Vaccine R&D for Influenza Pandemic Preparedness

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- Situation OF Pandemic/Avian influenza
- Pandemic Preparedness
- Critical path for LAIV and IIV vaccine development

Avian Influenza A Viruses

- Avian influenza A viruses do not normally infect humans, but sporadic human infections have occurred.
- Three subtypes of avian influenza A viruses are known to infect people (H5, H7 and H9 viruses).
- Highly pathogenic Asian avian influenza A H5N1 and low pathogenic Asian H7N9 viruses account for the majority of human infections with avian influenza A viruses.
- Human infections with avian influenza A viruses have most often occurred after exposure to infected poultry or their secretions or excretions, such as through direct or close contact, including visiting a live poultry market

Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2018

Country	2003-2009*		2010-2014**		2015		2016		2017		2018		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	6	1	1	0	0	0	0	0	0	0	8	1
Cambodia	9	7	47	30	0	0	0	0	0	0	0	0	56	37
Canada	0	0	1	1	0	0	0	0	0	0	0	0	1	1
China	38	25	9	5	6	1	0	0	0	0	0	0	53	31
Djibouti	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	120	50	136	39	10	3	3	1	0	0	359	120
Indonesia	162	134	35	31	2	2	0	0	1	1	0	0	200	168
Iraq	3	2	0	0	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	15	7	0	0	0	0	0	0	0	0	127	64
Total	**468**	**282**	**233**	**125**	**145**	**42**	**10**	**3**	**4**	**2**	0	0	**860**	**454**

* 2003-2009 total figures. Breakdowns by year available on subsequent tables.
** 2010-2014 total figures. Breakdowns by year available on subsequent tables.

Total number of cases includes number of deaths.
WHO reports only laboratory cases.
All dates refer to onset of illness.

Source: WHO/GIP, data in HQ as of 1 November 2018

World Health Organization

http://www.fao.org/ag/againfo/programmes/en/empres/h7n9/situation_update.html
(DEC 10-2018)

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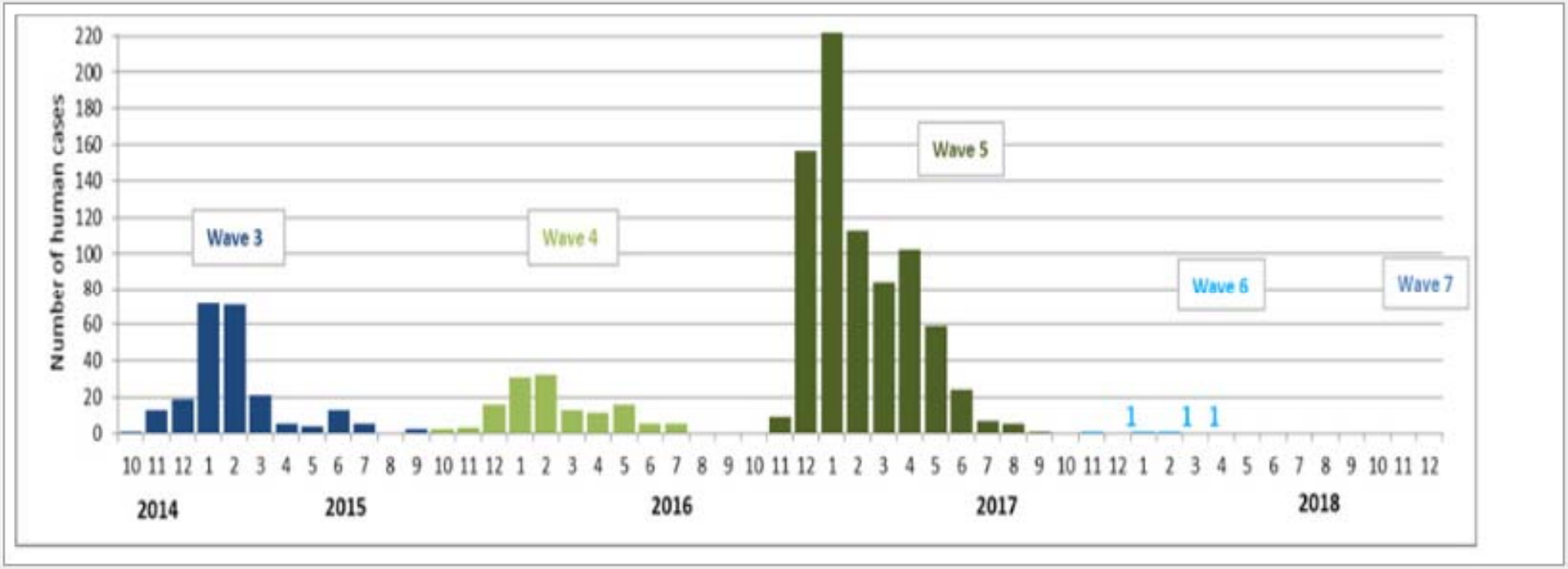
Figure 5. *Incidence of officially reported human cases by month, based on onset date from October 2013 (Beginning of wave 2) to 05 December 2018. Both high and low pathogenic H7N9 viruses are included.*



Click to enlarge - *Note:* For cases with unknown onset dates from wave 2 (n=2), wave 3 (n=146), wave 4 (n=27) and wave 5 (n=55), reporting dates were used instead.

