MedImmune
A member of the AstraZeneca Group

Update on Status of Investigation of Reduced LAIV Effectiveness

Helen Bright, PhD
Raburn Mallory, MD

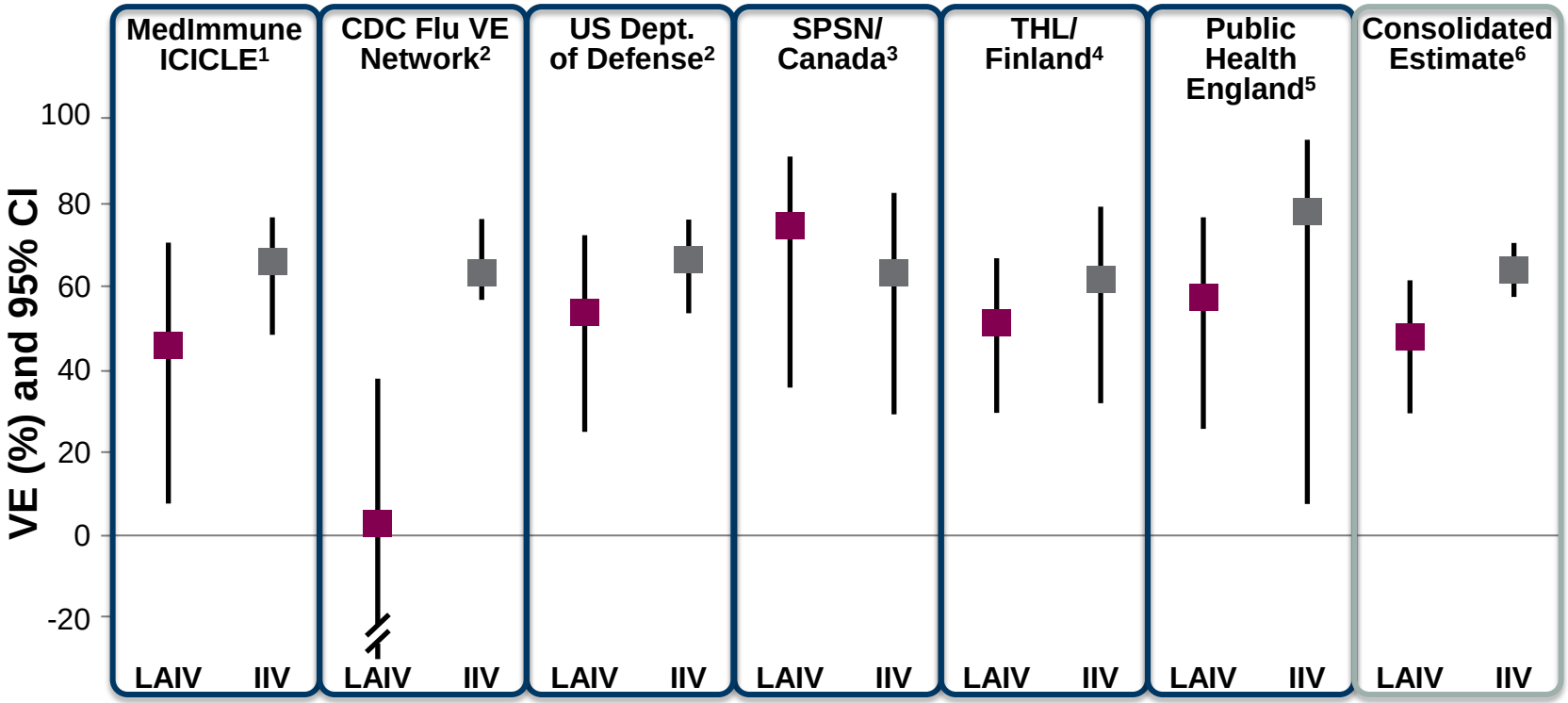
ACIP Meeting: Feb 22, 2017

Presentation Overview

- **Review of 2015-2016 vaccine effectiveness data including recent data on effectiveness of LAIV against influenza hospitalization**

- Progress on non-clinical investigation
- Update on A/H1N1 strain selection for 2017-2018 season
- Ongoing studies and timelines for data availability

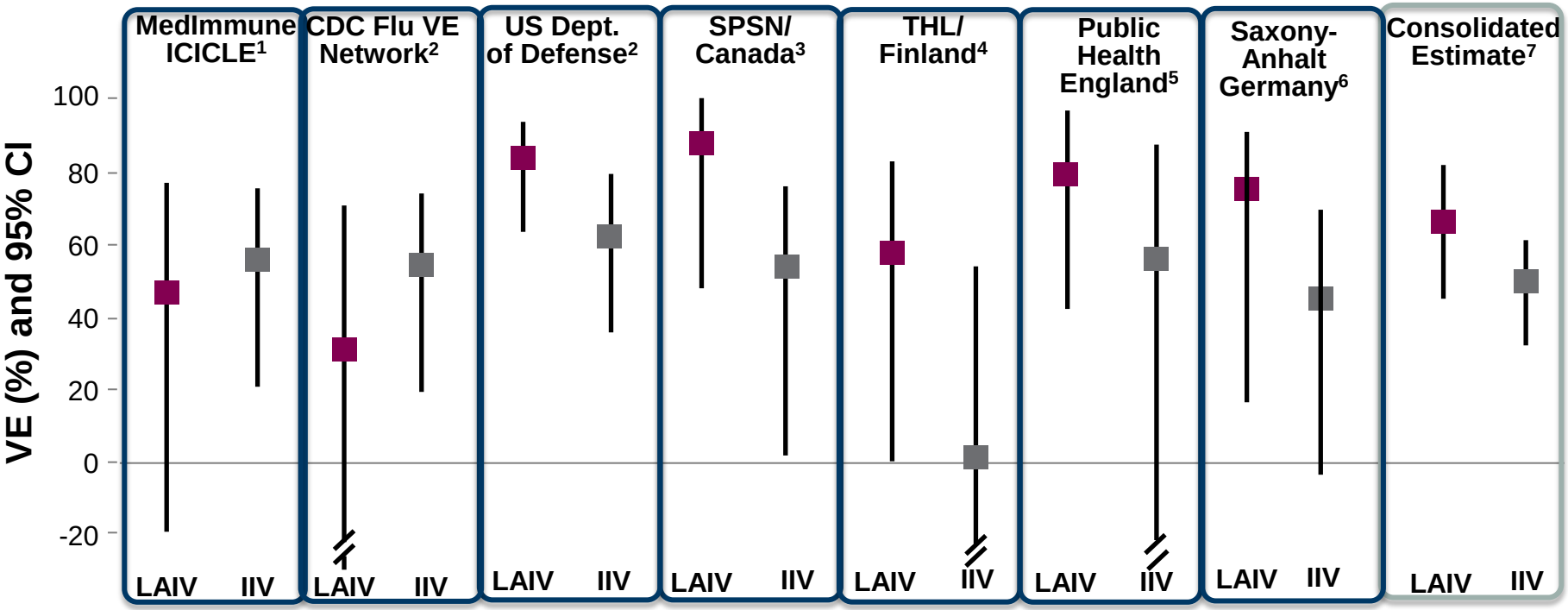
LAIV and IIV effectiveness estimates for all strains: 2015-2016 influenza season



Lower bound of CIs was truncated at –30.

