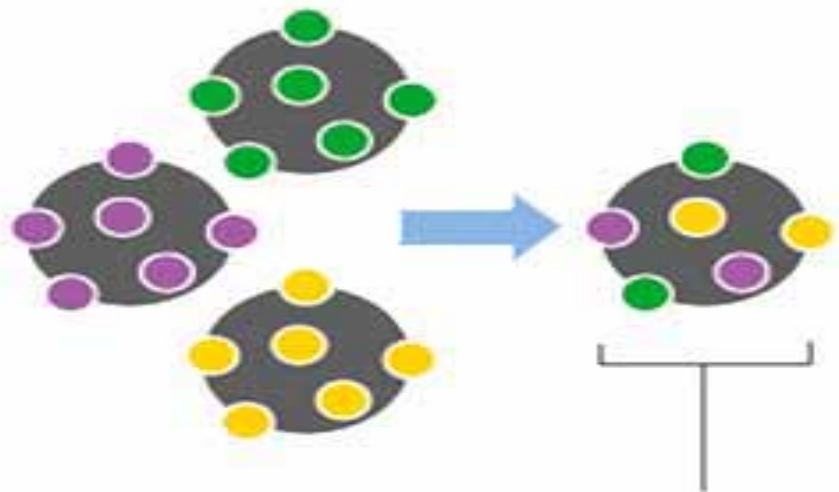# What Is influenza

- 3 types; A/B/C
- A and B- seasonal flu( A leads to pandemics)
- C no epidemics
- Influenza A : 2 main proteins determine the host tropism/ virulence and immunity [ N (1-11) & H (1-18)]
  - Most common is H1N1 and H3N2
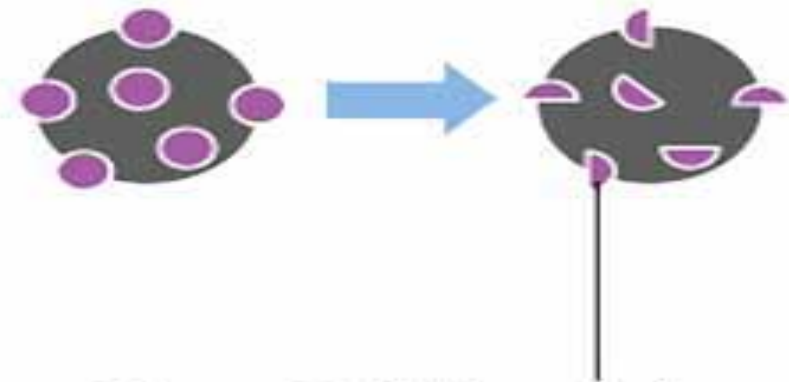- Influenza B
  - B/ Yamagata and B/ Victoria

# How they change

# Why is a pandemic threat is at large
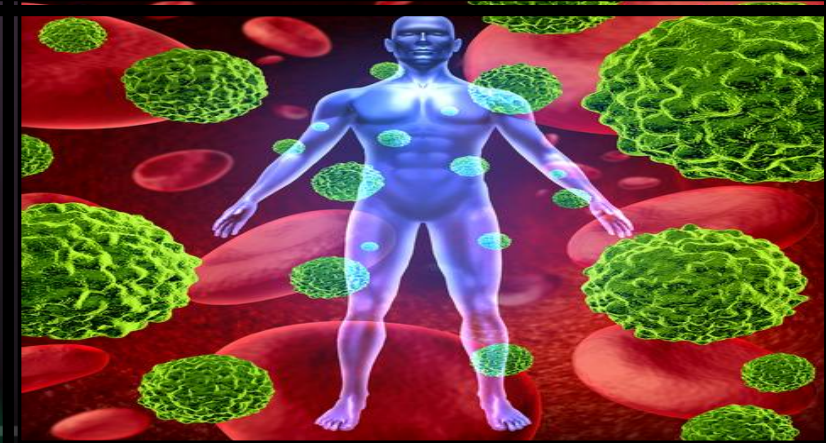
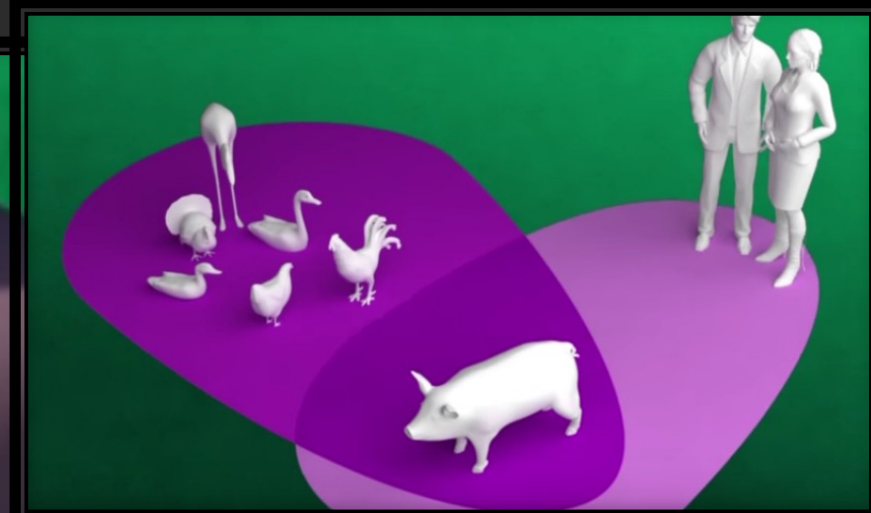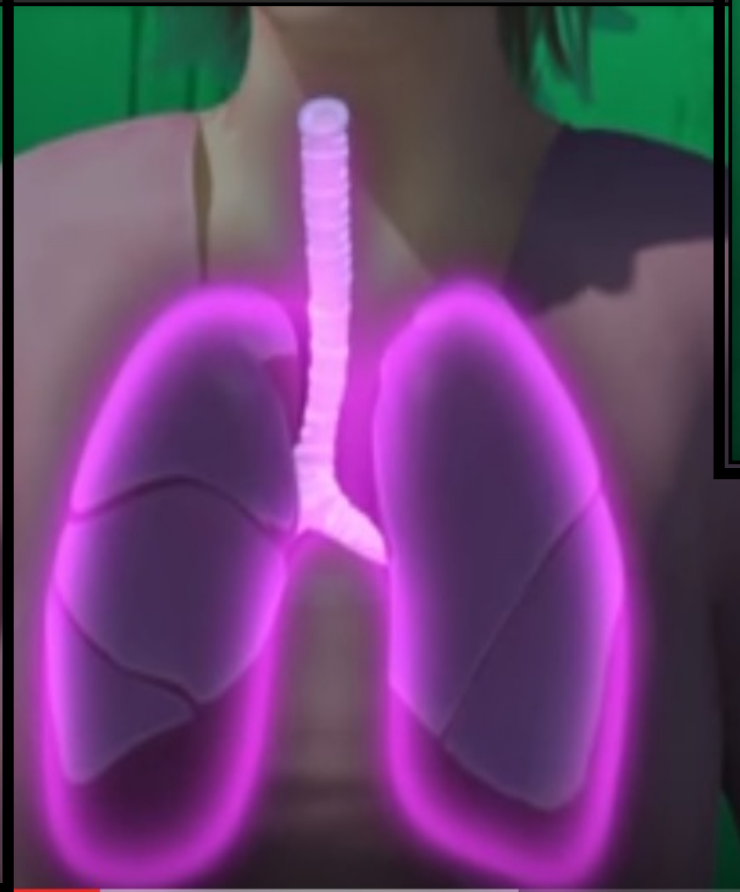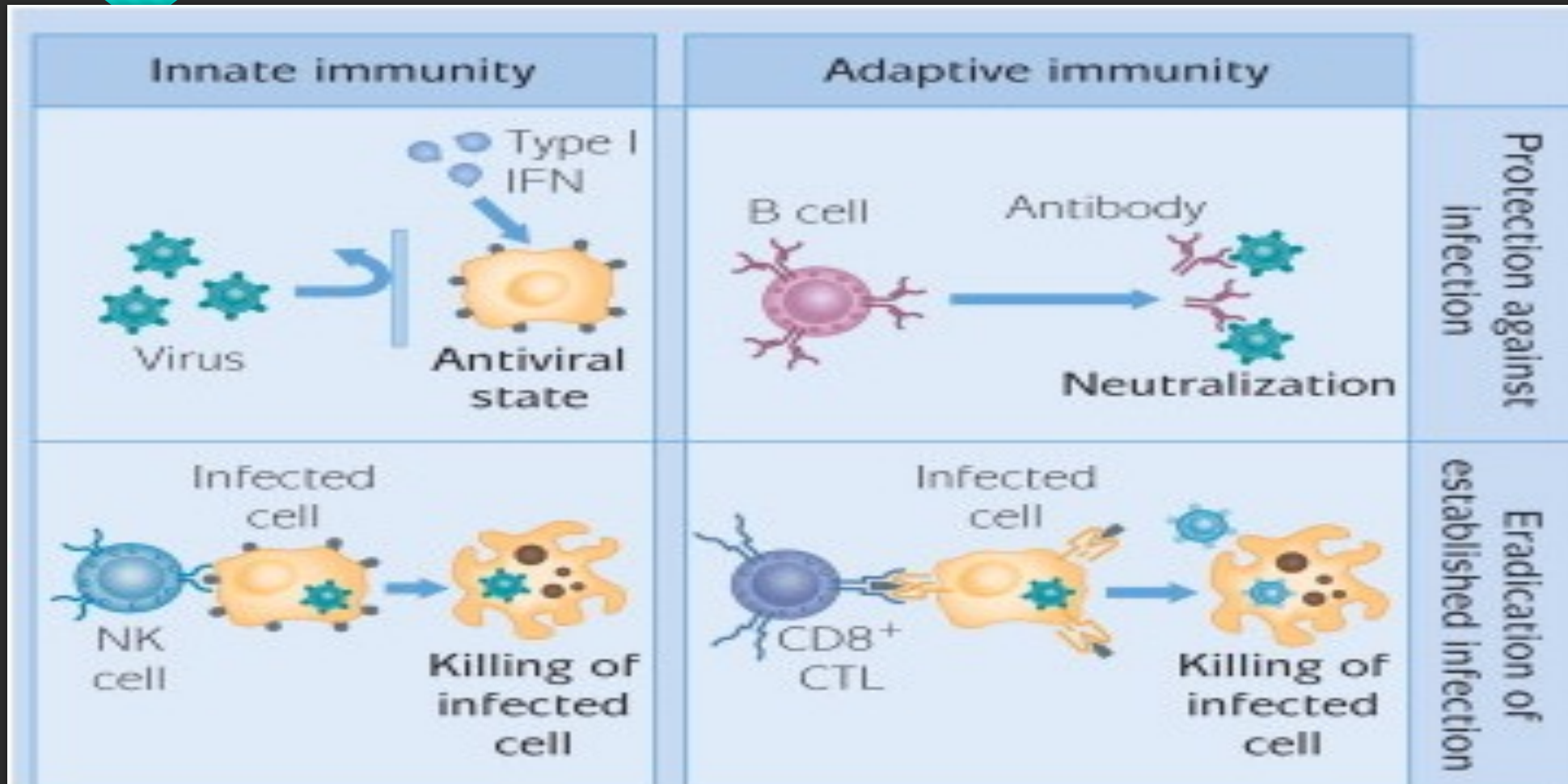# Pathophysiology

