

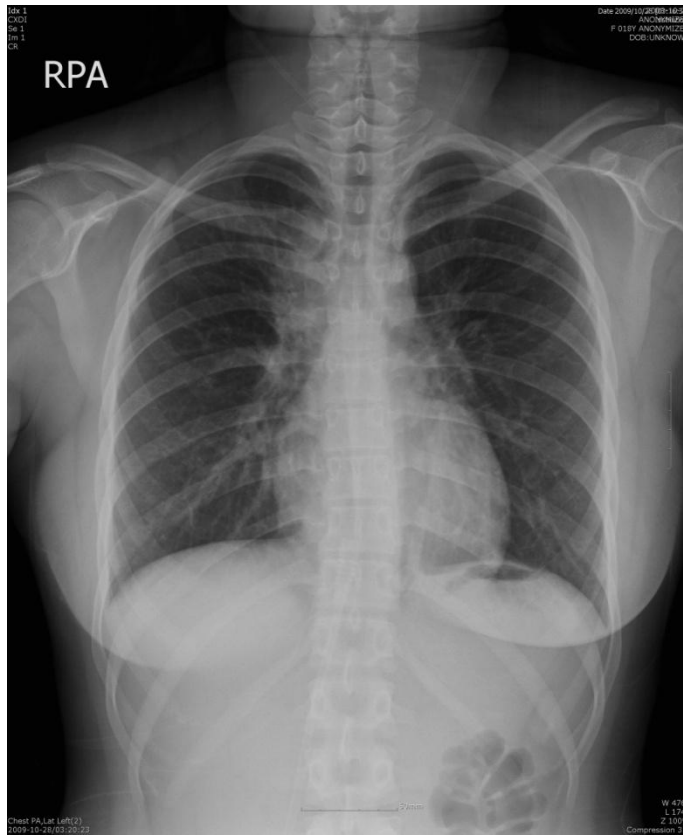
2009 H1N1/A Influenza

중앙대학교 의과대학 호흡기내과

김 재 열

여자 18세, 고열과 근육통

2009-10-28



2009-10-30



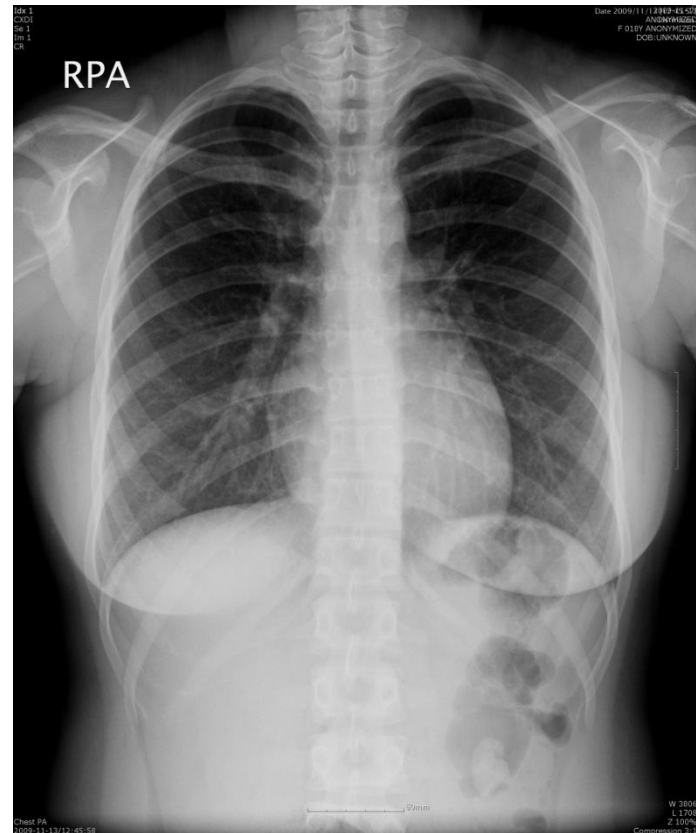
- Influenza A (H1N1) Rapid Real-Time PCR; Positive

임상 경과

Lab findings (2009-10-30)

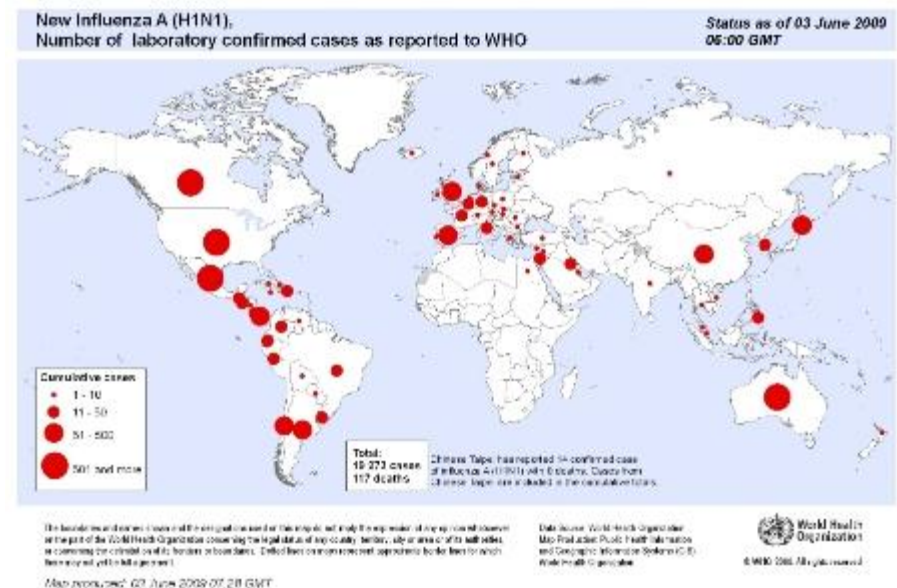
- ABGA
 - pH; 7.45
 - PCO₂; 30mmHg
 - PO₂; 58mmHg
- ICU transfer
- O₂ supply via Face mask with reservoir bag

2009-11-18



H1N1/A Influenza Pandemic

- 2009. 03
 - First case in Mexico
- 2009. 06.11
 - Pandemic alert by WHO
 - Phase 6, highest level
- Involved countries
 - More than 214 nations
 - 18,449 death
- Epidemiology in US
 - 61 millions cases
 - 12,470 deaths
 - Case fatality rate; 0.02%



H1N1/A Influenza in Korea

- 2009.05.02
 - First case report
- Confirmed cases
 - 750,000
- H1N1-related death
 - 252
- Case-fatality rate
 - 0.03%
- 2015 메르스
 - 확진자 186, 사망자 37
 - 사망률; 19.9%



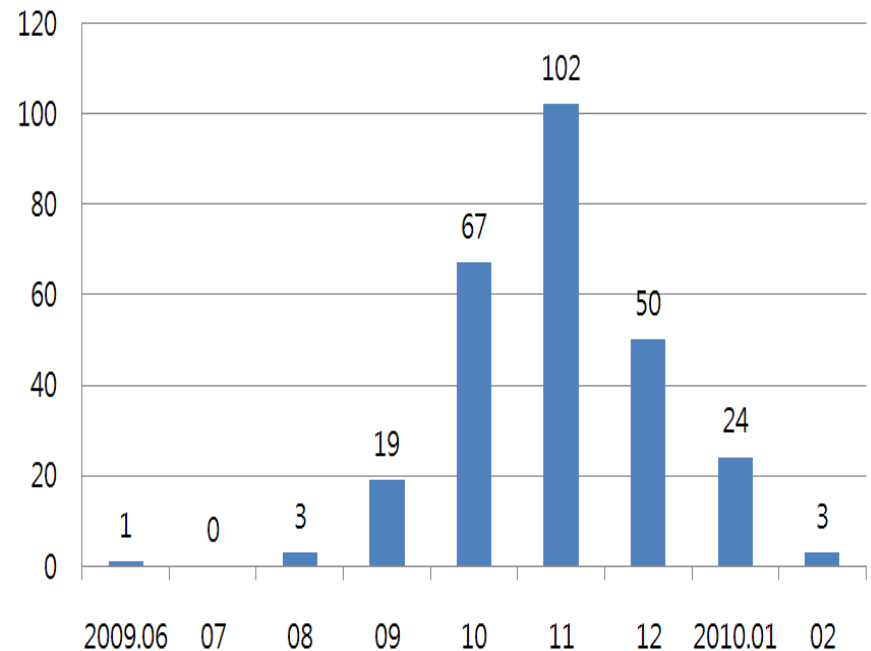
Clinical characteristics and outcomes of H1N1/A influenza-associated pneumonia among adults in South Korea

