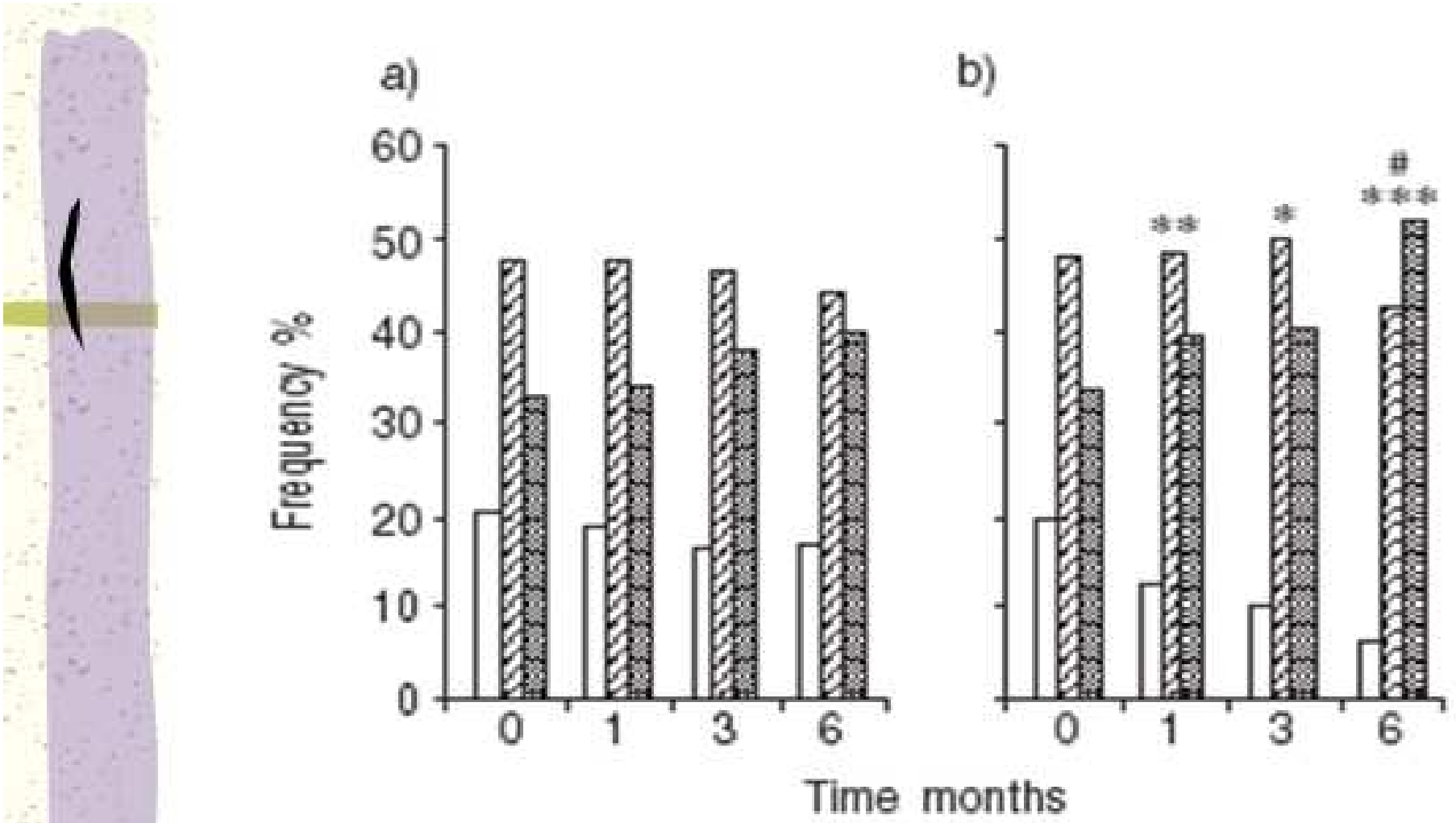


Fig. 3. – Effect of N-acetylcysteine (NAC) treatment on cell-mediated immunity. a) Placebo group; b) NAC-treated group. ▭ : anergy; ▨ : hypoergy; ▩ : normoergy. *:p <0.05; **: p<0.01; ***: p<0.001, significance of difference in the frequency of anergy, within the NAC group, after 1, 3 and 6 months, compared 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.