# Symptoms of Influenza



Complications

- Sinus and ear infection
- Myocarditis
- Pneumonia
- Encephalitis
- Myositis / Rhabdomyolysis
- Secondary bacterial infection
- Reyes syndrome

# Who are the high risk groups

| |
|---|
| Children <5 years, but especially <2 years* |
| Adults ≥65 years of age |
| Persons with chronic pulmonary (including asthma, chronic obstructive pulmonary disease, and cystic fibrosis), cardiovascular (except hypertension), renal, hepatic, hematologic (including sickle cell disease), endocrine (including diabetes mellitus), metabolic (including inherited metabolic disorders and mitochondrial disorders), and neurologic (including disorders of the brain, spinal cord, peripheral nerve and muscle such as cerebral palsy, epilepsy, stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, and spinal cord injury) disorders |
| Immunosuppression due to disease or medications (including HIV, cancer, and chronic glucocorticoids) |
| Women who are pregnant or postpartum (within two weeks after delivery) |
| Children and adolescents <19 years of age and receiving long-term aspirin therapy |
| Native Americans and Alaskan Natives |
| Extremely obese (body mass index [BMI] ≥40) |
| Residents of nursing homes and other chronic care facilities |

* In young children, rates of hospitalization and mortality are greatest among those <6 months of age.

# Diagnosis Of Influenza

- **Virus Isolation and culture-**
  - in egg culture media and takes 4-5 days

- **IF detection of antigens**
  - Direct and indirect staining for influenza antigen detection are screening tests that have slightly lower sensitivity and specificity than viral culture but have the benefit of yielding results within hours

- **Serology**
  - A 4 fold rise in ab 10- 14 days later is indicative of infection

- **Rt PCR**
  - Can be used to type/ subtype infection
  - 98% sensitive and specific
  - Rapid turnover

# Let History tell the story .....

## 1918: Spanish flu

1. Infected 1/3$^{rd}$ human population with >2.5% CFR
2. Death: 50 to 100million.
3. Attacked in 3 waves over 2years.-
4. Ancestors to the human and swine h1n1/ h3n2 and extinct h2n2 lineage.

## 1957 : Asian Flu; H2N2

1. China to Singapore to Hong Kong and US in a yr.
2. May have arisen reassorment flu virus from wild ducks and preexisting human strains
3. WHO CFR: 2million.
4. Demonstrated the success of vaccination program

## 1968 : HK Flu; H3N2

1. Descended from H2N2 by antigenic shift
2. Who CFR: 1million worldwide
3. Variable impact
4. Possible cross immunity from previous vaccination

## 2009: H1N1

1. 2009 H1N1 was first detected in the United States in April 2009
2. Unrelated to the human seasonal influenza
3. Quadruple reassortment of two swine strains, one human strain, and one avian strain
4. Estimated global mortality 284,000,

# A global disease burden



- One of the most common public health problem
- Seasonal epidemics esp during cold season in the northern and southern hemispheres and all year around in the temperate climates

- 3-5 million cases of severe illnesses every year
- 250 000 and 500,000 deaths every year

# Burden of influenza in asia

○ Literature is limited

○ SEA: 11 to 26% = outpatient fevers and 6-14 % of hospitalized pneumonia*

○ In Thailand : 10.4% of hospitalized pneumonia over 4 yr period (<5yrs and >75yrs)#

USA hospitalization rates children <5yrs with seasonal influenza 1.4/100,000
4yr period prior to 2009