1. Ambrose C. Presented at Advisory Committee on Immunization Practices Meeting; June 22, 2016; Atlanta, GA 2. Flannery B. Presented at Advisory Committee on Immunization Practices Meeting; June 22, 2016; Atlanta, GA 3. Caspard H et al. Presented at International Society for Influenza and Other Respiratory Virus Diseases (ISIRV) Options IX for the Control of Influenza Conference; August 25, 2016; Chicago, IL. 4. Nohynek H et al. *Euro Surveill.* 2016;21(38):pii=30346. 5. Pebody R et al. *Euro Surveill.* 2016;21(38):pii=30348. 6. Caspard H. Abstract Accepted for Publication PAS, May 6-9, 2017; San Francisco, CA.

LAIV and IIV effectiveness estimates for B Strains: 2015-2016 influenza season



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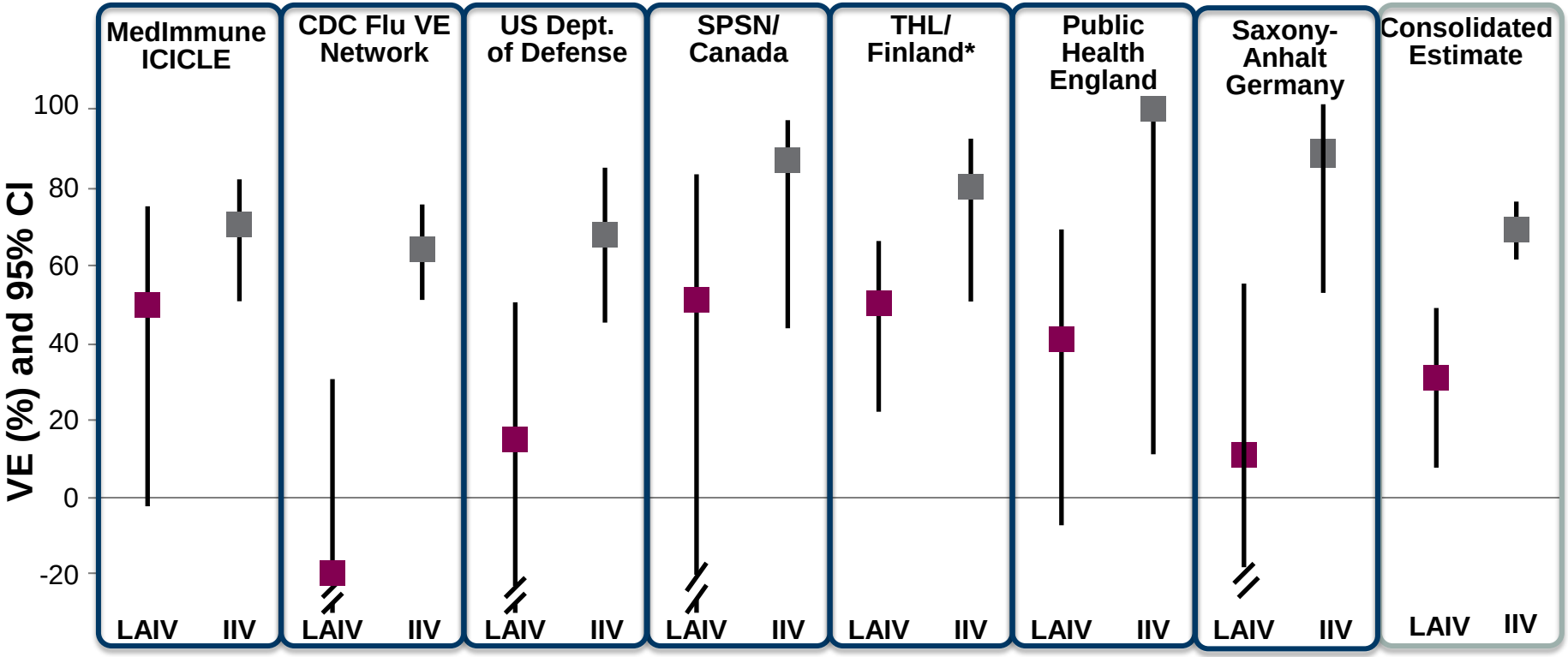
6. Helmeke C et al. http://www.verbraucherschutz.sachsen-anhalt.de/fileadmin/Bibliothek/Politik_und_Verwaltung/MS/LAV_Verbraucherschutz/hygiene/influenza/Effektivitaet_der_Influenzaimpfstoffe_2015-16.pdf 7.Caspard H. Abstract Accepted for Publication PAS, May 6-9, 2017; San Francisco, CA.

LAIV and IIV effectiveness estimates for A/H1N1pdm09 strains: 2015-2016 influenza season[1,2]



Lower bound of CIs was truncated at –30.* Effectiveness estimate against any A strain.

1. Caspard H et al. Abstract accepted for presentation at: Pediatric Academic Societies Meeting; May 6-9, 2017; San Francisco, CA.
2. Helmeke C et al. [poster]. Presented at: European Scientific Conference on Applied Infectious Disease Epidemiology; Nov 28-30, 2016; Stockholm, Sweden.

LAIV effectiveness against influenza hospitalization in England and Scotland: 2015-2016 Influenza Season

	Vaccine Effectiveness: Percentage (95% CI)	
Endpoint	**Public Health England[1]**	**Health Protection Scotland[2]**
Lab-confirmed influenza due to any strain	**54.5% (32, 68)**	**63% (50, 72)**
Lab-confirmed influenza due to H1N1 pdm09 strains	**48.3% (17, 68)**	**NA**
Lab-confirmed influenza due to B strains	**70.7% (33, 87)**	**NA**
Clinical diagnosis of influenza	**NA**	**68% (42, 83)**

[1] Peabody R et al. *Euro Surveill.* 2017; 22(4):pii=30450.
[2] Health Protection Scotland. http://www.hps.scot.nhs.uk/resourcedocument.aspx?id=5529. Accessed 16 February 2017.

Presentation Overview

- Review of 2015-2016 vaccine effectiveness data including recent data on effectiveness of LAIV against influenza hospitalization
- **Progress on non-clinical investigation**
- Update on A/H1N1 strain selection for 2017-2018 season
- Ongoing studies and timelines for data availability

Vaccine effectiveness investigation

- **Investigation currently focused on two potential hypotheses for root cause**
  - Reduced replicative fitness of H1N1pdm09 LAIV strains in human cells
  - Vaccine virus interference from quadrivalent formulation

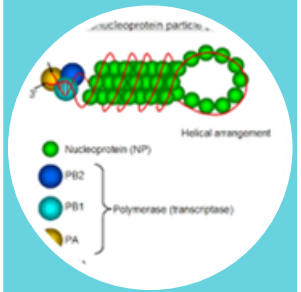
- **Investigation approach**
  - Biological characterisation of recent H1N1 strains vs historical effective LAIV strains
  - Focus on differences between pdm09 H1N1 CA09 & BOL13 vs pre-2009 H1N1 strains NC09 & SD07

Pre-pandemic strains	Post-pandemic strains
New Caledonia 1999 (NC99)	California 2009 (CA09)
South Dakota 2007 (SD07)	Bolivia 2013 (BOL13)
	Slovenia 2015 (SOLV15)
	Pandemic (pdm)

