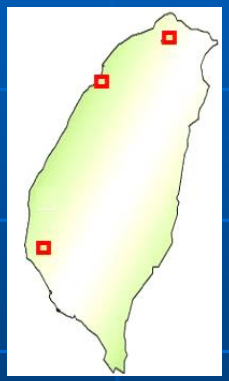
Development of MDCK Cell-Derived Influenza H7N9 Vaccines

Funded by NHRI and Taiwan MOHW

Min-Shi Lee (李敏西), MPH, PhD



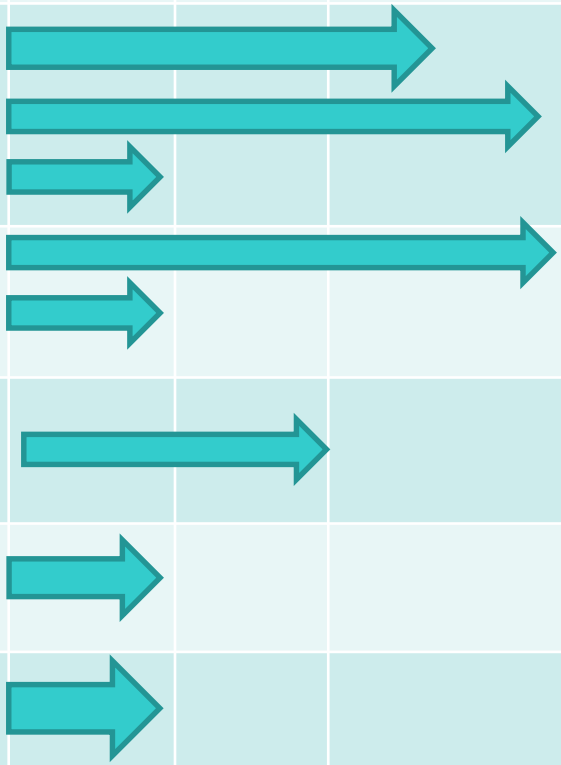
On behalf of Novel Influenza Vaccine Research Group

National Institute of Infectious Diseases & Vaccinology (NIIDV), National Health Research Institutes (NHRI)