– Choi WI....JY Kim, Int J Tuberc Lung Dis 2011;15:270

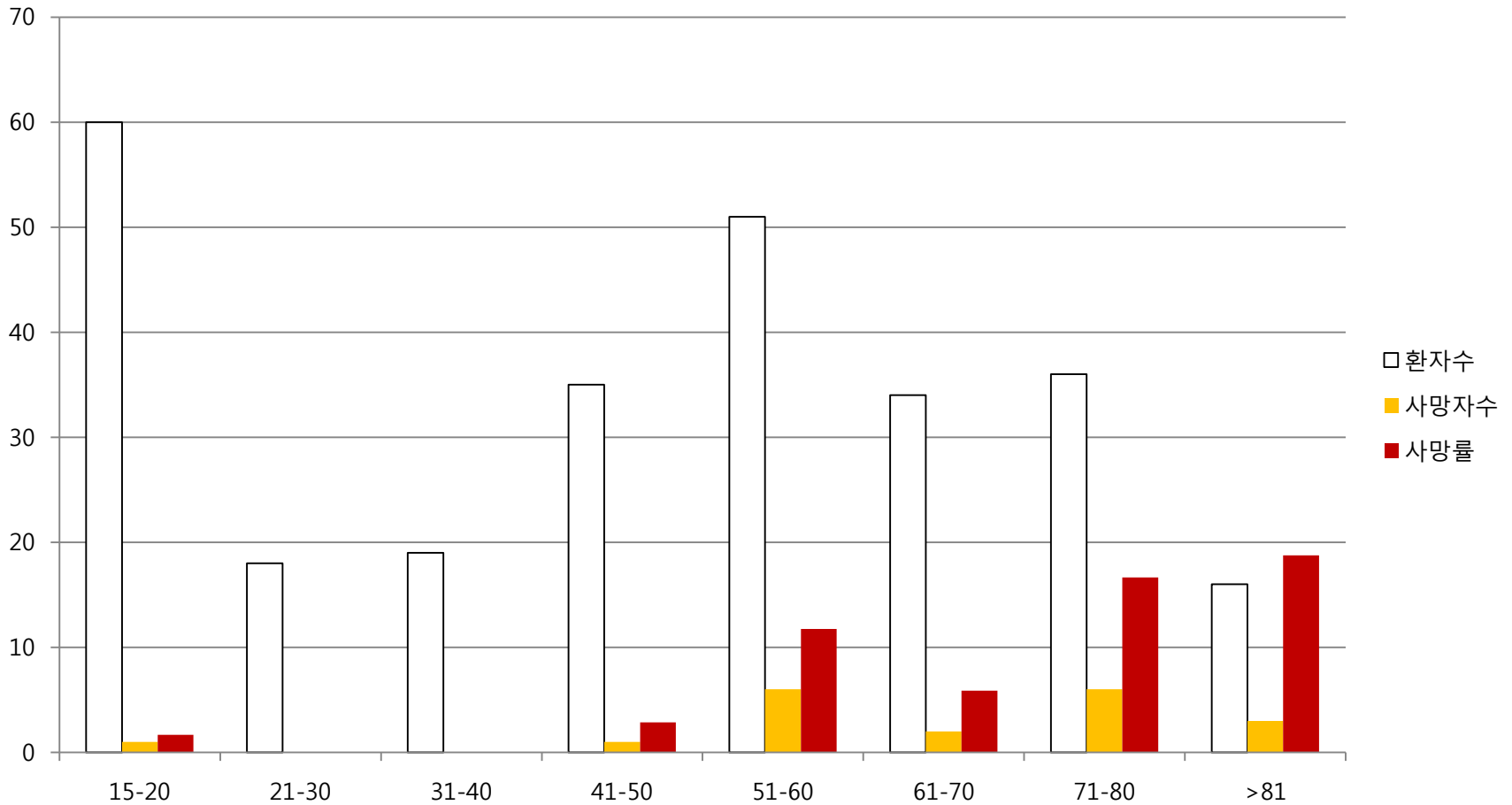
Study design

- Retrospective, multi-center trial
- 14 institutions
- 2009.06~2010.02
- 269 patients with H1N1 associated pneumonia
- 19 patients died(7.2%)

Monthly recruitment



연령대별 환자수, 사망자수, 사망률

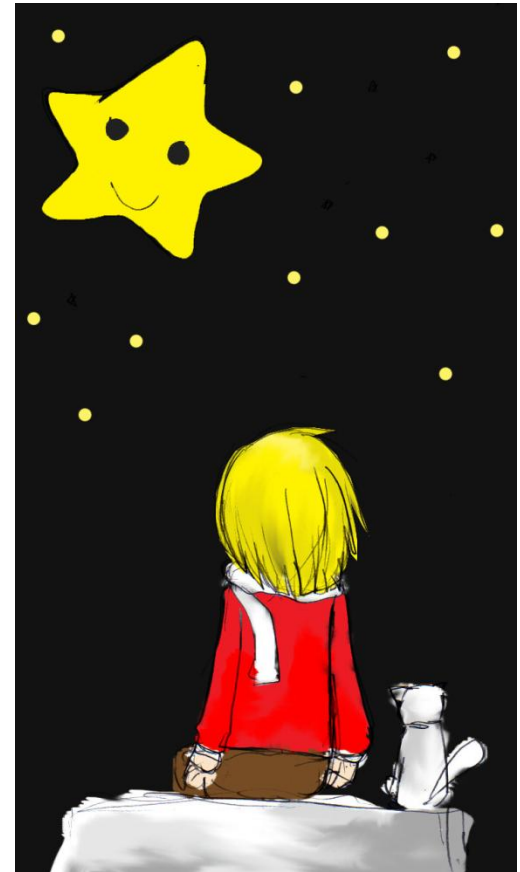


2009 H1N1/A Influenza 특징

- 구역 구토, 설사 등 위장 증상 비율 높다
- 중증 질환의 고 위험군
 - 고령, 비만, 동반질환, 하기도 질환
- 폐렴으로 진행되는 비율 높다
 - 원인균; *S. pneumoniae*, *S. viridans*,
S. aureus, *S. mitis*, *H. influenzae*
- 사망률은 seasonal flu와 비슷
 - 중증도와 사망률 감소에 neuraminidase inhibitor, 특히 Oseltamivir가 기여

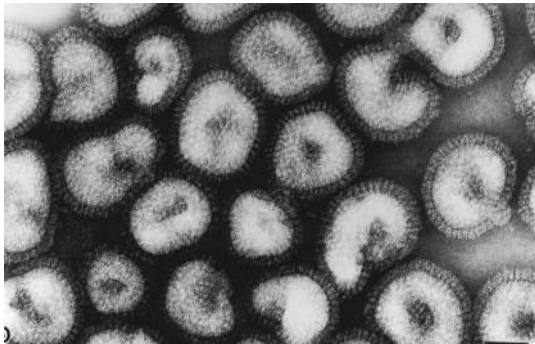
Influenza

“Influence from
bad star?”



