History of Influenza in India & Viral Changes.

Prof. (Dr.) A. K. Prasad,
Bhubaneswar, Odisha.

10-11 March 2018

<anilkpd2004@yahoo.com>

INFLUENZA WORKSHOP: (APACI-KIIT UNIVERCITY- IFI)

- Grateful acknowledgement to APACI, & KIIT's Univ. for inviting me to talk on "History of Influenza in India & viral changes".
- Mr. Chairman, Eminent dignitaries, on the Dias and off the dais, friends, colleague, Ladies & Gentleman. I am honored..
- My association with Influenza over time (in over 48 years) has become my passion, companion, & friend.
- I feel happy sharing what I learnt over years, with you all.
- Influenza, a Viral-infection of URT which we all know well.
- An infection, with no exception, all here, have suffered not once but few times in life and yet we ignore this as a common cold and loosely use "Flu" to express to all RTI. All are not Flu. Flu is caused due to Infl. group of viruses (Myxovirus) only.
- This is a self limiting infection and in case of no complication , recovers in 5-7 days but as soon fever subsides one starts mixing with all, little realizing that unconsciously, you pass the infection to others.

Virology- Influenza in India.

- History of Influenza in India is no different from the world history of influenza.

- I was surprised that hardly any publication was done on Influenza in India during the late sixties of the last century. There were only two published papers on Influenza, which I could locate.

Indian Reverences on Influenza Virus (till sixties)

- (1) Veeraraghva, N. (1961). Influenza viruses at the Govt. of India Influenza Centre, Connor during 1950-1960.

  Bull. WHO ,24, 679-689.
- (2) Seth. R. and Kalra, S, L. (1965). Viruses in respiratory infections in Delhi.

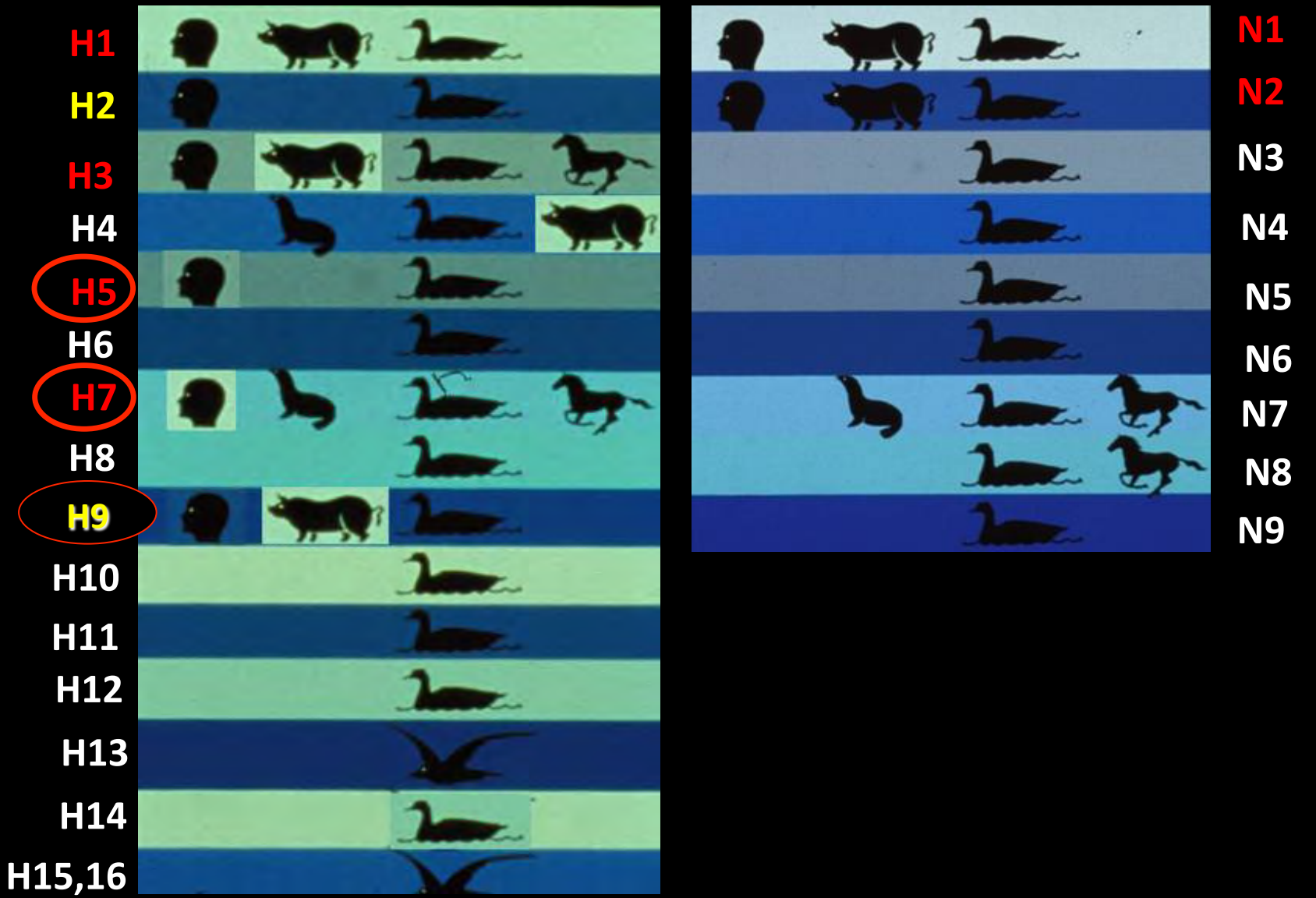
  Ind. J. Med. Res., 53, 1109-1111.

These are the two early references on Influenza from India (to my knowledge).

Virus: Influenza Subtypes.

- Three sub-types:
- Type A; Type B & type C.
- Type A causes infection in human & Mammals including birds. Most Pathogenic among all influenza viruses.
- Type B infects Man only.
- Type C infects man alone . Infection clinical to subclinical and one hardly one notices this. But very invasive. Virus isolation difficult but antibodies found all over the world population. Unstable virus in Lab.

Species Infected by Influenza A: HA and NA Subtypes



History of Influenza

- Epidemics of Influenza amongst man & animals are known for a long time. Epidemiologists in the past century have been fascinated by the OB's of the disease as its occurrence has been very erratic , both in time and space. From 1530 to 1930, some 30 widespread epidemics & pandemics have occurred and numerous less extensive OB's have been described. Thompson in 1852 wrote about the 1557 pandemic, describing the disease as starting with roughness of jaw, small cough followed by high fever with pain in head, back & legs. The symptom lasted for 3-days which decline with recovery. But some turned as Pleurisy and to fatal pneumonia.
- The 1743 & 1889 pandemics were observed very virulent but with less mortality.
- The most lethal was 1918-1919 which killed almost 20 million people. Fatal bronchopneumonia complications were seen mostly in young people.
- Indian references not known.

Continued from previous slide

- The 1782 pandemic was probably a turning point as idea about infectious & contagious nature , spread of disease etc. was changing over the metrological & telluric reason. It was no longer thought disease as "God's curse.
- However it took over 100 years to comple data for this. More scientific & precise knowledge about influenza was gained after the virus was isolated in laboratory by Smith, Andrews & Laidlaw in 1933 ; Francis 1934;Smith 1935; Burnet 1935; Hoyle & Fairbrother 1937.

Human Influenza type A virus & Other animal influenza type A viruses.

- During 1918-19 Influenza pandemic symptologically similar disease was seen in pigs for first time by a Veterinarian Koen (Dorset et al. 1922-23). Both the farmer & the pigs ran a similar course and used the name Flu for Swine Influenza. This was latter confirmed that Swine virus & human virus , influenza type A share a common CF antigen.
- Other animal & bird viruses (from equine, duck& fowl plague have common S-antigen with human infl. A virus.

Future Influenza pandemic (s)

- Epidemiologist think the pandemic time bomb may have been activated and we are powerless to control. It is like a tsunami, unimaginable devastating. Hundreds of hundred will die with no arsenal used like in world wars. Even today if we think about the deaths due to influenza as a single disease has killed 50-100M in the past last century pandemics. No country is immune & safe.
- History tells : healthy in morning , sick by lunch time and choking to death by evening.
- No country in the world has made enough life saving preventive courses of antiviral for its population.