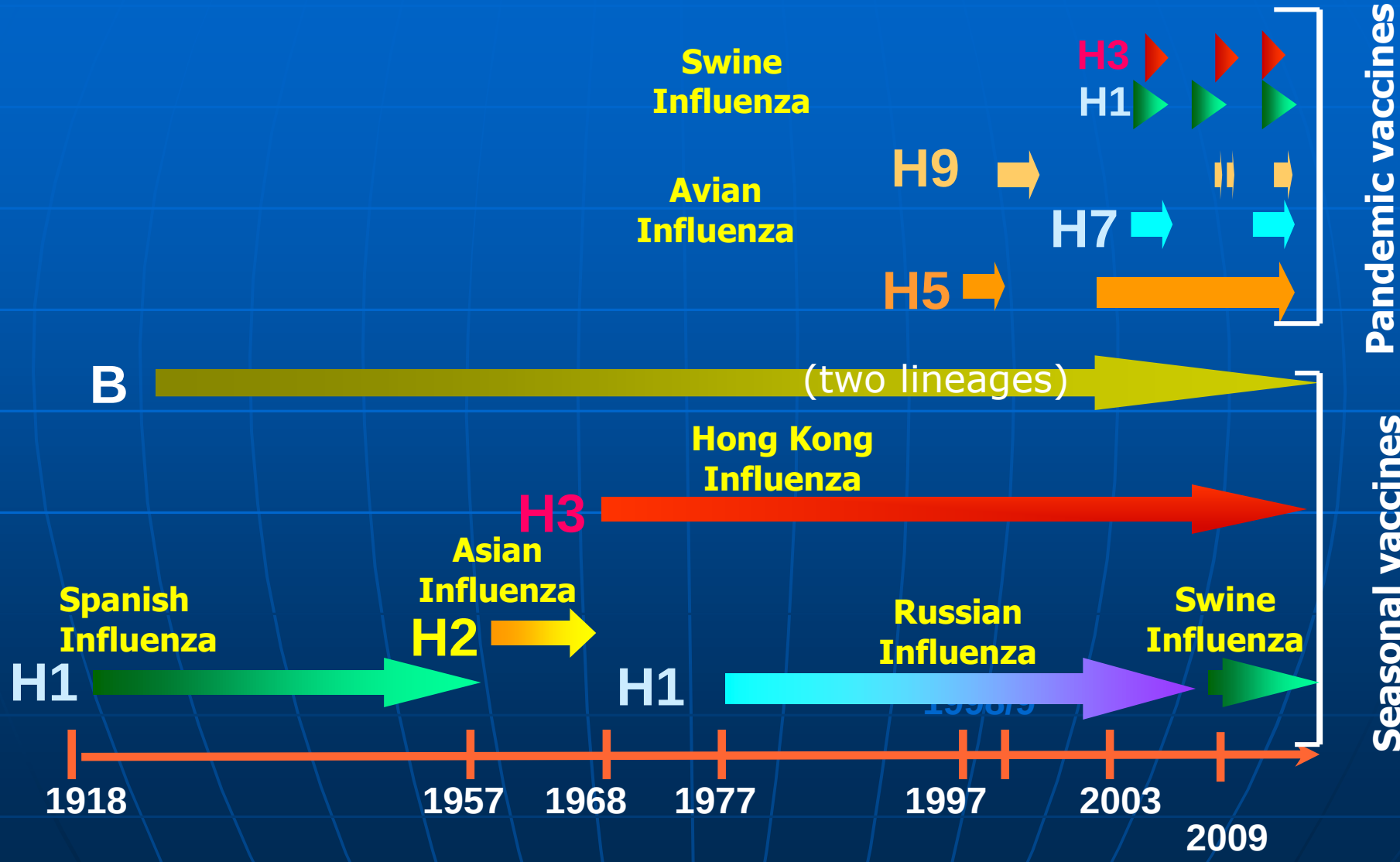
Zhunan, Taiwan

Pipeline of Product Development in NIIDV, NHRI, Taiwan

Group	Product	R&D	IND	Clinical Trial I II III	Market
I. Government Contract Production	BCG (licensed from Taiwan CDC)				
	Anti-venom horse sera (Taiwan CDC)				
II. National Security Project	Influenza H5N1 Influenza H7N9 Influenza H5N2				
	Enterovirus 71 (B4) High-growth EV71 (B5)				
III. PI-initiated project	Meningococcus B				
	Adeno-vector RSV				
	Therapeutic HPV vaccine				