Table 3. – Distribution of subjects as related to seroconversion towards A/H_1N_1 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

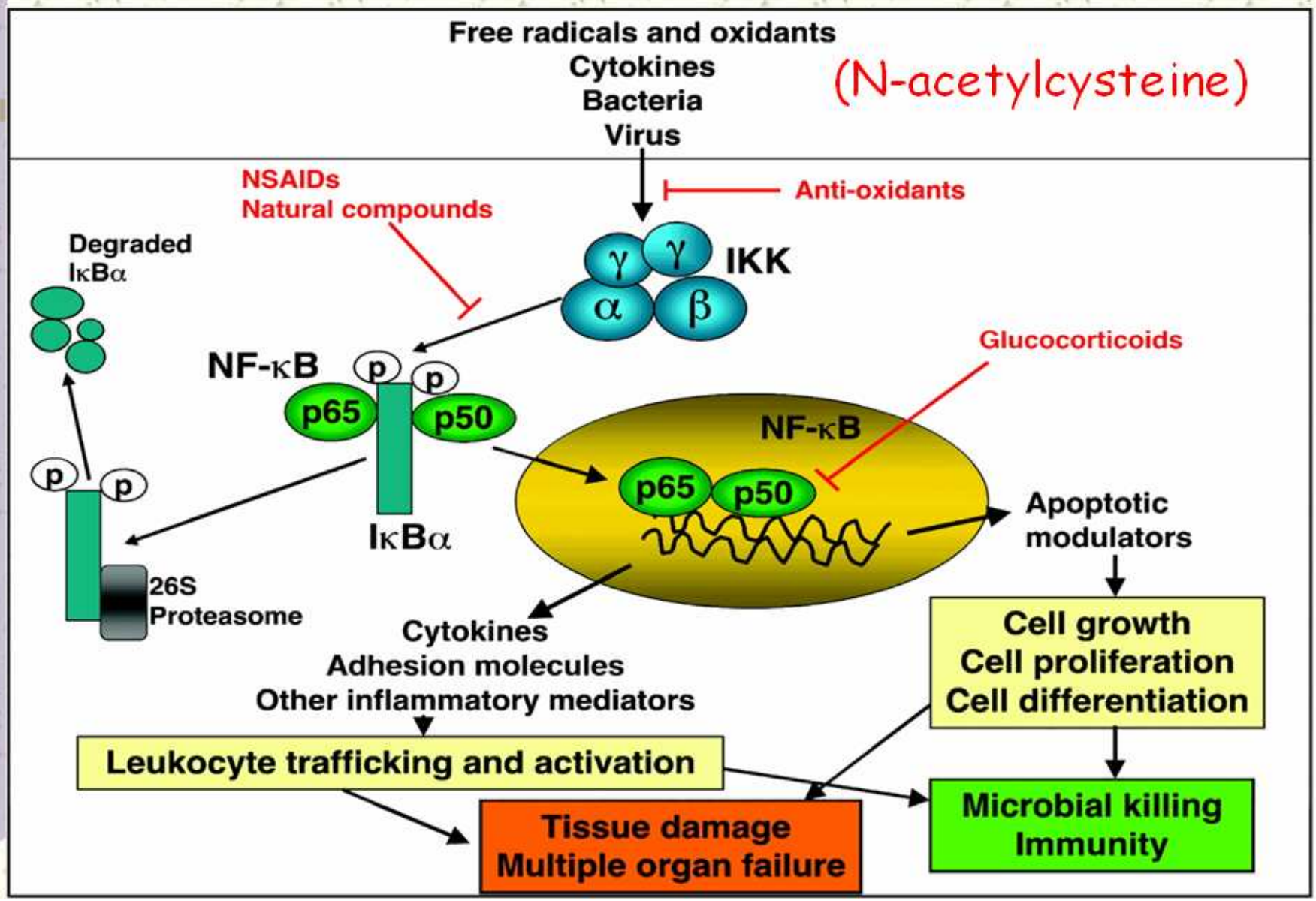
Role in Influenza Infection

Inhibition by NAC

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

TNF-[alpha]-induced activation of NF-κB activity was suppressed by N-acetylcystiene. *N*-acetylcysteine along with vitamin E suppressed **NF-κB** activation by oxidant stress .