Men who matters in Influenza say: H5N1: (Pandemic in waiting)

- H5N1 pandemic is an absolute certainty.
- The number of people infected will go beyond billions as 25-30% will fall sick.
- Under developed & developing countries will suffer more.
- The best prevention & protection for seasonal influenza is vaccine. (No total protection but this may only reduce the impact/ complication of the disease).
- This century (2009) was a surprise pandemic due to Swine virus pH1N1 when waiting for H5N1.

Influenza: Last century.

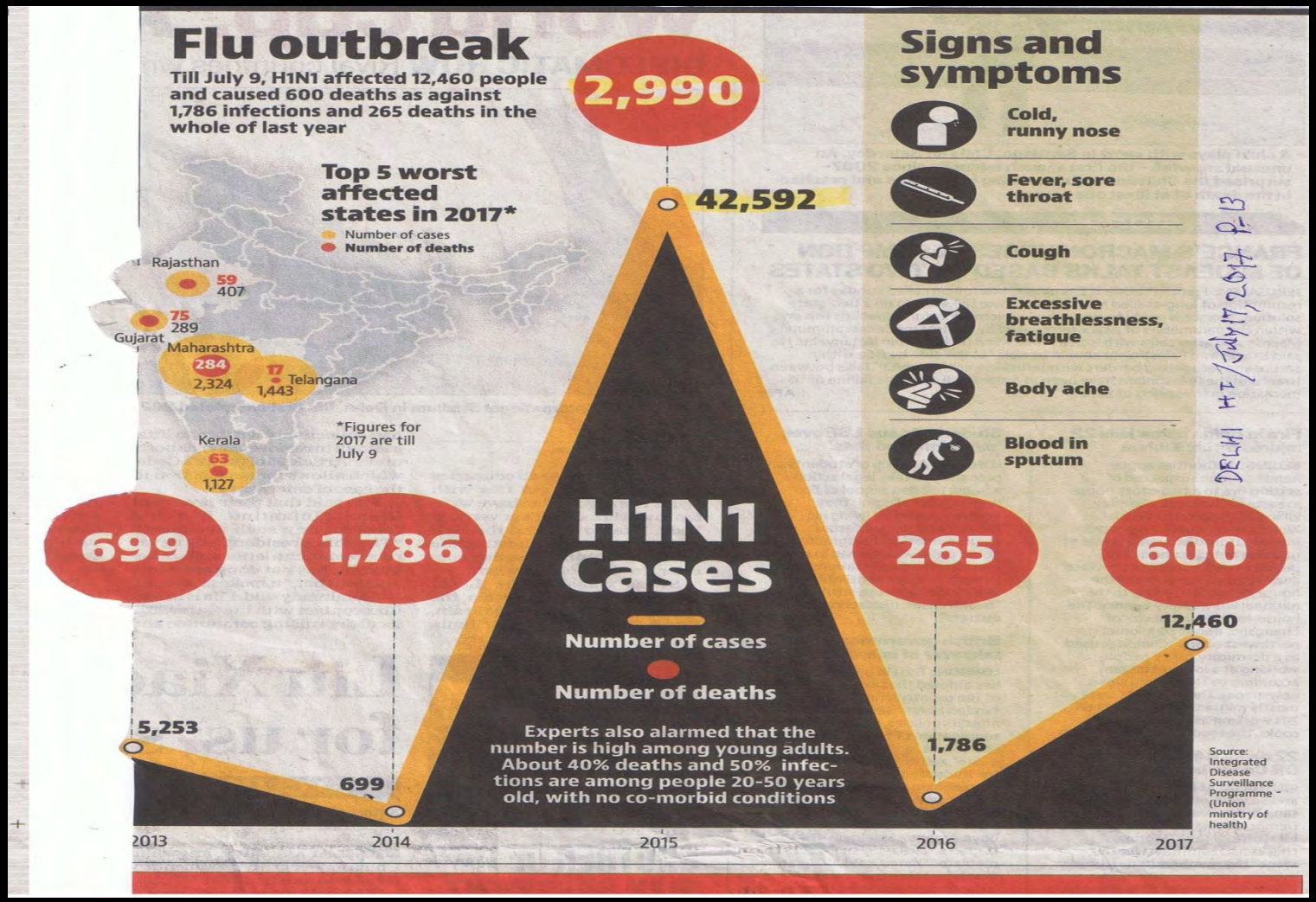
- Last century, three major influenza pandemics have been responsible for at least 50- 100 million deaths world wide. (Unheard for any one single disease; even WW I & II & natural calamities).
- In addition, annual winter influenza epidemics (Seasonal influenza) has enormous medical & economic impact in any country.
- A serious morbidity & mortality occurs among very young, old adults, persons with chronic conditions, and pregnant women.

Influenza

- No country is free & protected from the disease.
- Developing & under developed countries are more prone due to high density population & combined economic reasons with under to nil use of preventives suffer more.
- Pandemics occur over space & time. Surface antigens assortments in various hosts (Man, animals & birds)
- Human & mammals (swine) & birds play as biological incubators for antigenic recombination.
- Infection spreads fast like wild fire in short time over large area.


FOTOSEARCH

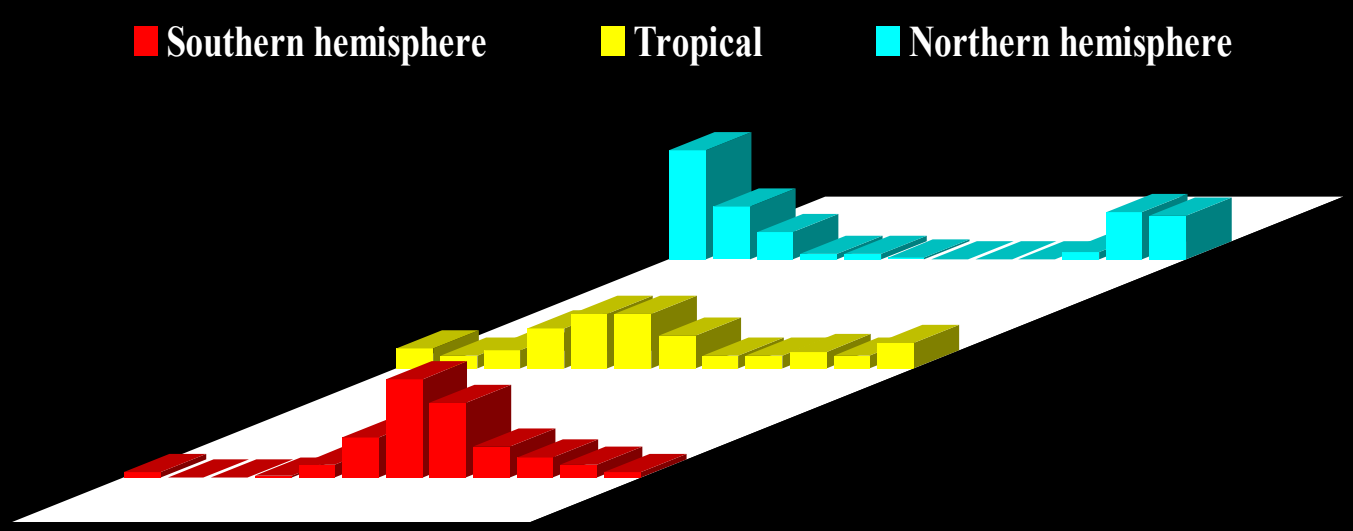
Latest Flu cases (H1N1) in India.



Preventive vaccine: I wish in a country like India, all available vaccines with no reservation to be made mandatory to use.

Influenza Viruses.

- Type A & B contains 8 segments ss RNA whereas Type C, contains seven.
- Interesting and worth noting. Type C still continues in this group.



Many people believe that influenza mainly occurs in colder climates. However, in tropical areas such as South China or Singapore, where there is a constant warm climate and little or no annual temperature change, influenza can occur at any time of the year. Influenza occurs somewhere in the world every month of the year.

4.2. Epidemiology and seasonality

In Pune, influenza outbreaks are observed during the "rainy" season, July–August (Fig. 1(f)), while in Delhi influenza activity is seen throughout much of the year, with the highest levels over the winter months (Fig 1(e)).