2.4

4.7

0.7-0.9
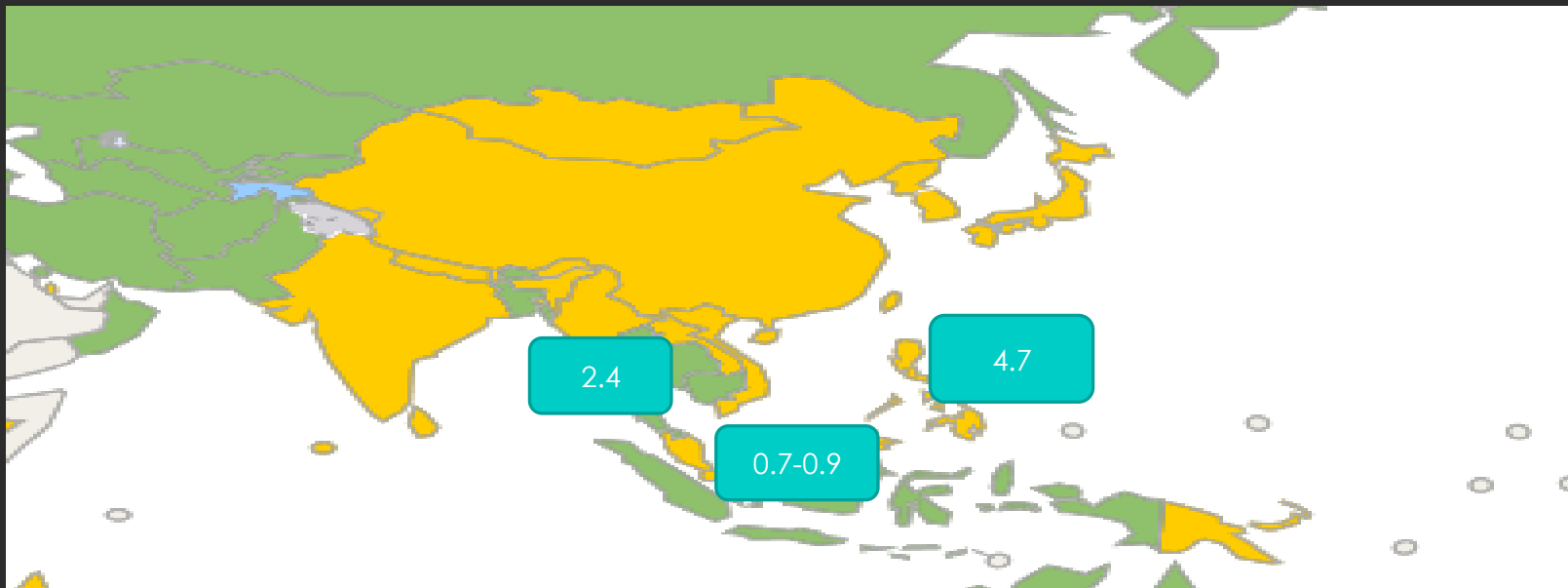
*Simmerman JM.Influenza Other RespirViruses. 2008; 2(3): 81-92.
#Simmerman JM,PLoS One. 2009; 4(11): e7776.

# Burden of influenza in Asia- a snapshot from Singapore



**Monthly Influenza Surveillance**

MINISTRY OF HEALTH SINGAPORE
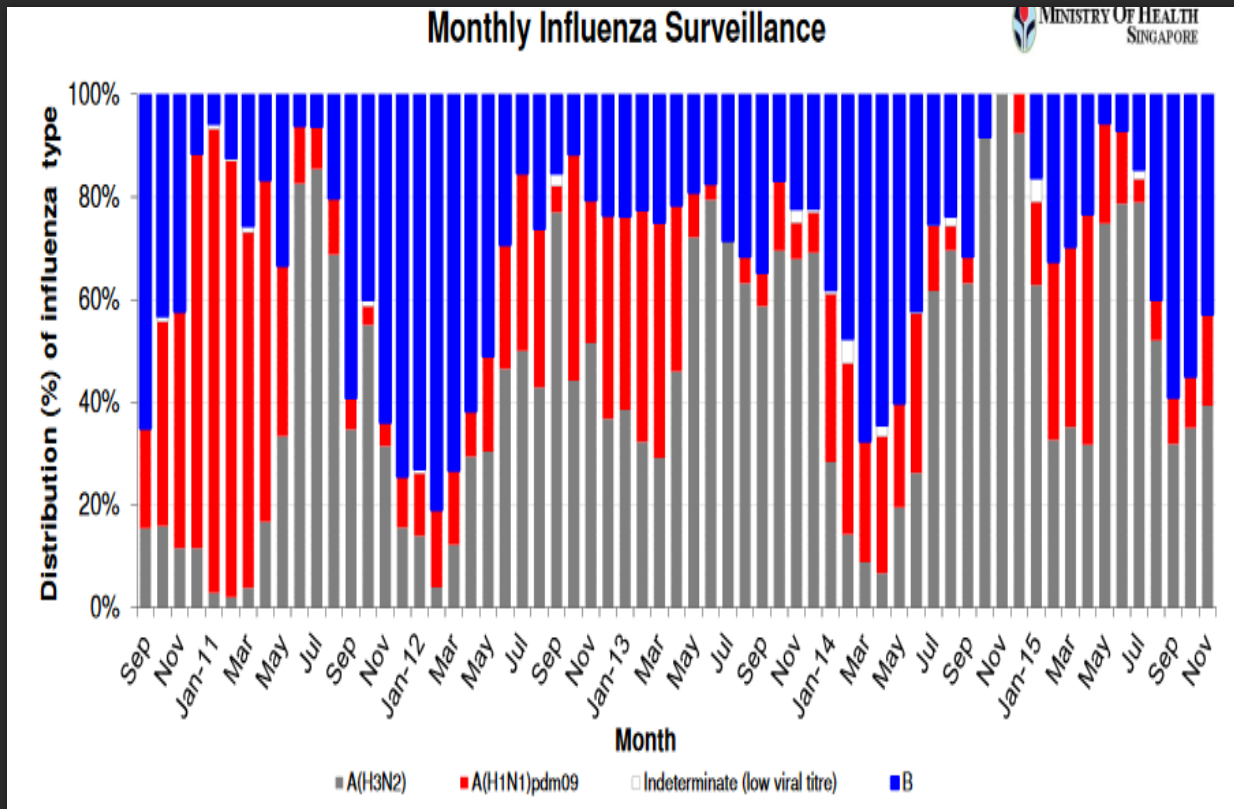
- Average daily number of patients over 5.5 WD seeking treatment for ARI in a week ranges from 2000-2455
  - ILI proportion is abt 1%
- NOV 2015: overall Influenza reported 27.1% from community
  - 45.8% Influenza B
  - 37.5% H3n2
  - 16.7% H1N1pm09

# Socio economic impact of influenza in Asia

- 2004 : in Thailand , identified all hospitalized pneumonia patients using an active, population-based surveillance system
  - Influenza was estimated to result between USD 23- 63 million in 2004 with main contribution due to missed work days
- In China
  - the cost of a child attending OPD with influenza was USD 127, which is about 30% of annual household income in urban setting
  - Direct cost of hospitalization was USD 624

# Seasonal Influenza trend in Malaysia
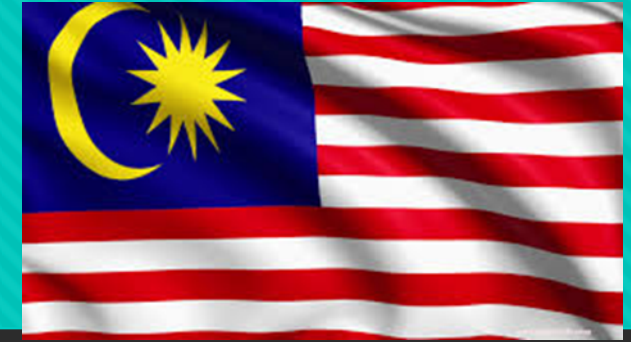
- Occurs year around with no clear seasonal trends

- Generally Influenza A is more common,

- Data capturing is still limited and underreported that can lead to mismatch in the circulating strain and the available vaccination

