“Thailand’s influenza surveillance networks and response for pandemic influenza”

JOINT INTERNATIONAL TROPICAL MEDICINE MEETING 2018 (JITMM2018)

12-14 December 2018
Amari Watergate, Bangkok, Thailand

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Influenza

Pandemic Influenza: an Evolving Challenge

2018 marks the 100th anniversary of one of the largest public health crises in modern history, the 1918 influenza pandemic known colloquially as "Spanish flu." The intensity and speed with which it struck were almost unimaginable – infecting one-third of the earth's population, which at the time was about 500 million people. By the time it subsided in 1920, tens of millions people are thought to have died.

Although influenza has been with humankind for millenia, the global spread and impact is in many respects a function accelerated in modern times. Urbanization, mass migration, global transport and trade accelerate the spread of pandemics.

Read the story

New Contributed Photographs Collection / Otis Historical Archives / National Museum of Health and Medicine

About influenza

– Fact sheet on seasonal influenza

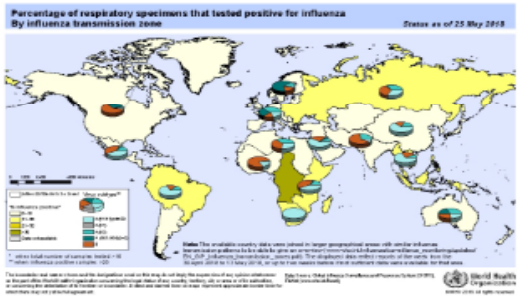
Global Influenza Programme

GISRS
GLOBAL INFLUENZA SURVEILLANCE & RESPONSE SYSTEM
Uniting the world in the fight against influenza

Global Influenza Programme

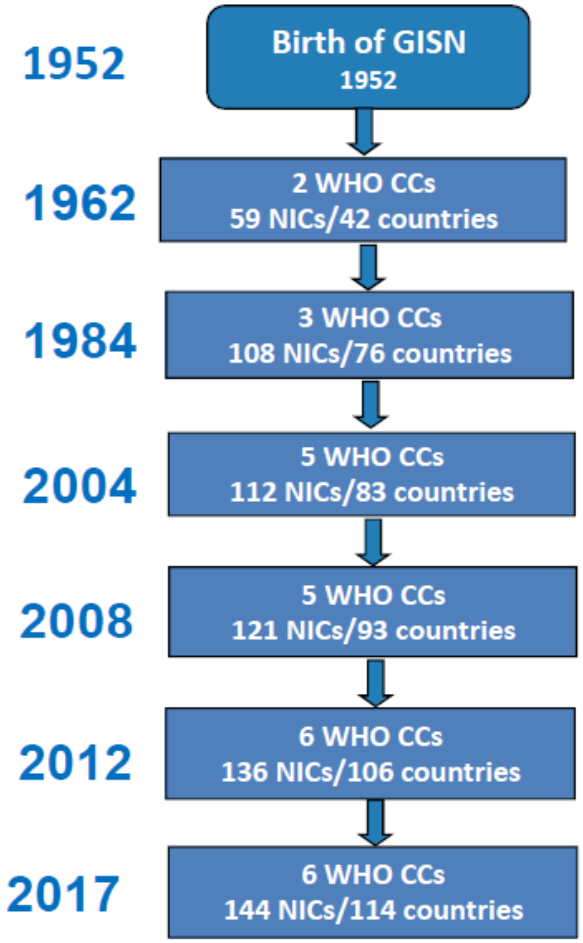
The Global Influenza Programme (GIP) provides Member States with strategic guidance, technical support and coordination of activities essential to

Current influenza situation



– Biweekly seasonal influenza updates and maps

Growth of the Global Influenza Surveillance and Response System (GISRS)

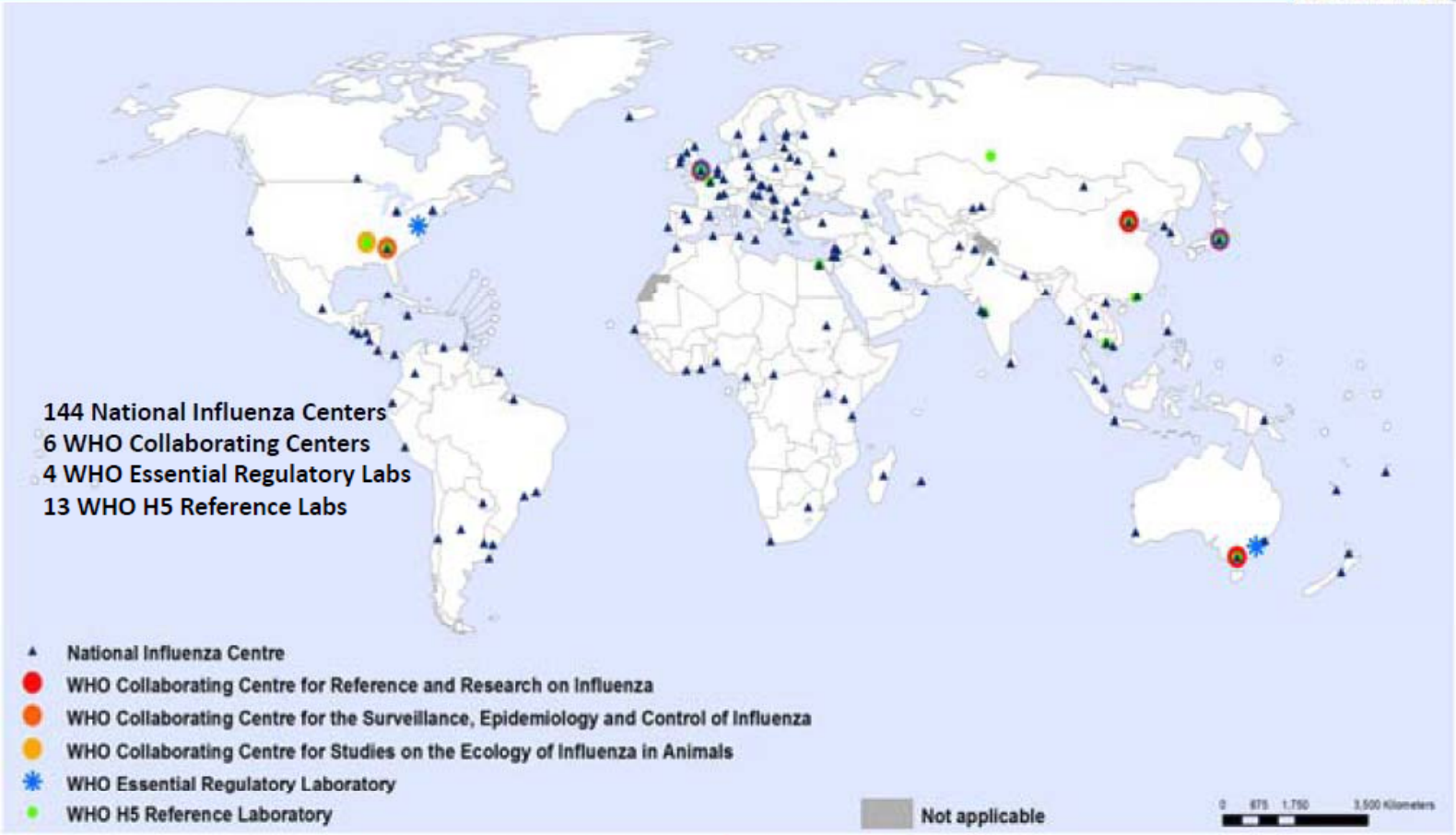


- Virus monitoring and risk assessment
- Integration of epidemiological data
- Laboratory diagnostics
- Vaccine virus selection
- Capacity building
- Communications and networking
- Regular interactions with industry
- **Serves as a model international surveillance system with a strong ethos of collaboration and cooperation**

WHO Collaborating Centers for Influenza: Atlanta in the mid-1950s, Melbourne in 1992, Tokyo in 1993, and Beijing in 2011; CC in Memphis for animal influenza, 1975

Nancy J. Cox, Ph.D.
WHO Meeting of National Influenza Centres
17-19 July 2017, Geneva, Switzerland