NK-kB'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. Behrends 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-kB leading to IL-8 expression and antioxidants inhibit influenza virus infection-induced NF-kB 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

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 formula79% ➔ 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

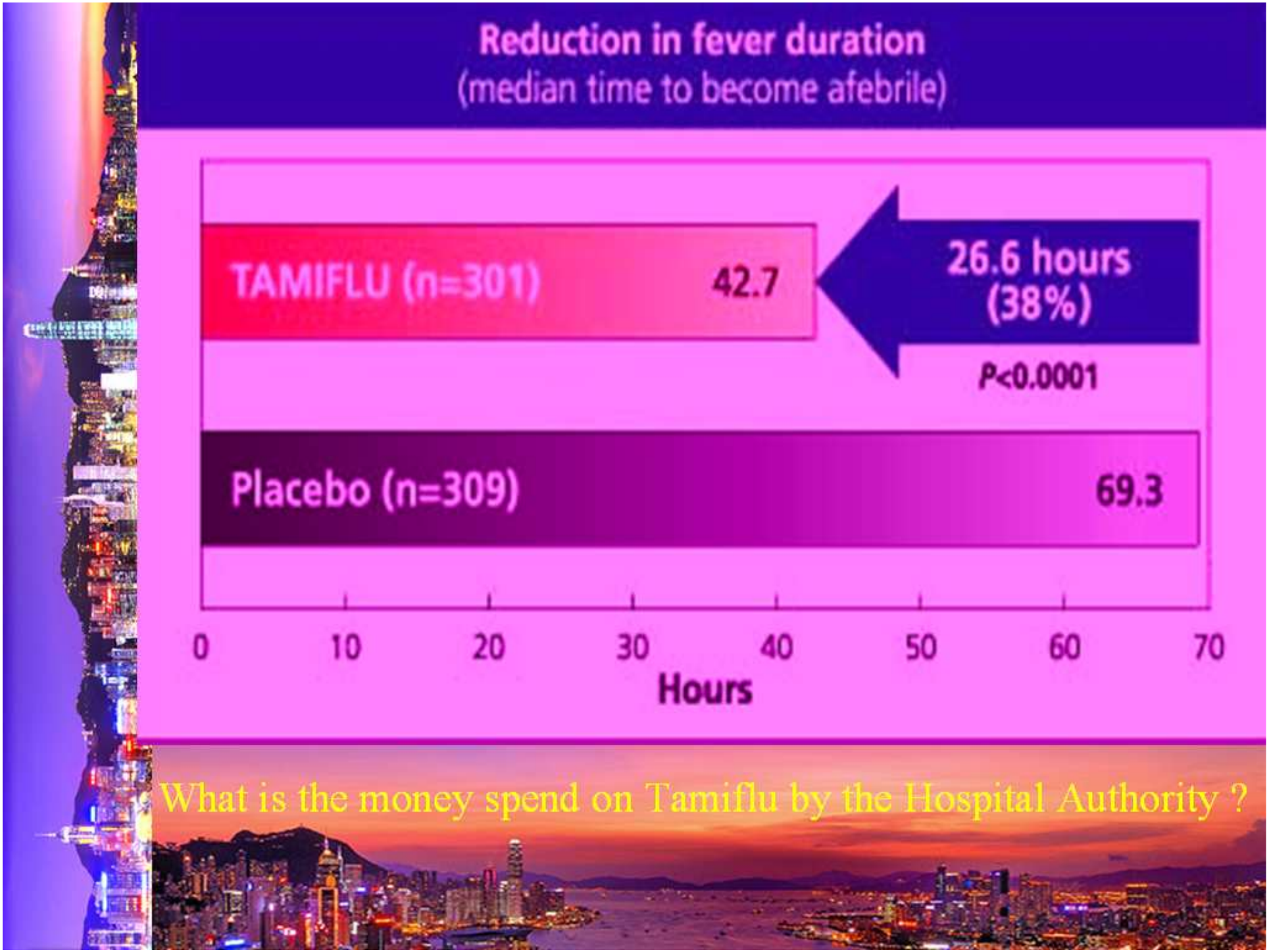
白醋消毒法

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)
TAMIFLU (n=301)
42.7
26.6 hours
(38%)
P<0.0001
Placebo (n=309)
69.3
0
10
20
30
40
50
60
70
Hours
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.