Proportions of Influenza A and B Viruses in Malaysia Surveillance 2003-2013

Influenza B    Influenza A

| Year | Influenza B | Influenza A |
|------|-------------|-------------|
| 2003 | 18% | 82% |
| 2004 | 32% | 68% |
| 2005 | 100% | 0% |
| 2006 | 48% | 52% |
| 2007 | 34% | 66% |
| 2008 | 18% | 82% |
| 2009 | 8% | 92% |
| 2010 | 11% | 89% |
| 2011 | 9% | 91% |
| 2012 | 81% | 19% |
| 2013 | 76% | 24% |
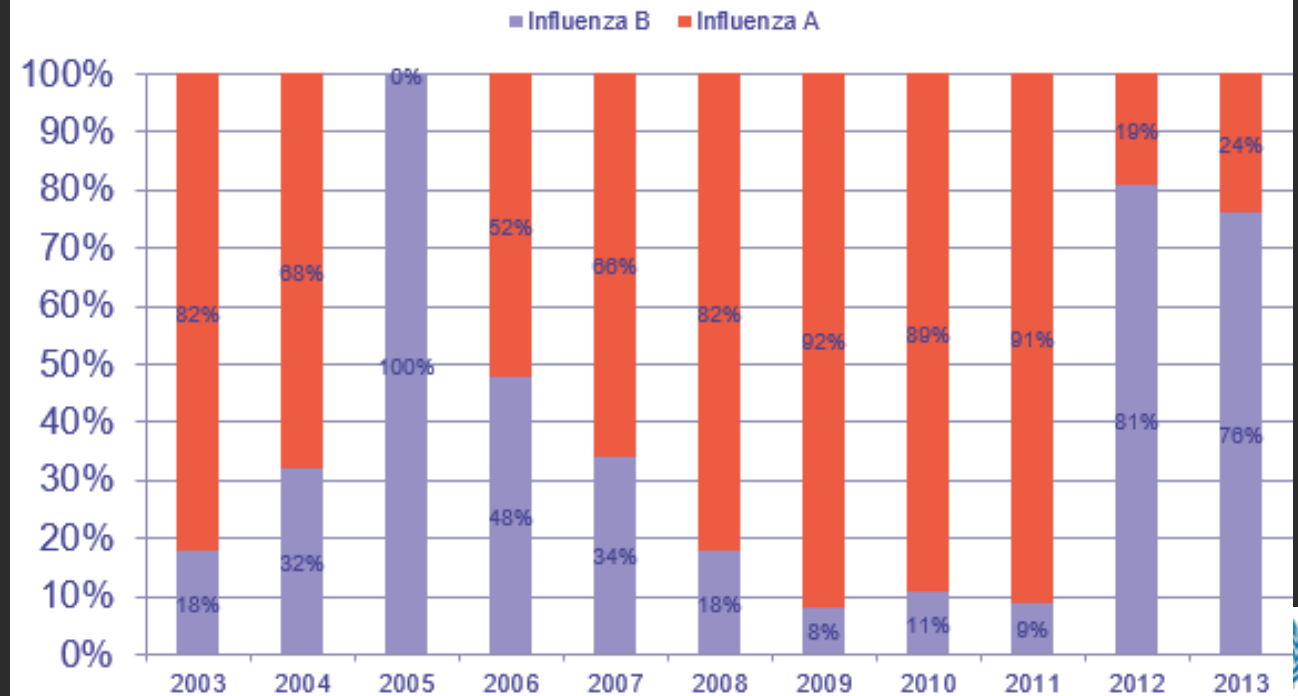
# Vaccine mismatch?

Circulating strains 2003-2015
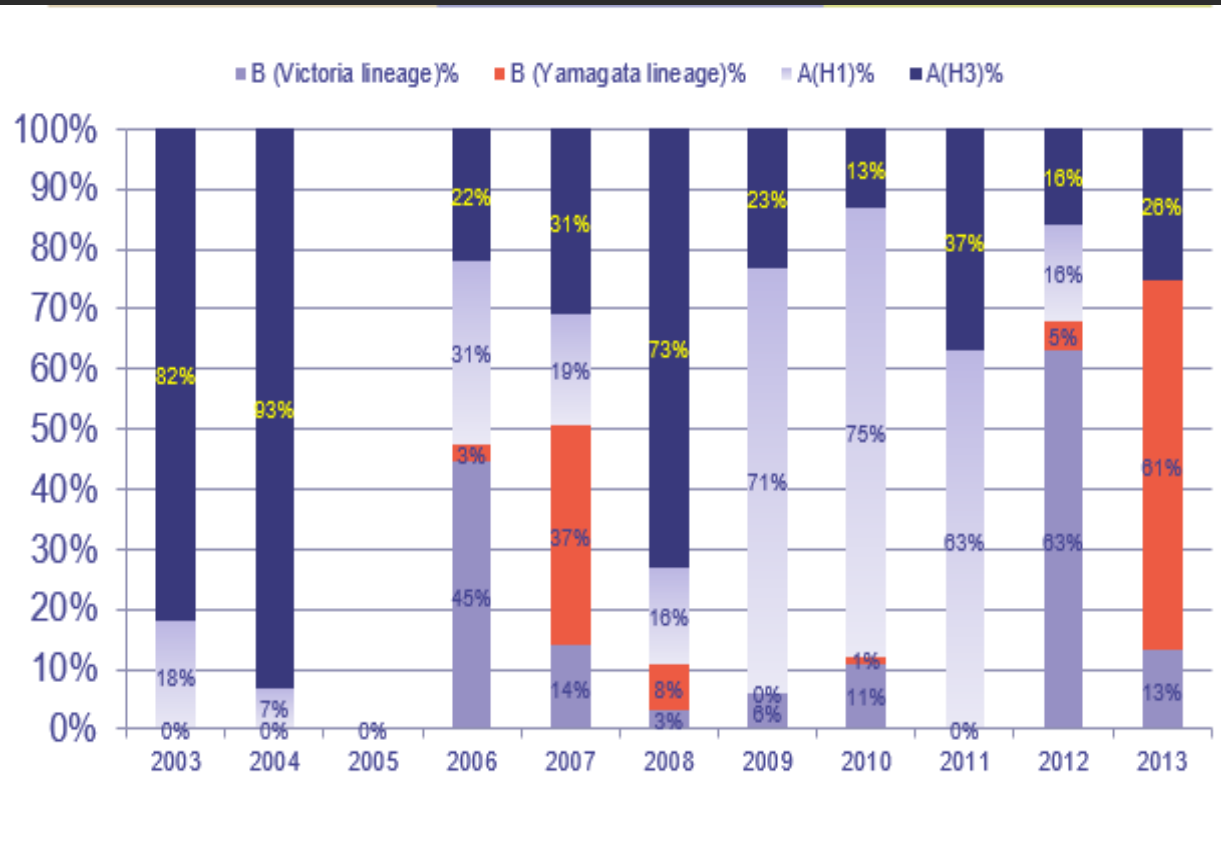


Circulating Influenza B lineages Malaysia 2003-2013
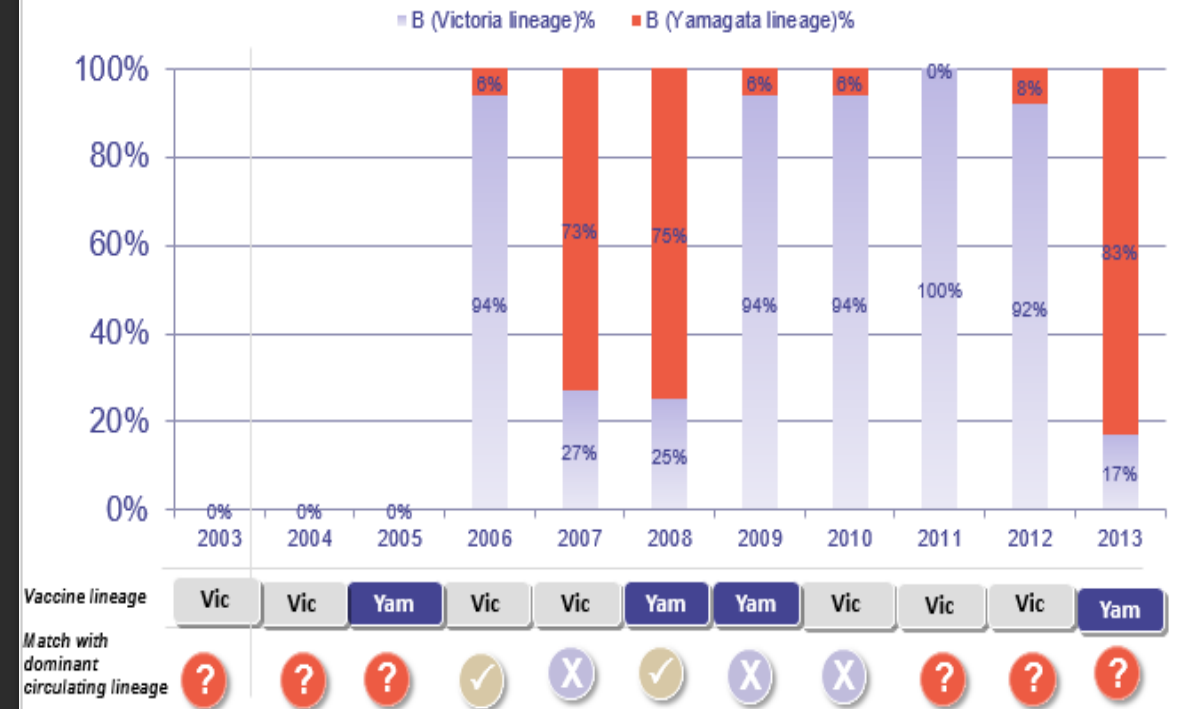
# Malaysian Influenza Surveillance System ( MISS)
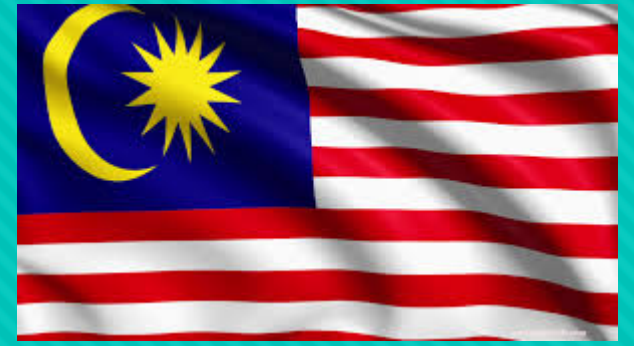
○ Collects data by disease based and laboratory based surveillance from preselected sentinel sites