Expansion of GISRS



2,000,000 specimens/yr tested in GISRS
> 20,000 viruses/yr shared with WHO CCs
~ 10,000 viruses/yr characterized by CCs

Nancy J. Cox, Ph.D.
WHO Meeting of National Influenza Centres
17-19 July 2017, Geneva, Switzerland

An Influenza WHO Influenza Collaborating Center Laboratory in 1976

Nancy J. Cox, Ph.D.
WHO Meeting of National Influenza Centre
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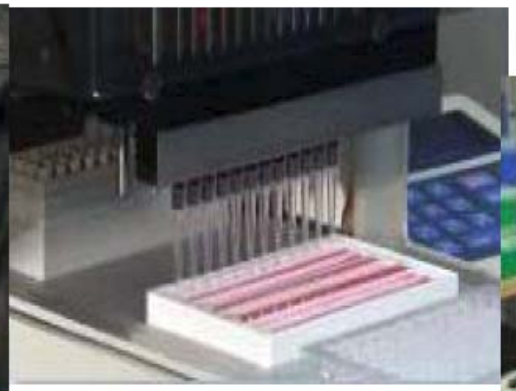
An Influenza WHO Collaborating Center Laboratory in 2017



Nancy J. Cox, Ph.D.
WHO Meeting of National Influenza Centre
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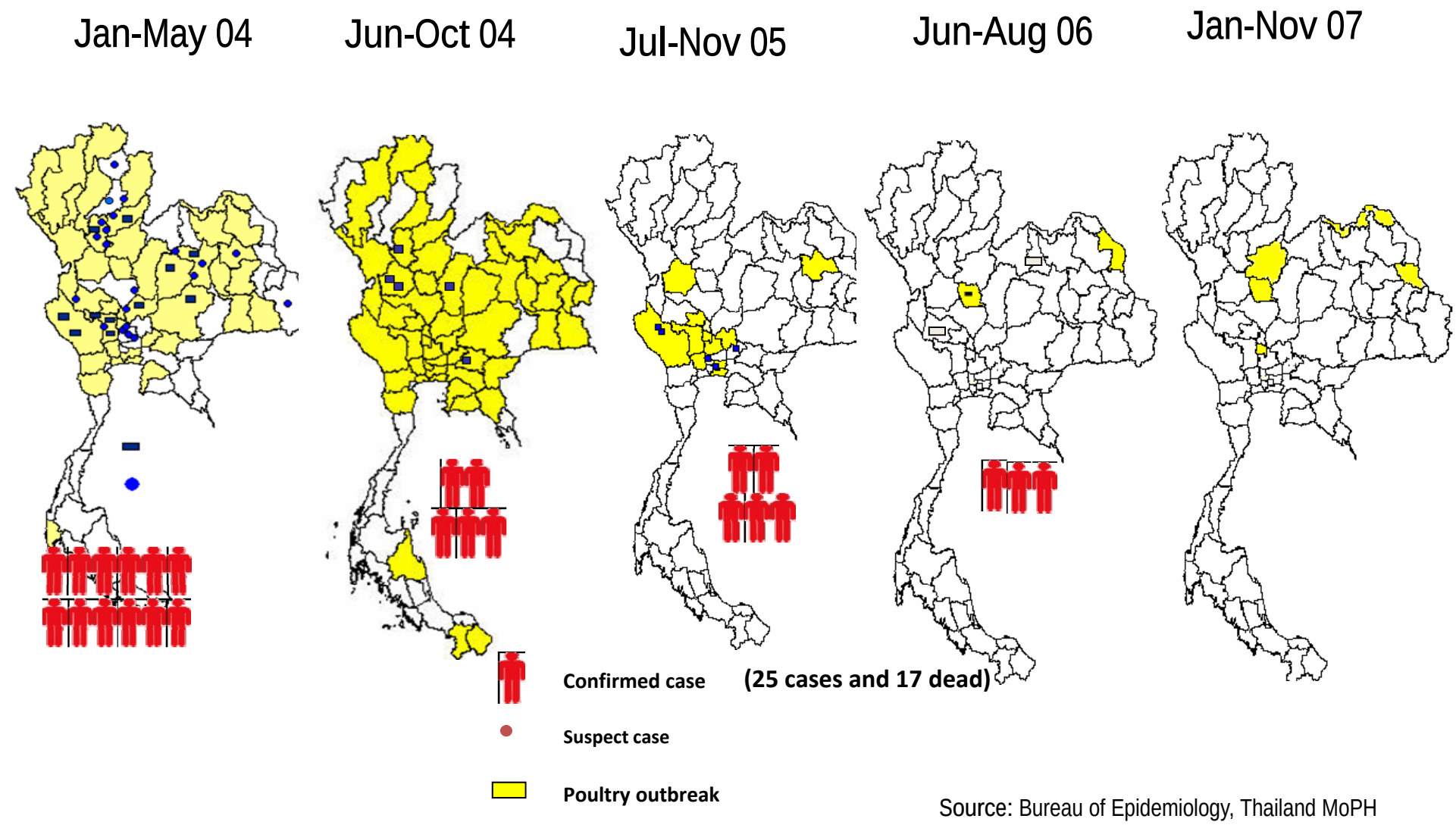
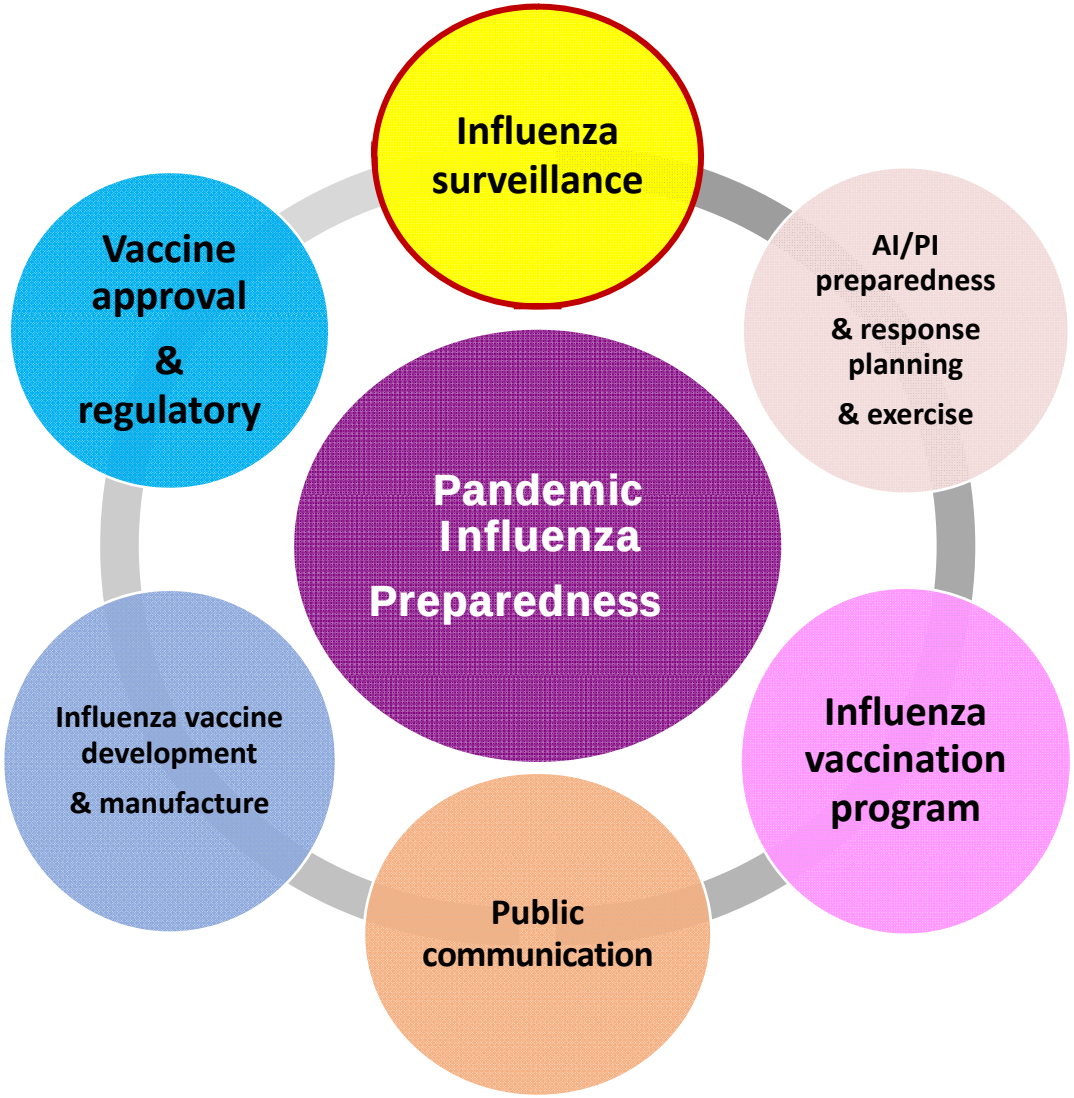
Thailand Influenza Surveillance System