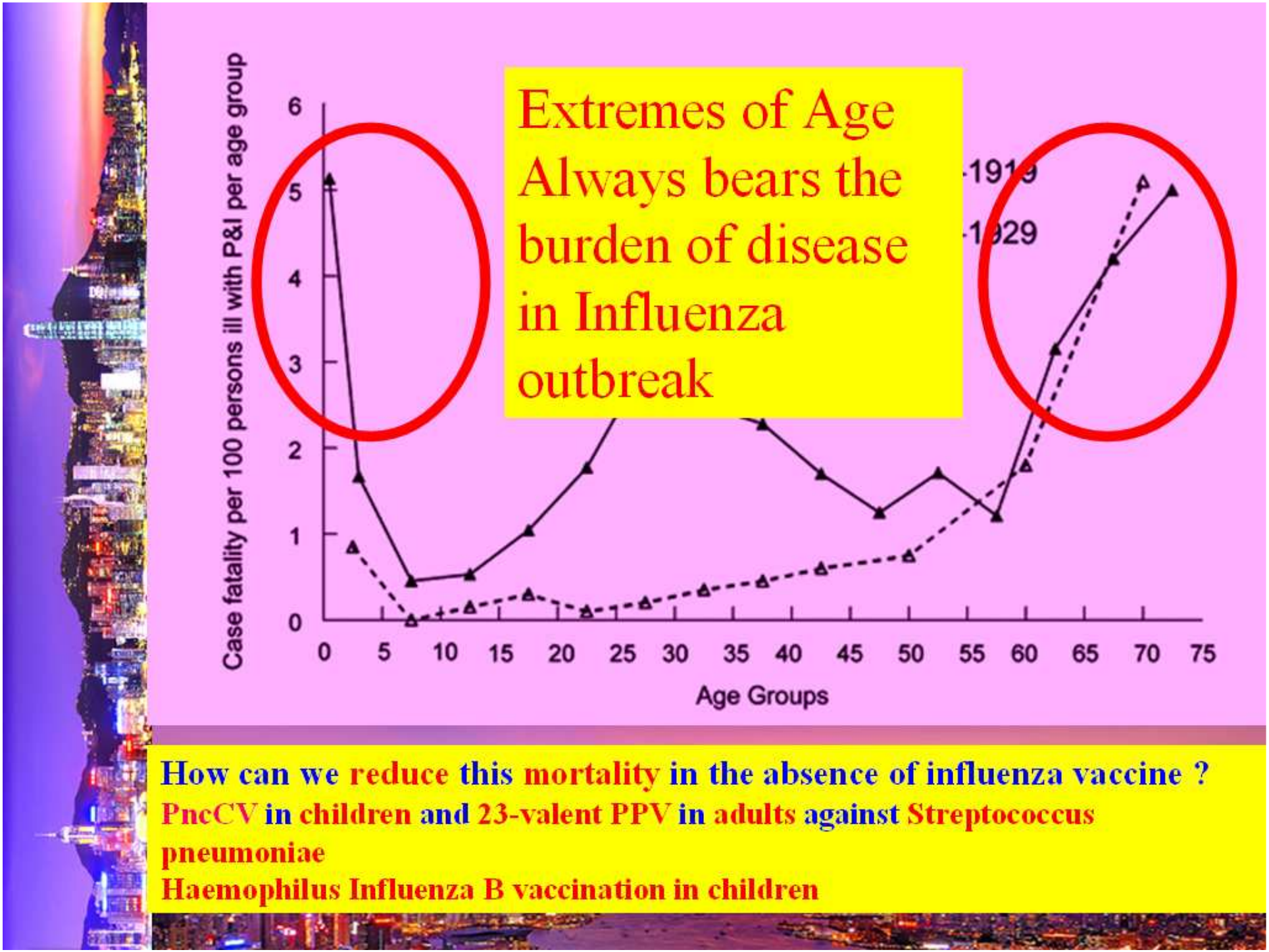
Garozzo A, Tempera G, Ungheri D, Timpanaro R, Castro A.
International Journal of Immunopathology & Pharmacology. 20(2):349-54, 2007 Apr-Jun.]