Challenges to the Development of (Pre) Pandemic Vaccines

- The difficulty in predicting which zoonotic virus will cause the next pandemic. (A/H5 and A/H7 subtypes are being developed)
- Moreover, antigenic evolution and diversity of zoonotic avian IAV pose a serious challenge for vaccine design and pandemic preparedness

To cope with the antigenic diversity the WHO has identified 38 H5 vaccine candidates, of which 32 are already available for distribution.

https://www.who.int/influenza/vaccines/virus/characteristics_virus_vaccines/en/

- For A/H7N9 viruses, three new candidate vaccines have been identified in 2017 to match the antigenic variation observed in recent A/H7N9 viruses

https://www.who.int/influenza/vaccines/virus/candidates_reagents/summary_a_h7n9_cvv_20180305.pdf?ua=1

H5N1vaccine :

Available as stock pile for human use

- Inactivated monovalent influenza virus vaccine manufactured by Sanofi

Under clinical trials:
H5 adjuvanted vaccine-prime and boost regimen

Sanofi 2017 H7N9 With/Without AS03 in Adults/Elderly
(https://www.clinicaltrials.gov/ct2/show/study/NCT03312231)

Co-Administration of AS03 Adjuvanted A/H7N9 IIV With IIV4
(https://www.clinicaltrials.gov/ct2/show/NCT03318315)

https://www.ncbi.nlm.nih.gov/pubmed/27814377

Situation in Thailand

11 Jan 2004		**Viet Nam** identifies H5N1 as the cause of human cases of severe respiratory disease with high fatality. Sporadic human cases are reported through mid-March.
12 Jan 2004	**Japan** first reports H5N1 in poultry, outbreaks continue in commercial poultry through March 2004.	
19 Jan 2004	**China Hong Kong SAR** reports H5N1 in a dead wild bird. (This is the first report of H5N1 in birds in China Hong Kong SAR since the poultry outbreak in 1997.)	
23 Jan 2004	**Thailand** first reports H5N1 in poultry. By the end of January, 32 provinces (throughout the north and several in the south) report outbreaks in many types of poultry, including fighting cocks, and outbreaks continue to be reported throughout the year. The virus appears closely related to the isolates	**Thailand** reports 2 laboratory-confirmed cases of human infection with H5N1. Sporadic human cases are reported through mid-March.
24 Jan 2004	**Cambodia** first reports H5N1 in poultry.	

H5N1

2004

2009 25 cases with 17 deaths

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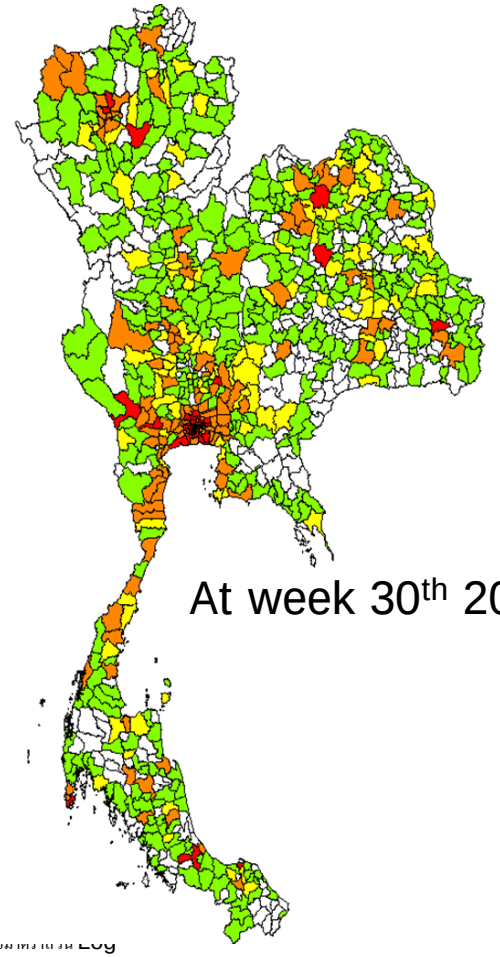
Distribution of confirmed influenza A (pandemic H1N1) cases by district in 9



สัญลักษณ์	จำนวนป่วย
	0
	1 - 5
	6 - 10
	11 - 50
	> 50

At week 30th 2009 (Late July)