Distribution of AI in poultry and human cases, 2004-2007



Source: Bureau of Epidemiology, Thailand MoPH

Thailand Pandemic Influenza Preparedness



Supamit Chunsutthiwat,
Assessment of Sustainability for PIP in Thailand_2017

National Strategic Plan for Prevention and Control of Avian Influenza and Preparedness for Pandemic Influenza (2005-2010)

The pandemic influenza preparedness planning was initiated in response to the outbreaks of avian influenza in 2004. The capacities were extensively tested in the response to pandemic H1N1 2009.

The National Strategic Plan on Avian and Pandemic Influenza was later transformed into the current National Strategic Plan for Prevention and Control of Emerging Infectious Diseases - EIDs(2013-2021)

The national committee has been upgraded to address EID as a whole and the new revision of national plan expanded to cover EID accordingly.

History of Thai National Influenza Center (Thai NIC)

อาคารสถาบันไวรัส เปิดทำการ 27 กุมภาพันธ์ 2506

Dr.Nadrirat Sangkawibha

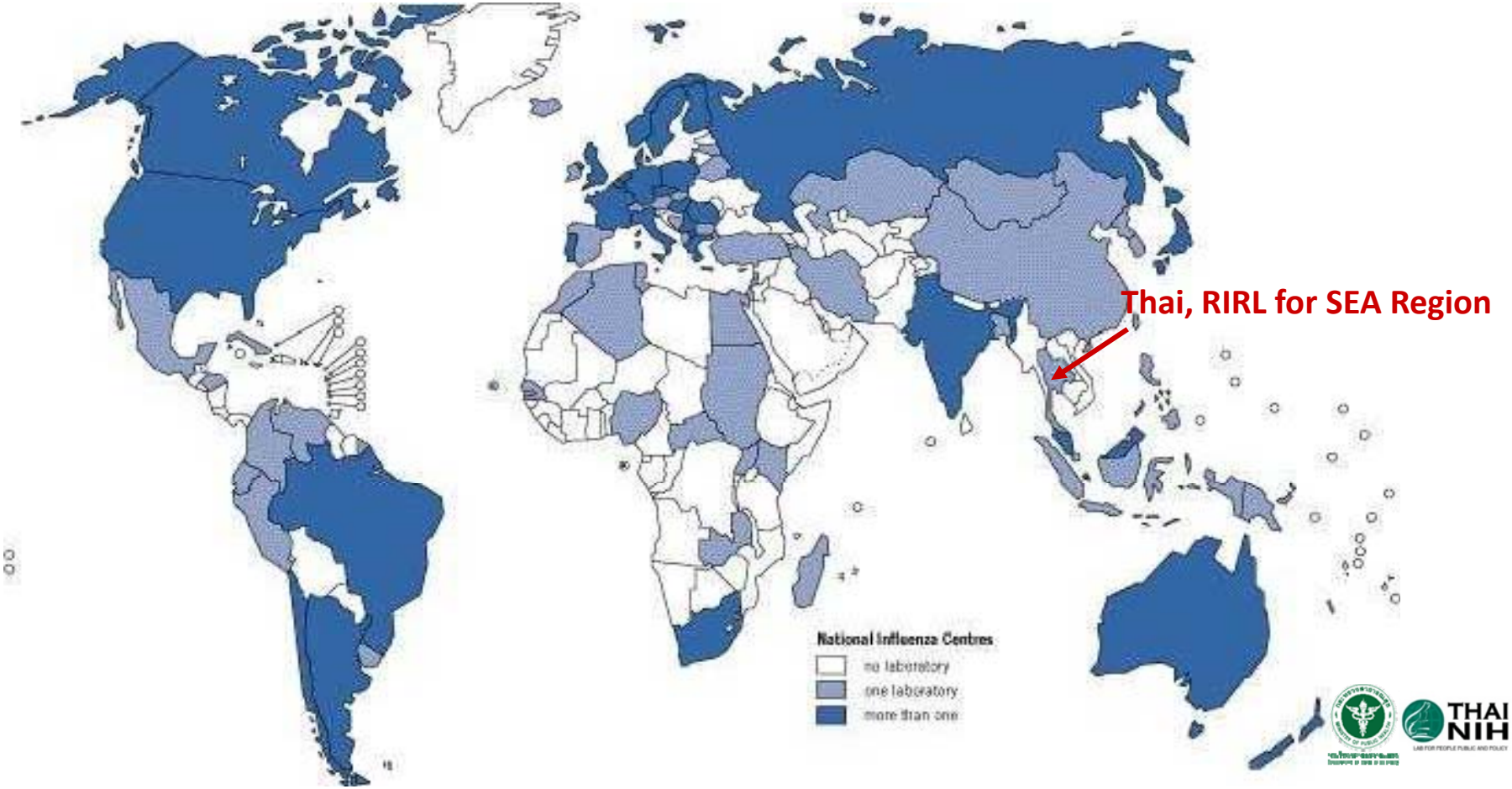
The first Director,Thai NIC

Department of Medical Sciences

WHO Global Influenza surveillance and Response System(GISRS)

WHO National Influenza Center, Thai NIC
has been established since 1972 at NIH, DMSc, Thailand

Regional Influenza Reference Laboratory (RIRL) for SEA Region
has been designated by WHO since 22 June 2010



Thailand 's Influenza Surveillance system

	Epidemiological (506) Surveillance	Virological (Laboratory) Surveillance
Objective	To monitor the epidemiology of 84 nationally notifiable diseases (ICD10code)	Document etiology and burden of influenza and other respiratory pathogens
Ownership	BoE ,Thai MoPH since 1973	1.Thai NIH,BoE,US-CDC since 2003 -2014 (NIH sentinel: ILI/SARI) 2. BoE,U-CDC,Thai NIH since 2010-2015 (BoE sentinel: SARI/pneumonia dead) 3. Thai NIH and BoE since 2015 – (NIH and BoE sentinel: ILI/SARI)
Patient type	outpatients and inpatients (Influenza ,admitted pneumonia)	OPD/ILI , SARI
Data type/ Timeliness	Epidemiological / weekly report	Laboratory, some clinical & Epi data/daily and weekly
Geographic	Nation wide	> 35 hospitals ,geographically representative

DMSc Laboratory network

★ Regional medical science center
(14 RMSc)

Laboratory	Facilities
NIH	Isolation,PCR ,Sequencing
RMSc 1 , Trang	PCR
RMSc 2 , Udornthani	PCR
RMSc 3 , Chonburi	PCR
RMSc 4 , Samutsongkram	PCR
RMSc 5 , Nakornrachasima	PCR
RMSc 6 , Khonkhen	PCR
RMSc 7 , Ubonrachathani	PCR
RMSc 8 , Nakornsawan	PCR, Sequencing
RMSc 9 , Pitsanulok	PCR
RMSc 10, Chaing Mai	PCR
RMSc 11, Suratthani	PCR
RMSc 12 , Songkhra	PCR, Sequencing
~~RMSc 13 , Chaing Rai~~	~~PCR~~
RMSc 14, Phuket	PCR