인플루엔자 바이러스 종류

- 원통형 ssRNA 바이러스



A형 인플루엔자 바이러스

- 사람, 동물 모두 감염
- 주요 타입; H1N1, H3N2

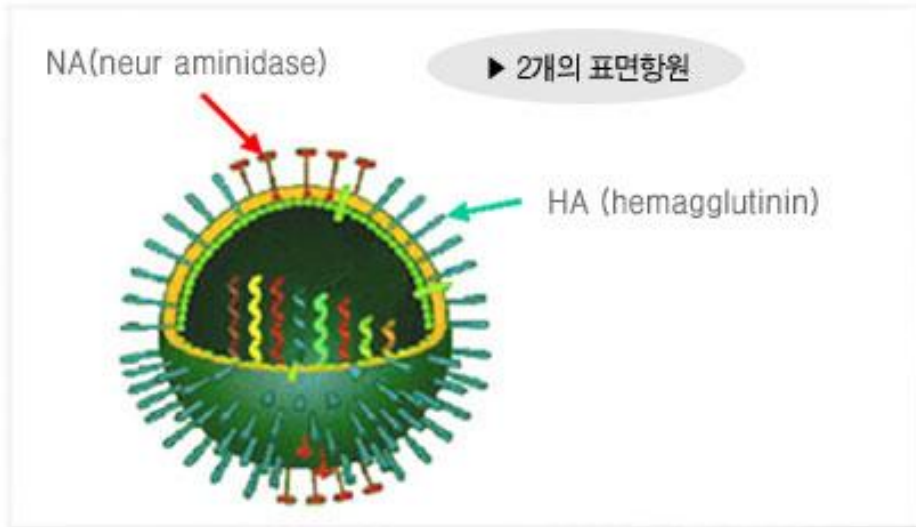
B형 인플루엔자 바이러스

- 주로 사람
- 두 계열: Victoria, Yamagata

C형 인플루엔자 바이러스

- 사람 감염 드물다
- 불현성 감염이 많다

독감 바이러스의 구조



RNA virus

▼ Hemagglutinin subtype

H1		H9	
H2		H10	
H3		H11	
H4		H12	
H5		H13	
H6		H14	
H7		H15	
H8			

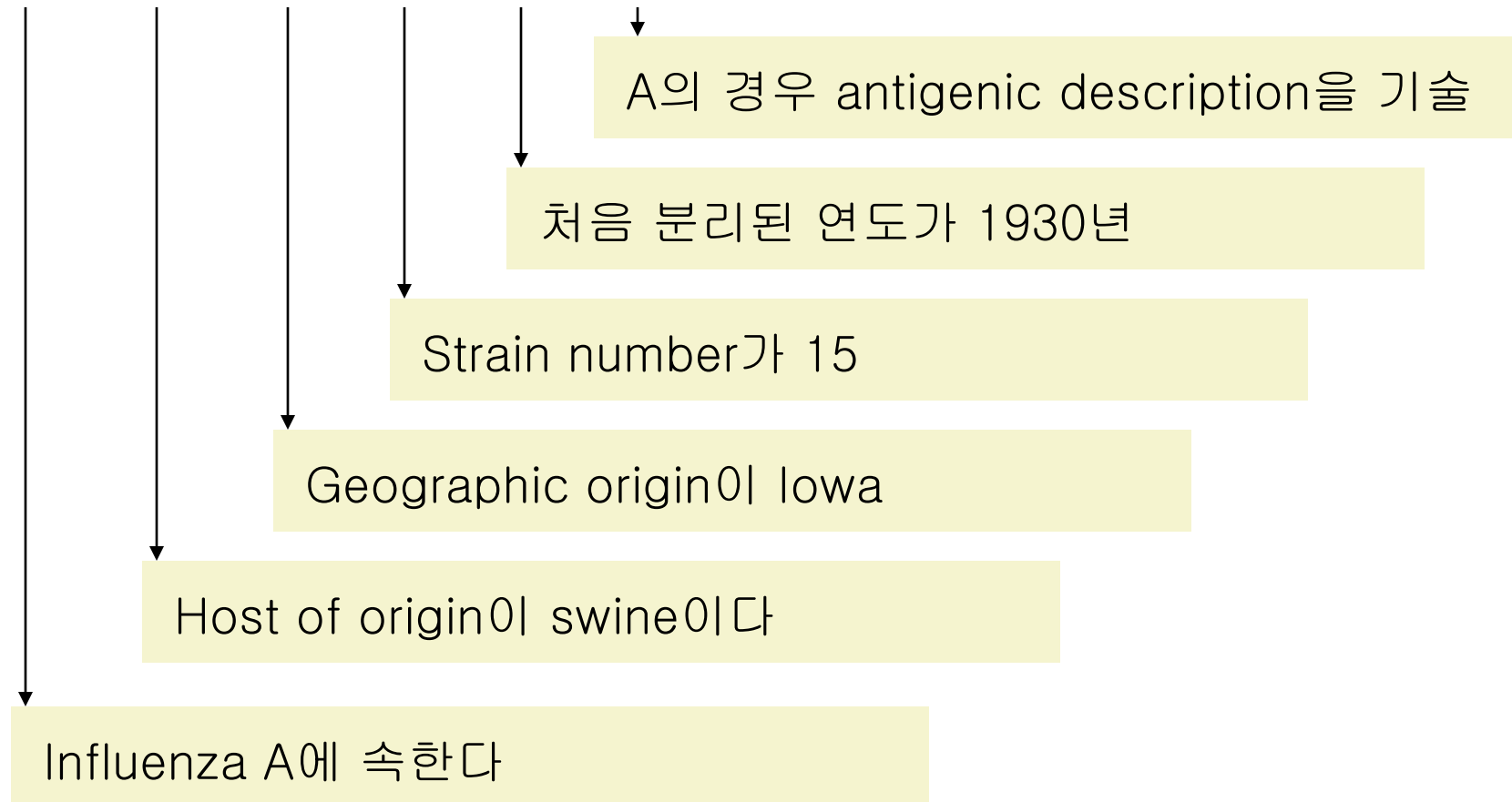
▼ Neuraminidase subtype

N1	
N2	
N3	
N4	
N5	
N6	
N7	
N8	
N9	

15 x 9 = 135

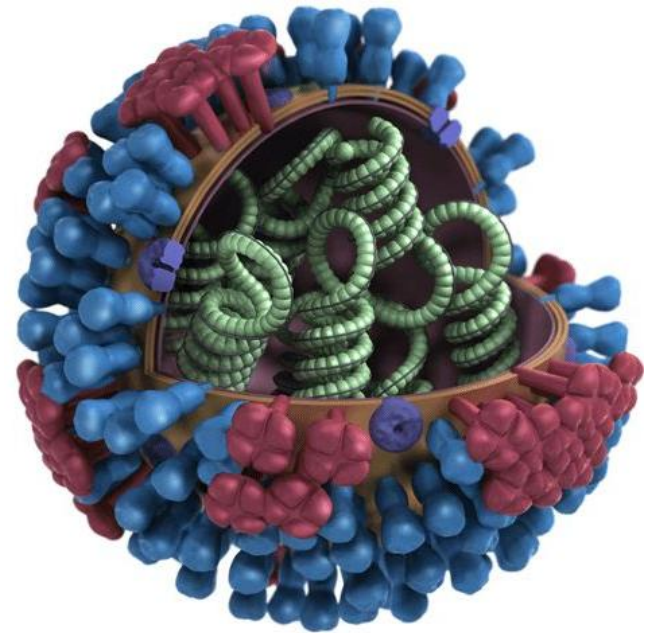
바이러스 명명법

- A/swine/lowa/15/30(H1N1)



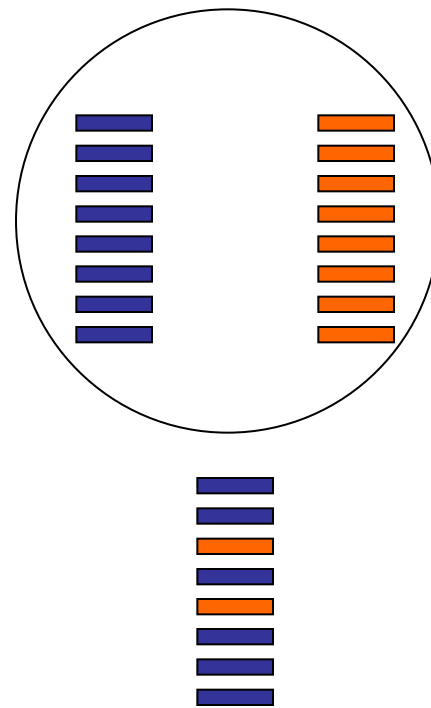
인플루엔자 바이러스의 유전적 변이

- 내부에 8개의 RNA 분절 포함
- 유전자변이
 - 돌연변이로 항원소변이 (drift) 발생
 - 두 종류의 바이러스가 한 숙주를 감염하면 유전자 재편성을 통한 항원대변이(shift) 발생
 - 항원대변이에 의해 pandemic 발생
- 이러한 항원변이 때문에 매년 새로운 백신이 개발되어야 함.



Pandemic의 기원

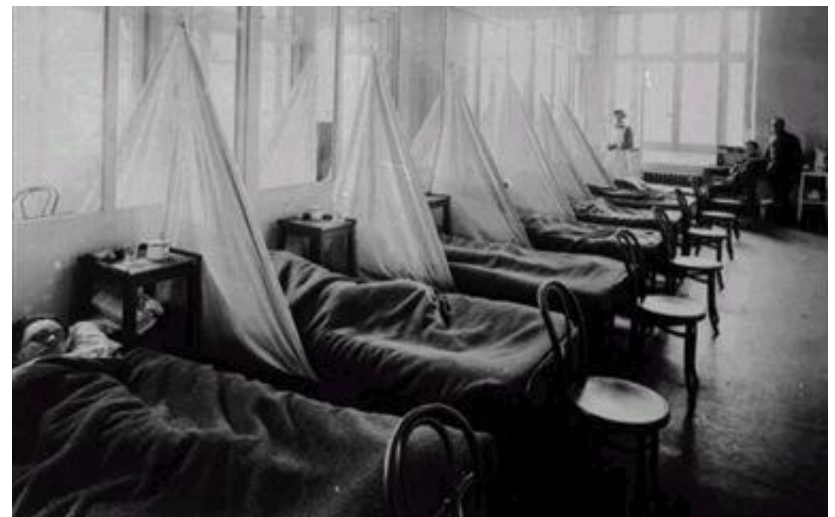
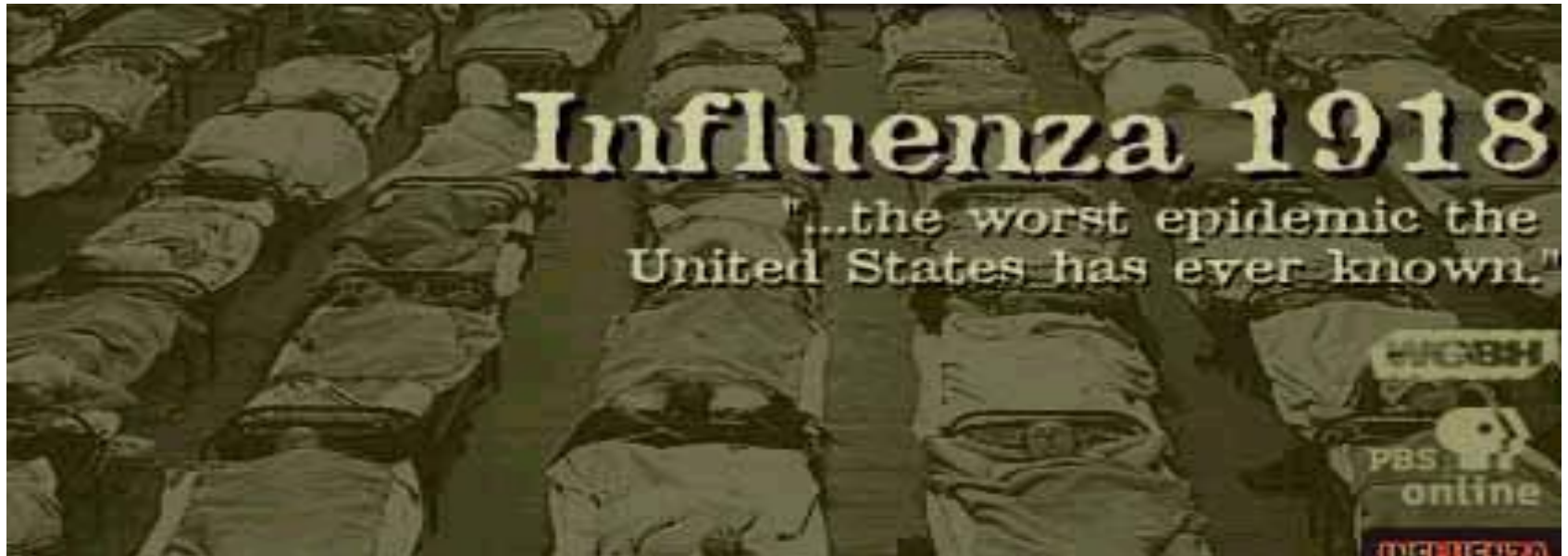
- 유전자 재조합 (Reassortment)