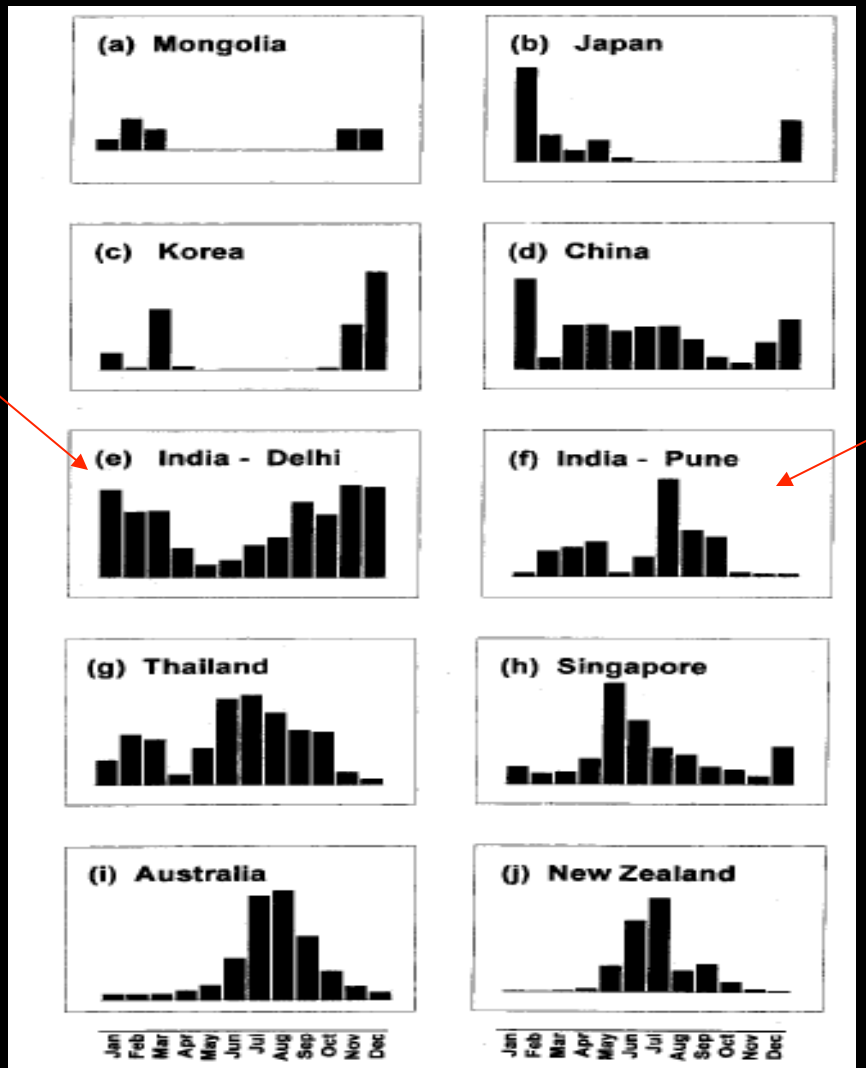
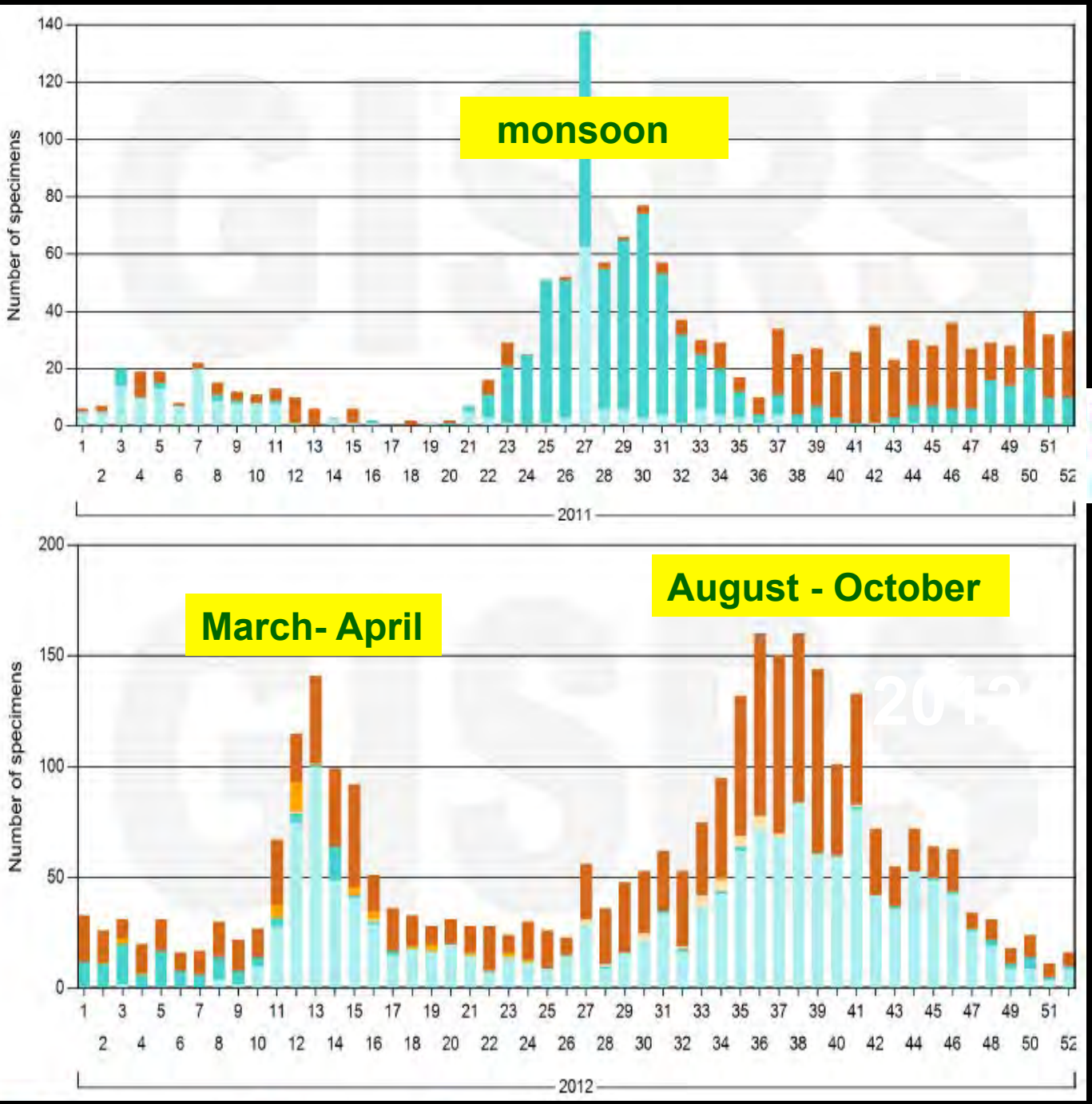