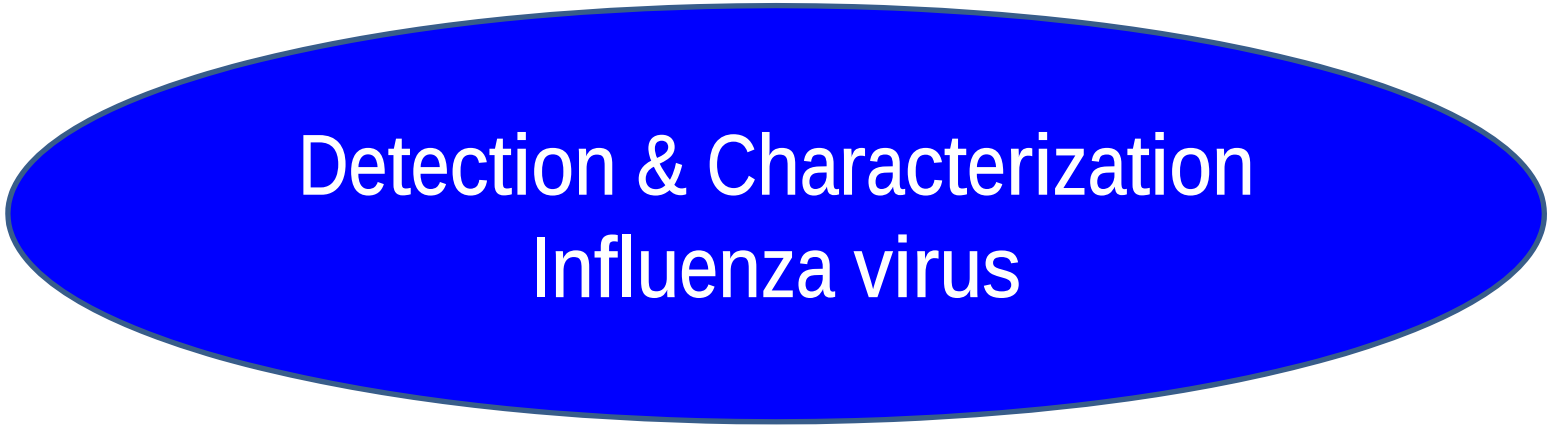
Laboratory-based Influenza Surveillance network partly supported by US-CDC & BOE

Phase I "Development of Influenza Surveillance Networks"
Five years : 15 Sep.2004 -14 Sep.2009
ILI : 5 sample/week/site

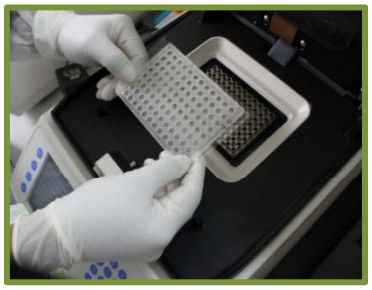
Phase II "Strengtening Thailand's Influenza Surveillance Network to Support Influenza Control Policy and Improve Pandemic Preparedness "
Five years : 15 Sep.2009 -14 Sep.2014
ILI : 10 sample/week/site
SARI : 5 sample/week/site

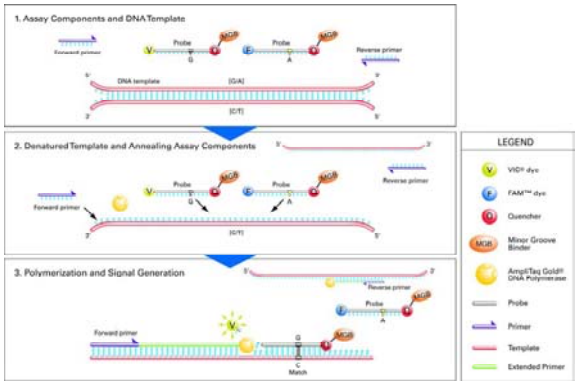
Current Influenza Virological Surveillance System by MoPH , Thailand (since 2016)

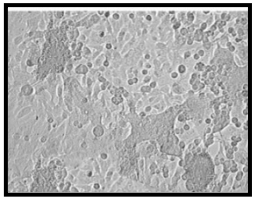
	Bureau of Epidemiology Department of Disease Control ,TUC
Project	“ Surveillance of viral etiology for respiratory diseases “
Type of patient	OPD/ILI , IPD/SARI
Type of virus	Subtype of Influenza/ AI , 26 respiratory pathogens (only SARI)
Number of sites	30 hospitals ,geographically representative
Reporting	Weekly on http://www.boe.moph.go.th , www.thainihnic.org (Sex, Age, lab results, site)

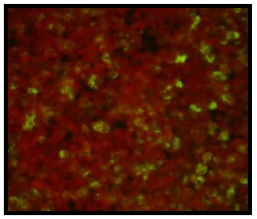

Detection & Characterization
Influenza virus

Testing Algorithm for Detection Influenza and Avian Influenza









Influenza A and B screening by realtime RT-PCR

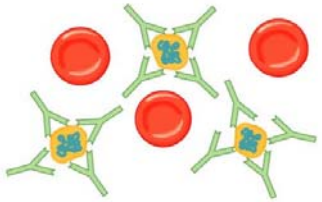
Influenza A positive

Subtying for H1pdm2009, H3 , H5 , H7, H9

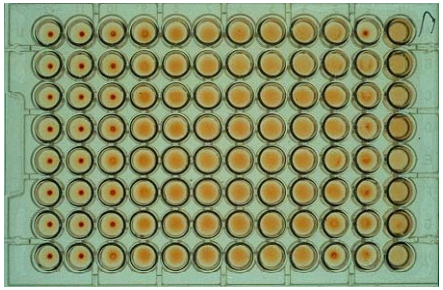
Sampled specimens are subculture on MDCK cell line or Embryonic chicken eggs

Strains characterization of local isolates by HI and gene sequencing

1. Antigenic characterization using WHO HI reagents kit



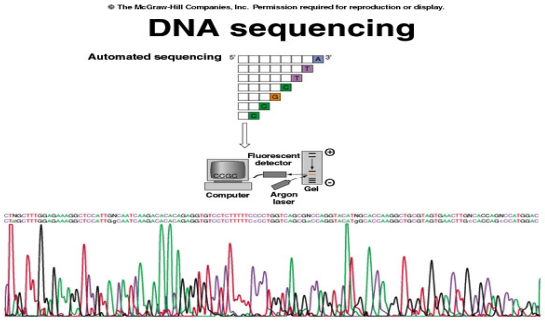
Viruses neutralized and hemagglutination inhibited