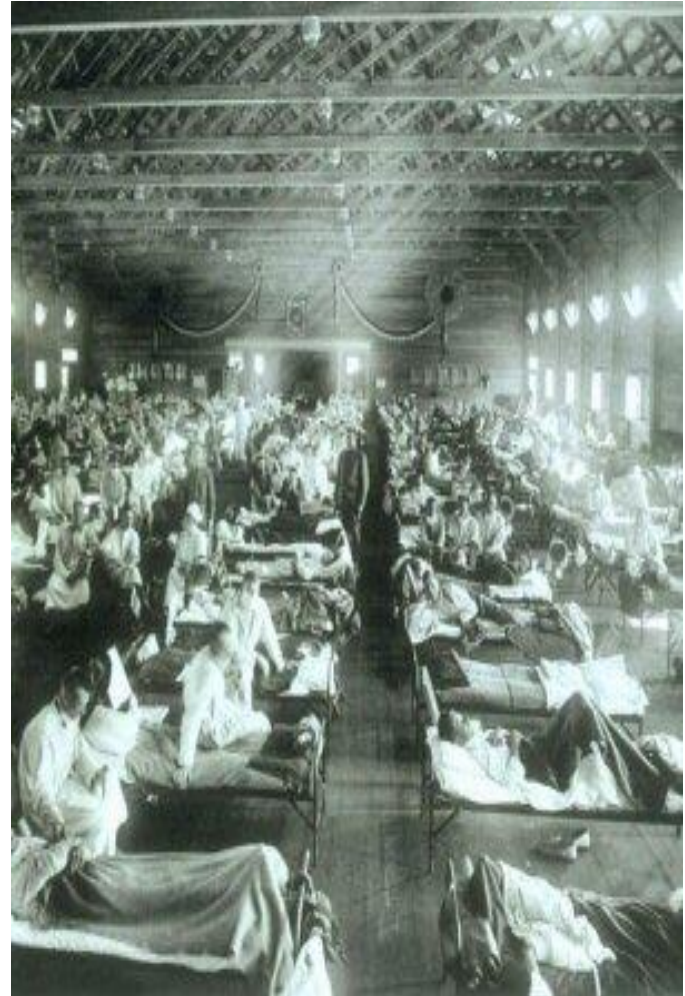
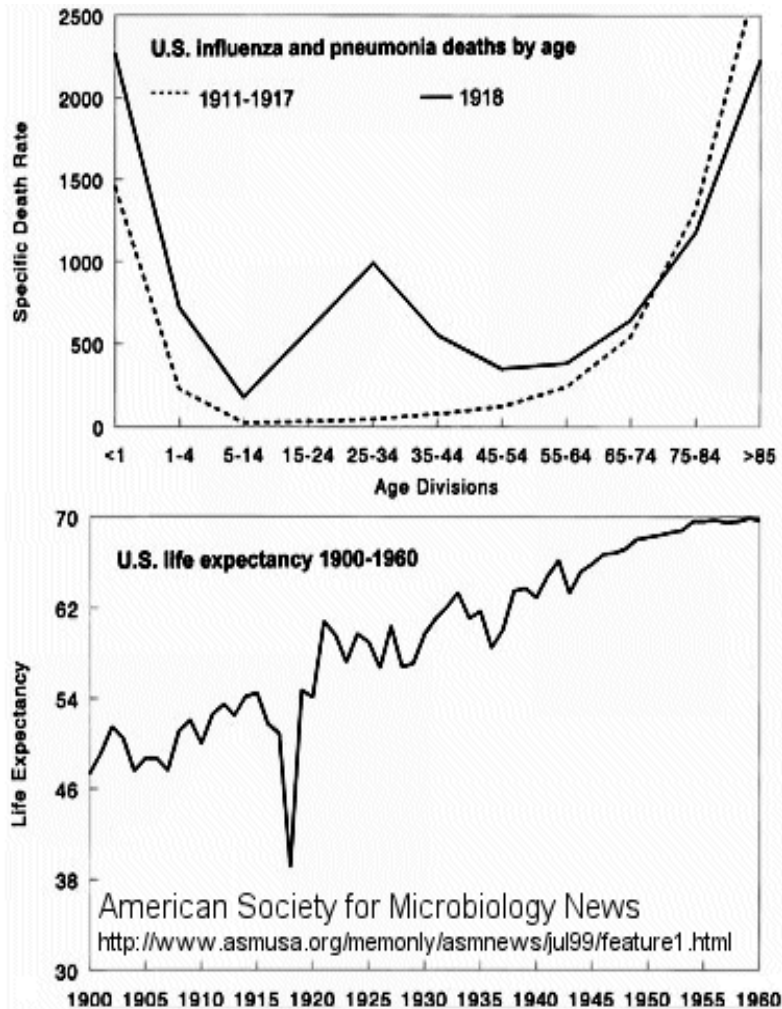
발생연도	Pandemic	Subtype	바이러스의 기원
1918-1919	스페인	H1N1	조류?
1957	아시아	H2N2	H1N1 + 조류
1968	홍콩	H3N2	H2N2 + 조류

- Direct adaptation to the human host

Spanish flu, 1918년



Spanish flu, 1918년



Spanish Flu의 원인은?

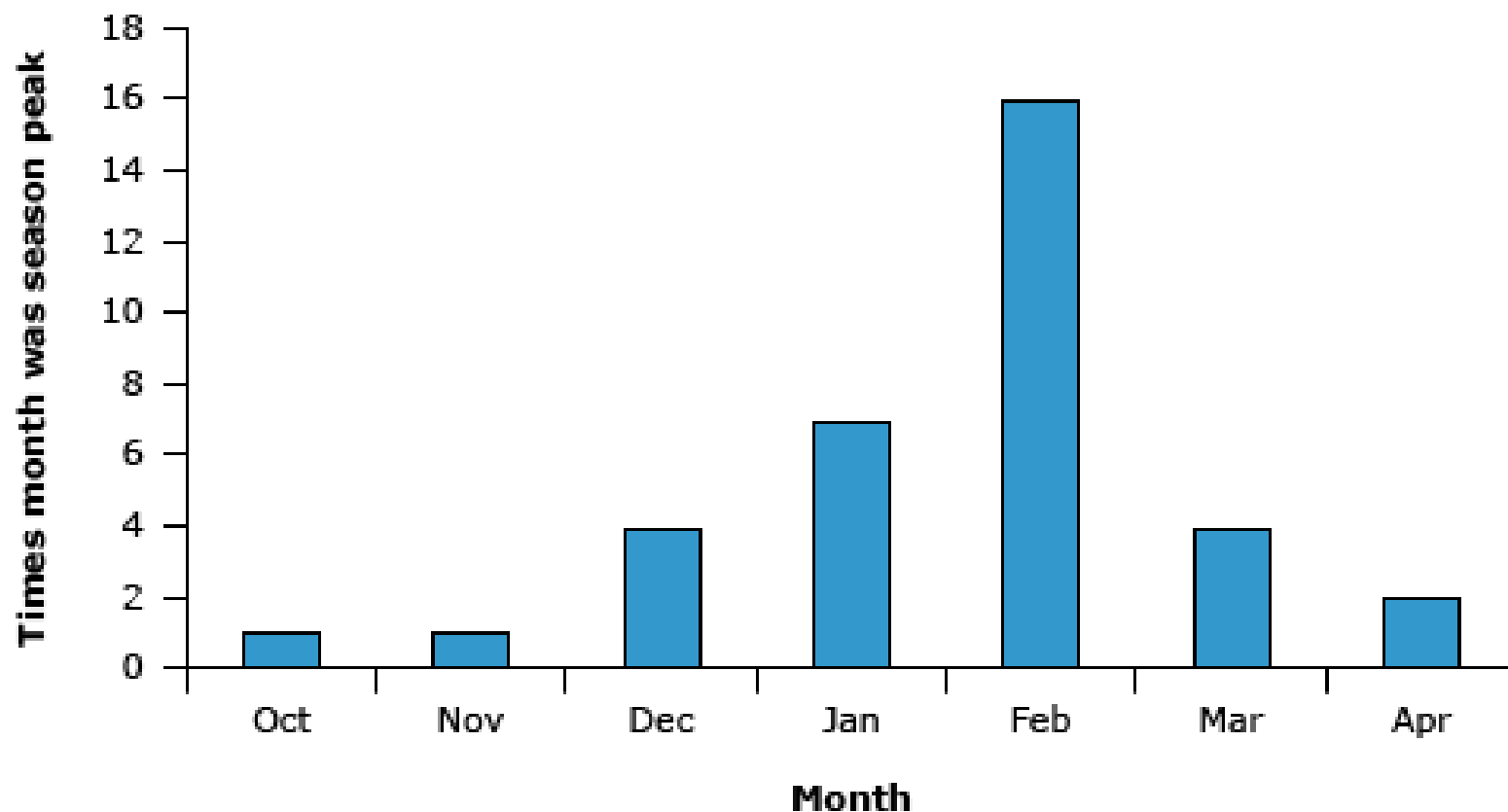
- Influenza virus 배양은 1933년에 이루어짐
- 그렇다면 1918년 바이러스는 어디에서 구할 수 있을까?
 - 알래스카 동토에 묻힌 Spanish flu 희생자의 폐
 - Paraffin block에 들어있는 Spanish flu 희생자의 폐조직



