Experiences with Live Attenuated Avian Influenza Vaccine Trials in Thailand

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Background

- Thailand one of 11 developing countries chosen to join WHO's influenza vaccine development scheme
  - Received ~$4million in funding
  - State-run drug maker Government Pharmaceutical Organization (GPO)
- GPO produced pandemic LAIV
  - Vaccine made in pilot plant in Saraburi Province for inactivated vaccine
  - Licensed for pandemic use by Thai FDA in July 2011
- Currently developing AVAIN FLU VACCINE-H5N2

Phase I safety and immunogenicity of live attenuated influenza H5 candidate vaccine strain A/17/turkey/Turkey/05/133 (H5N2) in healthy Thai volunteers

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Primary Objective

- To evaluate safety and reactogenicity of live attenuated 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

Study Design Part A

- It is a double blind randomized study using the dose 7.5-8.5 log EID_{50} per 0.5 ml
- 24 participants age 18 -45 years (16 vaccines and 8 placebos) were enrolled and admitted for 9 days twice 21 days apart
- Vaccine: *ca-ts* attenuated candidate strain A/17/turkey/Turkey/05/133 (H5N2) was prepared at Institute of Experimental Medicine (IEM) in St. Petersberg, Russia and was manufactured by GPO in Thailand.

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

- The formulation contains 6.84% sucrose, 1.00% porcine hydrolized Gelatin, 1.21% arginine, 0.094% Glutamate, 1.13% K_2HPO_4 and 0.48% KH_2PO_4. Storage at -20°C (± 5 °C)
- Each vial contains a single dose of Fluvac (H5N2) (0.5 ml); 0.25 ml of the contents is administered into each nostril by nasal sprayer.

Safety &Laboratory Evaluations

- Using diary card by nurse staff and each follow up visits and blood chemistry and CBCfor safety evaluation
- Nasal swabs **for monitoring vi**rus excretion on D2, D3, D5, D7, D9 after each immunization
- Nasal washing (d1,21,42,60) for local immune responses-sIgA.
- Specific antibodies to vaccine strain (HAI test, ELISA, micro-neutralization assay) at D1,7,21,42,60

Immunological end point

Vaccine is able to induce 2-4 folds rise of either HAI mNT, sIgA in 40% of vaccines.

Clinical Evaluations

Grading of reporting temperature are:

0 (no) ≤37 ˚C

1 mild >37˚C - ≤37.5 ˚C

2 (moderately high) >37.5 ˚C - ≤38.5 ˚C

3 (high) >38.5 ˚C

Other systemic reactions will be assessed in 4 scales as follow: 0 – no symptoms

1 –mild Ill-defined symptoms

2 –moderate Symptoms, affecting normal daily activity

3 –severe Symptoms markedly affecting normal daily activity and needed medication or clinic visit or activity limit