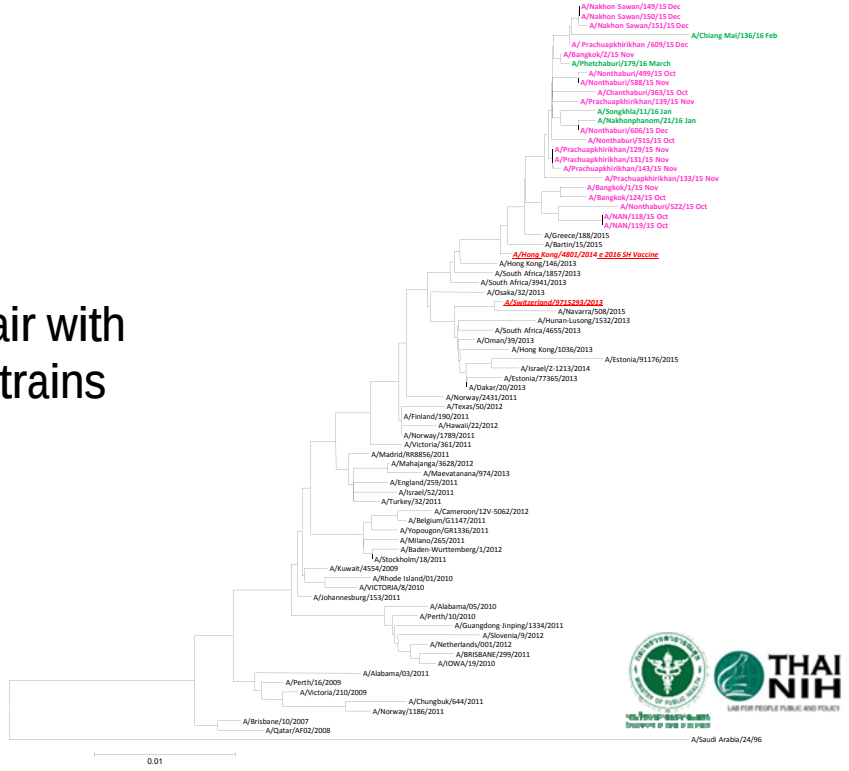
or

2. Genetic characterization by

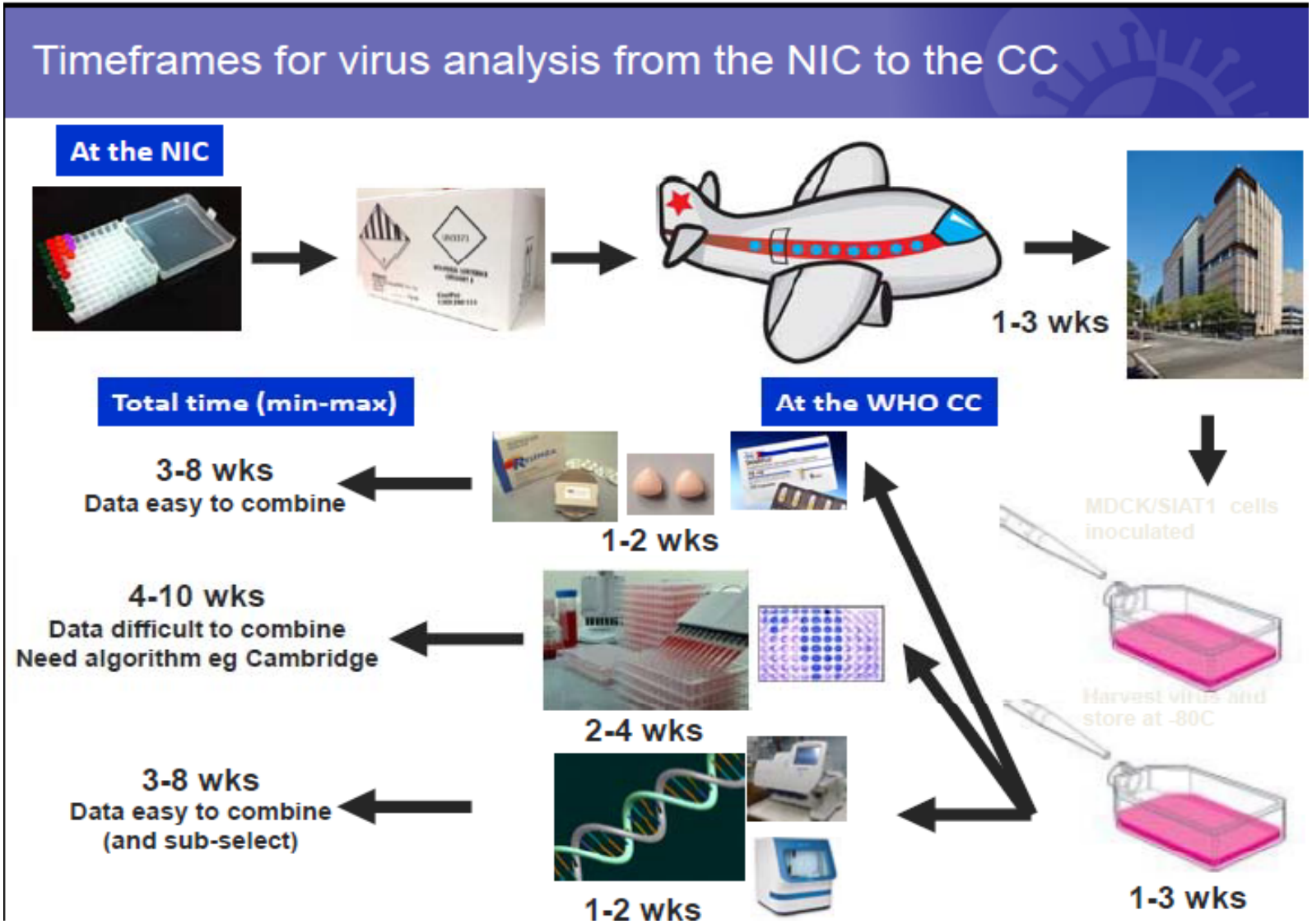
Gene sequencing & Phylogenetic tree



and compair with vaccine strains

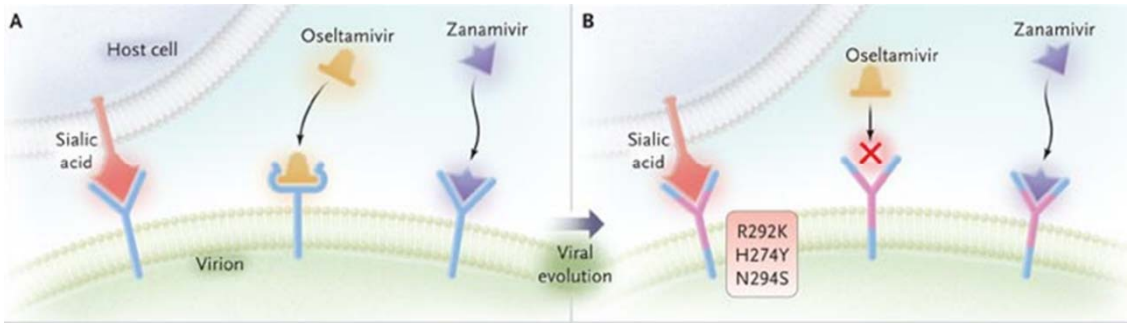


Represent of local isolates sent to confirm at
WHO CC in Atlanta and Melbourne (twice/year/WHO CC)



Source: Ian Barr, WHO CC , Melbourne

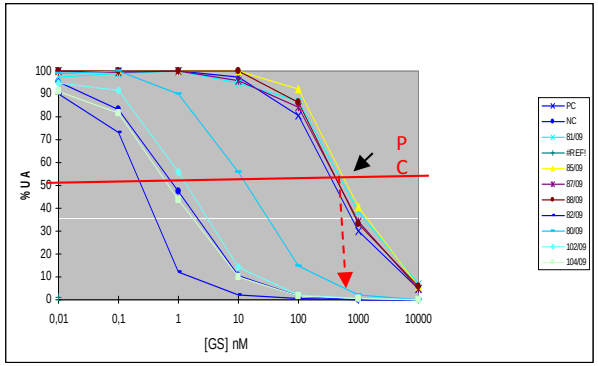
•Monitoring of drug resistant strains



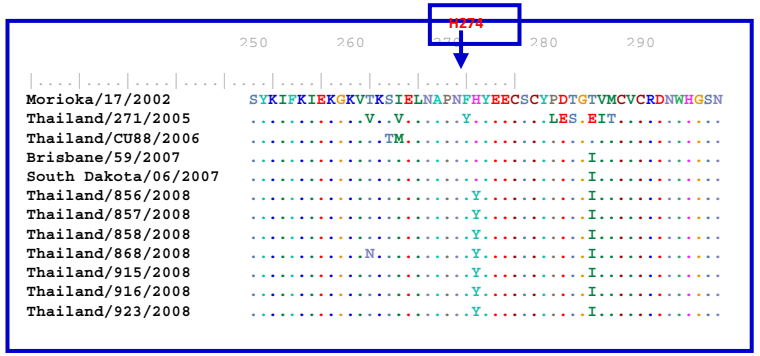
Detection of Drug resistant strains

Phenotypic

(Gold standard)



Genotypic



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IC$_{50}$ (50% Inhibition concentration)