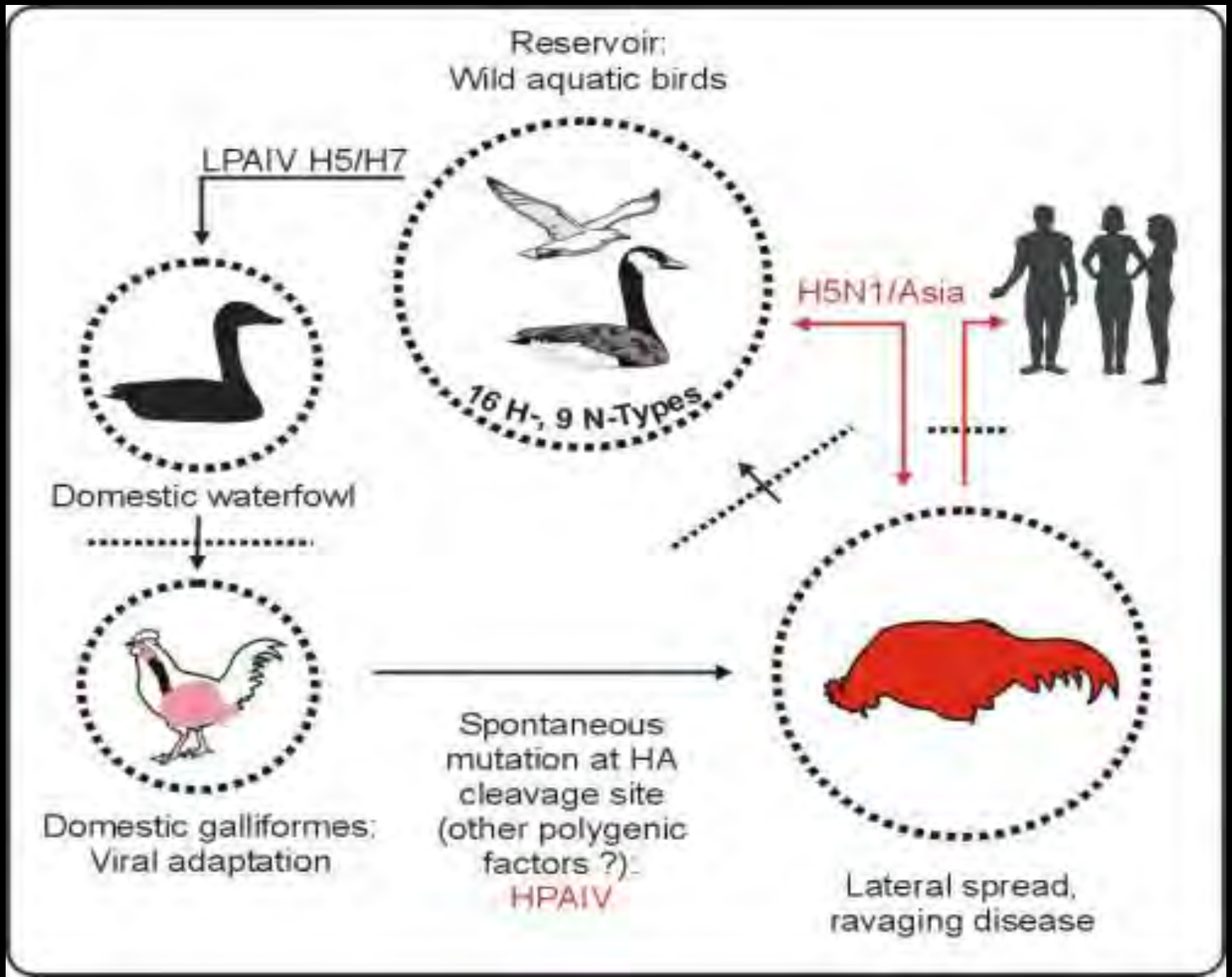
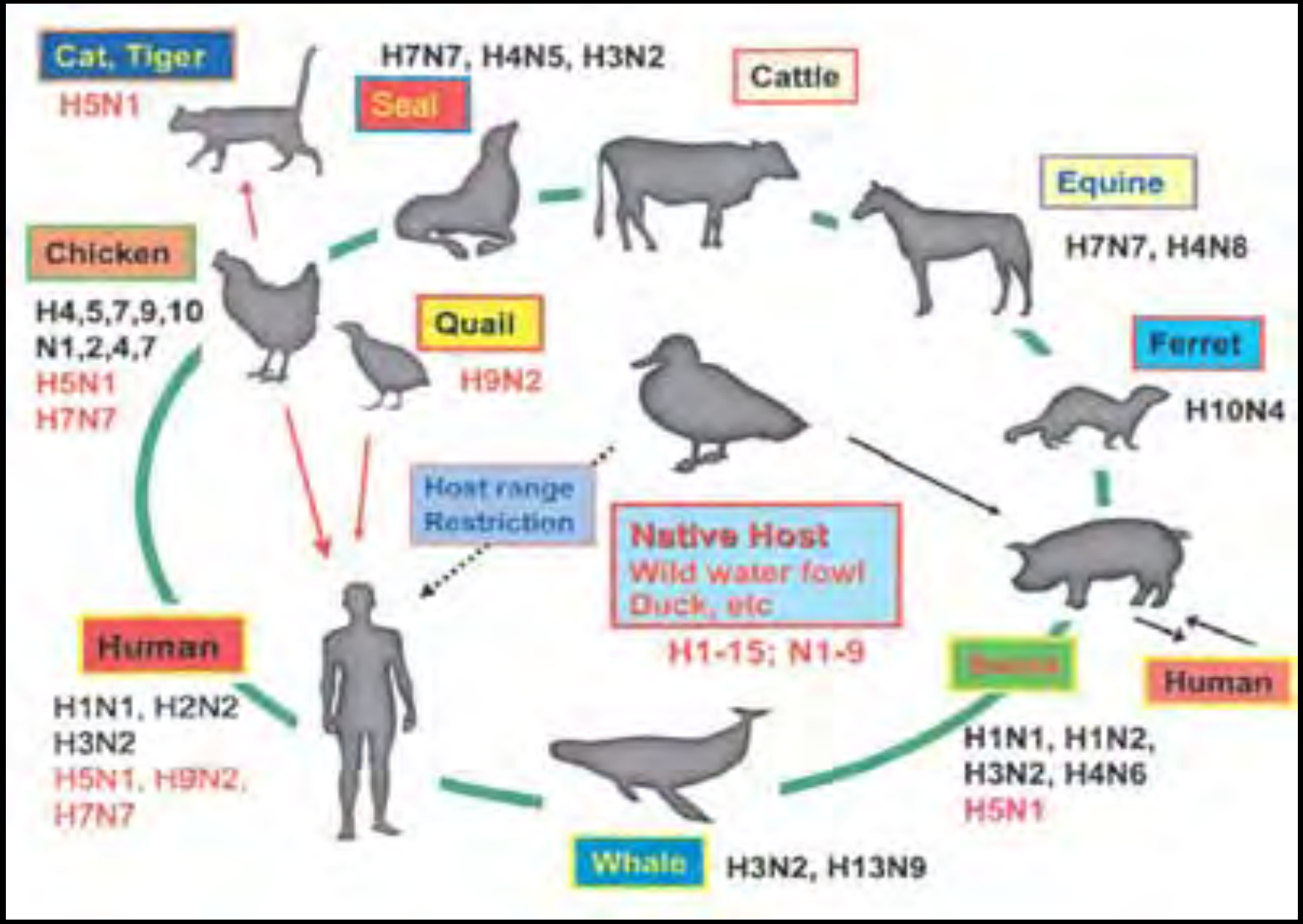