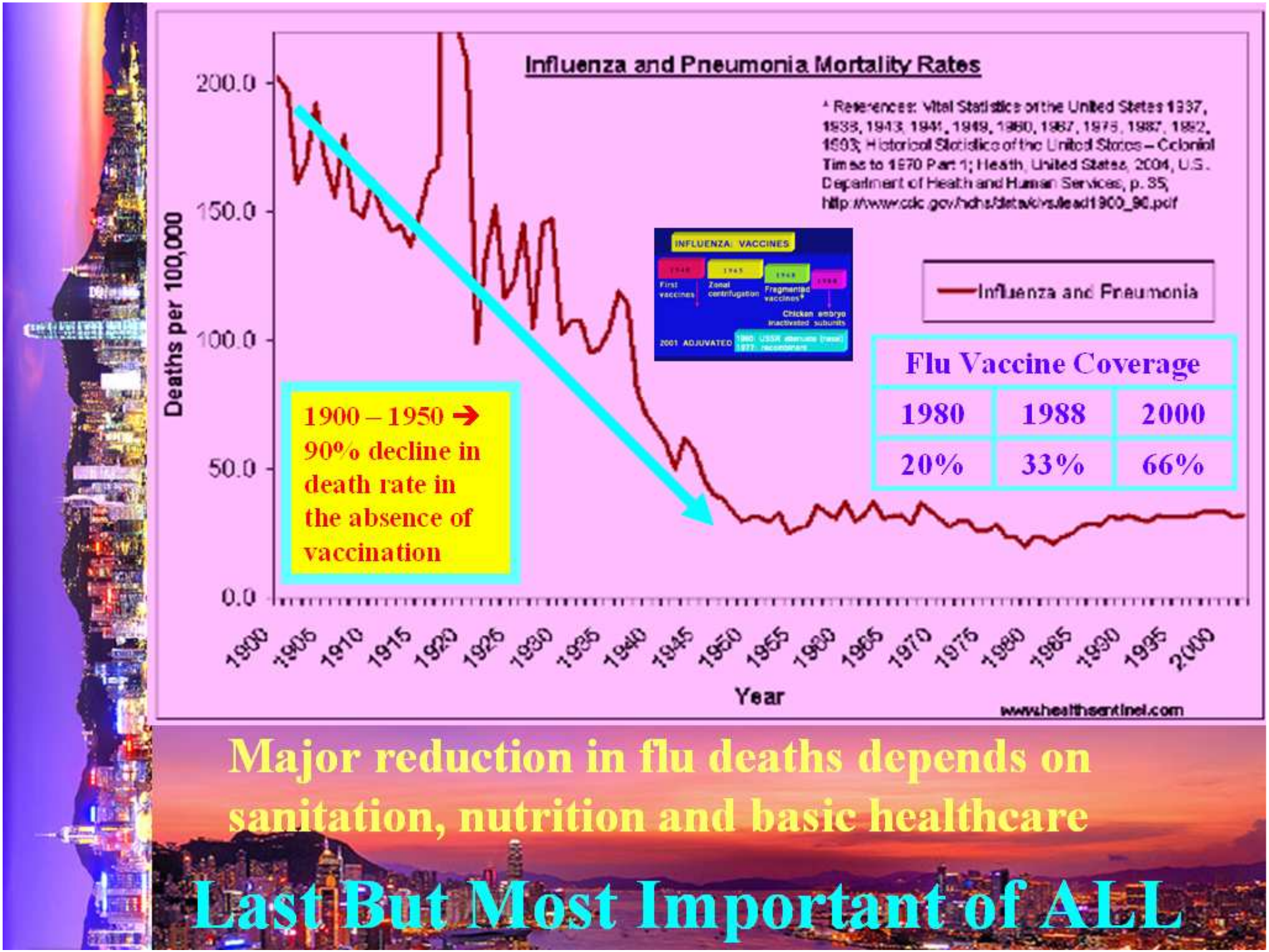
- NAC was given as a single daily dose of 1000 mg/kg starting from 4 h before infection and until day 4 after infection; Oseltamivir was given twice daily at dose of 1 mg/kg/die for 5 days, starting from 4 h before infection.
- 21-days survival.
  - **NAC alone 20%**
  - **Oseltamivir alone 60%**
  - **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.