**Sentinel Sites**

Collects data on ILI cases
Def :
- • Measured fever of ≥ 38oC;
- • and cough;
- • with onset within the last ten (10) days.

Collects data on SARI
History of fever or measured fever of ≥ 38oC;
- •and cough;
- •with onset within the last 10 days;
- • and requires hospitalization.

**NP swab/ throat Swab/ sputum/ BAL/ tissue**

**NPHL/ Virology Unit of IMR**
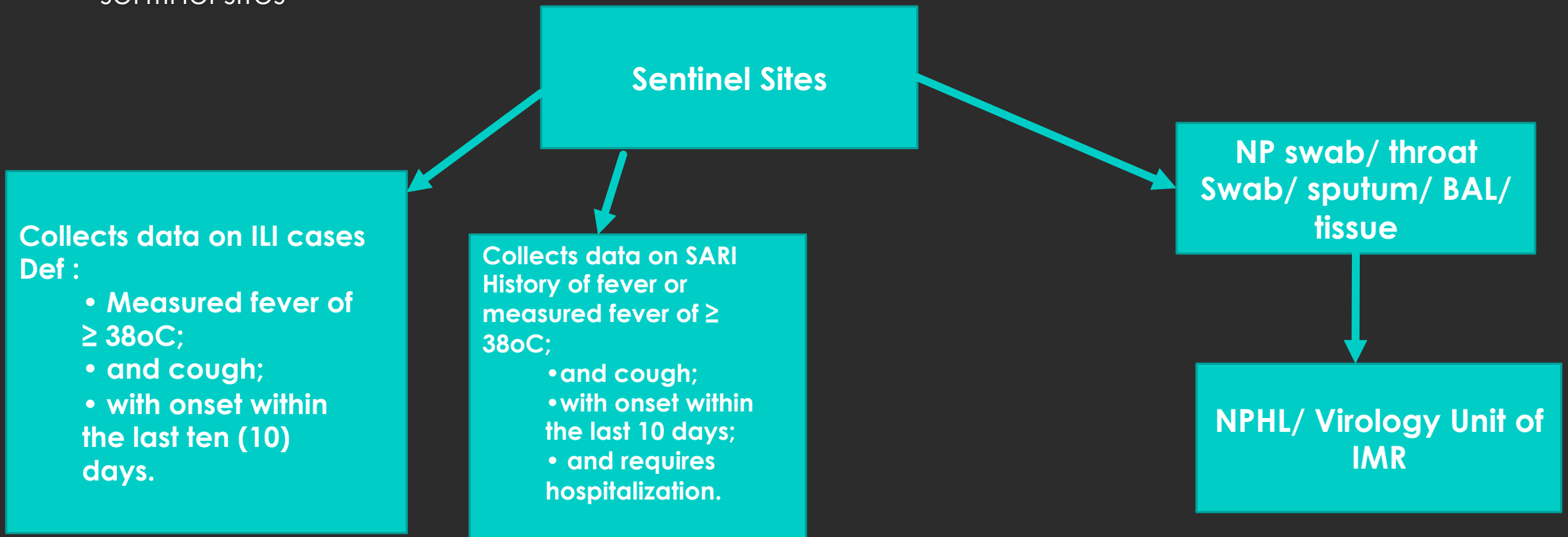
# Major cause of morbidity and mortality- Malaysian Health Facts 2016

## Ten Principal Causes of Hospitalisation in MoH & Private Hospitals, 2015[P]

| | | |
|---|---|---|
| 1. | Pregnancy, childbirth and the puerperium | 19.90% |
| 2. | Diseases of the respiratory system | 13.10% |
| 3. | Certain infectious and parasitic diseases | 11.12% |
| 4. | Injury, poisoning and certain other consequences of external causes | 7.54% 7.17% |
| 5. | Diseases of the circulatory system | |
| 6. | Certain conditions originating in the perinatal period | 6.36% |
| 7. | Diseases of the digestive system | 5.94% |
| 8. | Diseases of the genitourinary system | 4.96% |
| 9. | Neoplasms | 4.11% |
| 10. | Factors influencing health status and contact with health services | 3.75% |

## Ten Principal Causes of Death* in MoH Hospitals, 2015[P]

| | | |
|---|---|---|
| 1. | Diseases of the circulatory system | 22.77% |
| 2. | Diseases of the respiratory system | 18.54% |
| 3. | Neoplasms | 13.56% |
| 4. | Certain infectious and parasitic diseases | 13.20% |
| 5. | External causes of morbidity and mortality | 9.74% |
| 6. | Diseases of the digestive system | 4.82% |
| 7. | Diseases of the genitourinary system | 4.32% |
| 8. | Certain conditions originating in the perinatal period | 3.16% |
| 9. | Endocrine, nutritional and metabolic diseases | 2.08% |
| 10. | Disease of the nervous system | 1.51% |

# Number of influenza cases detected from 88 sentinel sites ( 2015)

PRELIMINARY DIAGNOSIS

| Count of DiagnosisPartCode | Column Labels | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Row Labels | Johor | Pahang | Perlis | Sabah | Sarawak | Selangor | wpkl&putrajaya | Grand Total |
| J10 | | | 98 | | | 89 | 54 | 241 |
| J10.1 | | 29 | 52 | | 9 | 94 | 62 | 246 |
| J10-J18 | 410 | 2 | 1514 | 114 | 53 | 5457 | 2307 | 9857 |
| J12 | | 23 | 25 | 30 | | 148 | 44 | 270 |
| J14 | | | | 23 | | | | 23 |
| J15 | 46 | | 265 | 617 | 12 | 279 | 277 | 1496 |
| Grand Total | 456 | 54 | 1954 | 784 | 74 | 6067 | 2744 | 12133 |