64 were screened for eligibility

24 were enrolled

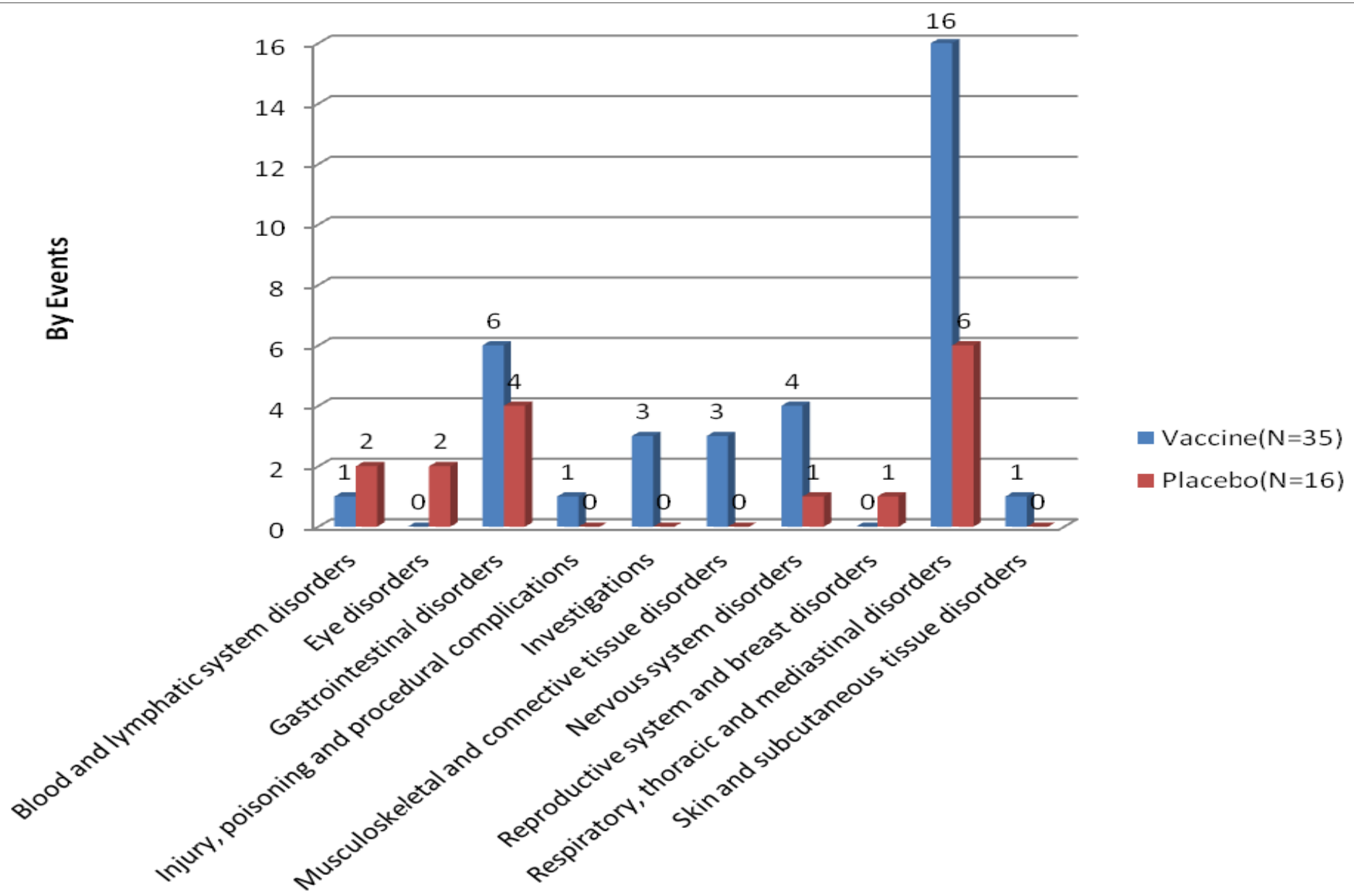
1st D1, **8** placebo

2nd D21, **8** r placebo

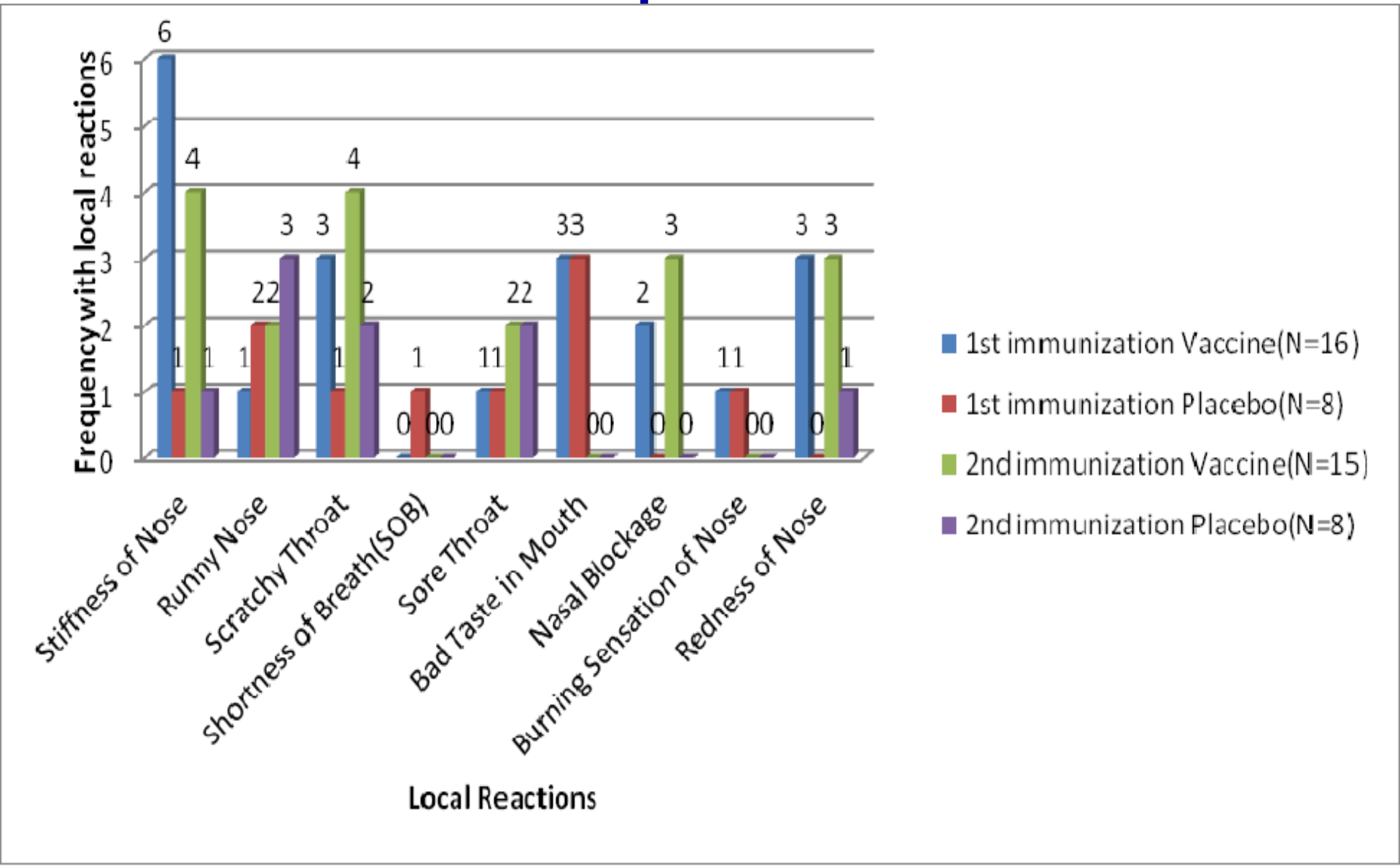
D1, **16** vaccinee

D21, **15** vaccine

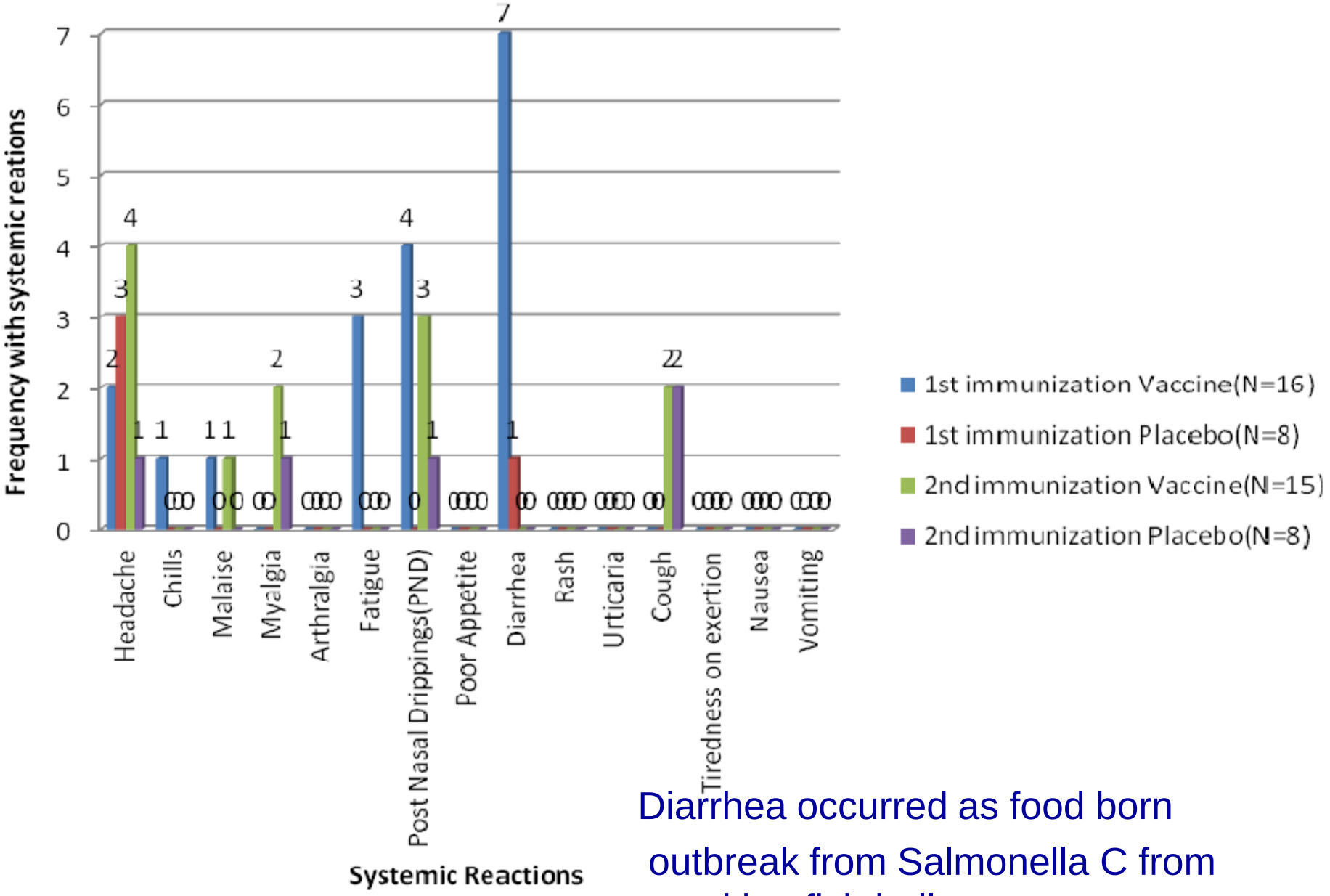
Adverse events by systemic organ class



Local reactions post-immunizations



Systemic reactions post-immunizations



Diarrhea occurred as food born outbreak from Salmonella C from taking fish balls

Comparison of summary of nasal swab (RT-PCR Oualitative)

Positive PCR	Vaccine n(%)	Placebo n(%)	p-value
Post 1st D2	14(87.50%)	0(0.00%)	<0.001*
D3	10(62.50%)	0(0.00%)	0.006*

All were negative after D3

Post 2nd			
D2	13(86.67%)	0(0.00%)	<0.001*
D3	5(33.33%)	0(0.00%)	0.122
D5	1(6.67%)	0(0.00%)	1.00

All were negative after D5

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

Amino acid substitutions found in the virus isolates recovered from nasal shedding