Note

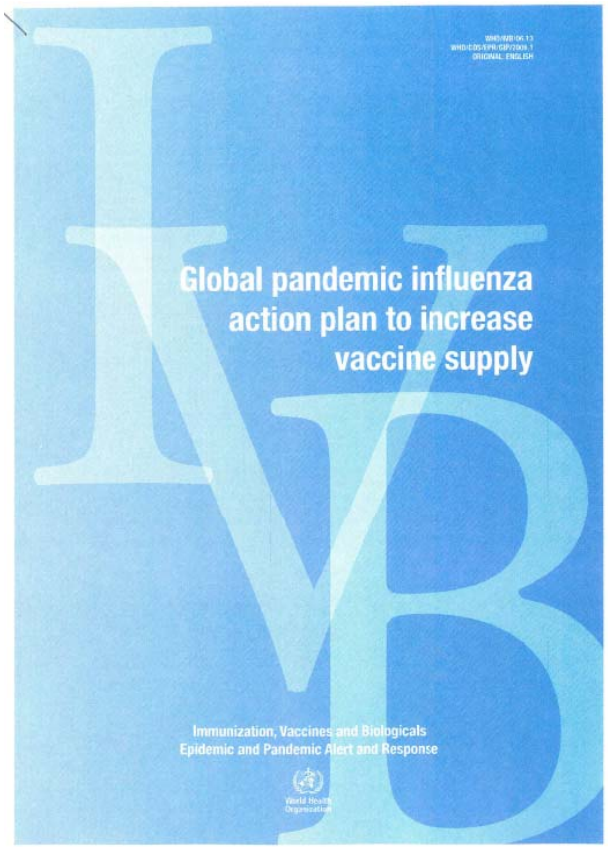
Situation of Flu Vaccine supply - 2009

- No domestic production of bulk influenza vaccine
- No experience of egg-based vaccine production before 2007
- Import 2.1 million doses of seasonal influenza vaccine in 2010
- GPO-MBP supplied approx. 800,000 doses, by formulating and filling imported bulk seasonal influenza vaccine, the remainder 1.3 million doses imported as finished products.

Influenza vaccine
A Far Dream

MARKET COMPITITON
FOR FLU PRODUCTION

Global Action Plan for Influenza Vaccine



Status 2009-Short-term potential availability of influenza vaccine (per year)	
Estimate of production capacity for current influenza vaccine:	350 million doses (inactivated trivalent vaccine containing 15µg of HA per dose).
Estimate of production capacity for potential influenza vaccine, if manufacturers optimize current output (e.g. by working 3 shifts/24 hours):	500 million doses (inactivated trivalent vaccine containing 15µg of HA per dose).
Planned expansion for extra vaccine production-capacity in the next 2-3 years (280 million):	780 million doses (inactivated trivalent vaccine containing 15µg of HA per dose).
Estimate if production should switch to monovalent pandemic influenza vaccine, assuming only 15µg of HA per dose (2009 projection):	2340 million doses of pandemic vaccine (inactivated monovalent vaccine containing 15µg of HA per dose)

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Major approaches to increasing supplies of pandemic influenza vaccine

- Develop regional and national plans for seasonal influenza vaccination programes
- Build a new production facilities in developing and/or industrialized countries
- Explore formulations of influenza vaccine other than those commonly used for seasonal vaccination

The National Pandemic Preparedness Plan (Thailand)

- First (2005-2007)

"Support research and development of vaccines, antivirals……."

- Second (2008-2010)

"To set up a local industrial-scale manufacturing plant for pandemic influenza vaccine based on international standard with production of specific pathogen free (SPF) eggs to support the vaccine production processes"

"To train staff for industrial-scale vaccine research and development processes"

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Clinical Trial Development Plan

- LAIV H1N1 vaccine
- Avian H5N2 vaccine
- Seasonal inactivated influenza vaccine

Why start with LAIV: Potential advantages of LAIVs

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- no down-stream processing required (harvested vaccine is simply packaged);
- high yield (20-50 doses of monovalent vaccine per an egg);
- needle-free delivery (administration is via an intra-nasal spray), which may facilitate administration in resource-poor settings;
- induction of a broad immune response including mucosal, systemic and cell-mediated responses (in contrast parenterally administered inactivated vaccines do not induce mucasal immunity);
- induction of cross-reactive immune responses;

History of LAIV Development in Thailand

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- 2004 outbreak of H5N1 in Thailand
- 2007 WHO/HQ started supporting developing countries to build up capacity to produce Influenza vaccine in 6 countries, including Thailand
- May 2009 Sublicensing agreement on LAIV with WHO based on Russian Technology from IEM, St Petersberg
- 16th July 2009 received the H1N1 (2009) pre-Master seeds from Russia, through WHO support and start MS, WS, vaccine viruses
- August 25,2009 first PLAIV clinical lot filled and tested

Live attenuated Vaccine H1N1 LAIV

2007 2008 2009 2010 2011 2012 2013 2014 2015 2016

1st WHO Grant US$ 1.996 million

2st WHO Grant US$ 2.064 million

Egg-based Monovalent PLAIV (H1N1)