Initiation of life-cycle focused investigation

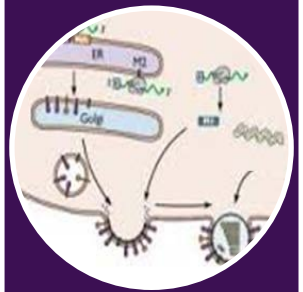
Viral entry

HA Stability
Receptor binding



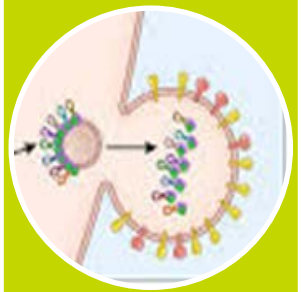
Replication & assembly

HA abundance
UTR mismatch



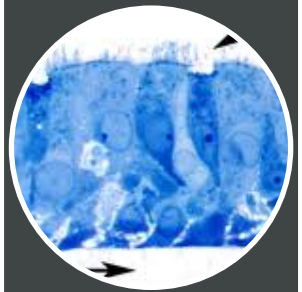
Biophysical

Size, shape
defective particles



Budding / spread

Multi-cycle replication
Neuraminidase



Primary human cells

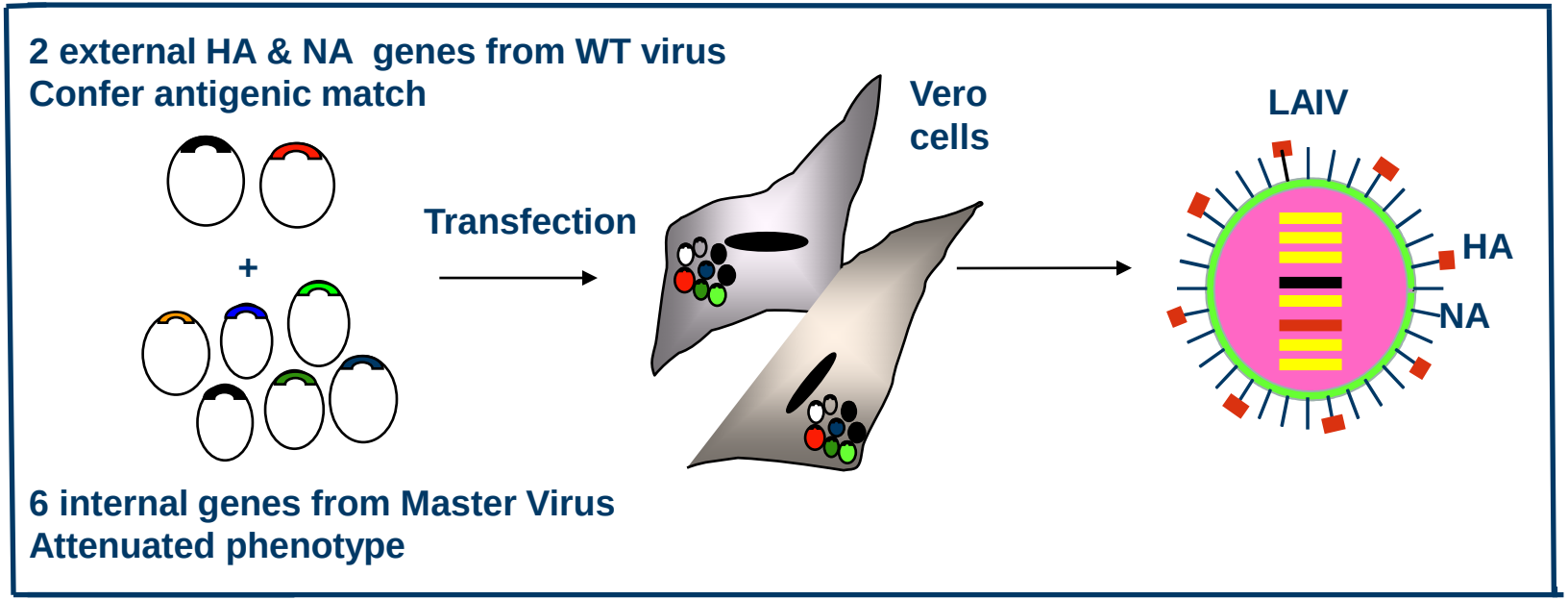
Growth curves
Competition

Ferret model

Infectivity
Immunogenicity
Competition

Biological profiling of effective vaccine strains → Performance in translatable models

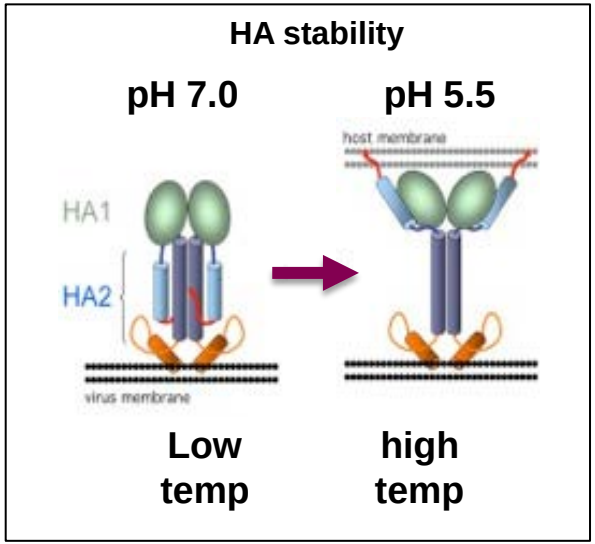
LAIV strains differ only in their external surface glycoproteins HA and NA



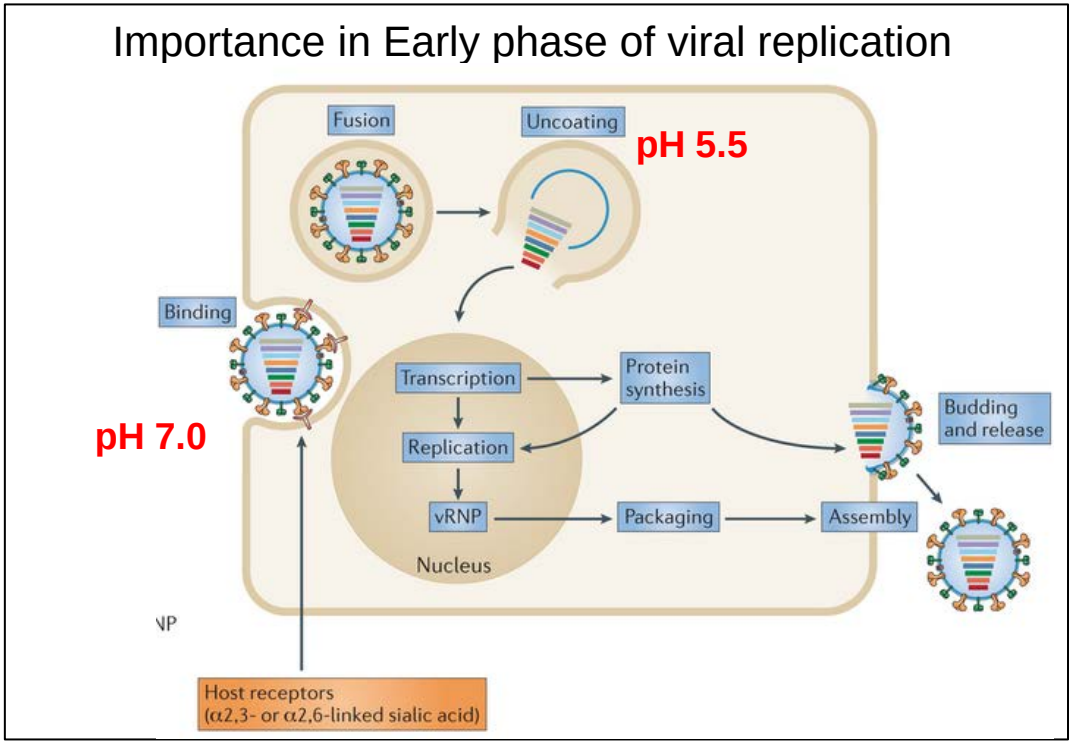
Hemagglutinin (HA) - responsible for the initial phase of virus replication
- cell binding and cell fusion