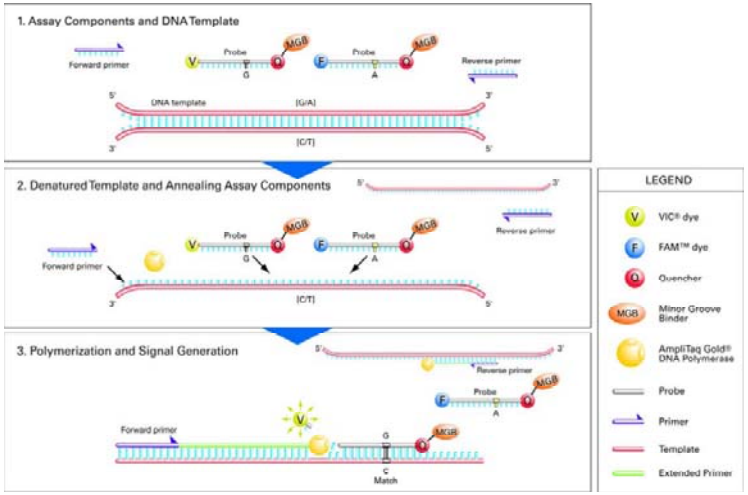
Mutation point on NA gene

Detection of Drug resistant strains by genotypic assay

1.Pyrosequencing

For A/H3 and B

2.Multiplex rRT_PCR

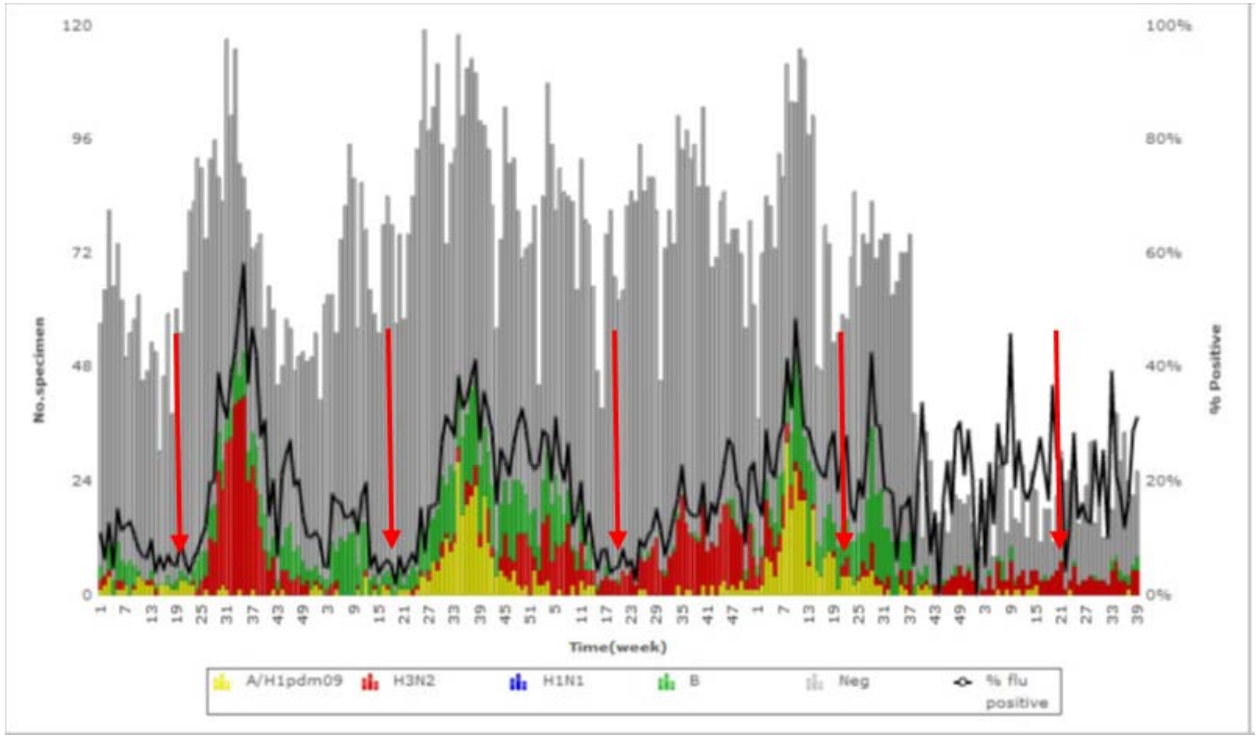


For pdm H1/2009

Virological Data Support

- Influenza Control Policy and Improve Pandemic Preparedness
- WHO Influenza Vaccine Selection
- National and Global Health Alert system

Data support the appropriate timing of vaccination campaign



- Influenza surveillance data from the past 10 years revealed that the high peak of flu run from June –July and small peak run from cool season November-February
- Vaccination campaign should starts in May each year (before flu season)

Source: National Influenza Center , Thailand MoPH

Support MoPH for Annual Influenza Vaccine Selection

Northern hemisphere(2018-2019)

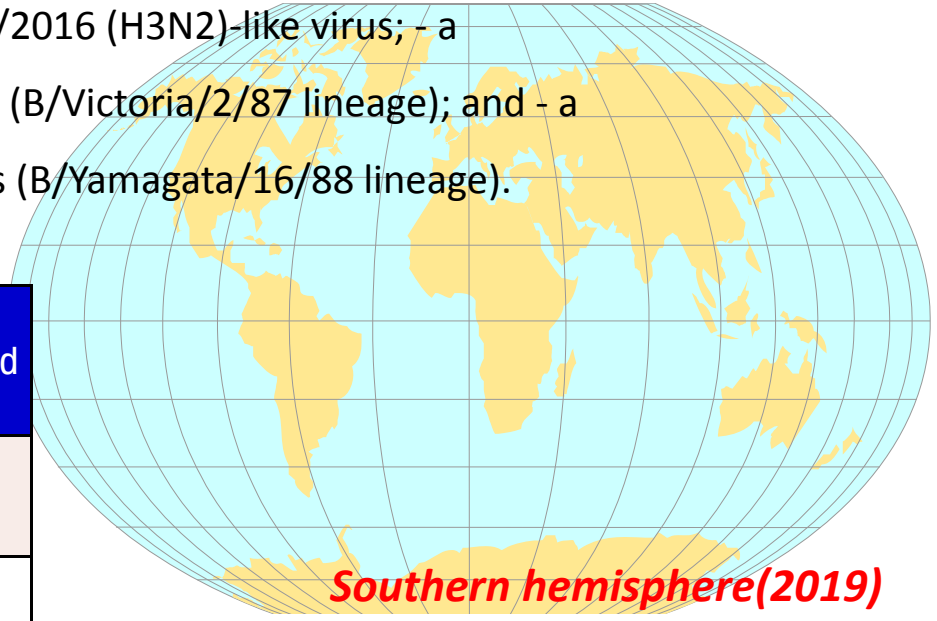
A/Michigan/45/2015 (H1N1)pdm09-like virus; - an ---

A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus; - a

B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and - a

B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

Percentage vaccine matching of Thai circulating strains by Sequencing method from Jan. –Oct. 2018	
A/Michigan/45/2015 (H1N1)	100
A/Switzerland/8060/2017(H3N2)	33.73
A/Singapore/INFIMH-16-0019/2014	66.27
B/Brisbane/60/2008 (Victoria lineage)	0
B/Phuket/3073/2013 (Yamagata lineage)	100



Southern hemisphere(2019)

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Switzerland/8060/2017 (H3N2)-like virus; and
-a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)
-a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)

Hemagglutinin Genes of Thai-Influenza A (H1N1pdm)