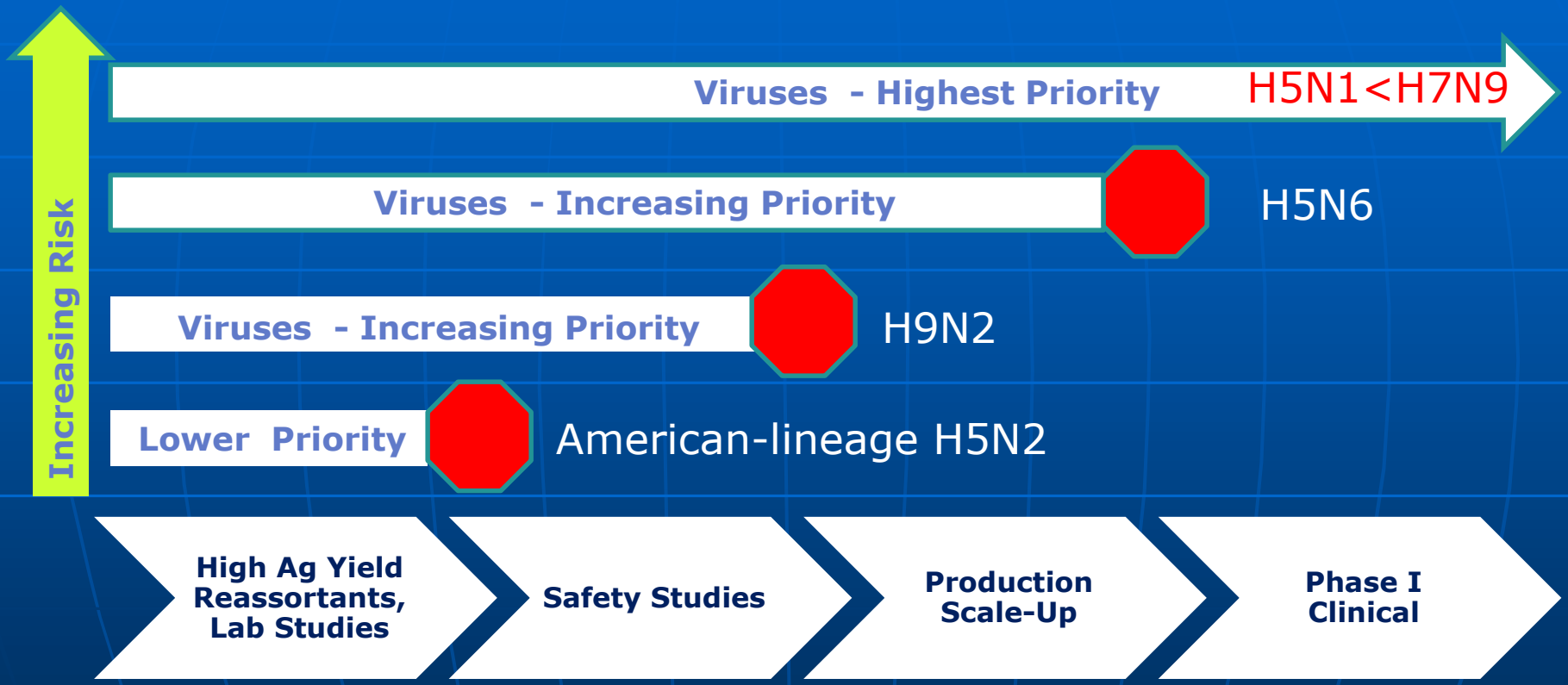


Timeline of Influenza Viruses in Humans



Expectations for an Influenza Risk Assessment

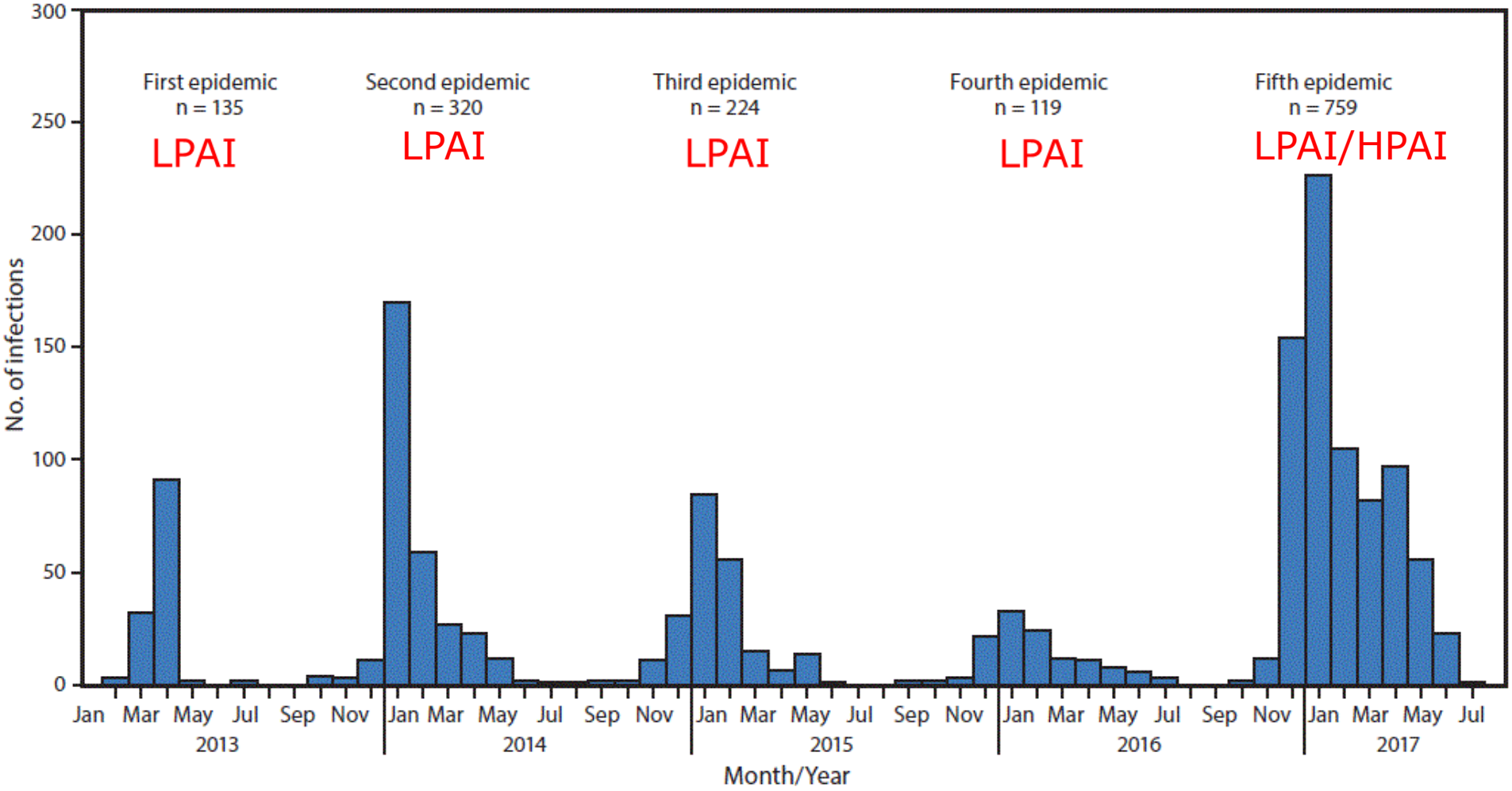
Courtesy of Dr. Ruben Donis, US CDC



Vaccine Development

Taiwan Influenza Risk Assessment Network (TIRAN): AHRI, Taiwan CDC, DOD, NHRI

Human Influenza H7N9 Cases Reported to WHO as of 7 Aug 2017 (1557 cases, 605 deaths) (MMWR, 8 Sep 2017)