Neuraminidase (NA) - responsible for late phase of virus replication
- virus release and spread

The hemagglutinin (HA) protein is responsible for cell binding and cell fusion

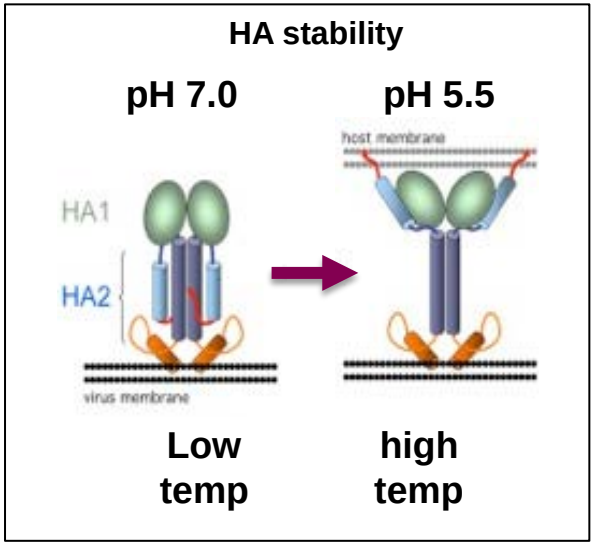


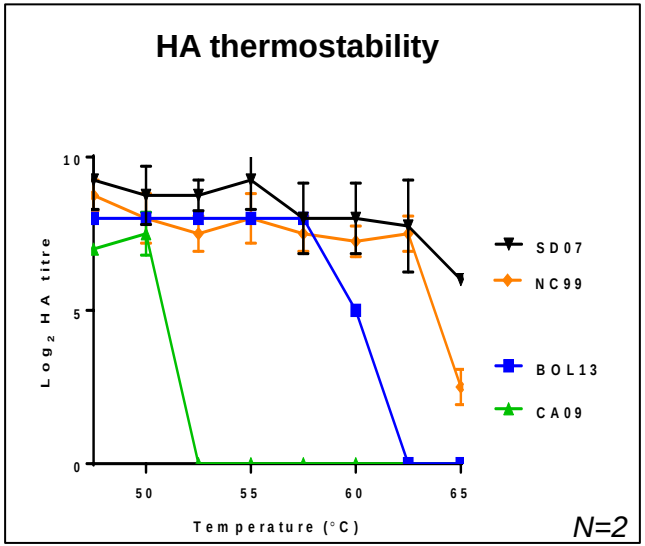
Lee KK - EMBO J. (2010)



Yi Shi, et al Nature Reviews Microbiology 12, 822–831 (2014)

The hemagglutinin (HA) proteins of post-pandemic H1N1 viruses have properties that differ from pre-pandemic H1N1 viruses



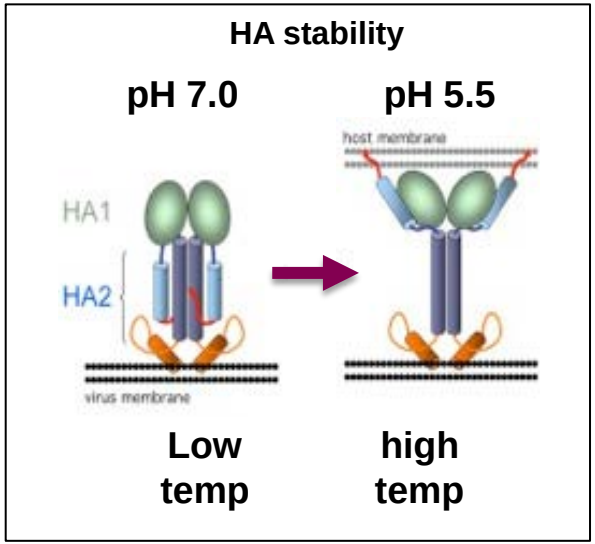


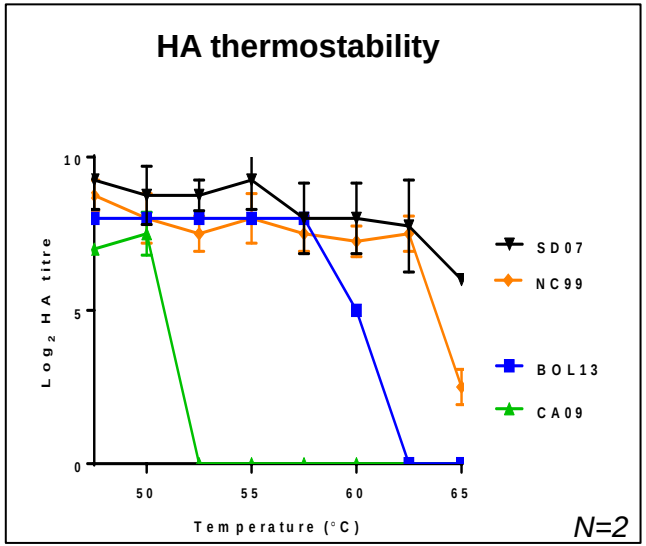
A/California differs as it is less thermostable

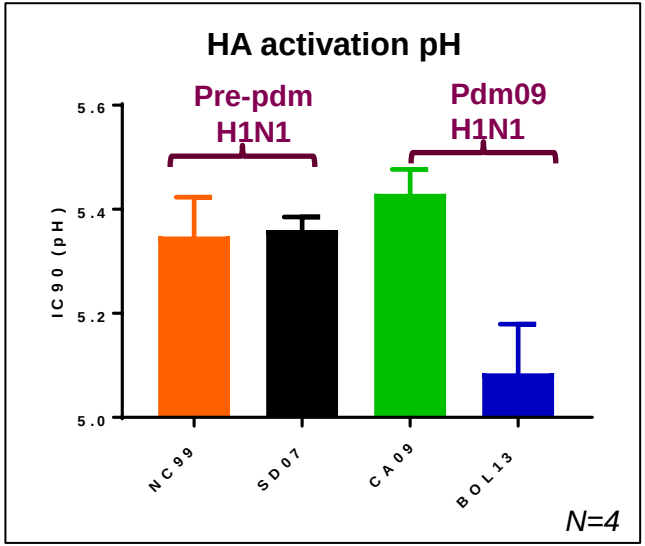
Potential susceptibility to heat

1. Internal Data, MedImmune. Speke UK, Feb 2017.

The hemagglutinin (HA) proteins of post-pandemic H1N1 viruses have properties that differ from pre-pandemic H1N1 viruses