인플루엔자 역학

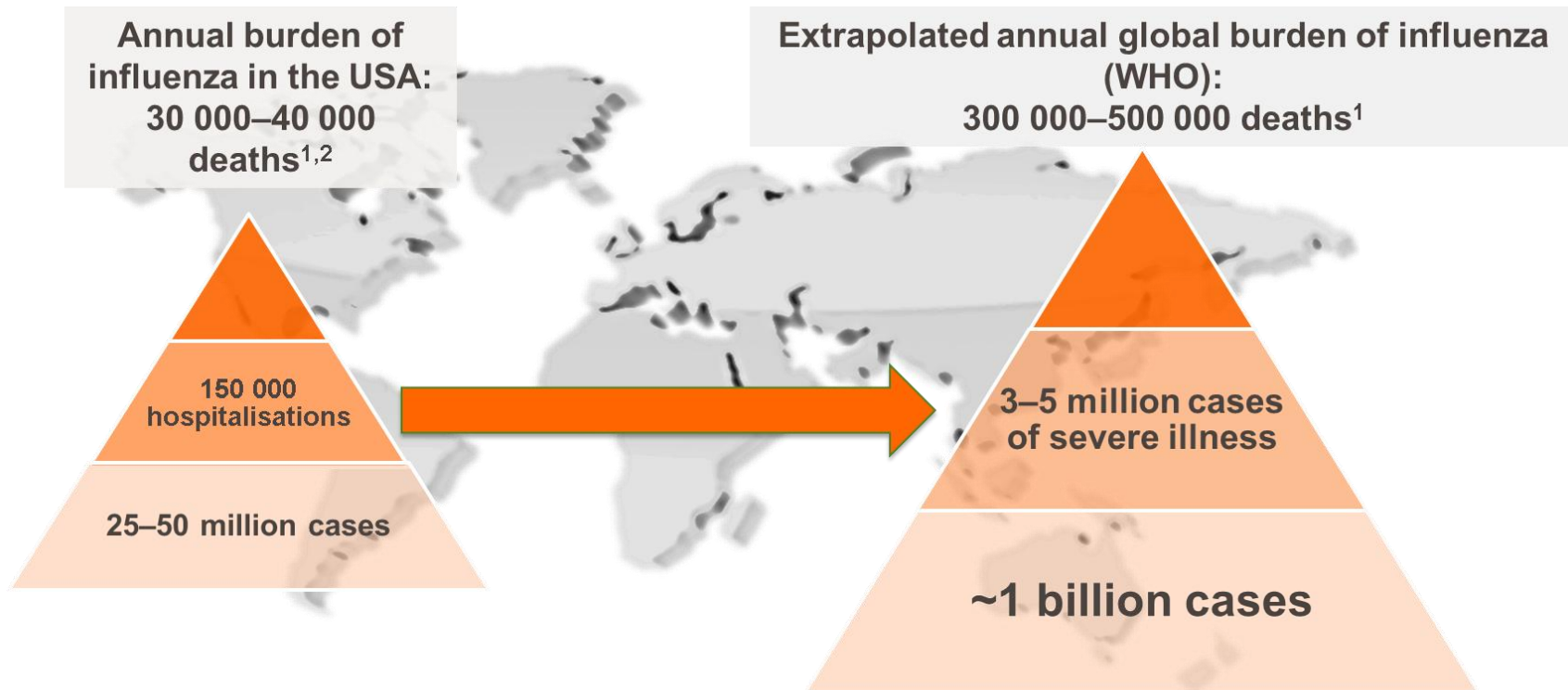
- 전 세계적으로 매년 성인의 5-10%, 어린이의 20-30%가 인플루엔자에 감염
- 온대지방은 주로 겨울철에, 열대지방은 년중 내내 발생
- 지역에 따라 유행하는 A형의 아형과 B형의 계열이 다르다.
- 새로운 종류의 바이러스가 생기면 범세계적 유행이 나타난다

Peak influenza activity, by month - United States, 1976 to 1977 through 2010 to 2011



Centers for Disease Control and Prevention. *The flu season*. Available at: <http://www.cdc.gov/flu/about/season/flu-season.htm>. Accessed on September 21,

인플루엔자; 유행윅과 사망윅



1. WHO. [Influenza](#). 2008 (accessed April 2014); 2. Thompson WW *et al.* *JAMA* 2003;289:179–86.

인플루엔자의 감염

- 감염자의 기침 또는 재채기에 의해 발생하는 에어로졸 혹은 비말의 흡입에 의해 발생
- 잠복기; 1 - 4일 (평균 2일)
- 바이러스 배출은 증상발생 하루 전부터 발병 후 5-7일까지 지속
- 어린이는 7일 이상까지 바이러스 배출 가능
- 밀집지역에서는 빠른 속도로 전파됨



인플루엔자의 임상상

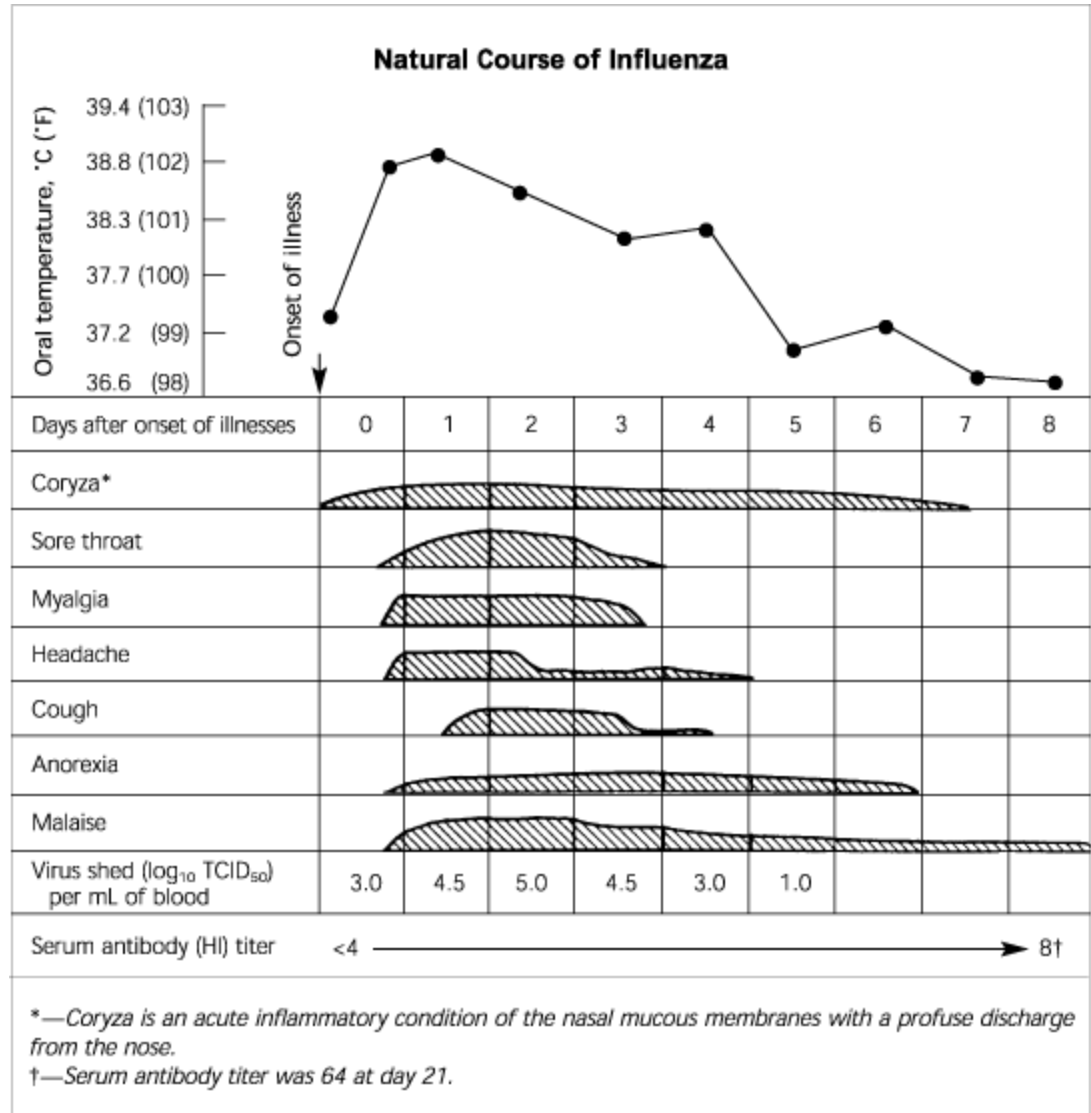
- 잠복기

- 2일 (1-5일)

- 가장 큰 특징은?

- 발열, 기침

- 전신 증상이 심하다는 것



Neuraminidase inhibitors

Tamiflu (Oseltamivir)/Relenza(Zanamivir)

- Active against influenza A & B
- 조기 투여시에만 효과
 - Within 48h of onset of symptoms
- Tamiflu
 - 75 mg bid for 5d
- Neuraminidase inhibitor, 특히 Oseltamivir는 2009 H1N1/A influenza의 중증도와 사망률 낮추는데 기여