Vaccine

Reference dataset

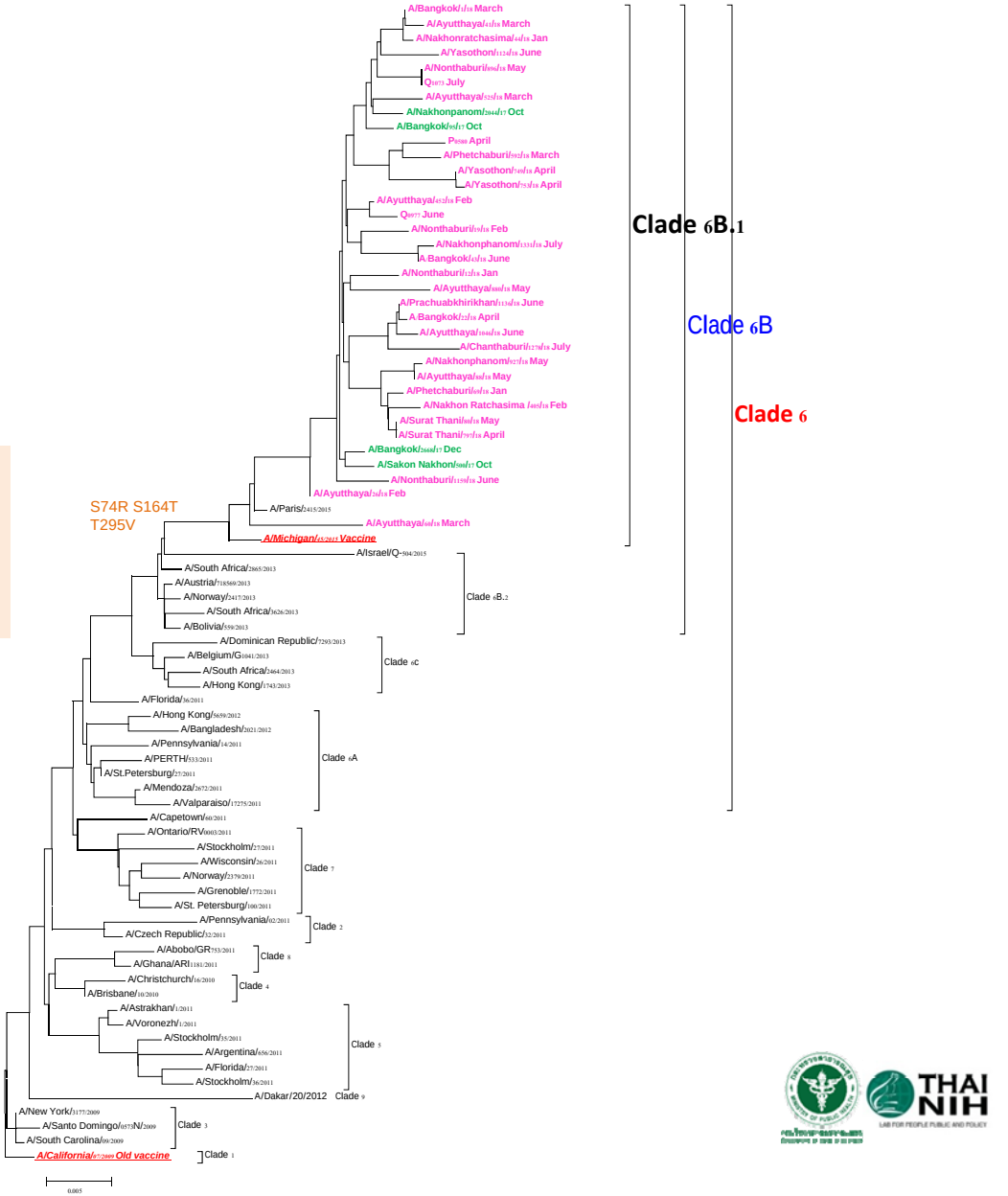
Local Isolates

(+/-)=gain/loss potential glycosylation site

-2017

-2018

The vast majority of HA gene sequences belonged to phylogenetic subclade 6B.1 with additional amino acid substitutions in the HA of S74R, S164T, and I295V



Hemagglutinin Genes of Thai-Influenza A (H3N2)

Vaccine

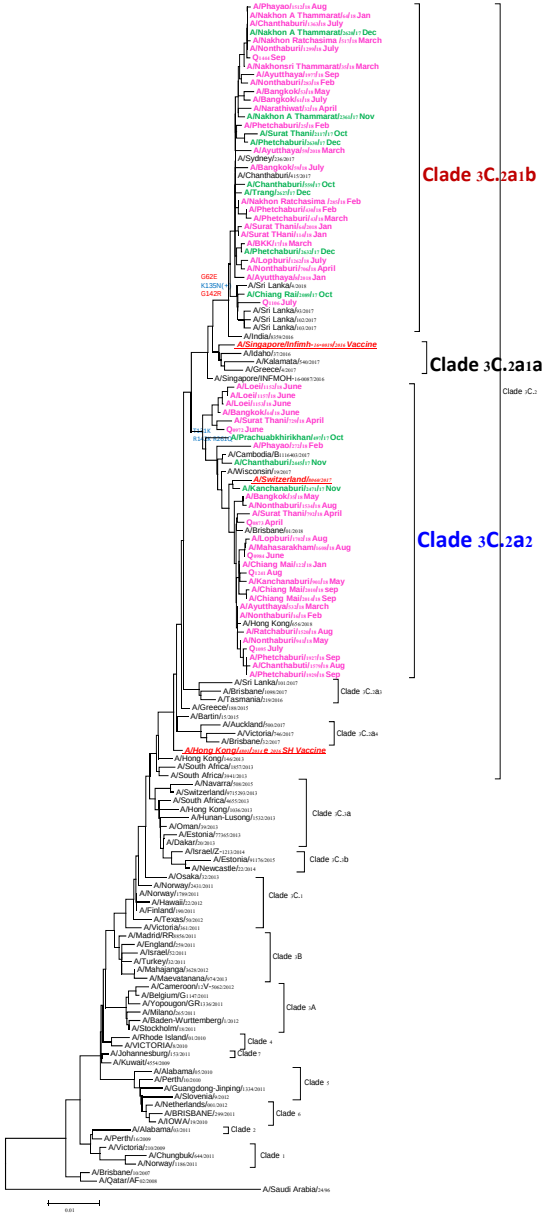
Reference dataset

Local Isolates

(+/-)=gain/loss potential glycosylation site

-2017

-2018



Hemagglutinin Genes of Thai-Influenza virus type B

Vaccine

Reference dataset

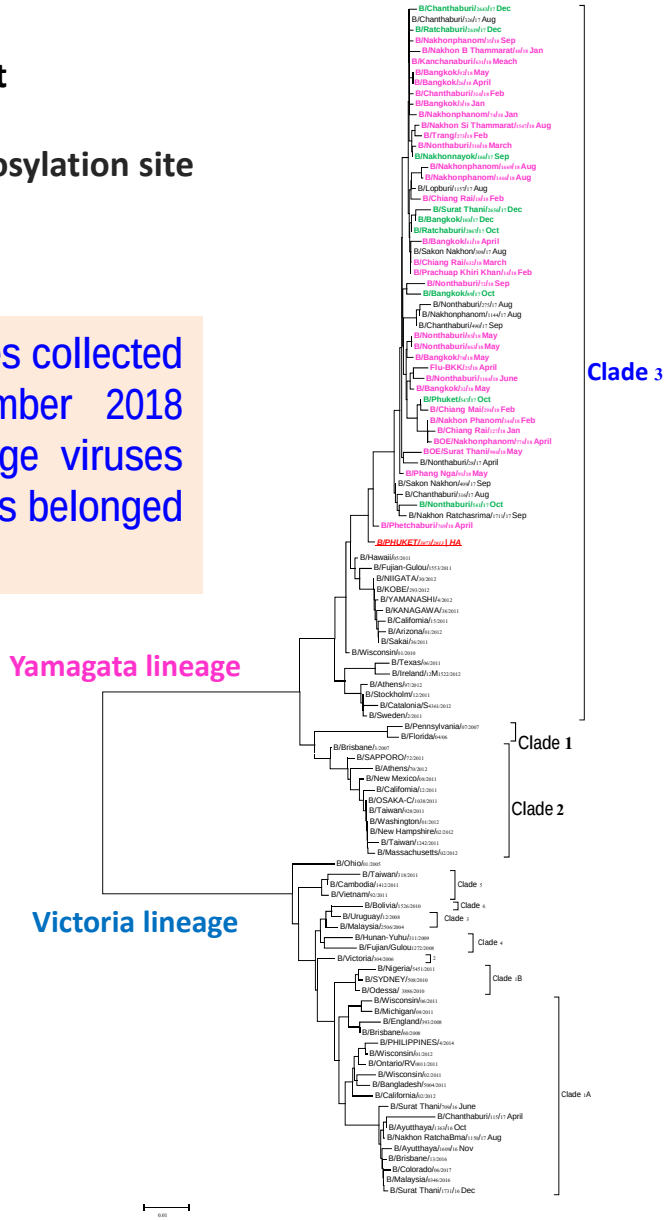
Local Isolates

(+/-)=gain/loss potential glycosylation site

-2017

-2018

The majority of influenza B viruses collected from October 2017 to September 2018 indicated that B/Yamagata lineage viruses predominated, and all of HA genes belonged to genetic clade 3



Data Contributed to Vaccine Policy Decisions

and National Alert System

หน้าหลัก | นสพ.ฉบับวันนี้ | ประเด็นร้อน | บริการข่าวไทยรัฐ | กิจกรรม

ไทยรัฐ

ไทยรัฐออนไลน์ > วันพฤหัสบดีที่ 16 มกราคม พ.ศ.2557

ข่าวในพระราชสำนัก | การเมือง | กีฬา | บันเทิง | ไลฟ์สไตล์ | วิทยาการ | เศรษฐกิจ | การศึกษา | ต่า