Pre-clinical study

- **Attenuation**
- **Challenge test in ferret**

Clinical Trial Phase I

Clinical Trial Phase II

3rd/1 WHO Grant US$ 0.552 million

Vaccine approved (EUA) from TFDA for 18-49 years

Vaccine approved (EUA) from TFDA for 12-65 years

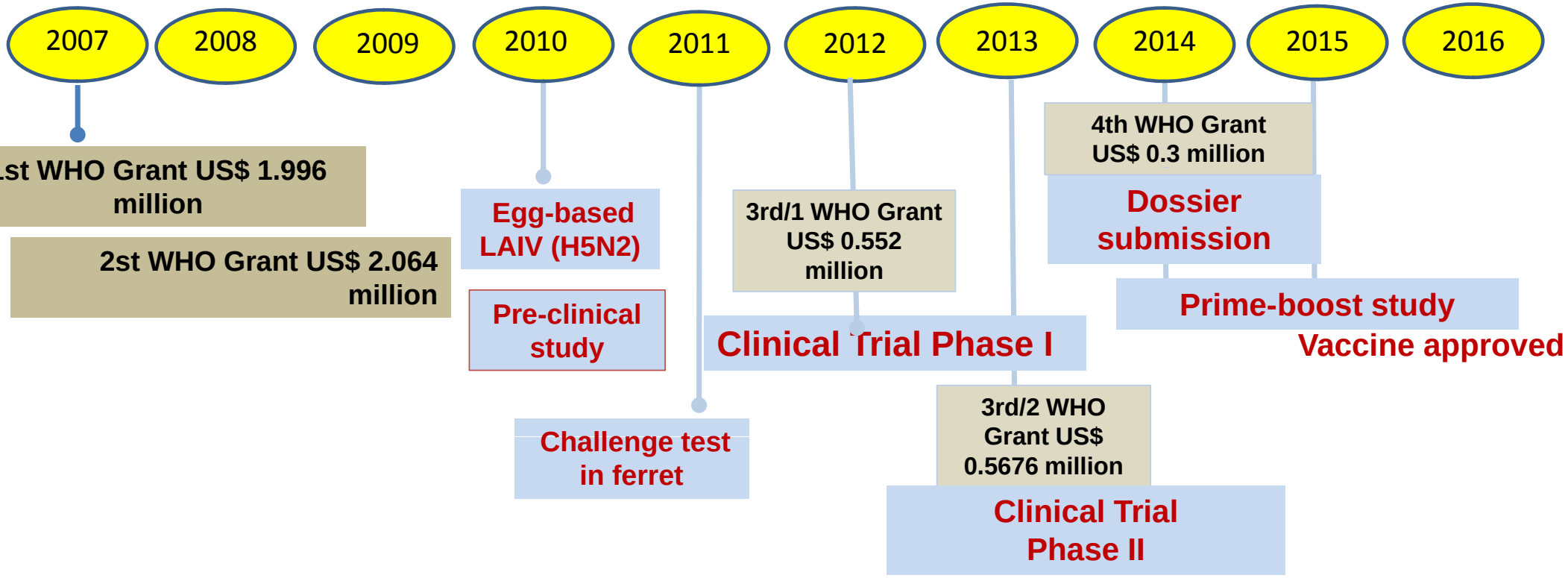
WHO FUND

H1N1LAIV

Construction of industrial plant

Acknowledgement : GPO expresses its appreciation for the support of all partners, particularly, WHO, BRADA, USCDC, US and Japan Government, IEM, KAKETSUKEN, NIBSC, and Thai partners including. MOPH, TFDA, DMSC, SU and MU.

Live attenuated Vaccine H5 LAIV



WHO FUND

H5N2LAIV

Construction of industrial plant

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Safety and Immune responses of Live attenuated influenza H5 candidate vaccine strain A/17/turkey/Turkey/05/133 (H5N2) in healthy Thai volunteers

- Phase I for initial safety
- Phase II FOR safety and immune responses

Phase I Primary Objective

- To evaluate safety and reactogenicity of live attenuated, temperature sensitive , cold adapted influenza H5 vaccine candidate strain A/17/turkey/Turkey/05/133 (H5N2) manufactured by GPO, in Thailand to previously healthy Thais

Secondary Objective

- To evaluate humeral immune response by using hemagglutination inhibition (HAI) test and micro neutralization assay, vaccine induced local IgA response by ELISA and assess shedding and stability of the viral strain by using PCR method

Vaccine :

vaccine is A/17/turkey/Turkey/05/133 (H5N2). The vaccine strain was produced by the method of classical genetic reassortment in chicken embryos (0.25 ml administered into each nostril) by nasal spray

- Immunization D1,D21
- Safety follow up for 9 days after each immunization,D42,60

- Nasal wash D1.D21,42,60
- Blood drawn D1, 7, 21,42,60

Comparison of summary of nasal swab (Viral Culture)

POSITIVE C/S	Vaccine n(%)	Placebo n(%)	p-value
Post 1st (D1)			
D2	5(31.25%)	0(0.00%)	0.130
Post 2nd			
D2	1(6.67%)	0(0.00%)	1.00