Fig. 1. Incidence of influenza isolates by month reported in: (a) Mongolia, (b) Japan, (c) Republic of Korea, (d) China, (e) India—Delhi, (f) India—Pune, (g) Thailand, (h) Singapore, (i) Australia and (j) New Zealand.

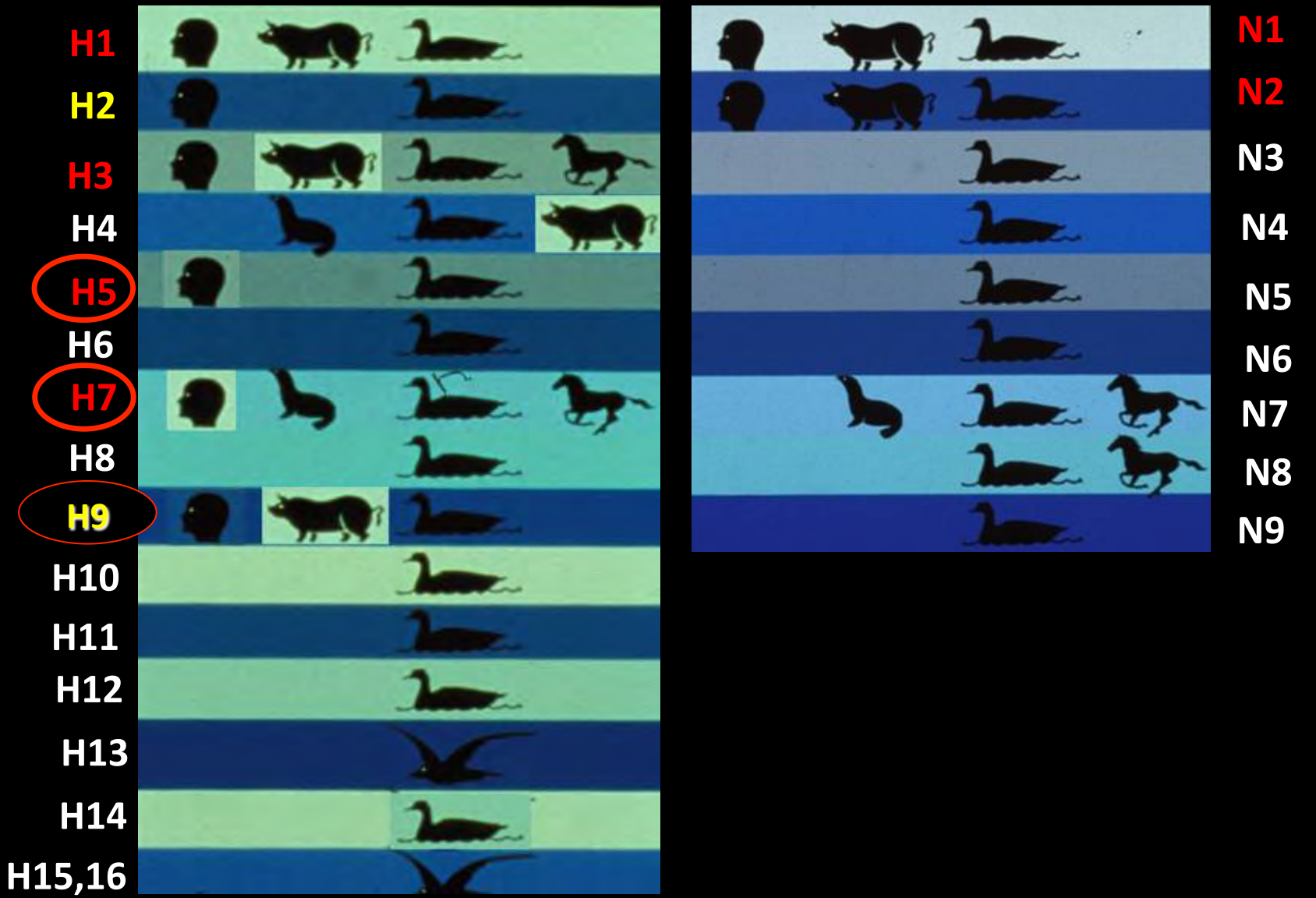
India


monsoon
March- April
August - October
Number of specimens
2011
2012
A (Not subtyped)
A(H3)
A(H1N1)pdm09
B (Lineage not determined)
B (Victoria lineage)
B (Yamagata lineage)


Reservoir:
Wild aquatic birds
LPAIV H5/H7
16 H-, 9 N-Types
H5N1/Asia
Domestic waterfowl
Domestic galliformes:
Viral adaptation
Spontaneous
mutation at HA
cleavage site
(other polygenic
factors ?):
HPAIV
Lateral spread,
ravaging disease


Cat, Tiger
H5N1
H7N7, H4N5, H3N2
Seal
Cattle
Equine
H7N7, H4N8
Chicken
H4,5,7,9,10
N1,2,4,7
H5N1
H7N7
Quail
H9N2
Ferret
H10N4
Host range
Restriction
Native Host
Wild water fowl
Duck, etc
H1-15; N1-9
Human
H1N1, H2N2
H3N2
H5N1, H9N2,
H7N7
H1N1, H1N2,
H3N2, H4N6
H5N1
Human
Whale
H3N2, H13N9

Species Infected by Influenza A: HA and NA Subtypes

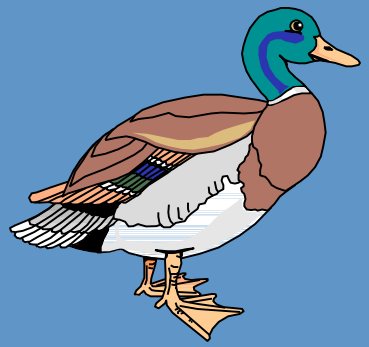


Natural Reservoirs for New Human Influenza A Virus Subtypes

Avian Influenza A viruses

H1 – H18

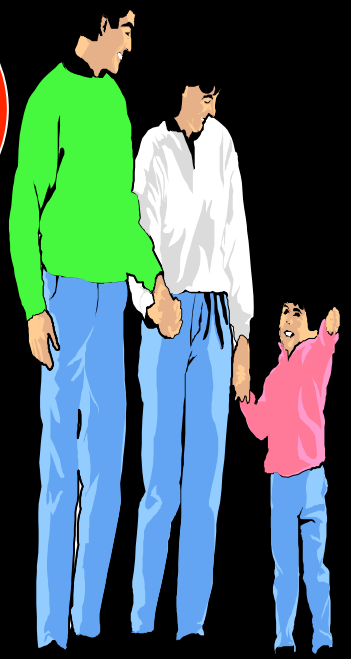
N1 – N11



Aquatic ducks and Geese

Human Influenza A Viruses

H1 - H3



INFECTION

- OVER 50% OF ALL HUMAN ILLNESSES ARE DUE TO INFECTIOUS AGENTS, AND VIRUSES ACCOUNTS FOR 60 % OUT OF THIS.
- RESP. VIRUSES ALONE, ACCOUNTS FOR 70 -85%.(out of above 60%)
- (This speaks VOLUME of importance of VIRUSES in CHEST INFECTION)
- (These figures are on higher side as the cases were all diagnosed and laboratory confirmed cases).

INFECTION

- INITIALLY MOST OF THE URTI STARTS WITH A VIRAL INFECTION.
- RECOVERY IN 2 -7 DAYS IN UN-COMPLICATED CASES WITH RISE OF SPECIFIC VIRAL ANTIBIDIES.(SELF LIMITING INFECTION).
- PATHOLOGY LIMITTED TO 1-2 LAYERS OF LINING M.M.

RESP. VIRUSES INCIDENCE

- MOST STUDIES & OUR STUDIES AT VPCI, SUGGEST THE COMMON RESP. VIRUSES ARE INFLUENZA, PARA-INFLUENZA, RSV, & (RHINO VIRUSES) IN VARIOUS AGE GROUPS.
- AT ANY TIME OF THE YEAR INFLUENZA VIRUS CIRCULATION VARIES 10-20% IN A POPULATION (based on serology & isolation of virus).

WHAT IS INFLUENZA & WHY IMPORTANT ?

- MOST PEOPLE KNOW ALL COLD OR URTI AS FLU.
- LACK OF AWARENESS LEADS TO COMPLICATION OF INFLUENZA.
- HIGH MORBIDITY, LOW MORTALITY RATIO GETS ALTERED. (MORE HOSP. ADMISSION).
- HIGHLY INFECTIOUS, SPREADS IN ALL CONTACTS.
- SPREAD ROUTE OF INFECTION IS BY RESP. ROUTE.
- LESS USE OF ANTI VIRALS & PREVENTIVES AVAILABLE.
- COUNTRY LOOSES MORE WORKING HOURS, INCRESED SCHOOL ABSENCE. (MORE ECONOMIC LOSS TO THE COUNTRY)
- SELF MEDICATION CREATES MORE PROBLEM & RESISTANT INFECTIOUS AGENTS.
- UNWANTED USE OF ANTIBIOTICS.