# Statistics on discharge (encounter) and death in MOH hospitals for influenza



## 2014
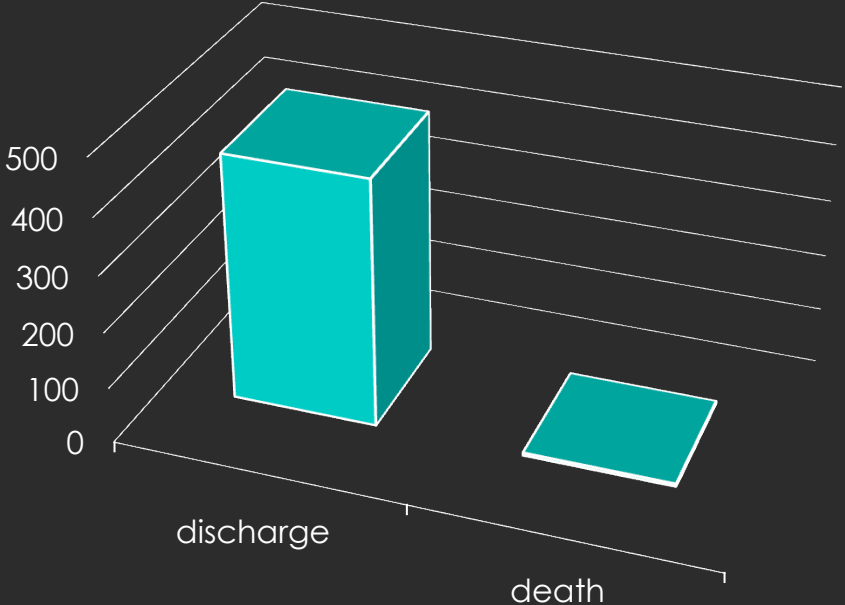
| | discharge | death |
|---|---|---|
| 2014 | 440 | 5 |

2014

## 2015
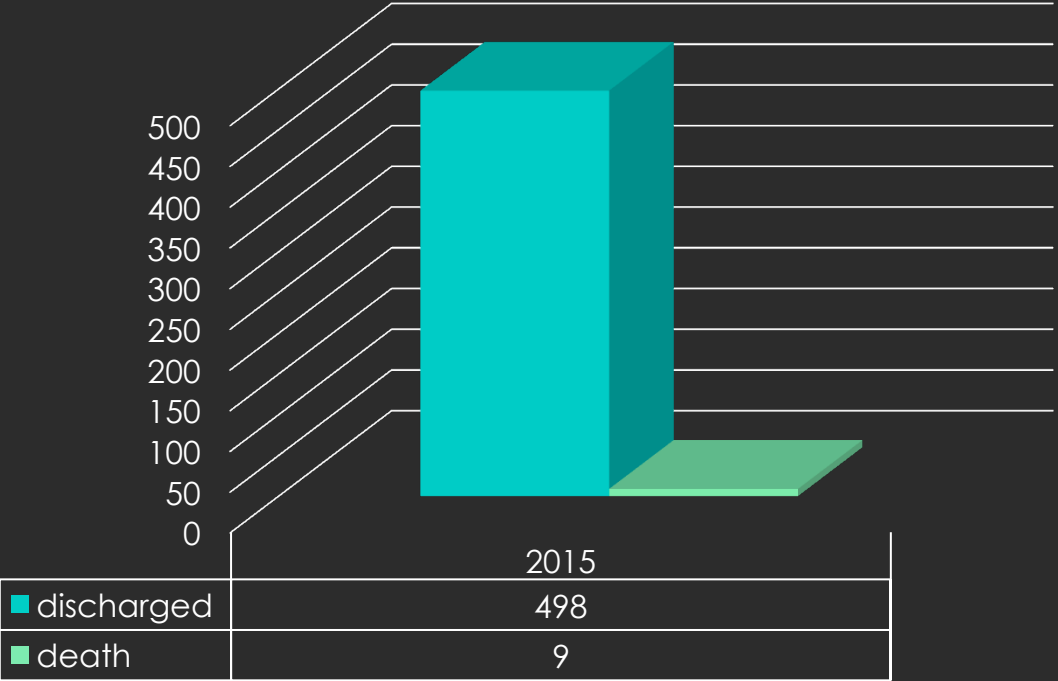
| | 2015 |
|---|---|
| discharged | 498 |
| death | 9 |

discharged ■ death

# Epidemiology and seasonality of respiratory viral infections in hospitalized children in Kuala Lumpur, Malaysia: a retrospective study of 27 years

Chee-Sieng Khor[1], I-Ching Sam[1,2], Poh-Sim Hooi[2], Kia-Fatt Quek[3] and Yoke-Fun Chan[1*]

- Retrospective Study from 27 years (1198-2008) carried out to look at the etiology of viral infections

- 10269 samples from children ≤ 5 years were sent for respiratory virus detection,

- 2708 (26.4%) were positive for the common respiratory viruses.
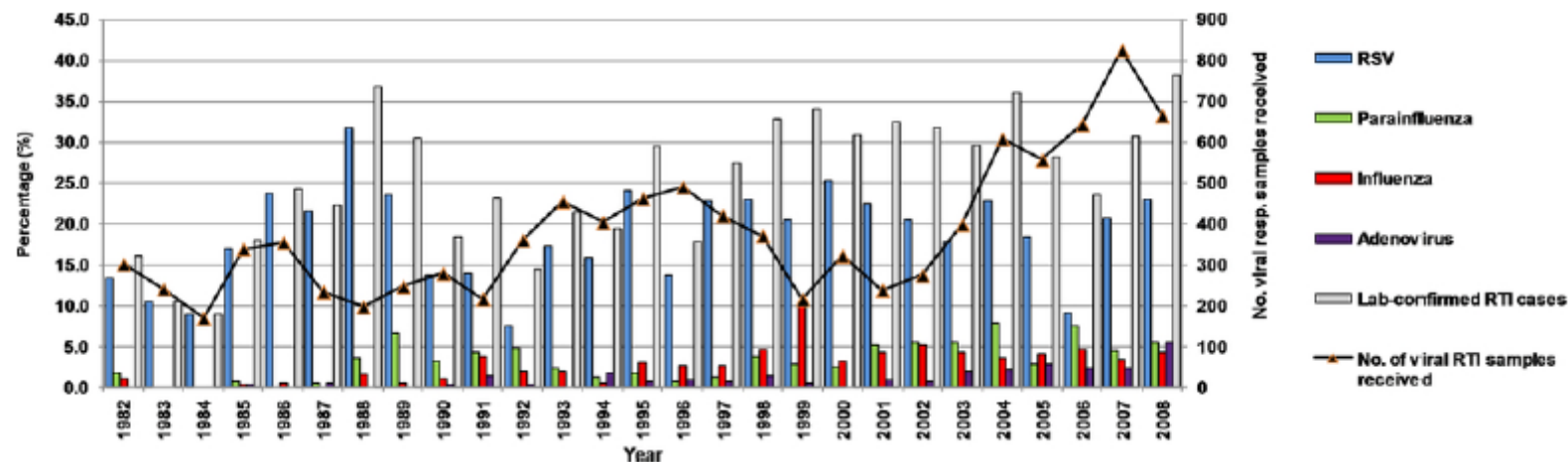


**Figure 1 Proportions of respiratory viruses detected between 1982 and 2008.** The detection of each respiratory virus as total number of positive respiratory virus samples is shown.