A/California differs as it is less thermostable

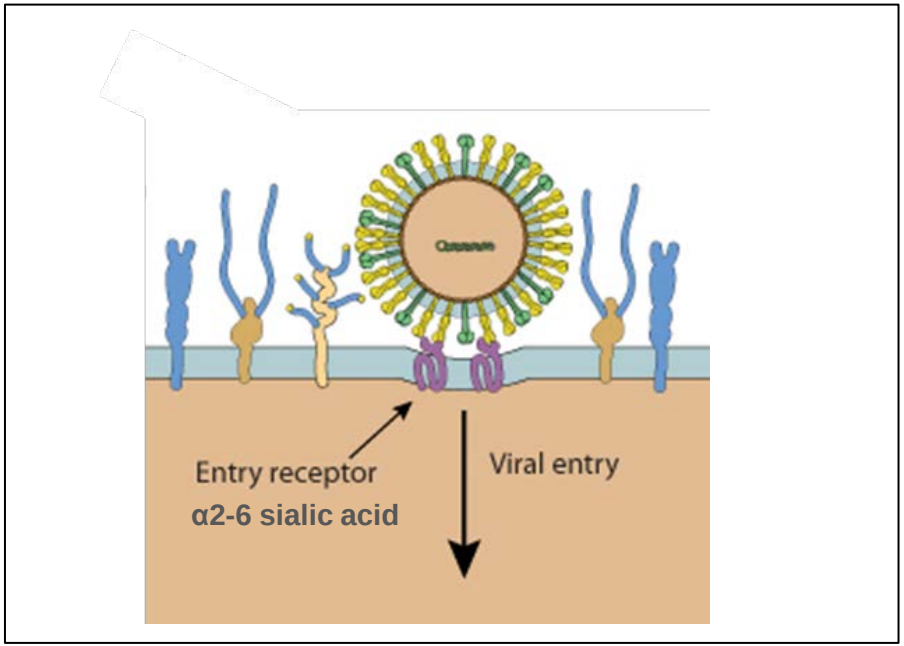
Potential susceptibility to heat exposure during shipping/handling

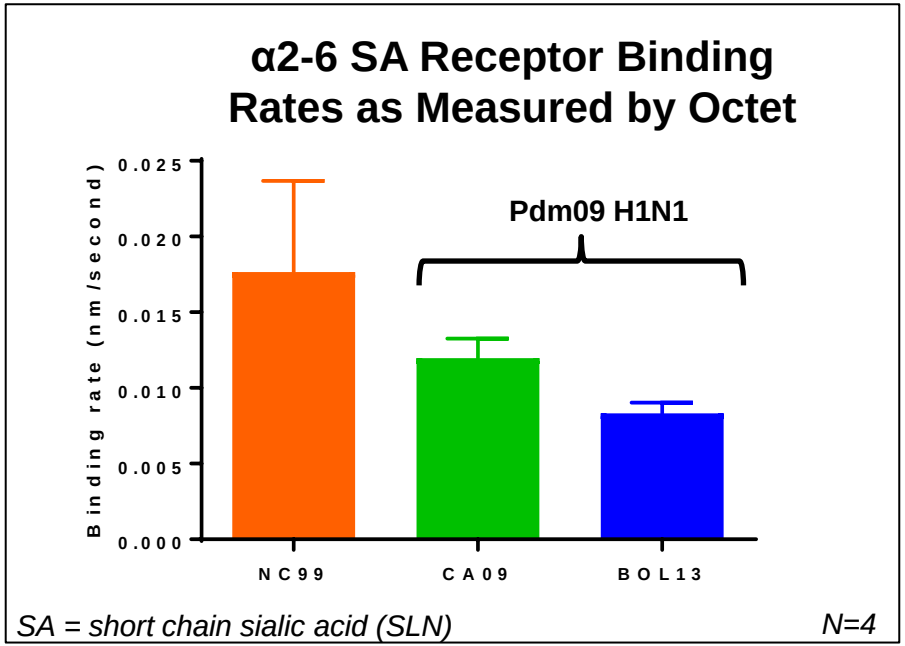
A/Bolivia differs as it is less pH sensitive

Potential impact on viral replication life cycle

1. Internal Data, MedImmune. Speke UK, Feb 2017.

Viral Entry: Post-pandemic H1N1 viruses have reduced binding to human α2-6 cell receptors[1,2]



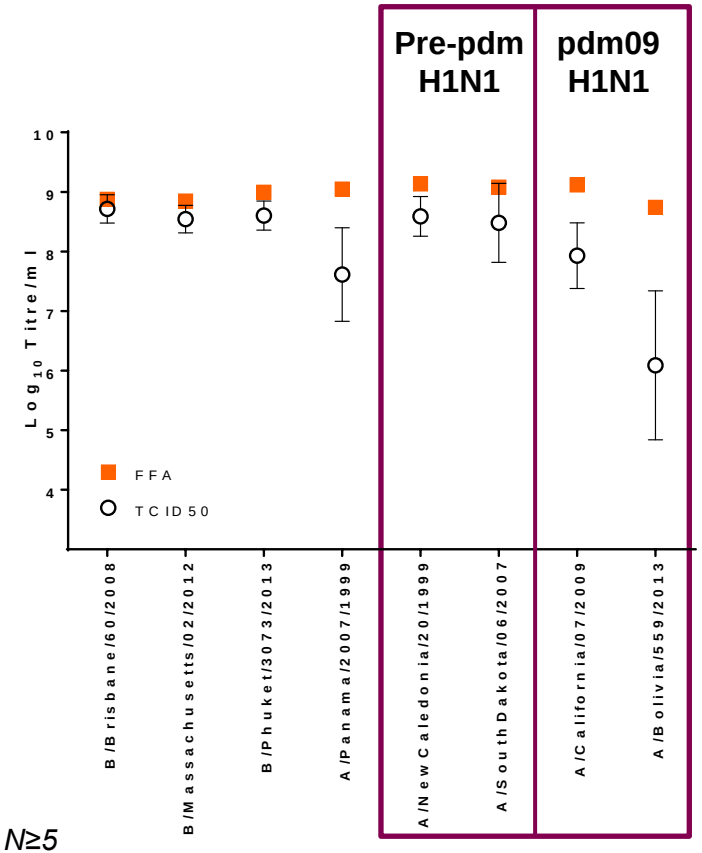


- **A/California and A/Bolivia strains have reduced binding to cell receptor**

1. modified from Swiss Institute of Bioinformatics http://viralzone.expasy.org/

2. Internal Data, MedImmune. Speke UK, Feb 2017.

Replication: Post-pandemic H1N1 viruses less able to support multiple rounds of replication compared to pre-pdm H1N1 viruses