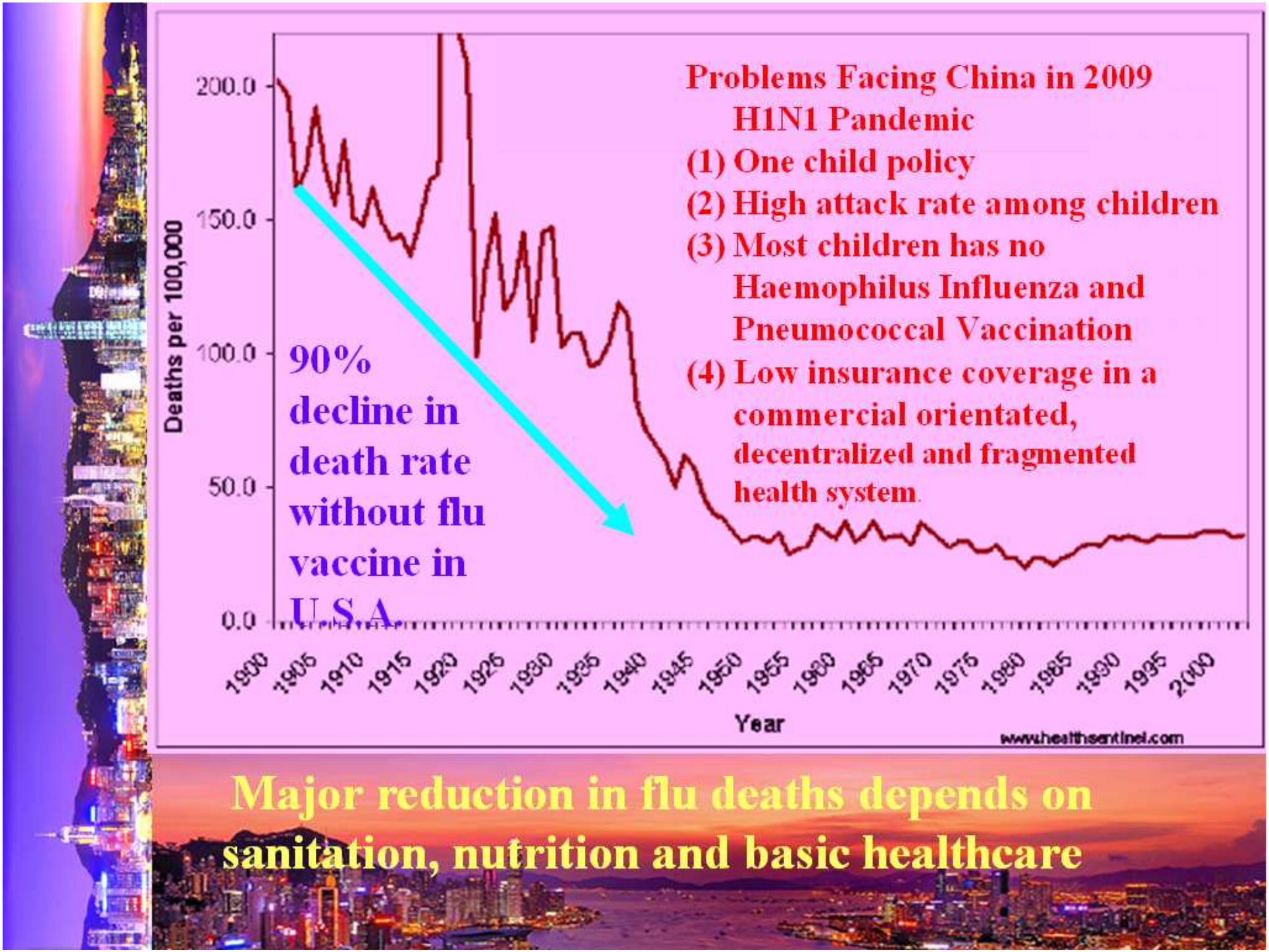
Synergistic combination of N-acetylcysteine and ribavirin to protect from lethal influenza viral infection in a mouse model.

[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.


Extremes of Age
Always bears the burden of disease in Influenza outbreak
Case fatality per 100 persons ill with P&I per age group
0
1
2
3
4
5
6
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
Age Groups
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


Influenza and Pneumonia Mortality Rates
* References: Vital Statistics of the United States 1937, 1938, 1943, 1941, 1949, 1960, 1967, 1975, 1987, 1992, 1993; Historical Statistics of the United States – Colonial Times to 1970 Part 1; Health, United States, 2004, U.S. Department of Health and Human Services, p. 85; http://www.cdc.gov/nchs/data/hus/tables/1900_90.pdf
INFLUENZA VACCINES
First vaccines
Zonal centrifugation
Fragmented vaccines
Chicken embryo inactivated subunits
2001 ADJUVATED
Influenza and Pneumonia
Deaths per 100,000
200.0
150.0
100.0
50.0
0.0
1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000
Year
1900 – 1950 → 90% decline in death rate in the absence of vaccination
Flu Vaccine Coverage
1980 1988 2000
20% 33% 66%
www.healthsentinel.com
Major reduction in flu deaths depends on sanitation, nutrition and basic healthcare
Last But Most Important of ALL