인플루엔자 사망 고위험군

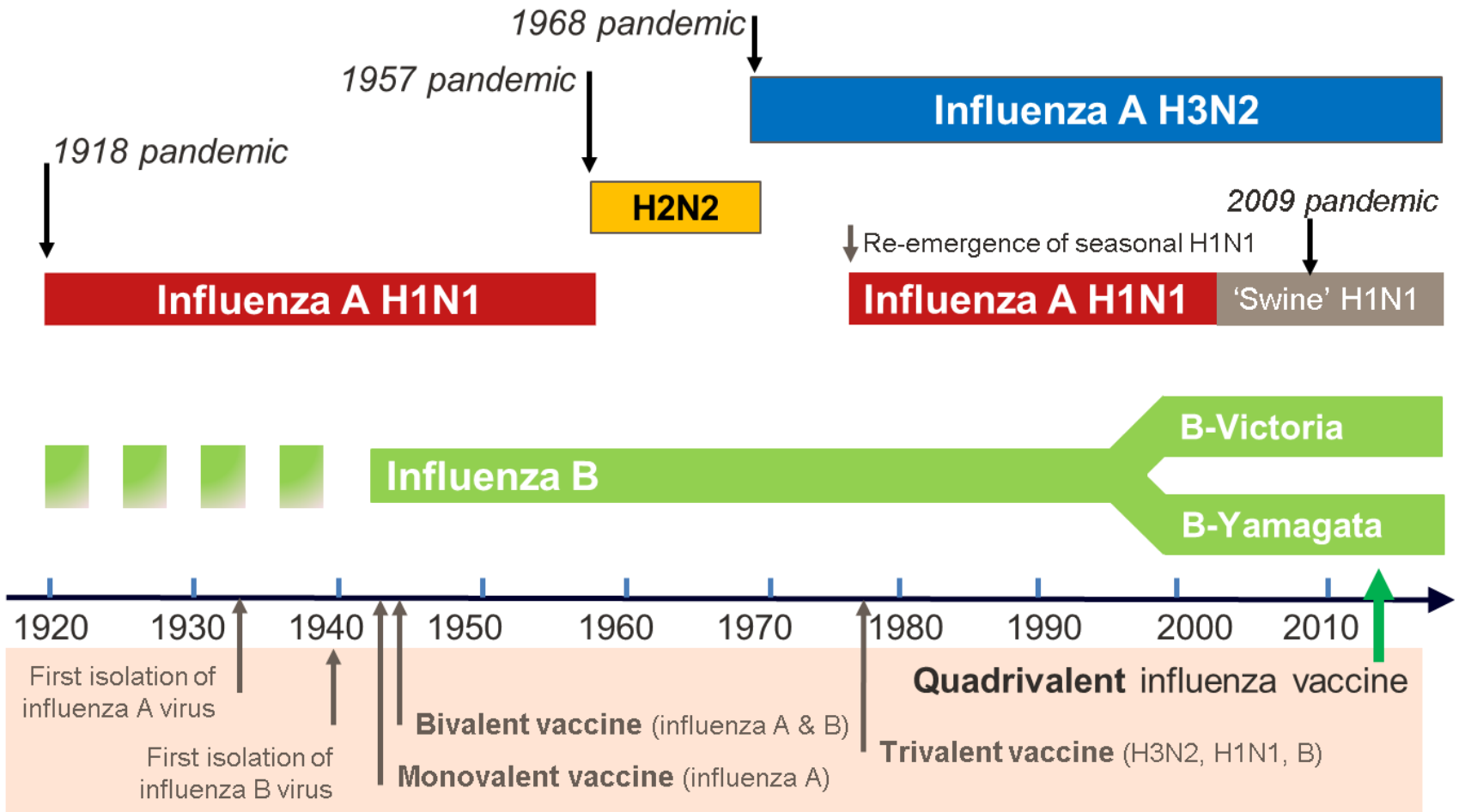
- Compared with otherwise healthy adults, influenza can cause more serious illness and greater mortality in:
 - Children aged <2 years
 - Adults aged ≥65 years
 - Pregnant women
 - Those with weakened immune systems
 - Those with certain medical conditions—eg, chronic heart, lung, kidney, liver, blood, or metabolic diseases
- Particularly high case-fatality rates can be seen among residents of long-term care facilities and in children younger than 6 months³
- Other groups, such as healthcare professionals, are at high risk because of occupational exposure

인플루엔자 예방접종

- ACIP 권고
; 6개월 이상 모두
- 백신공급 한정적
; 왼쪽 기준 참조

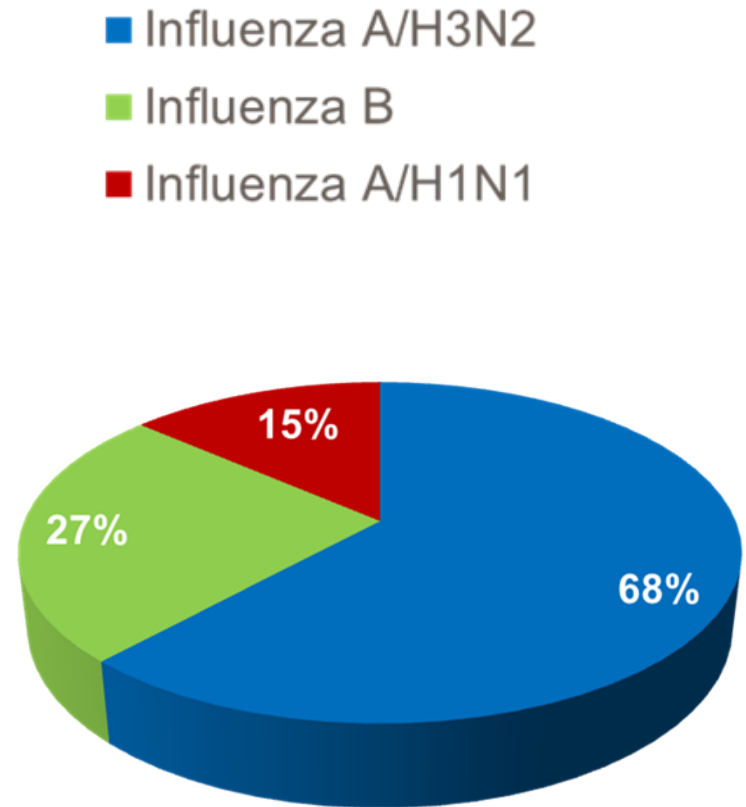
Are at high risk for influenza-related complications, including those who:
Are 6 months through 4 years (59 months) of age
Are ≥ 50 years of age
Have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematologic (including sickle cell disease), metabolic (including diabetes mellitus), neurologic, neuromuscular, and neurodevelopmental disorders (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, or spinal cord injury)
Are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus)
Are or will be pregnant during the influenza season
Are 6 months through 18 years of age and receiving long-term aspirin therapy (and may be at risk for Reye syndrome after influenza virus infection)
Are residents of nursing homes and other chronic-care facilities
Are Native Americans, including Alaska Natives
Are morbidly obese (body mass index [BMI] ≥ 40 for adults or BMI > 2.33 standard deviations above the mean for children)
Live with or care for persons at high risk of influenza-related complications, including:
Healthcare personnel
Household contacts or caregivers of children < 5 years and adults ≥ 50 years of age, with particular emphasis on contacts of children < 6 months
Household contacts or caregivers of persons with medical conditions that put them at increased risk for severe complications of influenza

인플루엔자 백신의 역사

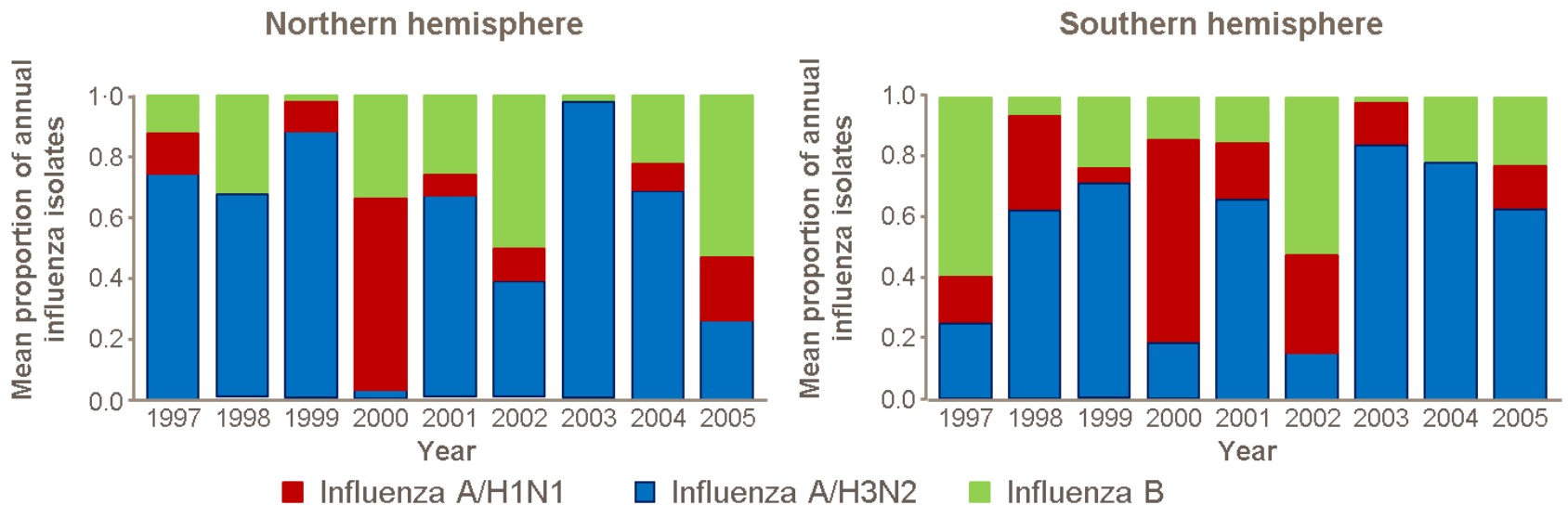


인플루엔자 B 역학

- 2 - 4년 마다 대유행
- 높은 사망률
- 모든 연령군 감염
 - 발병은 어린이와 젊은 성인에서 많고,
 - 사망은 노인에서 주로 발생
- 전 세계적으로 빈도는 A/H3N2보다 작으나 A/H1N1보다 크다