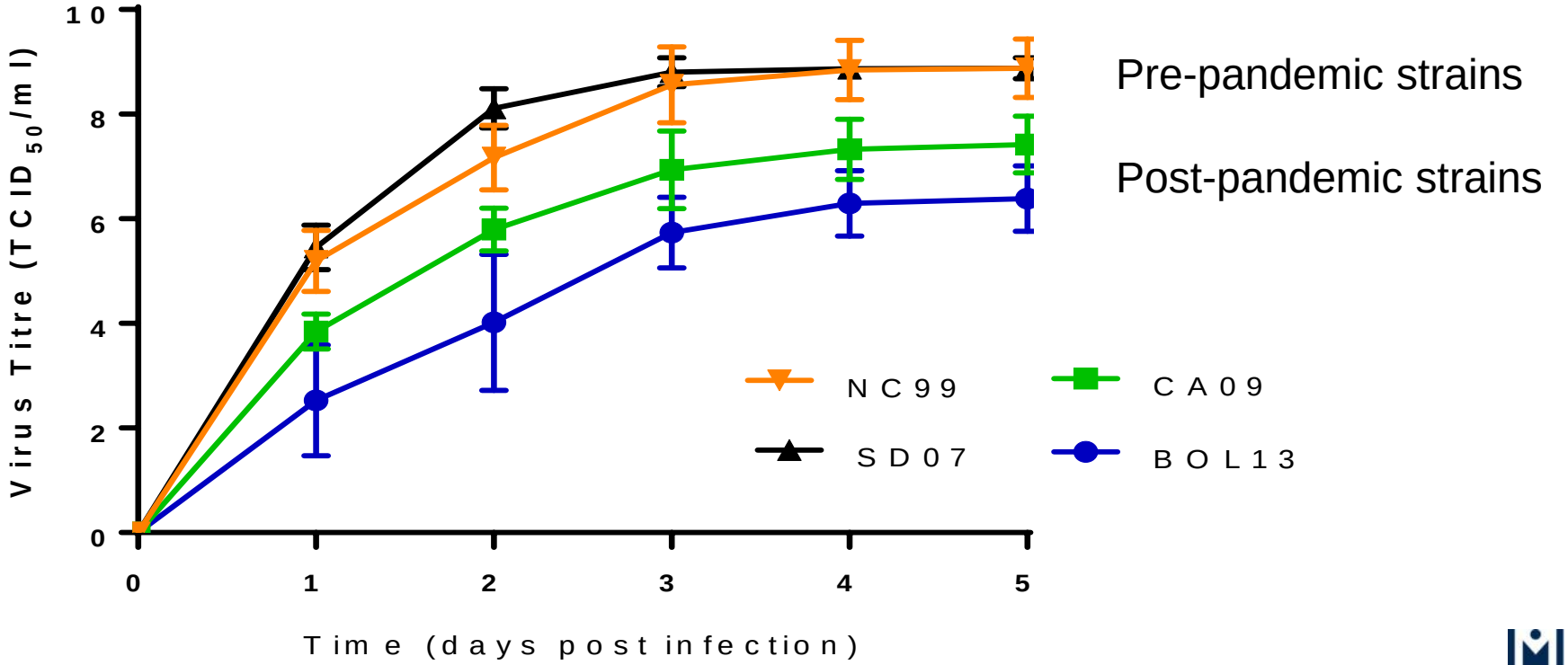


N≥5

- Two assays used to measure infectivity
  - Fluorescent Focus Assay (FFA): one round of replication
  - Tissue Culture Median Infectious Dose ($TCID_{50}$): multiple rounds of replication
- For previous LAIV viruses these assays have given very similar results
- For A/California and A/Bolivia results differ
- Suggests that H1N1pdm09 viruses are less able to support multiple rounds of replication

1. Internal Data, MedImmune. Speke UK, Feb 2017.

Replication: Post-pandemic H1N1 LAIV strains have reduced replication in primary human nasal epithelial cells



N≥9

1. Internal Data, MedImmune. Speke UK, Feb 2017.

Presentation Overview

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- Progress on non-clinical investigation

- **Update on A/H1N1 strain selection for 2017-2018 season**

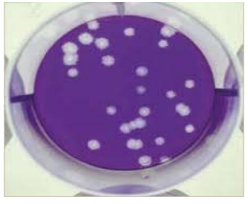
- Ongoing studies and timelines for data availability