BASICS OF INFLUENZA

- **HIGHLY CONTAGIOUS**
- **VIRUS ANTIGEN MUTATES.**
- **EACH YEAR 5 -15 % OF WORLD POPULATION SUFFERS.**
- **EVERY 2 YEARS EPIDEMIC IN SOME PART OF WORLD.**
- **WORLD PANDEMICS IN PERIODICITY**
- **ALL THE TIME VIRUS IS IN CIRCULATION IN A POPULATION**
- **OVER DUE HUMAN FLU PANDEMIC.**
- **HPIV – H5N1 : Bird Flu Virus trying to jump Human host-barrier.**

Viral Diversity And New Host Adaptation

Viral diversity led by two different ways:

- antigenic "drift" & "shift"

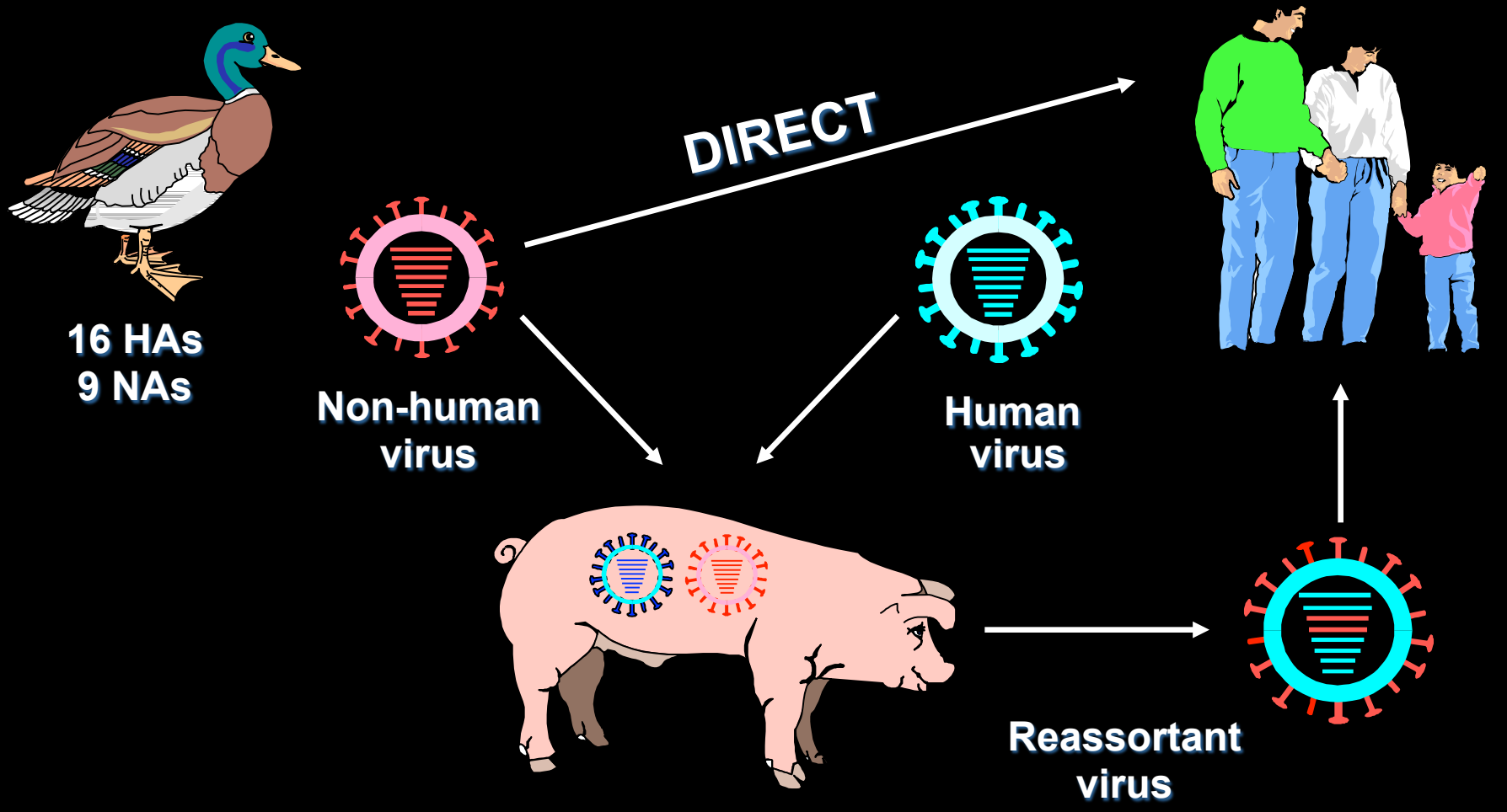
Antigenic Drift:

- Gene mutations result in new strain variants (OB)
- One variant "predominates" for 1-3 years
- As viruses evolve, people immune to older viruses become more susceptible to newer strains
- Necessitates annual updating of vaccine strains

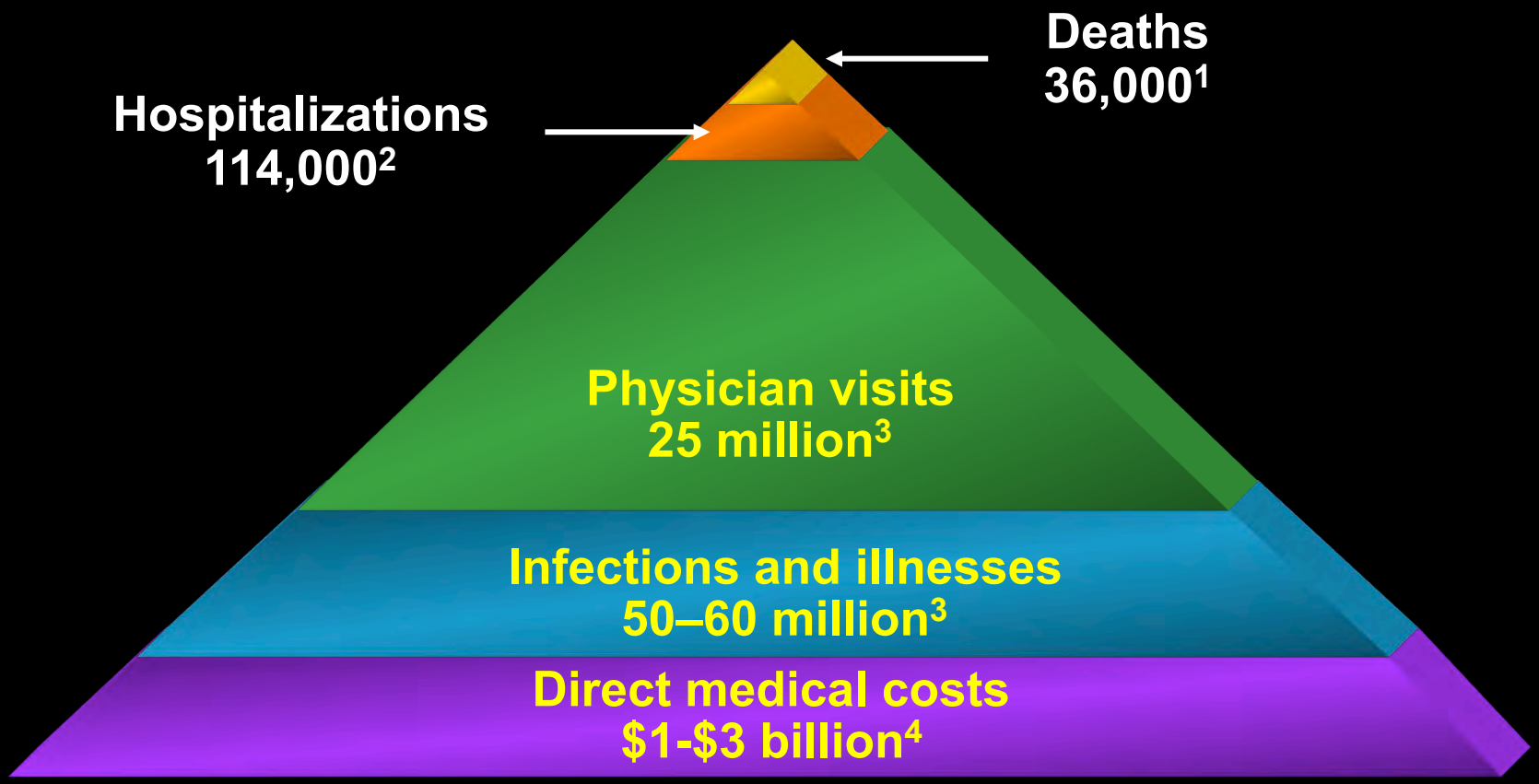
Antigenic Shift"

- Emergence of "novel" influenza A subtypes among humans
- Current candidates: H2 and H4-16 viruses
- Relatively Infrequent
- Potential for pandemic if person to person can be sustained