H3N2 > B > H1N1

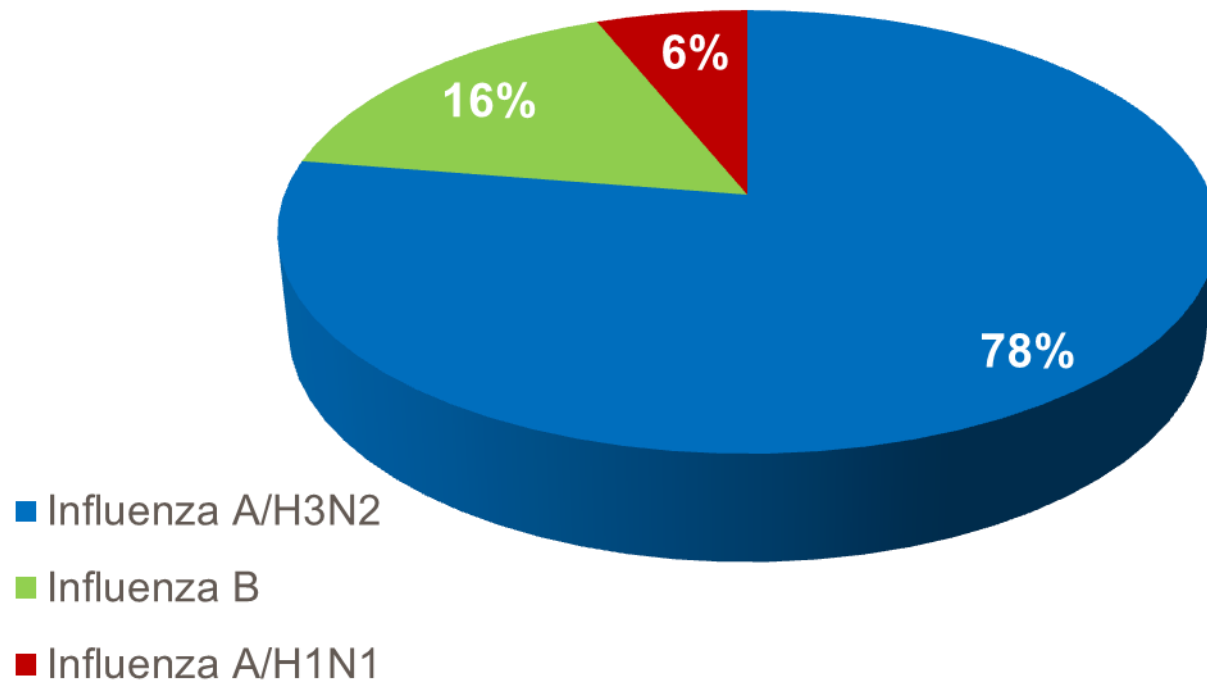


Over the past decade, influenza B viruses have, on average, caused around 25% of influenza cases worldwide¹⁻³

1. Finkelmann *et al.* *PLoS One* 2007;2:e1296; 2. ECDC. 2010. Annual epidemiological report on communicable diseases in Europe 2009 (accessed April 2014).
3. ECDC. 2011. Annual epidemiological report 2011 (accessed April 2014).

인플루엔자 B로 인한 사망

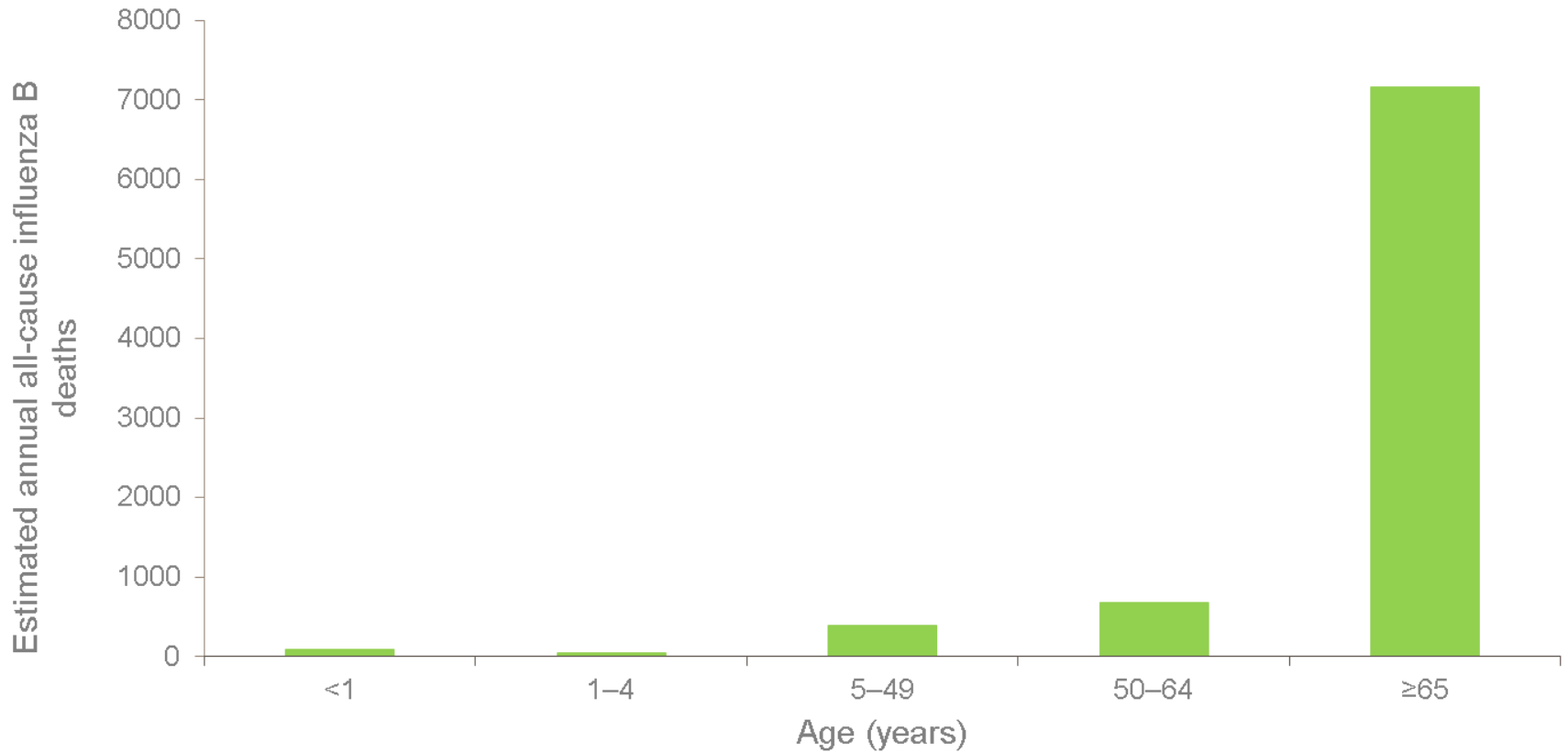
Influenza B causes 16% of influenza-linked mortality in the USA



Study design: analysis of laboratory-confirmed influenza surveillance data by type and subtype (A/H3N2, A/H1N1 and B) from 1997 to 2005^a Data were collected for 19 temperate countries in the Northern and Southern hemispheres^b

^aCompiled from a public database maintained by WHO (FluNet); ^bArgentina, Chile, South Africa, Australia, Israel, Japan, USA, Portugal, Spain, Italy, France, Romania, Switzerland, Germany, UK, Denmark, Latvia, Norway, and Finland