Assays previously used to select effective vaccine strains

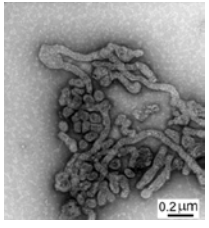
Virus Characteristics

Growth in Eggs

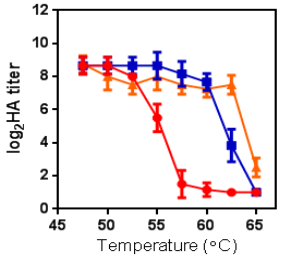
Plaque Morphology



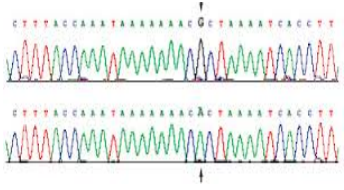
Morphology



HA Thermostability



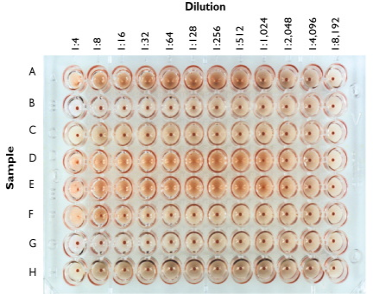
Sequence Stability



Immune-Response

Immunogenicity & Attenuation

Antigenicity
HAI & Neutralisation

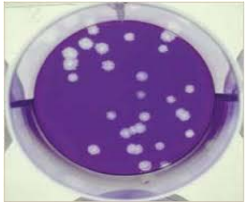


New characterization assays introduced into strain selection process

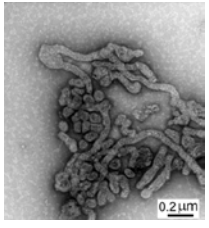
Virus Characteristics

Growth in Eggs

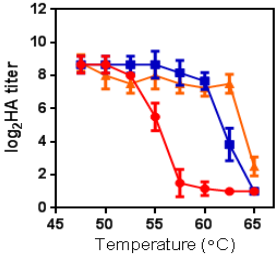
Plaque Morphology



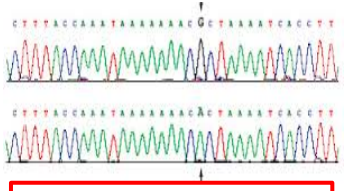
Morphology



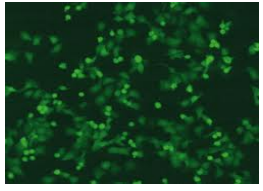
HA Thermostability



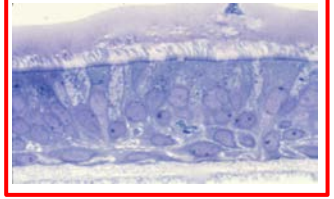
Sequence Stability



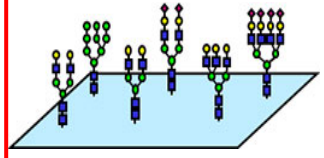
Acid stability and Fusion pH



Growth in Primary Human Nasal Epithelial Cells



Receptor Binding

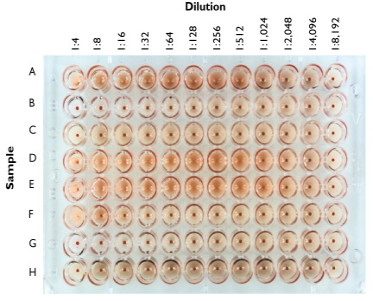


$TCID_{50}$ v FFA

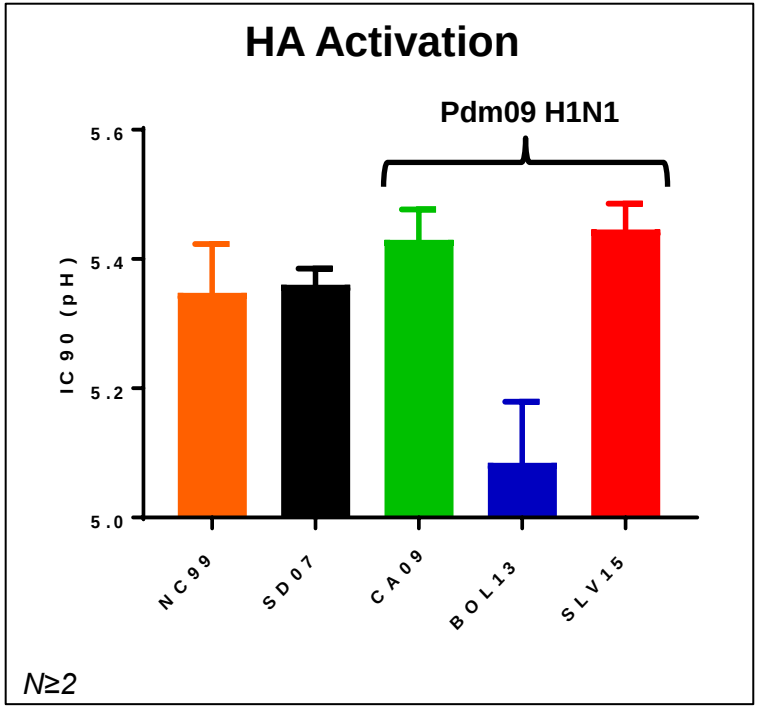
Immune-Response

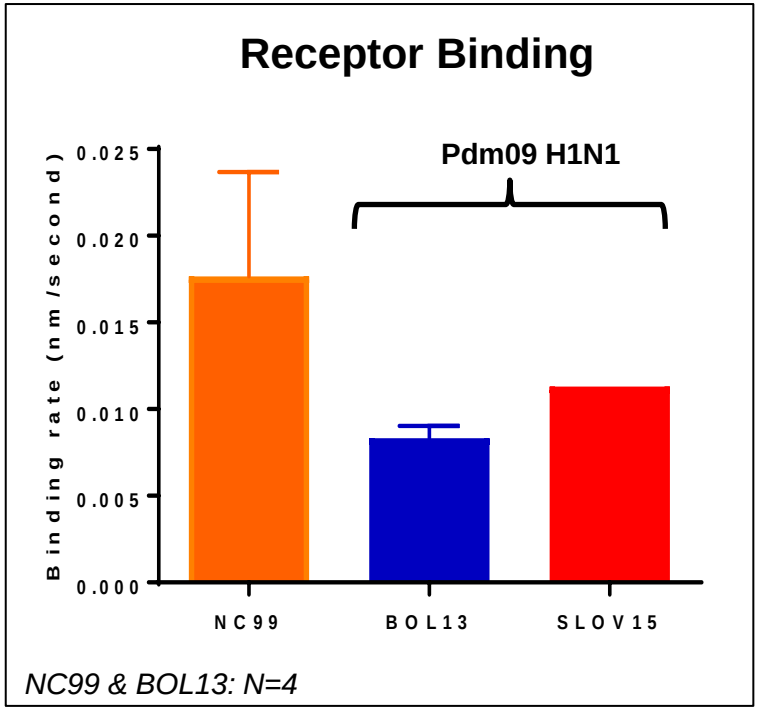
Immunogenicity & Attenuation

Antigenicity HAI & Neutralisation



A/Slovenia strain has improved HA properties

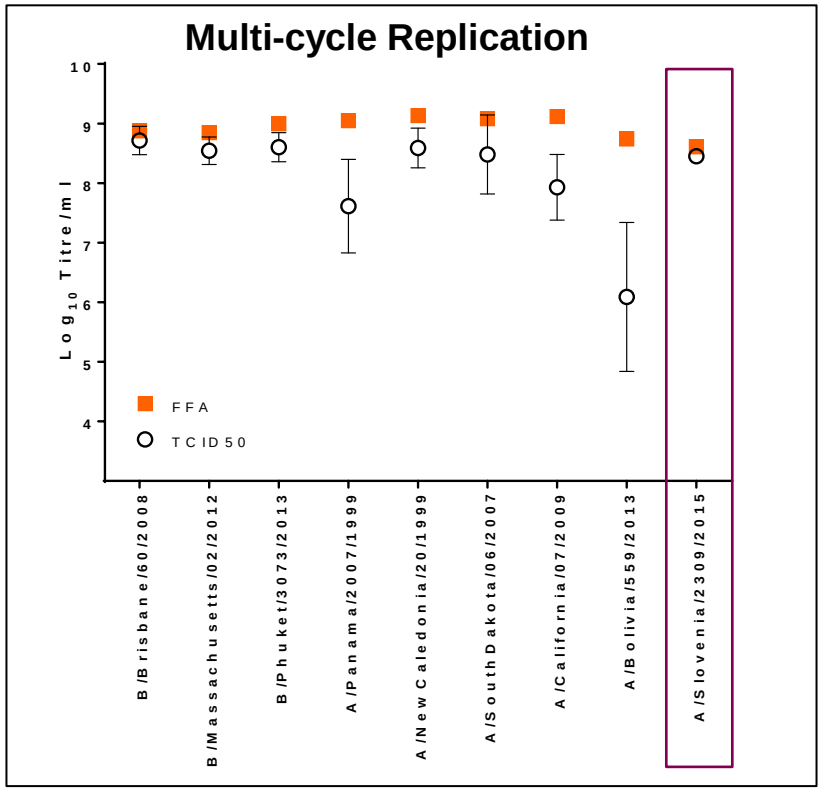




- **Higher activation pH compared to A/Bolivia strain**
- **Data suggest improved receptor binding vs Bolivia strain**

1. Internal Data, MedImmune. Speke UK, Feb 2017.

A/Slovenia strain has significantly improved replication kinetics compared to A/Bolivia strain