การศึกษา | การเกษตร | สาธารณสุข | วัฒนธรรม | คุณครูในดวงใจ | คนเก่งเปล่งประกาย | ข่าวทุน | สว

เรื่องเด่น : มหกรรมภาพแห่งความสำเร็จ รร.ไทยรัฐวิทยา | 'ประดิษฐ' โยน 'ปลัด สธ.' รับมือม็อบบุก |

สธ.ห่วงหวัดนก'H7N9' สั่งทุกจว.เฝ้าระวังหลังสงกรานต์

THAI NIH
LAB FOR PEOPLE PUBLIC AND POLICY

Influenza isolates are contributed to WHO influenza vaccine recommendations 2015-2016 and 2018

It is recommended that trivalent vaccines for use in the 2018 influenza season (southern hemisphere winter) contain the following:

an A/Michigan/45/2015 (H1N1)pdm09- like virus;

– an A/Singapore/INFIMH-16-0019/2014 (H3N2)-like virus;

– a B/Phuket/3073/2013-like virus

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008-like virus.

WHO selected B/Phuket/3073/2013 , Thailand influenza local strain which isolated from NIH sentinel surveillance system under BoE and US-CDC collaboration

Comparing of percentage pdmH1/2009 oseltamivir resistant strains at regional and national level

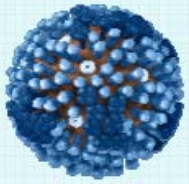
A(H1N1)pdm 2009	2009	2010	2011	2012	2013	2014	2015	2016	2017
WHO CC	1.1%	0.40%	0.1%	0.5%	0.70%	0.45%	0.51%	0.5%	0.3%
Thai NIC	1.2%	1.76%	0.0%	1.15%	0.0%	0.77%	0.0%	0%	0%

Surveillance update antiviral resistance in 2018 by WHO CC, Melbourne , Australia

Type/Subtype*	No. tested	Oseltamivir		Peramivir		Laninamivir		Zanamivir	
		Reduced inhibition	Highly reduced inhibition	Reduced inhibition	Highly reduced inhibition	Reduced inhibition	Highly reduced inhibition	Reduced inhibition	Highly reduced inhibition
A(H1N1)pdm09	851	-	2 (0.2%)	-	2 (0.2%)	-	-	-	-
A(H3N2)	338	2 (0.6%)	-	1 (0.3%)	-	1 (0.3%)	-	2 (0.6%)	-
A (mixed subtype)	3	-	-	-	-	-	-	-	-
B/Victoria	69	-	-	-	-	-	-	-	-
B/Yamagata	269	1 (0.4%)	-	1 (0.4%)	-	-	-	-	-
TOTAL	1530	3 (0.2%)	2 (0.13%)	2 (0.13%)	2 (0.13%)	1 (0.07%)	0	2 (0.13%)	0

source: The Newsletter, Volume 7, Issue 3, December 2018, WHO CC , Melbourne ,Australia

- CDC Influenza Risk Assessment Tool (IRAT)
  - Ten elements of the virus, population, and animal/human ecology are evaluated to develop a score



Virus

1. **Genomic variation**
2. **Receptor binding**
3. **Transmission in Laboratory animals**
4. **Antivirals and Treatment Options**

Population

5. **Existing Population Immunity**
6. **Disease Severity and Pathogenesis**
7. **Antigenic Relationship to Vaccine Candidates**

Ecology

8. **Global Geographic Distribution**
9. **Infection in Animals, Human Risk of Infection**
10. **Human Infections and Transmission**

https://www.cdc.gov/flu/pandemic-resources/national-strategy/risk-assessment.htm

Research and Development for Support the Early Warning System

- To explore more sequence data sets from unsubtypable influenza isolates and from severe cases as to support the early detection and rapid response to novel pathogens.
- Development of assay to monitor the antiviral resistant genes that cover the current drugs used in Thailand

NGS Platform and Methodolgy

- **Illuminar Miseq**
- **TruSeq based protocol and NEBNext Ultra RNA Library Prep kit**

Total RNA from patient / environmental sample

↓

Reverse transcription and 2nd strand cDNA synthesis

↓

Library prep using Nextera XT

↓

Sequencing using MiSeq

BioEdit
Biological sequence alignment editor for Win95/98/NT/2K/XP

MEGA Molecular Evolutionary Genetics Analysis

DnaSP
DNA Sequence Polymorphism

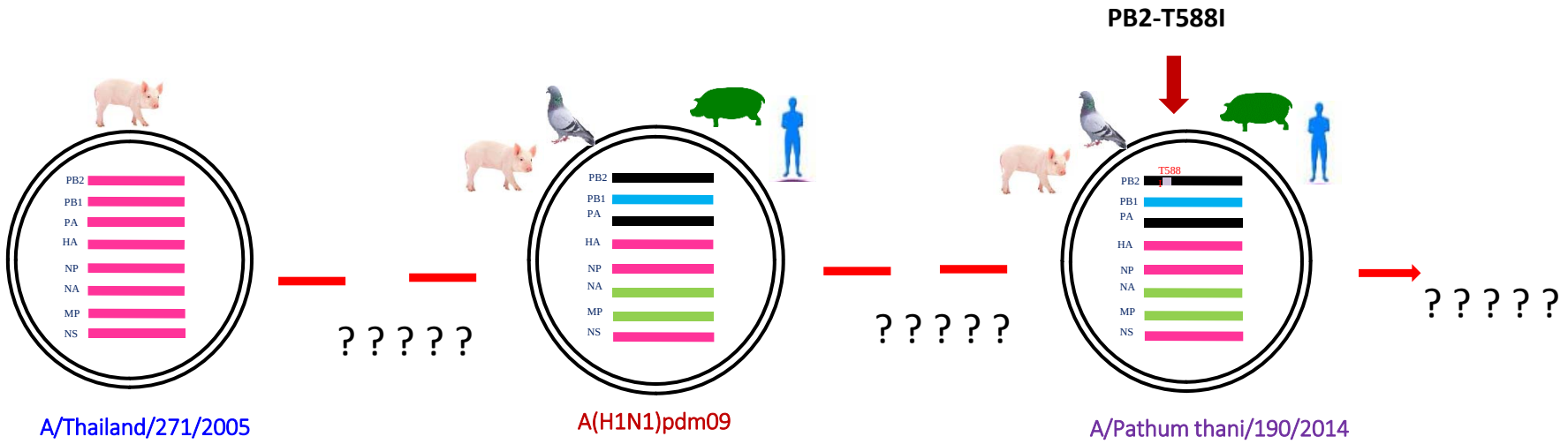
geneious

CLC Bioinformatics Database

DNASTAR Lasergene 14.1

THAI NIH

Genetic reassortment among Influenza viruse



- In 2014 ,pdmH1N109 virus was isolated from dead case in Pathum thani province.
- From conventional sequencing on PB2 gene ,shownT588I mutation and whole genome by NGS reveal all 8 gene segments are similar with H1N1pdm09 except on PB2 gene shownT588I mutation.
- The Chinese researcher team studied the mutation at PB2-T588I and found that it can enhance the virulence of A(H1N1)pdm09 by increasing viral replication and exacerbating PB2 inhibition of beta interferon expression using the experiment on reverse-genetic reassortant influenza virus in animal model .

- Are there any genetic re-assortment between swine influenza and human influenza in Thailand during 2005 to at present ? ? ? ? ?
- The further genomic study is needed to identify the linkage of transmission , the source of infection, the extent of the spread of virulence genes from Avian/Swine to human.

Challenges

➢Current issue

- MoPH budget for support influenza lab. surveillance system is unstable, this system should be integrated into National routine surveillance program as to obtain financial security

- Harmonization of multiple sources data of influenza surveillance programs in country by authorized focal point unit.

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- Thai Bureau of Epidemiology (BOE)
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Collaborating Agencies

- WHO Global Influenza Surveillance and Response System Network (WHO GISRS)
- Thailand MOPH – U.S. CDC Collaboration(TUC Thailand)