Inter-species Transmission and Influenza Re assortants

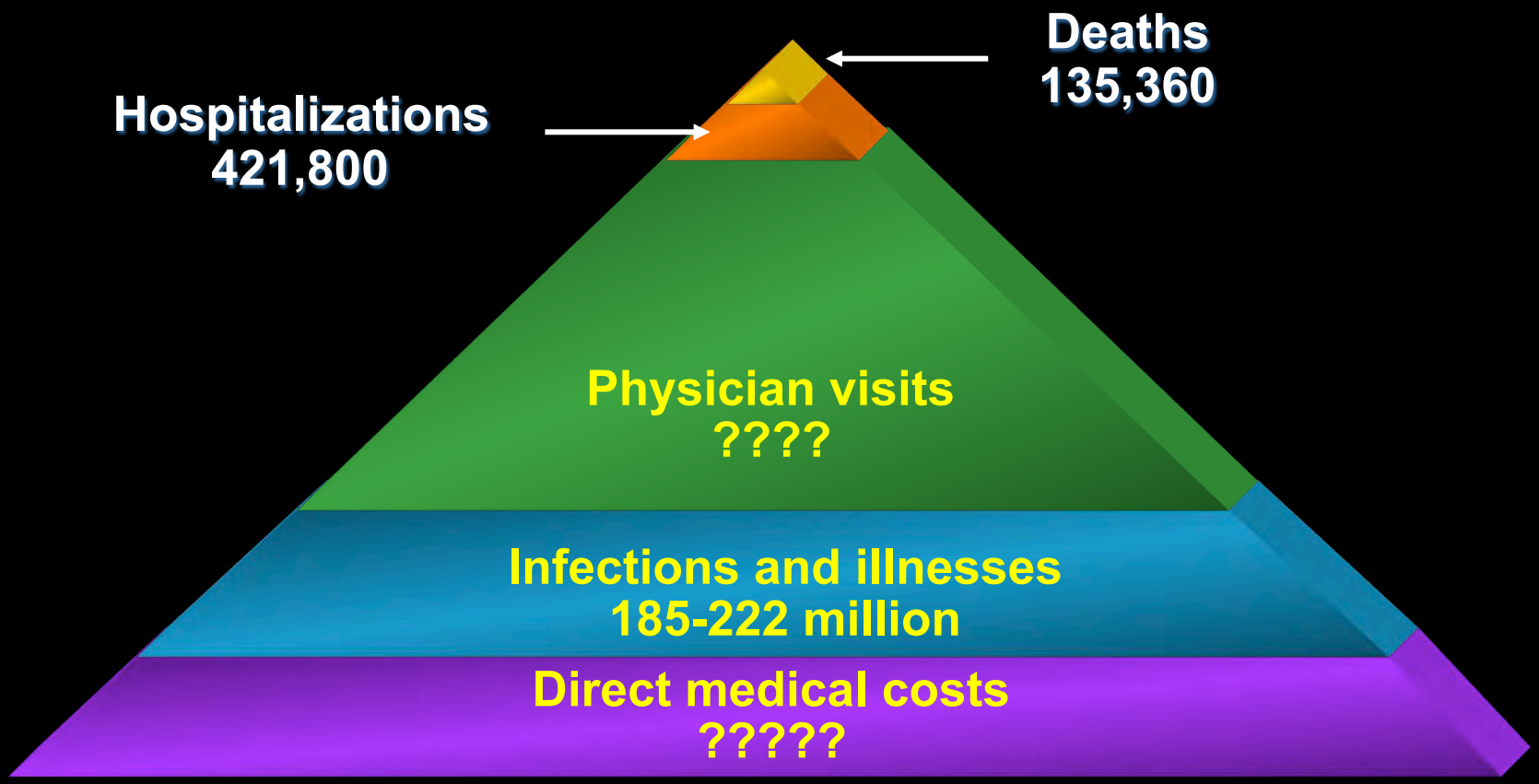


Seasonal Influenza Responsible for Much Disease in the United States



1. Thompson WW et al. *JAMA*. 2003;289:179-186.
2. CDC. *MMWR Recomm Rep*. 2003;58(RR-8):1-34.
3. Couch RB. *Ann Intern Med*. 2000;133:992-998.
4. Patriarca PA. *JAMA*. 1999;282:75-77.

Seasonal Influenza May Be Responsible for Much Disease in India

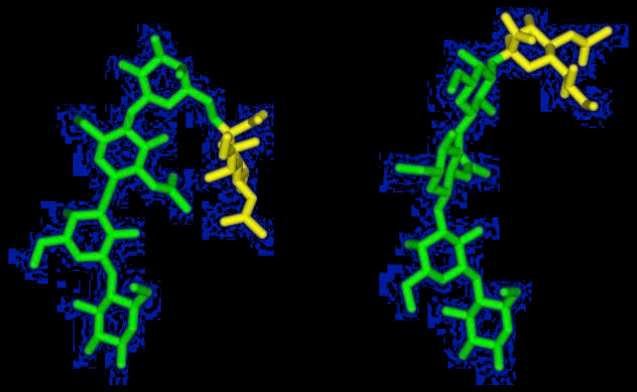


Assuming an estimated population of India of 1,129,866,000 and 301,000,000 in US, rate in India would be 3.76X US rate

Influenza HA Receptor Preference: Distribution of Sialic Acid

- Human influenza viruses prefer αlpha 2,6 linkages
- Avian influenza viruses prefer αlpha 2,3 linkages

Sia(2-6)Gal



AVIAN
Sia(2-3)Gal

Why is H5N1 (Bird Flu) Important ?

- Lethal to poultry (economic impact) and humans
- Infects many species of birds (endemic) and mammals

  Present in healthy waterfowl - shed in feces

  Potential for evolution to pandemic form
- No human H5N1 vaccine commercially available
- Limited supply of expensive antiviral medicines
- Potential for major economic, social and political impact

Human Exposed to Poultry

Current Challenges for Control of AI in Poultry

Poverty consumption of sick dead birds

- **Consumption of raw poultry products**
- **Inadequate compensation for farmers**
- **Co-habitation of humans and poultry**
- **Mixing multiple species of birds in wet markets**
- **Delays and transparency in reporting / detection of H5N1 in birds and humans**
- **Illegal trade and other activities**

Human H5N1 Epidemiology

- 267 human cases worldwide from 2003-06
- Primarily avian-to-human transmission
- No evidence of sustained person-to-person spread
- Limited probable person-to-person spread[1]
- Environment-to-human transmission possible