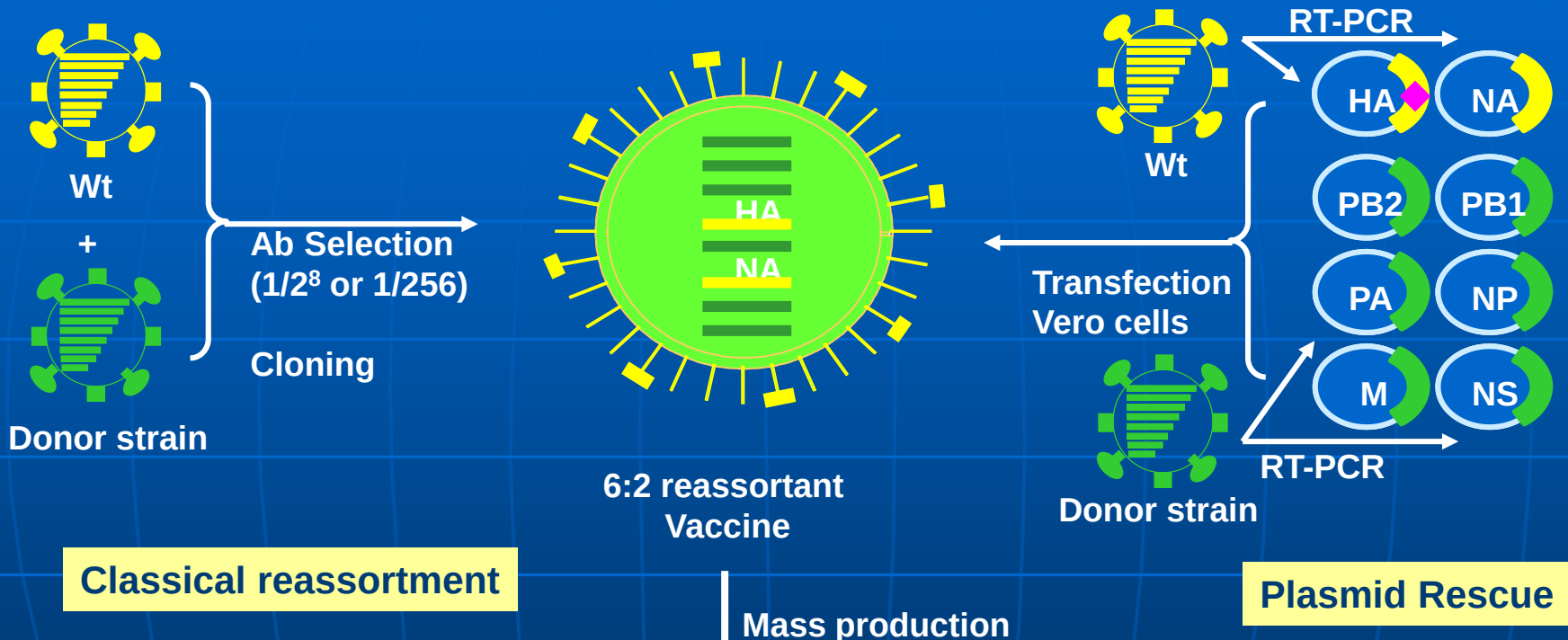


Control strategies in China, 2017: 1)promoting large-scale farming and centralized slaughtering, 2)improving poultry product cold chain transportation and storage at markets, 3)routine live poultry market closures with cleaning and disinfection, and 4) a national poultry vaccination program.

Viral and epidemiologic features identified during the fifth epidemic of Asian H7N9 in China (MMWR, 8 Sep 2017)

- Infections in humans and poultry were reported from most areas of China, including provinces bordering other countries.
- The risk to the general public is very low and most human infections were, and continue to be, associated with poultry exposure.
- During the fifth epidemic, mutations were detected among some Asian H7N9 viruses, identifying the emergence of high pathogenic avian influenza (HPAI) viruses as well as viruses with reduced susceptibility to influenza antivirals.
- The fifth-epidemic viruses diverged genetically into two separate lineages (Pearl River Delta lineage and Yangtze River Delta lineage), with Yangtze River Delta lineage viruses emerging as antigenically different compared with those from earlier epidemics.
- US CDC is working with partners to enhance surveillance for Asian H7N9 viruses in humans and poultry, to improve laboratory capability to detect and characterize H7N9 viruses, and to develop, test and distribute new candidate vaccine viruses (CVV).

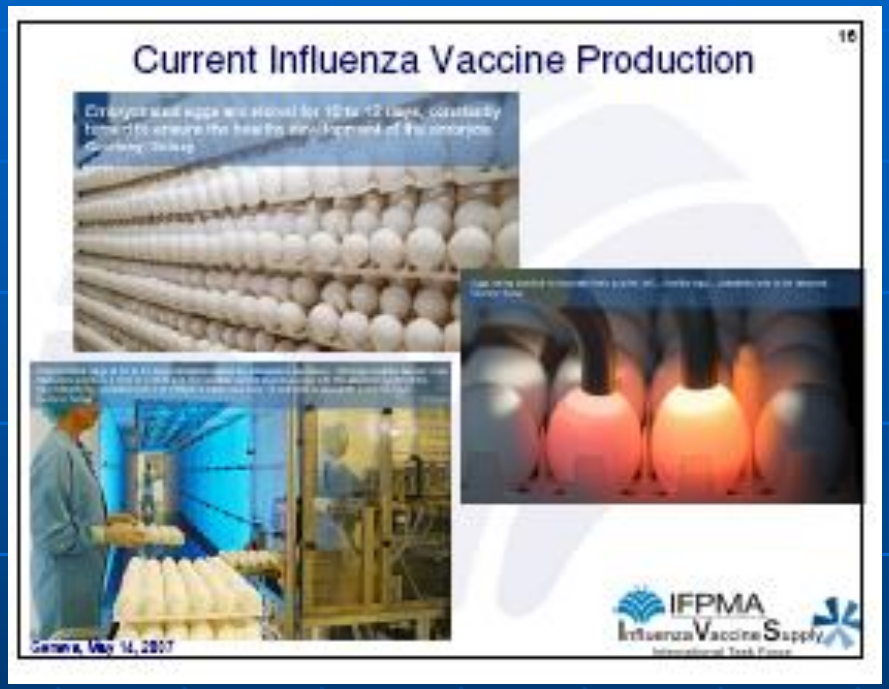
Generation of Influenza Vaccine Seed Viruses



NIBRG-14 vaccine strain from UK NIBSC: NA & modified HA from A/Vietnam/1194/2004 (H5N1) and the other 6 gene segments from egg-adapted A/PR/8/1934 (H1N1)

Production of Influenza Vaccines

Egg-Based



Advantage: history of success, low technology
Disadvantage: hard to scale up, biosafety concern, labor-intensive, egg supply during pandemics caused by HPAI

Cell-Based

Vero cells
MDCK cells
Insect cells (rHA, 2013, USA)
Duck cells (H5 in 2014, Japan)