Infleunza : 3% of cases

Khor et al. BMC Pediatrics 2012, 12:32

# Influenza and respiratory syncytial viral infections in Malaysia: Demographic and clinical perspective

M.M. Rahman[1], K.K. Wong[2], A. Hanafiah[3], I. Isahak[4]
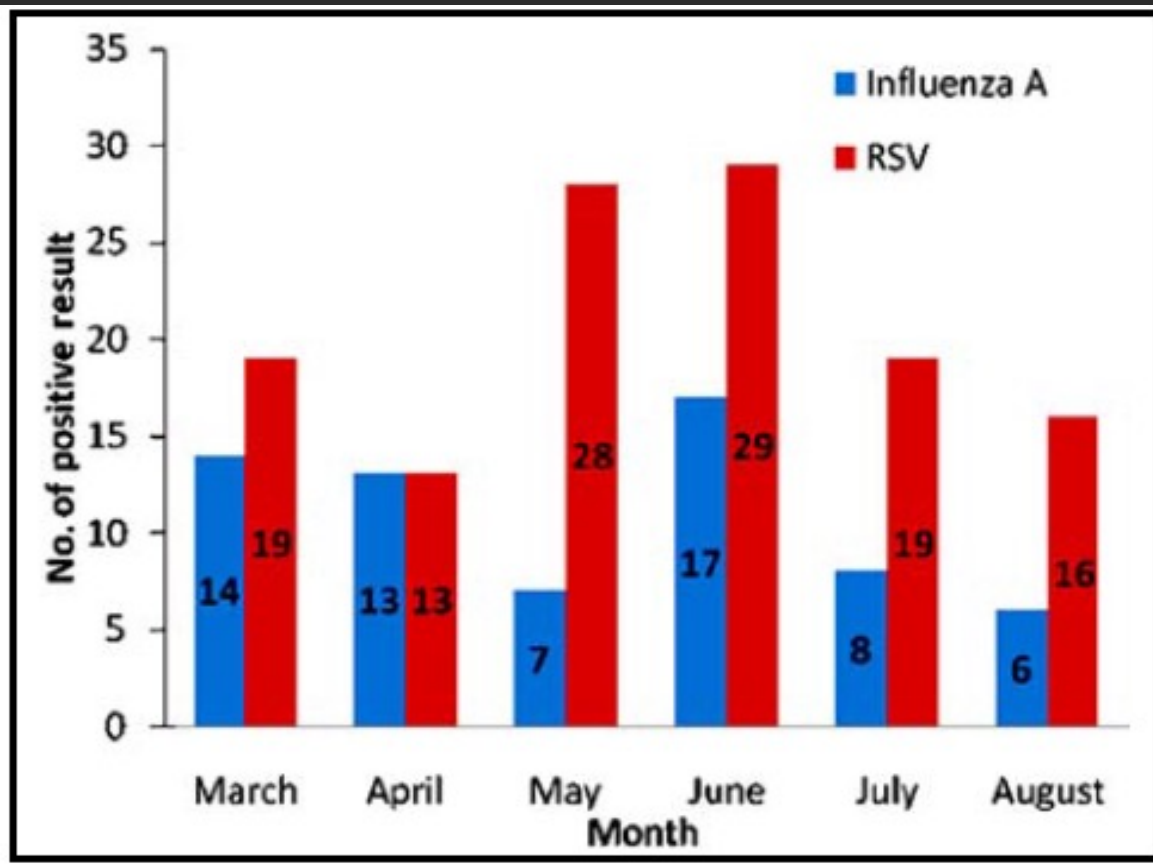


- Used viral propagation cell culture / IFA as well as PCR methods to isolate .
- Out of 505 samples, Influenza A : 13% of cases and RSV 24.8% of cases
- No significant difference in clinical presentation

# Clinical features of Malaysian children hospitalized with community-acquired seasonal influenza

I-Ching Sam [a,*], Aizuri Abdul-Murad [a], Rina Karunakaran [a], Sanjay Rampal [b], Yoke-Fun Chan [a], Anna Marie Nathan [c], Hany Ariffin [c]

| Predictor | n (%) | No. with severe influenza, n (%) | Crude OR (95% CI) | p-Value | Adjusted OR (95% CI) | p-Value |
|---|---|---|---|---|---|---|
| Age | | | | | | |
| <12 months | 43 (32.6) | 11 (25.6) | 5.78 (1.86–17.93) | 0.02 | 8.76 (2.31–33.14) | 0.01 |
| >12 months | 89 (67.4) | 5 (5.6) | 1.0 | | | |
| Sex | | | | | | |
| Male | 75 (56.8) | 6 (8) | 1.0 | | | |
| Female | 57 (43.2) | 10 (17.5) | 2.45 (0.83–7.19) | 0.10 | 3.69 (1.01–13.43) | 0.048 |
| Ethnicity | | | | | | |
| Malay | 97 (73.5) | 11 (11.3) | 1.0 | | | |
| Indian | 18 (13.6) | 0 | 0 | 1.00 | | |
| Chinese | 15 (11.4) | 4 (26.7) | 2.84 (0.77–10.49) | 0.12 | | NS[c] |
| Other[a] | 2 (1.5) | 1 (50) | – | – | | |
| ACIP condition | | | | | | |
| No | 84 (63.6) | 9 (10.7) | 1.0 | | | |
| Yes | 48 (36.4) | 7 (14.6) | 1.42 (0.49–4.10) | 0.51 | | |
| Duration of symptoms (days), mean | 5.0 | – | 0.84 (0.68–1.03) | 0.13 | | NS[c] |
| Clinical features on admission[b] | | | | | | |
| Rhinitis | | | | | | |
| No | 33 (25) | 10 (30.3) | 6.74 (2.22–20.46) | 0.001 | 8.66 (2.43–30.80) | 0.001 |
| Yes | 99 (75) | 6 (6.1) | 1.0 | | | |
| Cough | | | | | | |
| No | 12 (9.1) | 4 (33.3) | 4.50 (1.18–17.29) | 0.03 | | NS[c] |
| Yes | 120 (90.9) | 12 (10) | 1.0 | | | |
| Seizures | | | | | | |
| No | 117 (88.6) | 12 (10.3) | 1.0 | | | |
| Yes | 15 (11.4) | 4 (26.7) | 3.18 (0.88–11.57) | 0.08 | | NS[c] |
| Influenza diagnosis | | | | | | |
| Positive IF | 72 (54.5) | 9 (12.5) | 1.0 | | | |
| Virus culture only | 60 (45.5) | 7 (11.7) | 0.96 (0.33–2.75) | 0.94 | | |
| Influenza type | | | | | | |
| A | 97 (73.5) | 13 (13.4) | 1.0 | | | |
| B | 35 (26.5) | 3 (8.6) | 0.61 (0.16–2.27) | 0.46 | | |
| Respiratory virus co-infection | | | | | | |
| No | 127 (96.2) | 15 (11.8) | 1.0 | | | |
| Yes | 5 (3.8) | 1 (20) | 4.00 (0.67–23.86) | 0.13 | | NS[c] |

# Characteristics of Children Hospitalized for Pandemic (H1N1) 2009, Malaysia

Table 2. Concurrent conditions in children hospitalized for pandemic (H1N1) 2009, Malaysia, June 18, 2009–March 1, 2010*

| Condition | No. (%) children | | | OR (95% CI) | p value |
|---|---|---|---|---|---|
| | Total | Survived | Died | | |
| None | 860 (63.1) | 845 (64.7) | 15 (29.4) | 0.2 (0.1–0.4) | <0.001 |
| Chronic lung disease | 258 (18.9) | 246 (18.8) | 12 (23.5) | 2.5 (1.1–5.6) | 0.02 |
| Neuromuscular disease | 33 (2.4) | 27 (2.1) | 6 (11.8) | 2.5 (4.5–34.8) | <0.001 |
| Cardiovascular disease | 54 (4.0) | 46 (3.5) | 8 (15.7) | 9.8 (3.9–24.3) | <0.001 |
| Renal disease | 18 (1.3) | 16 (1.2) | 2 (3.5) | – | – |
| Immunosuppression | 18 (1.3) | 15 (1.1) | 3 (5.9) | – | – |
| Obesity | 14 (1.0) | 13 (1.0) | 1 (2.0) | – | – |
| Malnutrition | 14 (1.0) | 13 (1.0) | 1 (2.0) | – | – |

*OR, odds ratio; CI, confidence interval; –, numbers too small to infer from study sample.

Hussain Imam.et al.Emerg.Inf. Dis.(17).4. 2011
Sam etal. Int J Inf Dis. 14S(2010)

# Impact of influenza in pts with comorbidities

- Influenza related to multiple athereoclerotic events including heart disease and Stroke
    - 3 case control studies have shown vaccination offers protection

- In patients with cirrhosis , influenza infection was associated with poorer outcome with more episodes of severe pneumonia/ ARDS / hepatic decompensation.