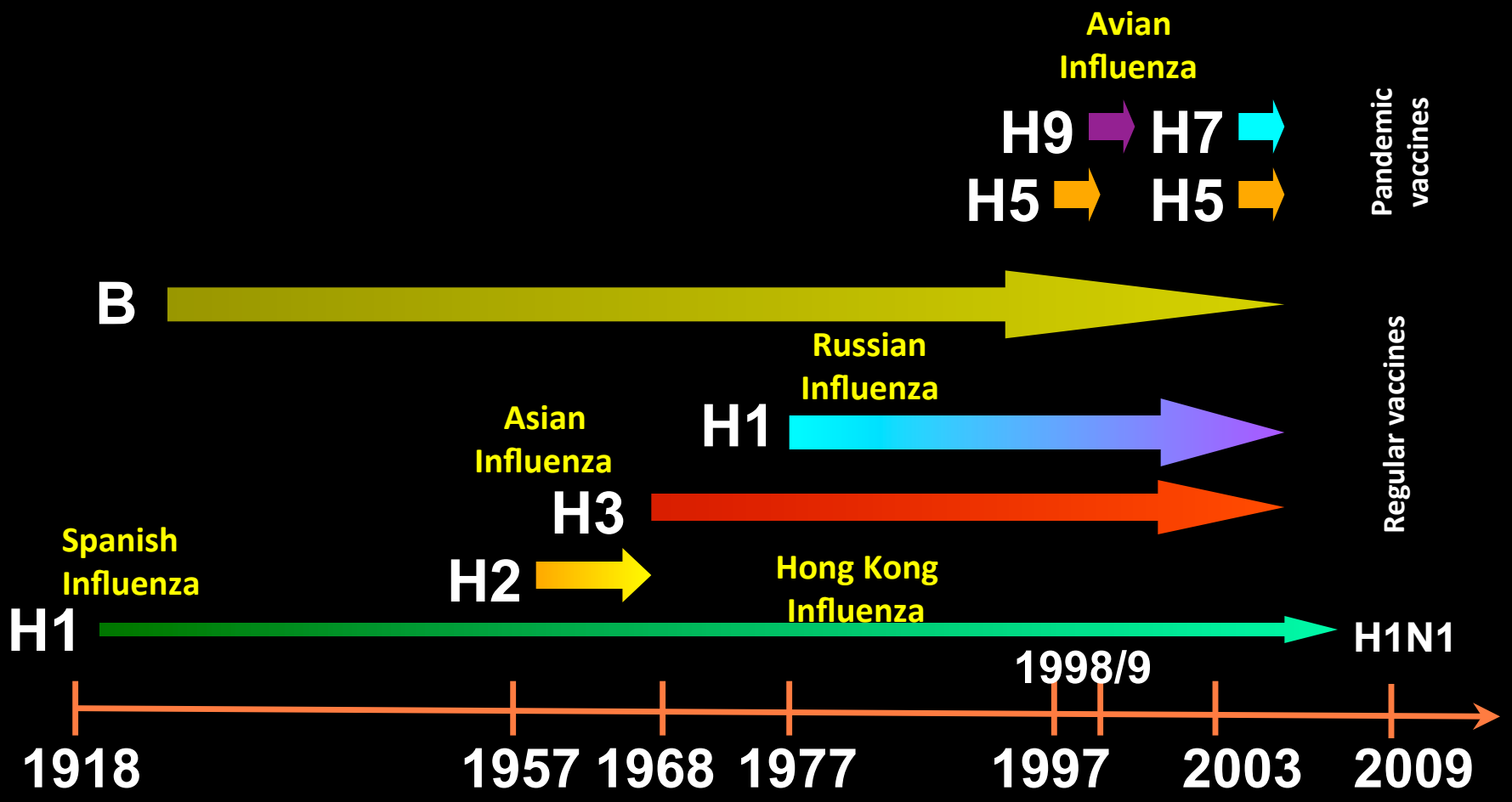
[1] N Engl J Med 2005;352:333-340

Human infections with HPAI

Mild to severe human illness with HPAI:
(usually associated with poultry outbreaks)

- H7N7 (mild illness, conjunctivitis)
  - 2003 Netherlands (89 cases, 1 death)
    - Most cases were poultry workers
- H7N3 (mild illness, conjunctivitis)
  - 2004 Canada (2 cases, 0 deaths)
- H5N1 (severe respiratory disease)
  - 1997 Hong Kong (18 cases, 6 deaths)
    - Risk factor: visiting live poultry market
  - 2003 Hong Kong (2 cases, 1 death)
  - 2003-06 (267 confirmed cases/ 161 deaths)

Timeline of Emergence of Influenza Viruses in Humans



Avian Influenza: Summary

- H5N1 Avian Influenza is currently spreading through birds with occasional outbreaks among humans
- While there is evidence of rare human to human transmission, sustained transmission has not occurred
- If H5N1 virus obtains the ability to easily transmit from person to person, a pandemic may result

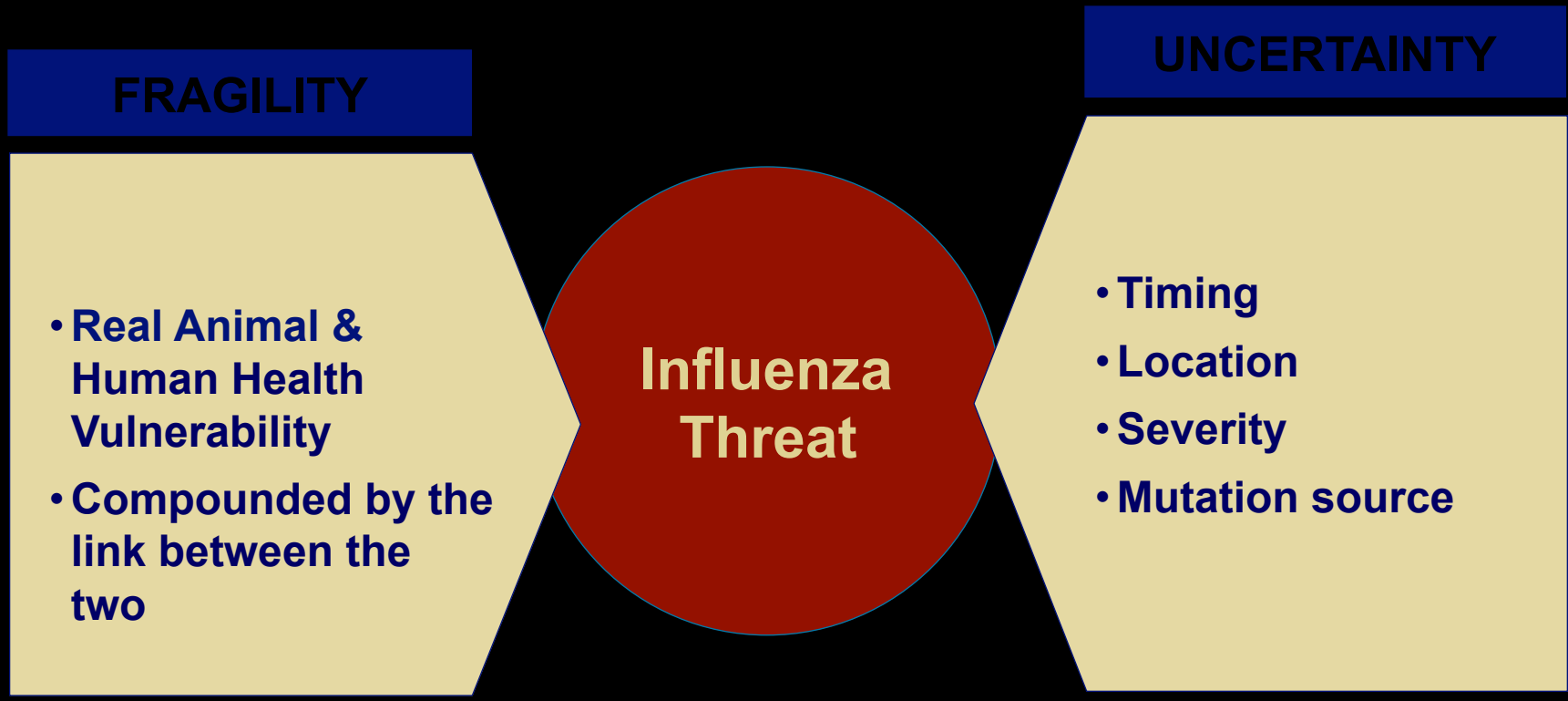
Seasonal Epidemics vs. Pandemics

Seasonal Influenza	Influenza Pandemics
- A public health problem each year	- Appear in the human population rarely and unpredictably
- Usually some immunity built up from previous exposures to the same subtype	- Human population lacks any immunity
- Infants and elderly most at risk	- All age groups, including healthy young adults, may be at increased risk for serious complications
- Result of Antigenic *Drift*	- Result of Antigenic *Shift*

Influenza A (H5N1) and the Threat of Pandemic Influenza

- Is H5N1 evolving into a pandemic ?
- Can critical events be identified "early" enough?
  - Viral changes suggesting adaptation to humans
  - Outbreaks associated with human-to-human spread
- Is "containment" realistic?
- What preparations can & must be done?

The Complexity of the Threat



Possibly the greatest global human security vulnerability today


I'M SO GLAD WE LIVE FAR FROM ALL THOSE DISASTER-PRONE AREAS OF THE COUNTRY...
MONSTER HURRICANES BATTER GULF COAST
AH-CHOO!
BIRD FLU
MORA
The Miami Herald

Influenza : A point to be noted.

- High-dose influenza vaccine provides better protection against influenza when compared with standard-dose vaccine among persons aged 65 years and older.

(N Eng J Med. 2014;371:635-645. Abstract)

Antigenic Mutation in Influenza Virus in India

- All influenza viruses have evolved in a pattern similar to the global evolution. Indian strains have been by and large similar to the vaccine strains in the corresponding years. In years when the strain has changed, our viruses were seen to be similar to the Southern Hemispheric vaccine.

  (NIV, Pune)

THANK YOU