Positives only for one days post each immunization

Phase II (Part B)for assessing safety and immune response Study Design

- Using 7.5-8.5 log EID50 dose which is the same dose as being tested in phase I.
- Randomized placebo controlled
- 150 participants (100 vaccines and 50 placebos) age 18-49 years old ,each will be admitted for 4 nights 5days in 4 batches; Batch 1: 36 participants (24 v and 12 p)

  Batch 2: 38 participants (25 v and 13 p)

  Batch 3: 38 participants (25 v and 13 p)

  Batch 4: 38 participants (26 v and 12 p)

Study Design

- Two doses of vaccination given by intranasal route D 1 and D 28.
- Follow up for nasal swab culture D2,3,5 and will be discharge if culture negative .if any one remains to be positive ,Tamiflu will be given.
- Blood drawnD1, D 49 and D 60
- 45 subjects were randomized for nasal wash specimen AT D 1,14,28,49

Stopping Rules

* The trial may be prematurely terminated if the subject experienced disability or severe adverse event or death and such event is definitely related to study vaccine in the investigator's opinion.
* DSMB judge to terminate the trial.
* The sponsor can terminate the trial for any reason which may not relate to the safety reason of the volunteer

DSMB meeting: After the first dose administration of the first half of volunteers, after the first dose administration of all volunteers and closed out

Summary of treatment emergent adverse event

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Adverse Event	Vaccine		Placebo	
	Event (n=95) n (%)	Case (n=101) n (%)	Event (n=43) n (%)	Case (n=51) n (%)
ADVERSE EVENT				
Relation to Study Vaccine				
• AE Definitely not related to treatment	15(15.79%)	11(21.57%)	11(25.58%)	9(32.14%)
• AE Definitely related to treatment	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
• AE suspected probably related to treatment	80(84.21%)	40(78.43%)	32(74.42%)	19(67.86%)
• AE **suspected to be related**** to treatment which cause no discontinuation of treatment	77(96.25%)	37(92.50%)	32(100%)	19(100%)
• AE **suspected to be related**** to treatment which cause permanent discontinuation of treatment	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
• AE **suspected to be related**** to treatment which cause temporary discontinuation of treatment	3(3.75%)	3(7.50%)	0(0.00%)	0(0.00%)

Comparison of summary of nasal swab (Viral Culture)

POSITIVE C/S	Vaccine n(%)	Placebo n(%)	p-value
Post 1st (D1)			
D2	5(31.25%)	0(0.00%)	0.130
Post 2nd			
D2	1(6.67%)	0(0.00%)	1.00

Positives only for one days post each immunization

H5N2 LAIV : Only 14% of the participants received H5 N2 LAIV had > 4 fold HAI antibodies

Potential Immune Correlates

- LAIV induced both humoral and cellular immune response :cytotoxic cells, different T-helper populations, local antibodies and virus specific immune memory cells.
- Recent study conducted in US by K. Subbarao showed that LAIV recipients showing poor immune response were boosted with inactivated influenza H5N1 vaccine 52, 54 or 56 months later.

H5 Boosted Protocol

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Objectives :

- Aims to evaluate the effect of H5N2 LAIV priming on an inactivated sub unit H5N1 vaccine boost with prime-boost intervals of approximately 1 year.

Vaccine

- Subunit aluminium hydroxide adsorbed H5 influenza vaccine contain HA and NA protein from A/turkey/Turkey/1/05 (H5N1)

60 participants (40 V, 20 P phase II) have been enrolled and received 1 dose of H5 IIV (June30,14)

Serum antibody responses by influenza strain after inactivated H5N1 vaccine boosting between participants who had previously received vaccination (LAIV H5N2 vaccine; n=40) and participants who were naive (placebo; n=20) in the ITT population (1)