- In patients with HSCT, those who were lymphopenic and after transplantation developed pneumonia
    - Viral shedding was prolonged in the ones who had high dose steroid use and use of oseltamivir was associated with less duration of shedding and nosocomial transmission

Van Lenten BJ.Circulation 2001;103:2283–8
Marzano A.J Med Virol. 2013 Jan;85(1):1-7.
W. Garrett Nichols. Clin Infect Dis. (2004) 39

# Timeline Of Influenza Pandemics in Malaysia since 1968

**19Aug 2004**
**H5N1** outbreak in poultry Scattered outbreak thru sept 2004

**9 feb 2006**
**H5N1** outbreak in poultry with scattered outbreak No human cases reported

**May 2009**
Influenza **H1N1** pandemic outbreak

**12th Feb 2014**
**H7N9** in a Chinese tourist visiting Sabah had a stop over in KL No local transmission case reported
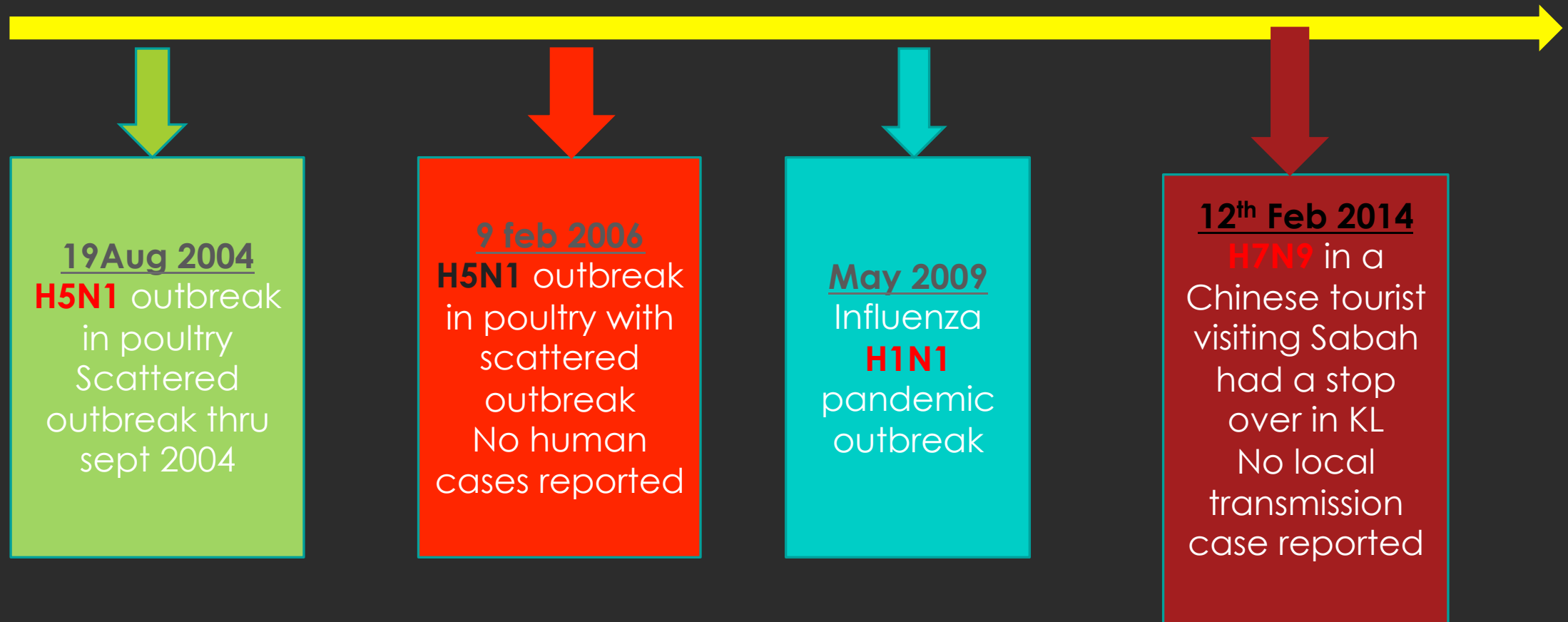
# H1N1 pandemic Influenza in Malaysia

**159 (27.7%)**

**So far 11 confirmed cases- all imported**

**12,307 reported 78 deaths**

**Containment Phase**



9 July: move to mitigation phase

4-8 July: Cluster of 20 cases at conference, Penang

21 June: 1st school closure

17 June: 1st local transmission

11 June: WHO declares phase 6 pandemic alert

15 May: 1st confirmed case

No. of confirmed cases

Cumulative % of total cases

18 May | 25 May | 1 Jun | 8 Jun | 15 Jun | 22 Jun | 29 Jun | 6 Jul

■ Local transmission cases
▨ Imported cases
— Cumulative % of cases which are local transmissions

# Influenza A H1N1 in Malaysia

## Clinical features and outcomes of hospitalized patients in a tertiary healthcare centre

- In a review of 117 adult patients admitted with confirmed H1N1 ( rt- pCr) in Kuala Lumpur
  - 30% had no underlying medical condition
  - 12% had severe disease
  - 6% mortality ( patients with more than 1 comorbidities
  - Duration of hospitalization is longer  for the severe group (10.9 vs 2.9 days, p>0.001)

# Epidemiology and clinical characteristics of hospitalized patients with pandemic influenza A (H1N1) 2009 infections: the effects of bacterial coinfection

Amreeta Dhanoa[1*], Ngim C Fang[2], Sharifah S Hassan[1], Priyatharisni Kaniappan[3] and Ganeswrie Rajasekaram[3]

| Characteristics | No of patients (N = 50) | % |
|---|---|---|
| Male sex | 25 | 50 |
| Age < 50 | 45 | 90 |
| Paediatric (≤ 15 years) | 23 | 46 |
| Cough | 50 | 100 |
| Fever | 49 | 98 |
| Dyspnoea | 24 | 48 |
| Rhinorrhoea | 24 | 48 |
| Sore throat* | 16 | 36.4 |
| Vomiting | 12 | 24 |
| Myalgia* | 7 | 15.9 |
| Headache* | 7 | 15.9 |
| Hypoxaemia | 12 | 24 |
| Tachypnoea | 16 | 32 |
| Pneumonia | 25 | 50 |
| Comorbidity** | 24 | 48 |
| Lung disease[¶] | 11 | 22 |
| Hypertension | 5 | 10 |
| Diabetes mellitus | 5 | 10 |
| Malignancy[Ψ] | 3 | 6 |
| Autoimmune[×] | 2 | 4 |
| Others[£] | 6 | 12 |

- Coinfection seen 17 (34%) /50
- Mycoplasma pneumoniae (n =5) Staphylococcus aureus (n = 3), Klebsiella pneumoniae (n = 2)
- Mutivariate analysis showed
  - age>50 (OR 12.577; 95% CI 1-165.24; p = 0.05)
  - combined complication(OR 9.01; 95% CI 1.70-47.67; p= 0.01) are risk factors for bacterial coinfection

# H7N9 virus

**Details of the case are as follows:**

A 67 year old woman tourist from Guangdong Province, China, arrived in Malaysia on 3 February in a tour group of 17 persons, including relatives, and stayed overnight in Kuala Lumpur, Malaysia. The tour group then went on a visit to Sabah, Malaysia from 4 to 6 February. On 7 February, she was admitted to hospital and later transferred to another hospital in Sabah. The patient is currently in a stable condition.

Four days prior to travelling to Malaysia, on 30 January 2014, she was treated in China for symptoms of fever, cough, flu, fatigue and joint pain. Given the onset of symptoms, and travel dates, the most likely exposure occurred before arrival in Malaysia.

# Treatment slide

TABLE 2. Summary of antiviral resistance among influenza viruses worldwide, December 2010*

| Antiviral | Influenza A viruses | | Influenza B viruses[†] |
| --- | --- | --- | --- |
| | 2009 H1N1 | H3N2 | B |
| Adamantanes (not recommended currently) | Resistant | Resistant | No activity |
| Oseltamivir | Susceptible | Susceptible | Susceptible |
| Zanamivir | Susceptible | Susceptible | Susceptible |

*Information regarding antiviral resistance is updated weekly and is available at http://www.cdc.gov/flu/weekly. Rare instances of infection with oseltamivir-resistant 2009 H1N1 virus strains have been reported; >99% of influenza viruses circulating since September 2009 have been sensitive to oseltamivir.
[†] Yamagata and Victoria lineages

# Bridging the gaps

- **Surveillance! Surveillance! Surveillance !**
  - **Population rates in Influenza assoc clinic visits**
  - **Influenza associated hospitalization**
  - **Mortality**
- **Important to guide vaccination – determine the strains circulating→ effective choice of vaccine and timing**
- **Need rapid more available detection kits**
- **Increase awareness in HCW**