Problems Facing China in 2009
H1N1 Pandemic
(1) One child policy
(2) High attack rate among children
(3) Most children has no Haemophilus Influenza and Pneumococcal Vaccination
(4) Low insurance coverage in a commercial orientated, decentralized and fragmented health system.
90% decline in death rate without flu vaccine in U.S.A.
Deaths per 100,000
200.0
150.0
100.0
50.0
0.0
1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000
Year
www.healthsentinel.com
Major reduction in flu deaths depends on sanitation, nutrition and basic healthcare

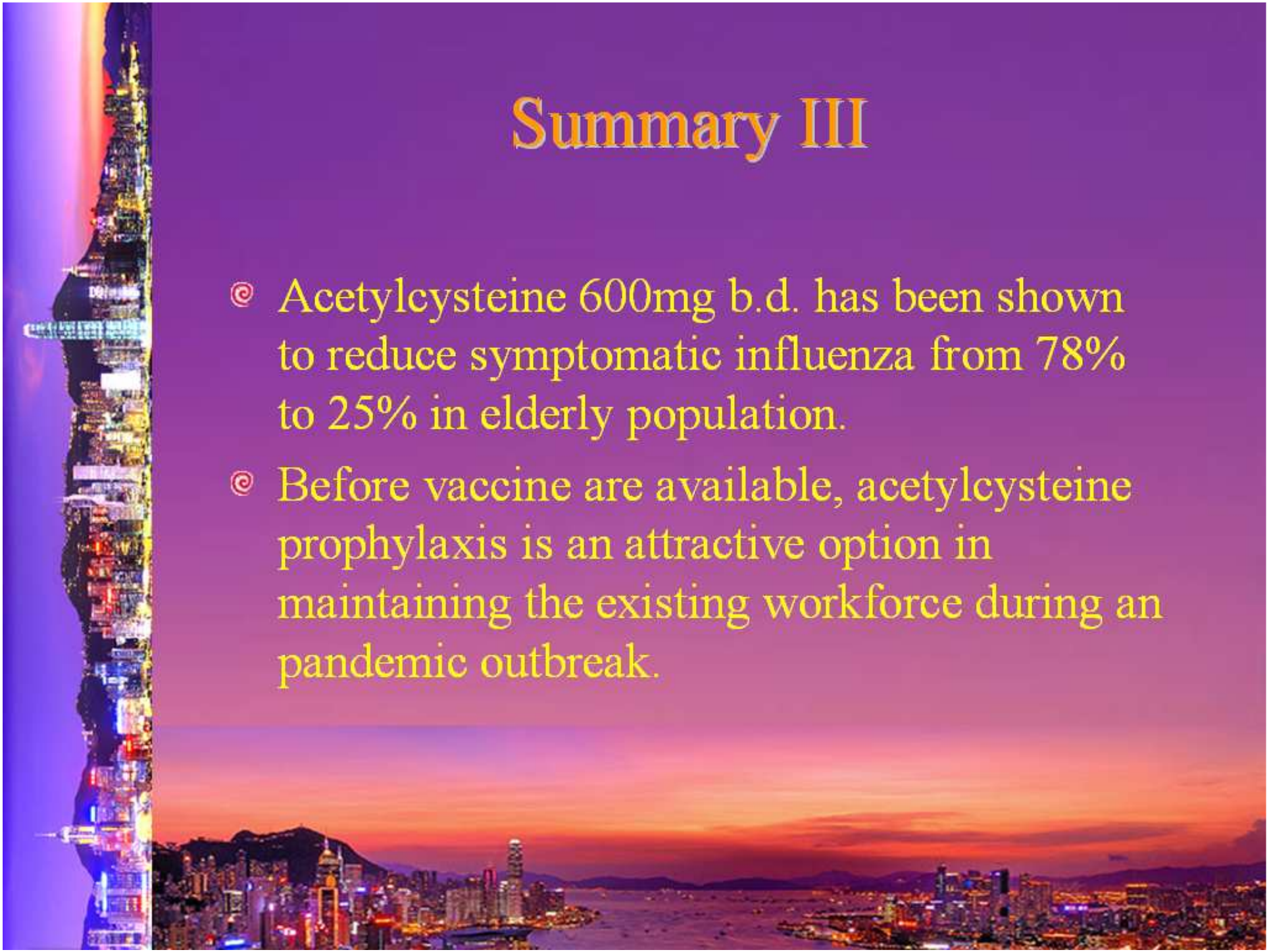
Summary I

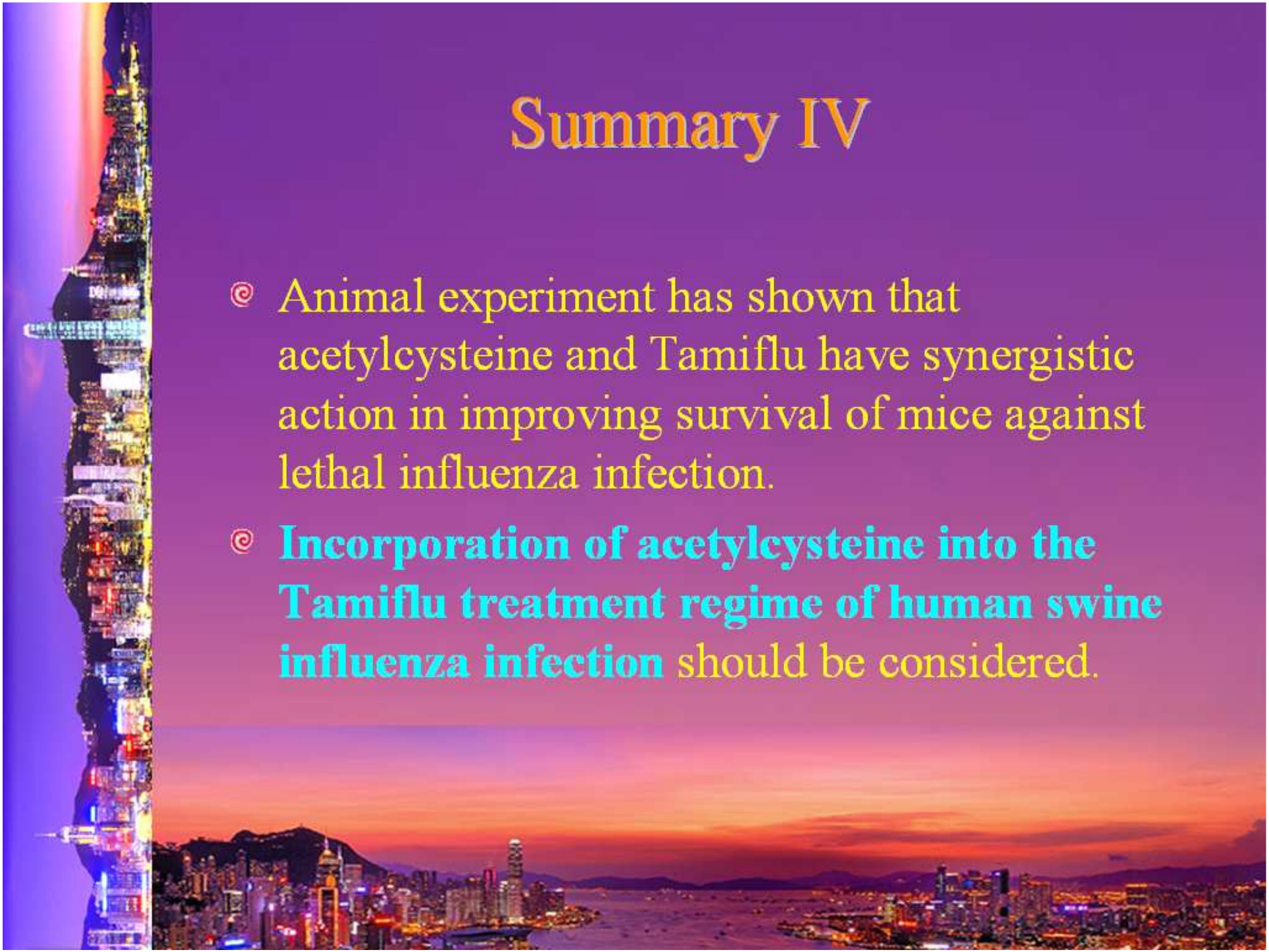
- The 2009 H1N1 Human Swine Influenza has a high attack rate among children.
- The mortality rate would increase 10x in the present of bacterial co-infection.
- 30-80% of the co-infection are related to pneumococcus and Haemophilus influenza which are vaccine preventable.
- **The government should prevent such complication by vaccination 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.
- Hong Kong pneumococcal population has high rate of penicillin resistance.
- **The government should prepare the above at risk population against pneumococcal co-infection by vaccination before pandemic.**


Summary III
Acetylcysteine 600mg b.d. has been shown to reduce symptomatic influenza from 78% to 25% in elderly population.
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!"