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	Before vaccination		7 days after vaccination		28 days after vaccination		90 days after vaccination	
	Seroconversion	GMT	Seroconversion	GMT	Seroconversion	GMT	Seroconversion	GMT
Haemagglutination-inhibition antibodies								
A/turkey/Turkey/05/133								
Vaccinated	0/40 (0%; 0·00–0·00)	3·92 (3·24–4·75)	39/40 (98%; 92·66–100·00)	211·12 (134·45–331·52)	* 40/40 (100%; 100·00- 100·00)	566·89 (436·97–735·44)	39/40 (98%; 92·66–100·00)	245·11 (183·44–327·53)
Naive	0/20 (0%; 0·00–0·00)	2·59 (2·41–2·78)	3/20 (15%; 0·00–30·65)	3·66 (2·60–5·15)	14/20 (70%; 49·92–90·08)	25·49 (11·82–54·96)	15/20 (75%; 56·02–93·98)	26·39 (13·52–51·52)
p value	..	0·0019*	<0·0001†	<0·0001*	0·0008‡	<0·0001*	0·0031‡	<0·0001*
A/Thailand/1 (KAN-1)/04								
Vaccinated	0/40 0%; 0·00–0·00)	2·59 (2·46–2·72)	35/40 (88%; 77·25–97·75)	32·49 (22·01–47·96)	40/40 (100%; 100·00–100·00)	98·49 (75·44–128·58)	38/40 (95%; 88·25–100·00)	30·64 (22·93–40·94)
Naive	0/20 (0%; 0·00–0·00)	2·50 (··)	0/20 (0%; 0·00–0·00)	2·77 (2·46–3·12)	3/20 (15%; 0·00–30·65)	5·18 (2·90–9·25)	4/20 (20%; 2·47–37·53)	5·36 (3·48–8·26)
p value	..	0·3254*	<0·0001†	<0·0001*	<0·0001†	<0·0001*	<0·0001†	<0·0001*
A/Indonesia/5/2005 clade 2.1.3.2								
Vaccinated	0/40 (0%; 0·00–0·00)	2·59 (2·46–2·72)	38/40 (95%; 88·25–100·00)	68·45 (42·91–109·17)	39/40 (98%; 92·66–100·00)	187·00 (133·79–261·38)	38/40 (95%; 88·25–100·00)	59·14 (43·08–81·19)
Naive	0/20 (0%; 0·00–0·00)	2·68 (2·42–2·96)	2/20 (10%; 0·00–23·15)	4·51 (3·12–6·52)	14/20 (70%; 49·92–90·08)	9·01 (5·55–14·64)	12/20 (60%; 38·53–81·47)	8·71 (5·28–14·36)
p value	..	0·4792*	<0·0001†	<0·0001*	0·0042‡	<0·0001*	0·0004‡	<0·0001*
A/Laos/Nong Khai/1/2007 clade 2.3.4								
Vaccinated	0/40 (0%; 0·00–0·00)	2·50 (··)	35/40 (87%; 77·25–97·75)	33·06 (22·34–48·93)	38/40 (95%; 88·25–100·00)	105·56 (77·53–143·73)	37/40 (93%; 84·34–100·00)	35·95 (27·17–47·58)
Naive	0/20 (0%; 0·00–0·00)	2·50 (··)	0/20 (0%; 0·00–0·00)	2·59 (2·41–2·78)	3/20 (15%; 0·00–30·65)	4·35 (2·58–7·34)	4/20 (20%; 2·47–37·53)	4·51 (2·84–7·15)
p value	..	1*	<0·0001†	<0·0001*	<0·0001†	<0·0001*	<0·0001†	<0·0001*

Source: Pitisuttithum P, et al. Lancet Infect Dis. 2017 Aug;17(8):833-842.