Progress in pre-pandemic & pandemic vaccine development

Egg-based technology

inactivated vaccines


whole virus


split virus


subunit

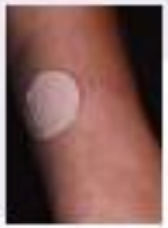

embryonated egg


adjuvants

other immune-enhancing mechanisms Such as virosomes


injection


intranasal


patch


intradermal


live attenuated


SPF embryonated egg

IFPMA Influenza Vaccine Supply International Task Force

Milestones of Cell-based Influenza H7N9 Vaccine in NHRI, Since May 2013

1. Virus adaptation in MDCK and Vero cells
2. Validation of master virus bank
3. Process development: disposable bioreactor and liquid chromatography
4. Obtaining potency assay (SRID) reagents
5. Mice immunogenicity
6. Ferret immunogenicity and protection study
7. Preclinical toxicology in rats and rabbits
8. Tech transfer to an industry partner (Medigen Vaccinology, Inc., April 2014)
9. Conduct phase I & II clinical trials (April 2015~1Q2017)
10. Taipei Biotech Award (台北生技銅牌獎), July 2016
11. Give a talk in the DCVMN's Annual Meeting, Sep 2017

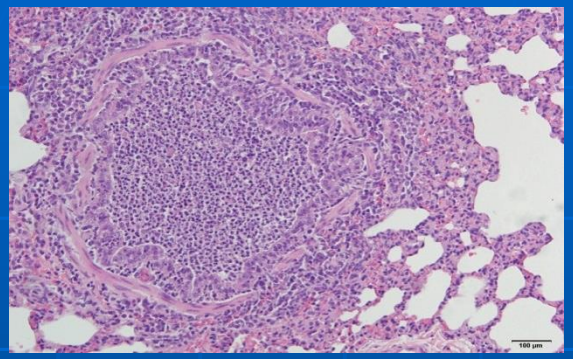
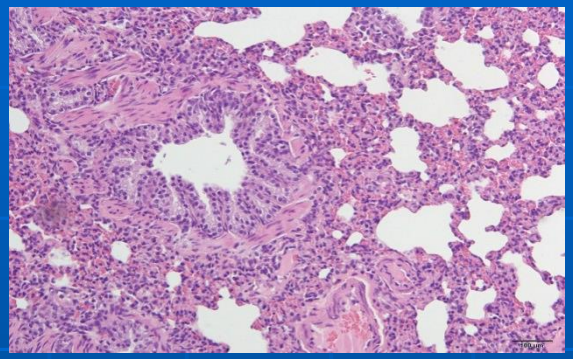
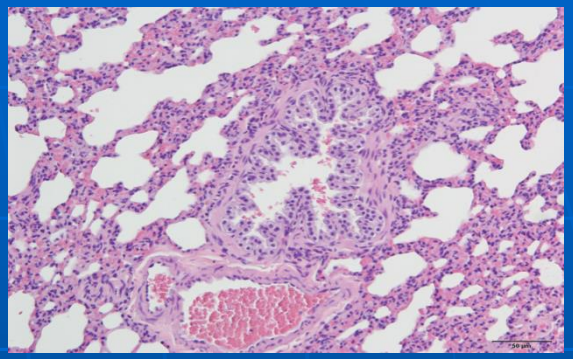