- 6 isolates were obtained from 5 subjects at day 2 or 24 hr after immunization only.
- All viruses were isolated from chick embryonated eggs, none from MDCK cells.
- Only one amino acid change was found in 4 viruses, but at different positions. Mixed virus populations between vaccine strain and mutant were found in 2 virus isolates.
- One virus underwent nucleotide change in *NA* gene, but no amino acid substitution occurred.

Nucleotide/amino acid changes were found in *NP, NA* and *PB1*, but not in *PA, PB2, M, NS* and *HA* genes. These changes are suggestive of virus replication or vaccine in take.

Antibody responses

- 3 developed 4 folds rise of HAI antibody
- 2 had two folds rise of HAI antibody
- No local Ig A detected from nasal wash

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

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* 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.

Closed out

- Initial approval from TM EC
- Waiting for WHO EC expected to be this week-24-25 Jan 2013
- Screening is planned to start first week of Feb,2013
- Admission will be started third week of Feb 2013

Acknowledgement

Clinical : Vaccine Trial Centre and Department of Clinical Tropical Medicine, Mahidol University

Laboratory : Department of Microbiology, Faculty of Medicine, Siriraj Hospital, Mahidol University

Statistical : Center of excellence for biomedical and public health informatics (BIOPHICS) Faculty of Tropical Medicine, Mahidol University

Consultants: Suwit Wibulpolprasert, MD, Ministry of Public Health, Pratap Singhasivanon, MBSS, DTM&H, PhD, Faculty of Tropical Medicine, Mahidol University

Manufacturer: The Government Pharmaceutical Organization (GPO)

Sponsor: World Health Organization (WHO)

US-CDC

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