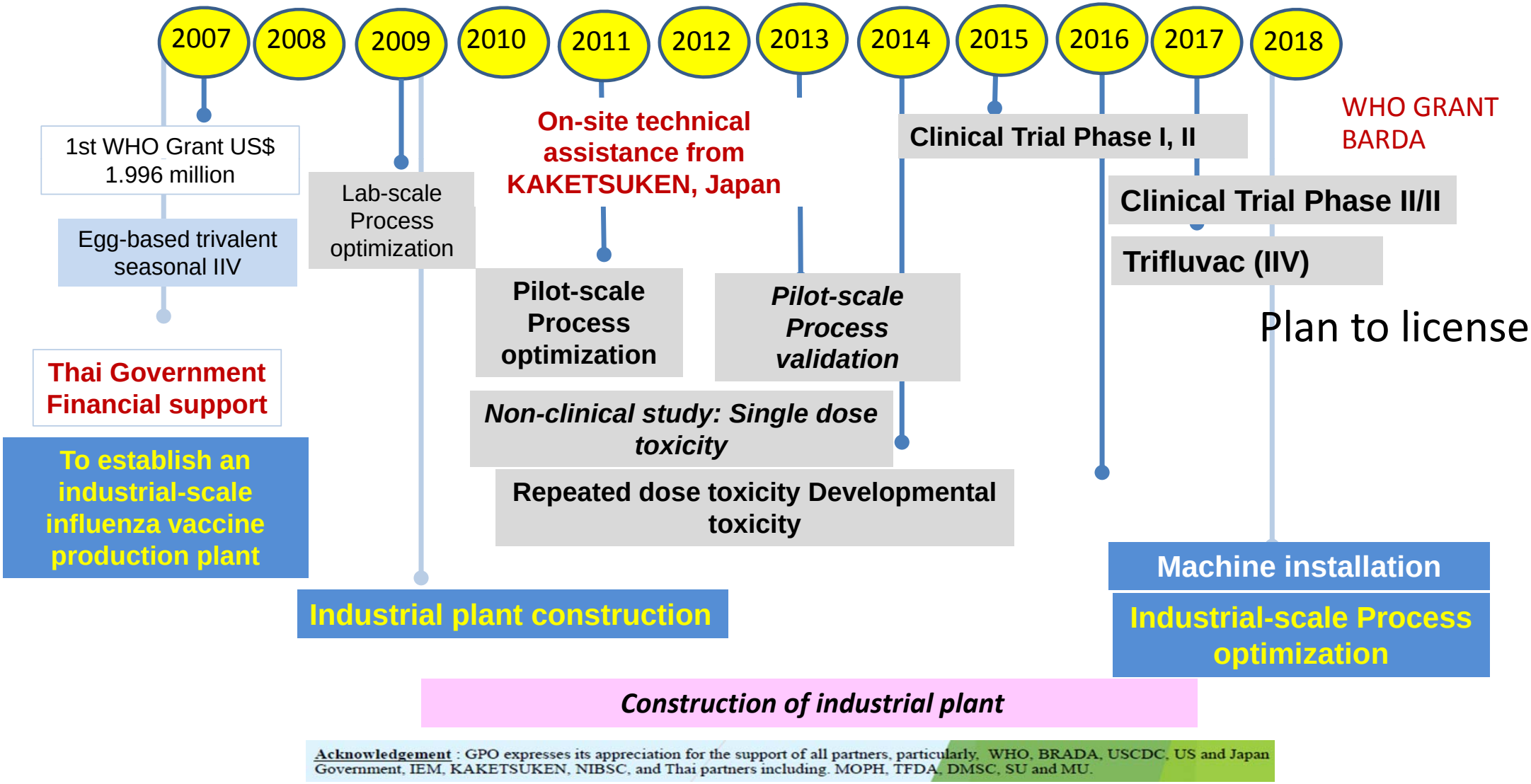
Inactivated Influenza Vaccine-GPO

- In accordance with the resolution of a special meeting held by the Ministries of Public Health of the ASEAN countries+3,

the KAKETSUKEN Institute has provided technical assistance in the development of technologies to produce seasonal inactivated influenza vaccines on both a pilot and an industrial scale, as well as providing recommendations for the design of the manufacturing plant, the management of the chicken eggs, which are a raw material of great import, the management of documentation and the completing of applications for the registration of the vaccines.

Source: Government Pharmaceutical Organization

Inactivated Vaccine- Trivalent Seasonal IIV



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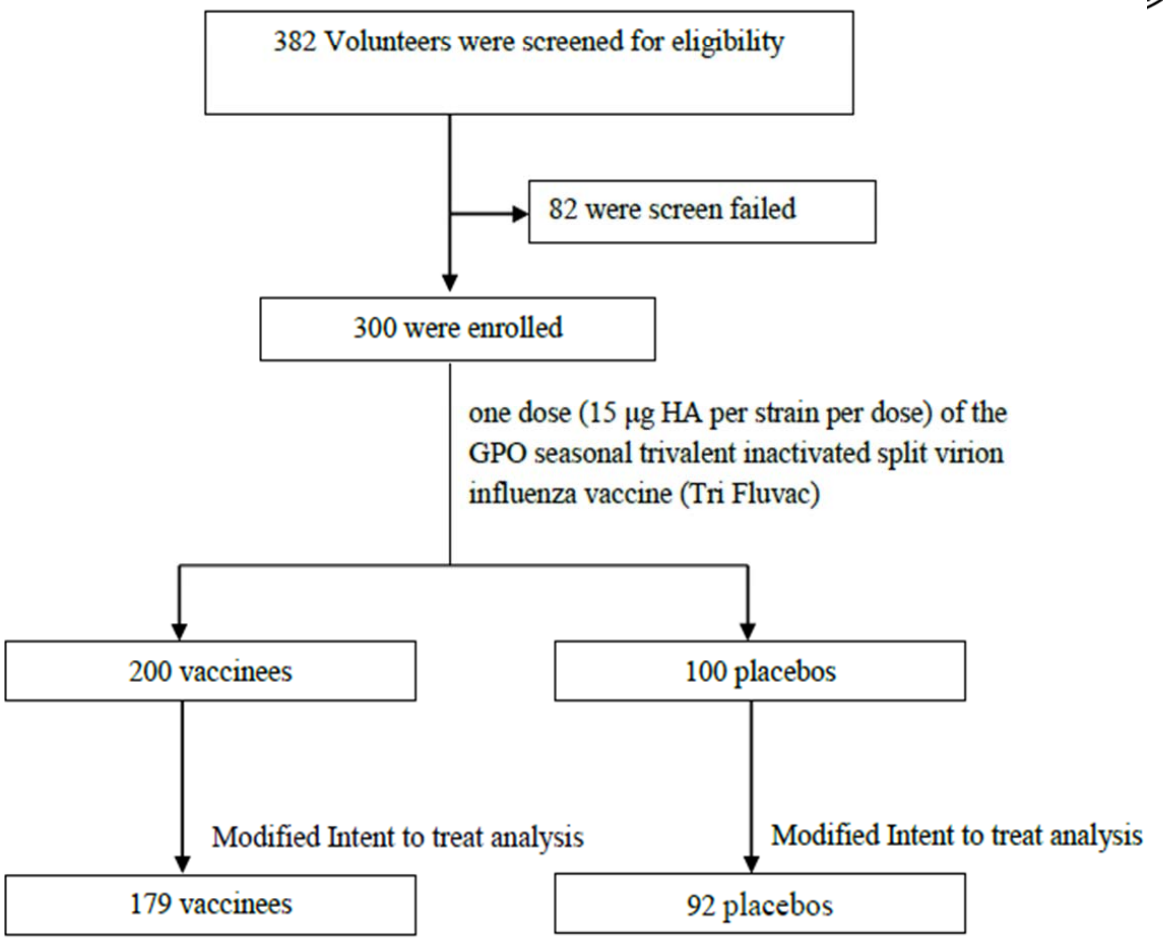
A Phase I/II Randomized Double Blind Controlled Study to Evaluate the Safety and Immunogenicity of GPO Seasonal Trivalent Inactivated Split Virion Influenza Vaccine in Healthy Thai Adults Aged Between 18 years to 49 years