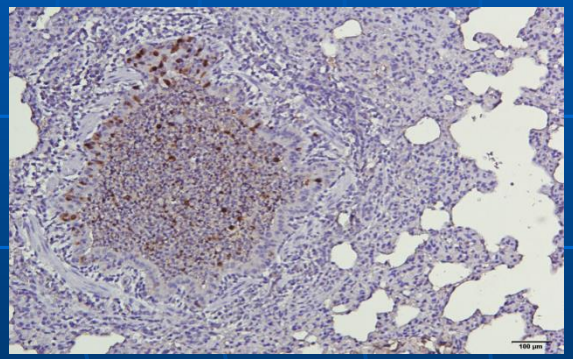
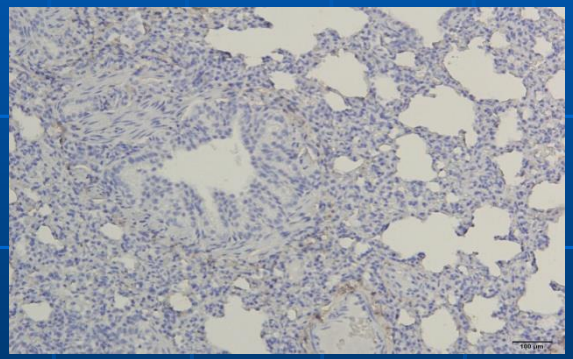
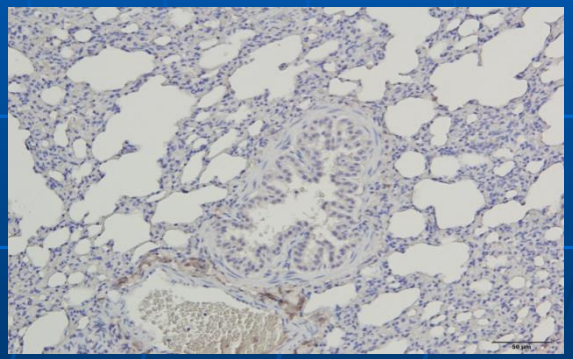
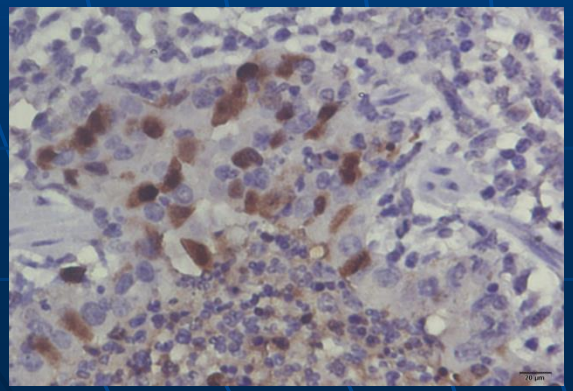
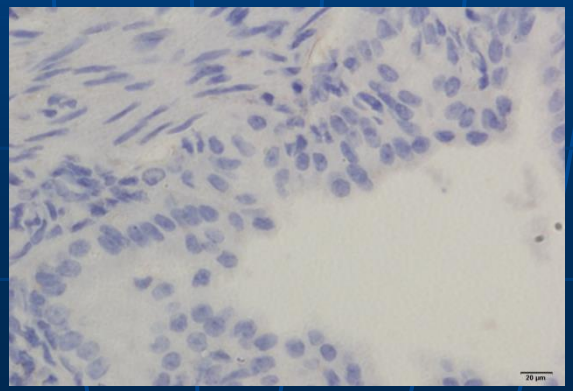
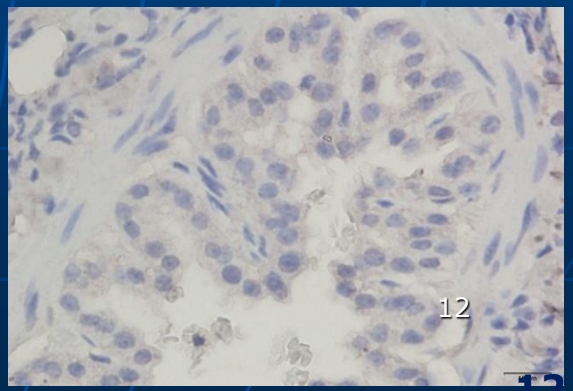
Ferret Study (immunogenicity & protection)

- **Materials & Methods：**
- **Age： 4~8 months of age (4 ferrets / group)**
- **Time: Nov 18 ~ Dec 30 (vaccinated at day 0 and 14, challenged at day 28, sacrificed at day 31 and 42)**
- **Control group：vaccine solvent (PBS) + adjuvant**
- **Vaccine : inactivated H7N9 whole virus vaccines**
- **Challenge study: A/Anhui/1/2013 (H7N9) in BSL-3**

	Group 1	Group 2	Group 3
HA (ug)	0	1.5	1.5
Alum (ug)	300	0	300
HI (Nt) GMT Post dose 1	<10 (<40)	<10 (<40)	48 (48)
HI (Nt) GMT Post dose 2	<10 (<40)	17 (80)	190 (640)

Chia et al. PLoS One 2015

Pathological Examination in Lung Tissues of Ferrets Infected with Influenza A/Anhui/1/2013 (H7N9)

	Group1: Alum only	Group2: HA only	Group3: HA+ Alum
	F180 (DPI 3)	F187 (DPI 3)	F191 (DPI 3)
H&E 100X			
Anti-NP (ATIT) 100X			
Anti-NP (ATIT) 400X			

Clinical Trials of MDCK Cell-based Influenza H7N9 Vaccines in Taiwan (Medigen Vaccine Biologics Co.)