- **FFA and $TCID_{50}$ similar, unlike A/California and A/Bolivia**

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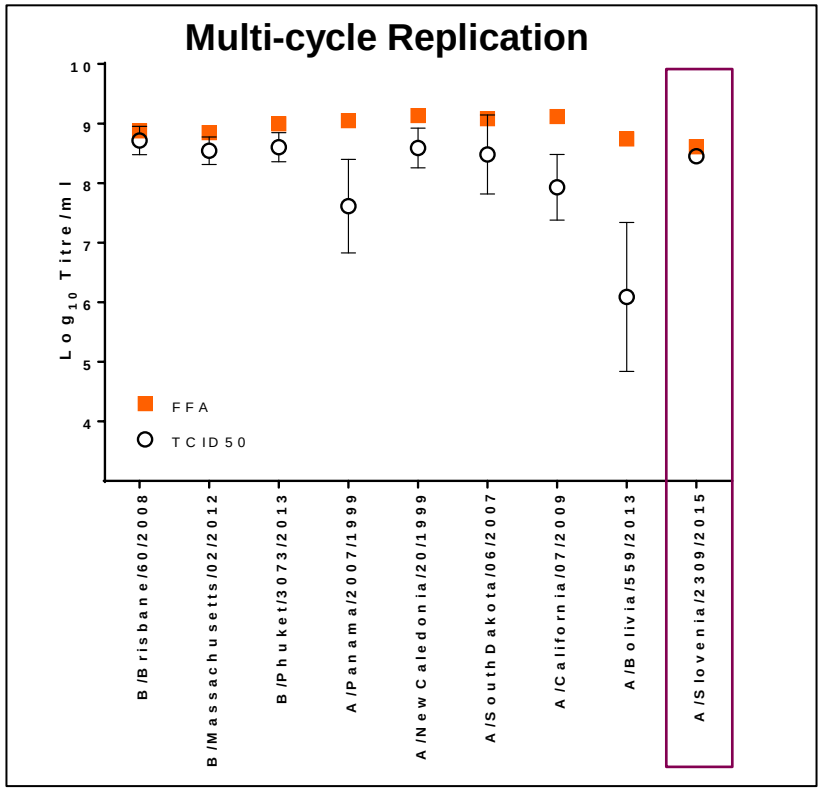
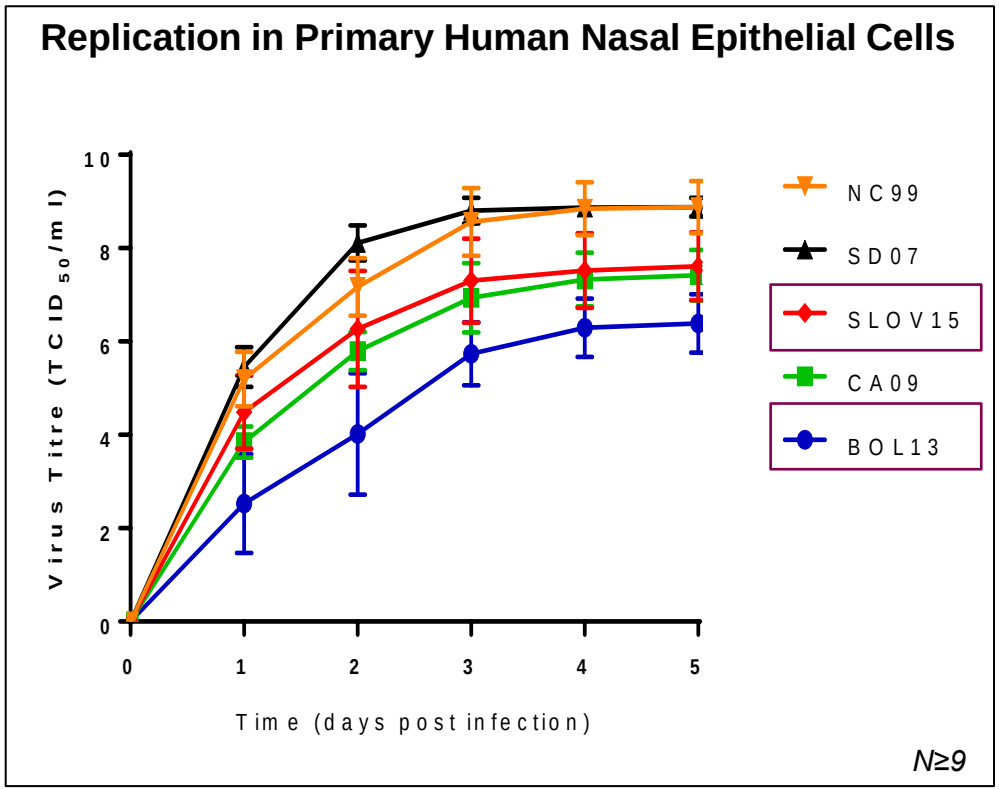
A/Slovenia strain has significantly improved replication kinetics compared to A/Bolivia strain





- FFA and $TCID_{50}$ similar, unlike A/California and A/Bolivia
- Improved replication in primary human cells compared to A/Bolivia

1. Internal Data, MedImmune. Speke UK, Feb 2017.

Summary of non-clinical data

- Initial findings of reduced replicative fitness with H1N1pdm09 viruses

- Underlying mechanism likely to be multi-factorial :
  - E.g. HA stability, HA activation pH, receptor binding, neuraminidase

- Current lead H1N1 candidate (A/Slovenia) identified for 2017-2018 LAIV:
  - No deficiency with multiple rounds of replication (FFA and $TCID_{50}$ match)
  - Higher HA activation pH vs. A/Bolivia
  - Higher replication in nasal epithelium vs. A/Bolivia

- Investigation ongoing:
  - Cell and ferret studies evaluating interference and formulation
  - Planned clinical study with 2017-2018 LAIV

A pediatric study is being planned to further compare the new A/Slovenia strain to the previous A/Bolivia strain

Randomized, double-blind, study will enroll ~ 200 children 24 to <48 months of age

Subjects will be randomized (~65 subjects per group) at 1:1:1 ratio to receive two doses of:

- LAIV4 2017-2018 (A/H1N1 Slovenia strain)
- LAIV4 2015-2016 (A/H1N1 Bolivia strain)
- LAIV3 2015-2016 (A/H1N1 Bolivia strain)

Primary endpoint:

- HAI antibody seroconversion rates after each dose

Secondary endpoints:

- Neutralizing antibody seroconversion rates after each dose
- Mucosal IgA increases after each dose
- Shedding after each dose
- Safety

Presentation Overview

- Review of 2015-2016 vaccine effectiveness data including recent data on effectiveness of LAIV against influenza hospitalization
- Progress on non-clinical investigation
- Update on A/H1N1 strain selection for 2017-2018 season

- **Ongoing studies and timelines for data availability**

Timeline for data availability

February 2017

- 2015-16 VE meta-analysis
- 2015-16 VE hospitalized flu
- Preliminary 2017-18 H1N1pdm09 strain characterization

June 2017

- Final 2017-18 H1N1pdm09 (A/Slovenia) strain characterization
- 2016-17 VE (H3N2) data: UK, Finland, Canada

October 2017

- US pediatric shedding / immunogenicity data (new H1N1pdm09 strain)
- Japan 2016-17 pediatric efficacy study data (A/H3N2)

Conclusions

- LAIV demonstrated overall effectiveness in most studies conducted in 2015-16:
  - H1N1 effectiveness more variable and lower than IIV in all studies
  - Effectiveness against influenza hospitalization recently demonstrated

- Initial findings from investigation indicate that post-pandemic strains have reduced replicative fitness compared to pre-pandemic strains

- Based on investigation, new assays introduced into strain selection process:
  - Replacement A/H1N1 Slovenia strain selected for 2017-2018 has characteristics similar to pre-pandemic strains
  - Final nonclinical strain characterization data for the new A/Slovenia strain will be available in Q2 2017

Back up slides

Vaccine effectiveness investigation

- Following in-depth investigations, no support for the following:
  - H1N1 A/Bolivia development
    - Homology to circulating strains, antigenic match to A/California, growth in eggs, morphology, thermostability, ferret immunogenicity, MDCK cell infectivity, fusion pH
  - Manufacturing / Processing
  - QC Testing
  - Storage Stability
  - Distribution / Logistics

Pre-existing immunity among vaccinated children

- No statistically significant effect of prior season vaccination on LAIV VE was observed in either CDC or ICICLE studies in 2013-14 or 2015-16

- In ICICLE and Finland studies, H1N1 VE estimates trended higher among previously vaccinated vs. not previously vaccinated
  - ICICLE: 19% vs. 9% (2013-14); 60% vs. 35% (2015-16)
  - Finland: 74% vs. 25% (2015-16)

- Considered an unlikely root cause of the reduced VE

1. Ambrose C. Presented at Advisory Committee on Immunization Practices Meeting; June 22, 2016; Atlanta, GA 2. Nohynek H et al. *Euro Surveill.* 2016;21(38):pii=30346.