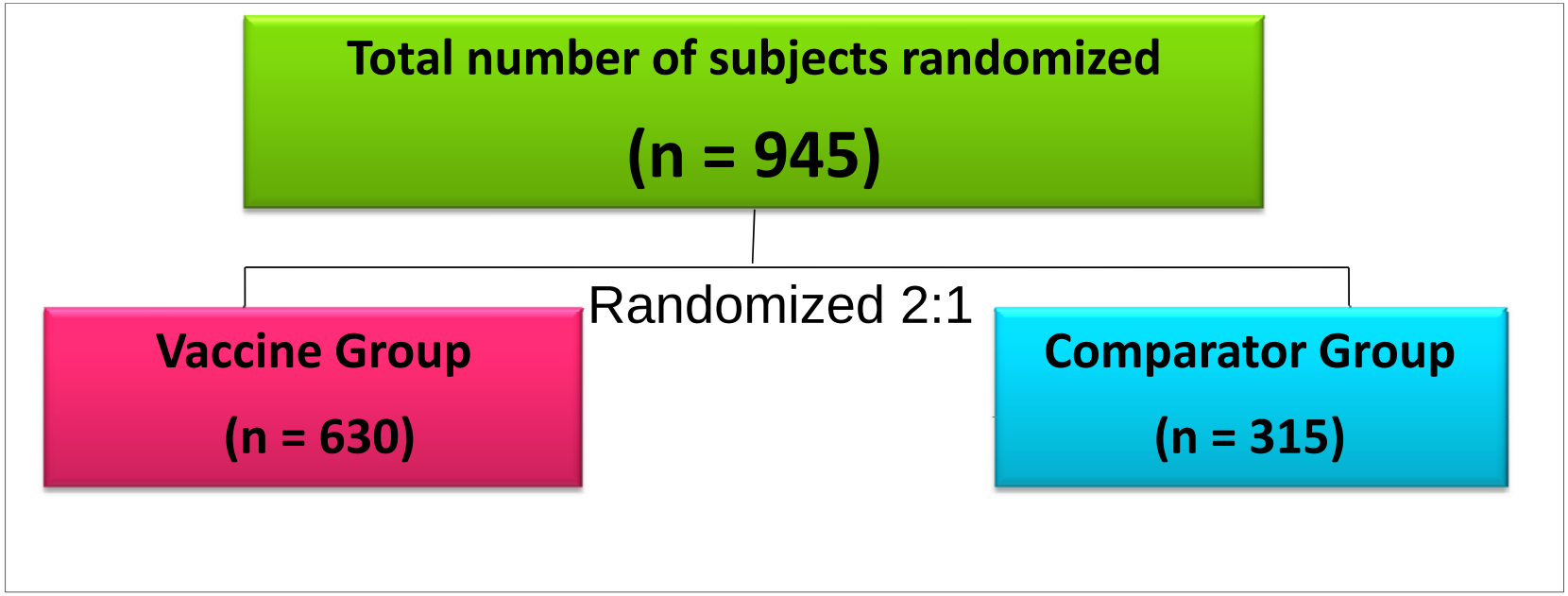


Supported by WHO-BARDA

GPO Tri Fluvac Vaccine Phase II/III

STUDY DESIGN

- Phase II/III, non-inferiority double-blinded, randomized, and controlled trial
- Study Site: Vaccine Trial Centre or its mobile sites, Faculty of Tropical Medicine, Mahidol University.



Supported by WHO-BARDA

Clinical part has been completed upto D90 FU
July 2017- Feb 2018

Inactivated Influenza Vaccine

- GPO's vaccine manufacturing plant is situated in Tub Kwang Sub-District, Kaeng Khoi District, Saraburi Province and is being built with a budget of 1.116.19 million baht.
- The goal of the plant is in the first instance to have the capacity to produce 2 million doses of seasonal influenza vaccines. THEN increase to 10 million doses in the near future
- Able to increase up to 60 M DOSE DURING EPIDEMIC/OUTBREAK

Source: Government Pharmaceutical Organization

CONCLUSION

Successful program in helping local manufacturer (GPO) to be able to manufactured (Both LAIV AND IIV) it own influenza vaccine as part of self reliance and national security

Remain challenges remain for policy support and sustainability

LAIV OR IIV ? FOR PANDEMIC SITUATION

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- Silpakorn U
- NVI,Thailand
- IEM, Russia Dr. Larissa
- Kaketsuken, Japan

Thank you for your attention