(Phase I & II in 200 Healthy Adults, NCT02464163)

Group	HA dosage	Alum hydroxide	N	Post dose 2 HI antibody GMT, titer>=40	
I	15 μg	0	45	24,	42%
II	15 μg	300 μg	48	22,	40%
III	30 μg	0	49	33,	51%
IV	30 μg	300 μg	48	36,	65%

Wu et al. Vaccine 2017

Clinical Trials of Influenza H7N9 Vaccine Candidates

Vaccine Antigens	Sponsor	Adjuvant	Status
類病毒顆粒流感疫苗 (VLP)	Novavax	ISCO	Phase II
次單位疫苗 (MDCK cell-derived H7N9 subunit Vaccine)	Novartis Vaccines	MF59	Phase I
去活化流感病毒裂解疫苗 (Egg-derived H7N9 Split Vaccine manufactured by Sanofi)	National Institute of Allergy and Infectious Diseases (NIAID), NIH	MF59 or AS03	Phase II
去活化流感病毒裂解疫苗 (Egg-derived H7N9 Split Vaccine)	GSK	AS03	Phase I
去活化流感病毒裂解疫苗 (Egg-derived H7N9 Split Vaccine)	AdImmune (國光)	Alum	Phase II
去活化全流感病毒疫苗 (MDCK cell-derived inactivated whole virion Vaccine)	Medigen Vaccinology (基亞疫苗)	Alum	Phase II
活性減毒疫苗 (egg-derived LAIV)+去活化流感病毒次單位疫苗	NIAID, NIH	None	Phase I
活性減毒疫苗 (egg-derived LAIV)	俄國流感研究中心		
DNA 疫苗)+去活化流感病毒次單位疫苗	NIAID, NIH	None	Phase I
H7重組蛋白疫苗	Protein Sciences Corporation	2% SE	Phase II

Clinical Evaluation of Influenza H7N9 Vaccines Worldwide

Vaccine type	Production platform	Antigen type	Adjuvant	Antibody titers in clinical trials
1	Egg	Split	None	Low
2	Egg	split	AS03	High
3	Egg	Split	MF59	Intermediate
4	Suspensive MDCK cell	Subunit	MF59	Intermediate
5	Suspensive MDCK cell	Subunit	None	Low
5	Adherent MDCK cell	Virion	None	Intermediate
6	Adherent MDCK cell	Virion	$Al(OH)_3$	Intermediate
7	Insect cell	VLP	None	Low
8	Insect cell	VLP	ISCO	High
9	Egg	Live virus	None	Intermediate

More formulations: inactivated whole virion and adjuvants.

Conclusions

1. Based on published clinical studies, influenza H7N9 inactivated whole virus antigens seem to be more immunogenic than VLP, split and subunit antigens.
2. Influenza H7N9 inactivated whole virus antigens formulated with emulsion-based adjuvants (MF59 or PELC) are highly immunogenic in ferrets and clinical evaluations are warrant.
3. To encourage development of pandemic influenza vaccines, national stockpile policy for pandemic influenza vaccines is necessary.
4. Since influenza pandemic is not predictable, it is desirable to separately stockpile vaccine antigens and adjuvants.

Development of Influenza H5N2 and H7N9 Vaccines: teams and advisors

Nov 2012 Influenza Symposium

10 April 2013 Vaccine Strain Selection Meeting

26 March 2014 Advisor Meeting

17 Oct 2014 Advisor Meeting

Acknowledgements

- Scientific Advisors, NIIDV, NHRI, Taiwan
- IPM, National Defense Medical Center, Taiwan
- AHRI, COA, Taiwan
- MOHW, Taiwan
- CDC, Taiwan
- MOST, Taiwan
- FDA, Taiwan
- CDE, Taiwan
- NIBSC, UK
- NIID, Japan
- US CDC
- US FDA

National Project:Asia-Pacific Network for Enterovirus Surveillance (APNES) , Annual Workshop: 30 Oct 2017

Postdoc positions are available. Please contact minshi@nhri.org.tw.