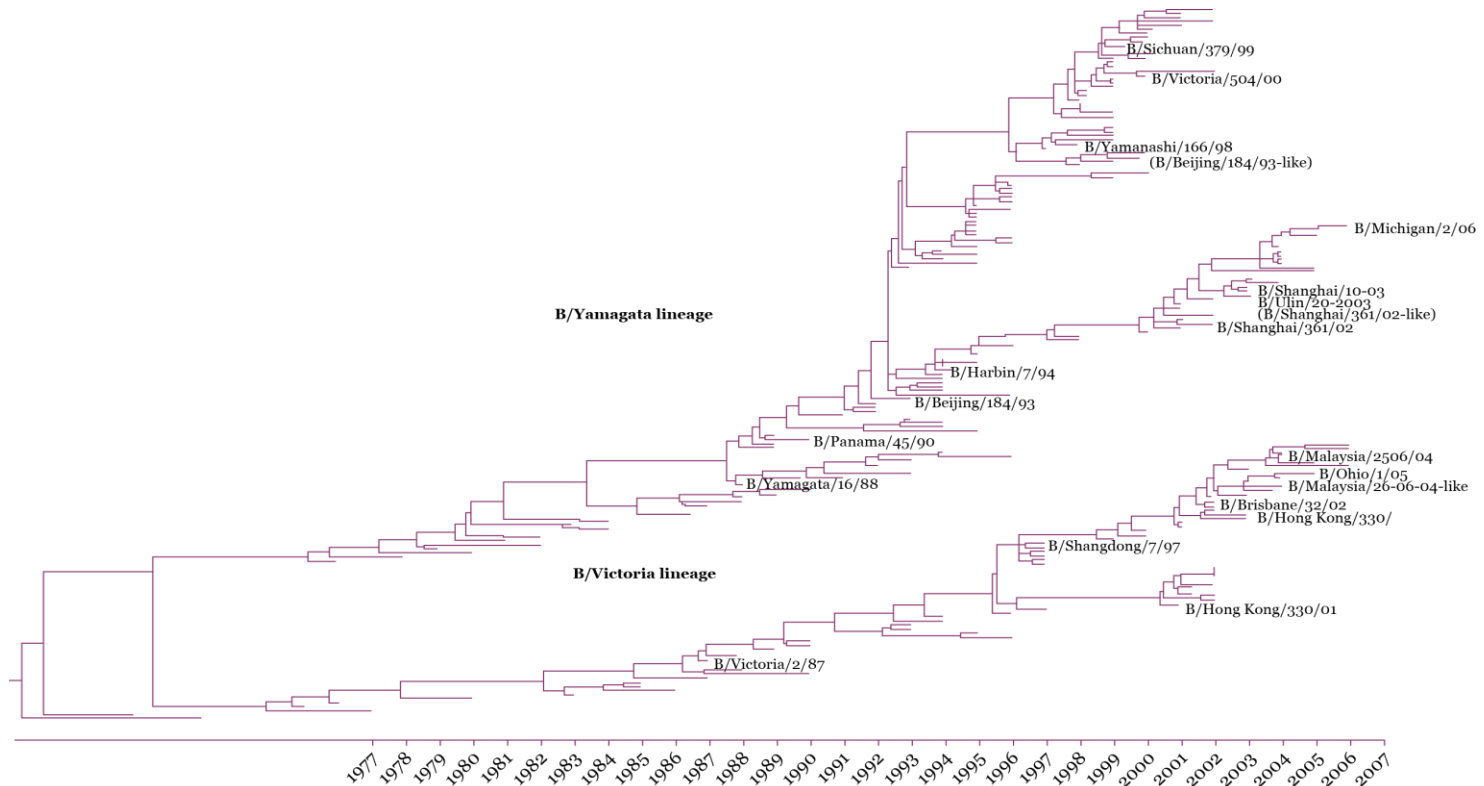
인플루엔자 B 연령별 사망자수



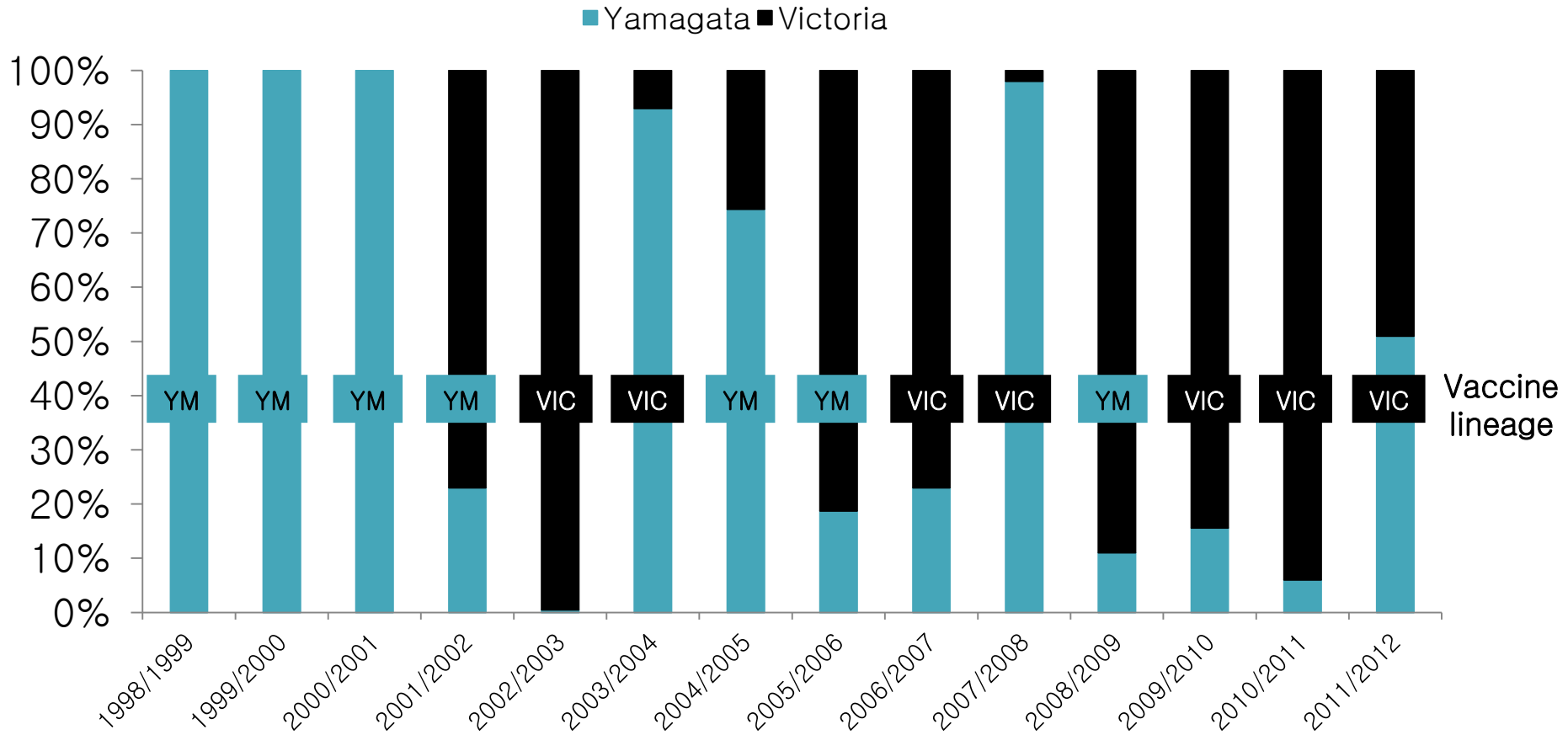
Thompson *et al.* JAMA 2003;289:179-86.

인플루엔자 B 바이러스

- Victoria & Yamagata
- 1980년대 중반 이후 동시 감염 빈발



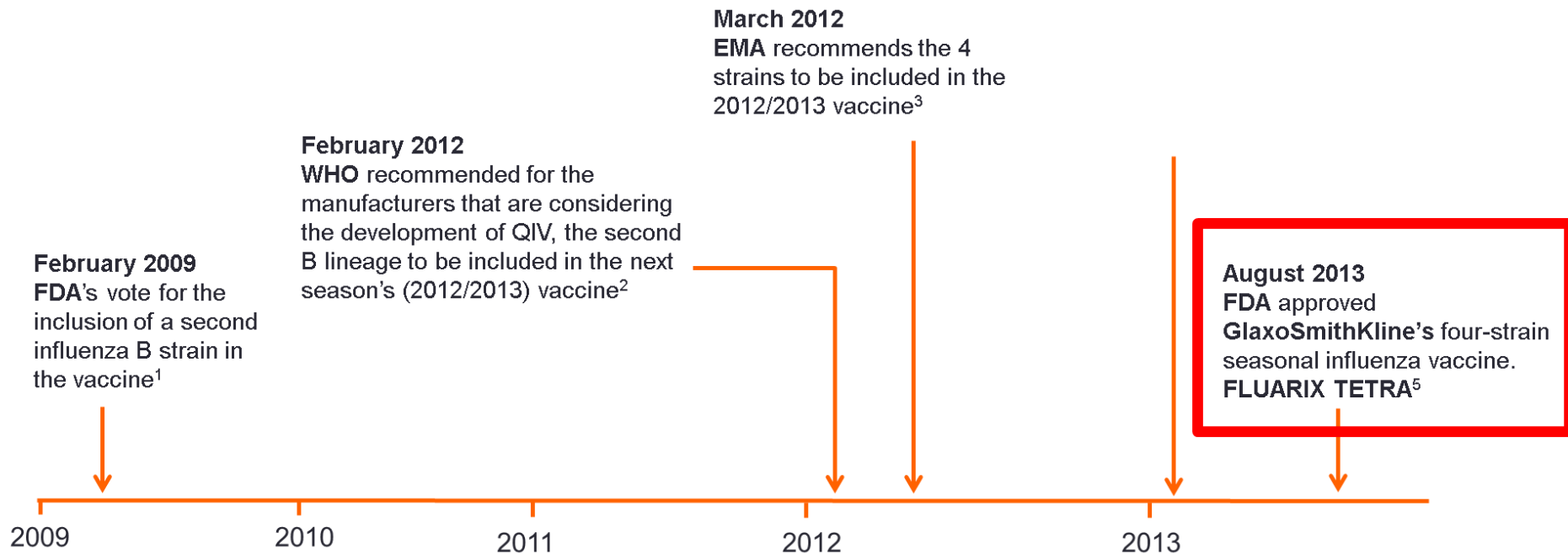
인플루엔자 B 유행 예측 불일치



한국의 인플루엔자 B 상황

Year	No. of total samples	Victoria	Yamagata	Vaccine lineage
2007-08	79	42 (53.2%)	37 (46.8%)	Victoria
2009-10	99	90 (90.9%)	9 (9.1%)	Victoria
2011-12	154	63 (40.9%)	91 (59.1%)	Victoria
2013-14	230	96 (41.7%)	134 (58.3%)	Yamagata

Global alignment to solve the influenza B problem



1. FDA. www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm129568.htm (accessed July 2012); 2. WHO. Influenza vaccines – WHO position paper. *Wkly Epidemiol Rec* 2012;87:461–76; 3. EMA. www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/03/news_detail_001467.jsp&mid=WC0b01ac058004d5c1 (accessed July 2012); 4. WHO. www.who.int/influenza/vaccines/virus/recommendations/201202_recommendation.pdf (accessed July 2012); 5. FDA. August 15, 2013 Approval Letter- Flulaval® Tetra. <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm112845.htm> (accessed Nov 2013)

Summary: 2009 H1N1/A Influenza

- 2009. 3. 2. 멕시코에서 첫 케이스
- 2009. 6. 11. Pandemic alert, Phase 6 by WHO
- 2009 H1N1/A Influenza in Korea
 - 2009. 5. 2. 첫번째 확진 환자
 - 750,000 확진, 252명 사망 (치명률; 0.03%)
 - 폐렴이 합병될 경우 사망률 수백배 이상 증가
- Neuraminidase inhibitor (특히 Oseltamivir)로 인해 중증도와 사망률이 감소되었다고 평가됨.
- 2015년 부터 2개의 A형(H3N2, H1N1)과 2개의 B형(Victoria, Yamagata)을 포함한 4가 백신 접종 시작됨