Update on Live Attenuated Influenza Vaccine (LAIV)

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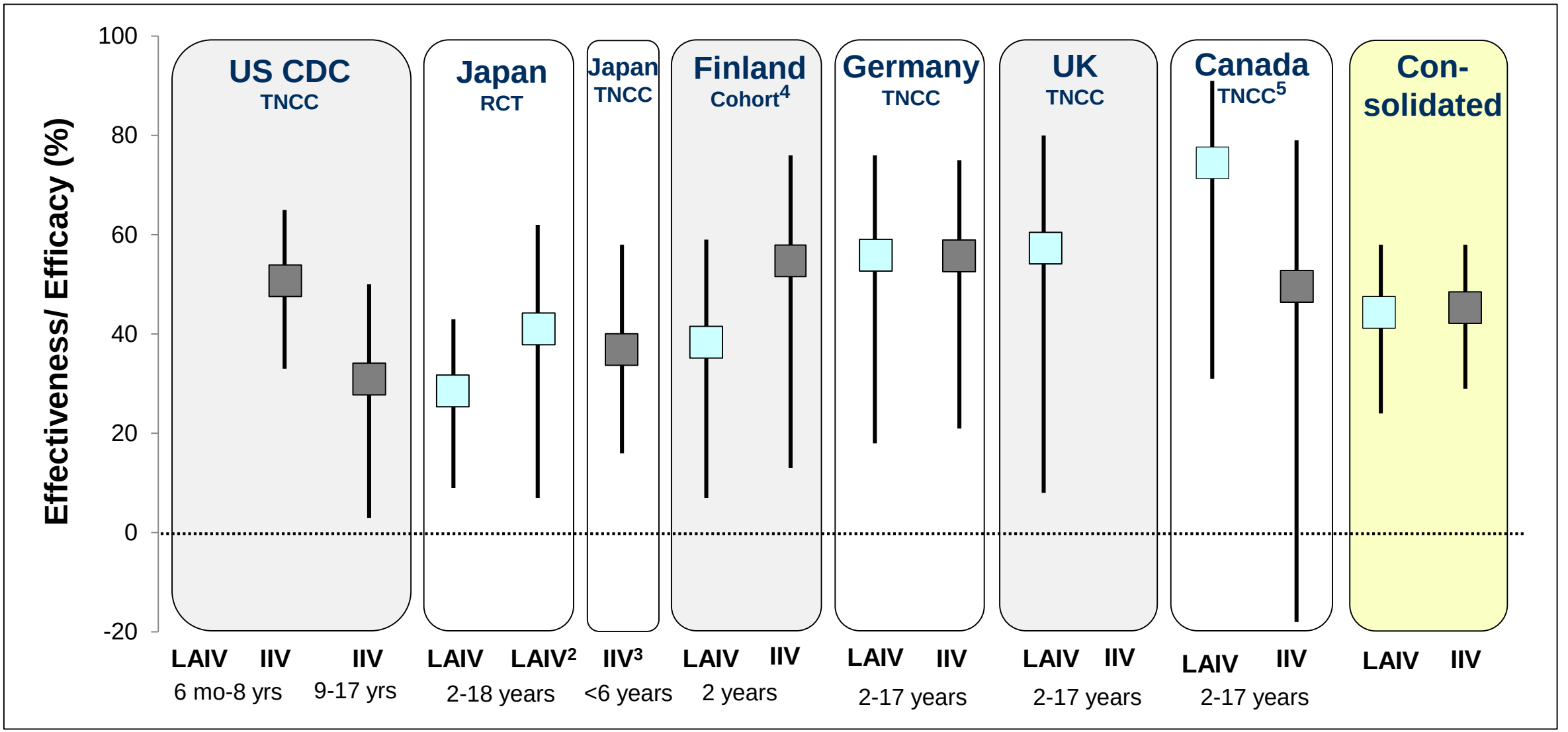
Update on *in vitro*, *in vivo*, and clinical investigations to improve H1N1pdm09 effectiveness of LAIV

- LAIV showed reduced effectiveness against H1N1pdm09 strains in the 2013-14 and 2015-16 seasons, resulting in ACIP recommendation not to use the vaccine in the US
- In 2016-17, LAIV effectiveness for H3N2 strains was moderate and comparable to IIV
- *In vitro* investigations identified reduced replicative fitness of post-pandemic H1N1 strains as the likely root cause of reduced effectiveness (presented at Feb 2017 ACIP meeting)
  - A/Slovenia strain with improved replicative fitness selected for 2017-18 LAIV formulation
- Since February, an improved ferret efficacy model has been developed
  - A/Slovenia provided greater protection than recent H1N1pdm09 LAIV strains, similar to a previous clinically highly efficacious H1N1 strain
- Data available in December from randomized study in US children comparing A/Slovenia and 2015-16 H1N1pdm09 LAIV strain (A/Bolivia)
  - Anticipated that study results, combined with improvements made to strain selection process, will help inform ACIP recommendation on future use of LAIV in US within the next 4 months

LAIV was effective against H3N2 in 2016-2017, comparable to IIV[1]

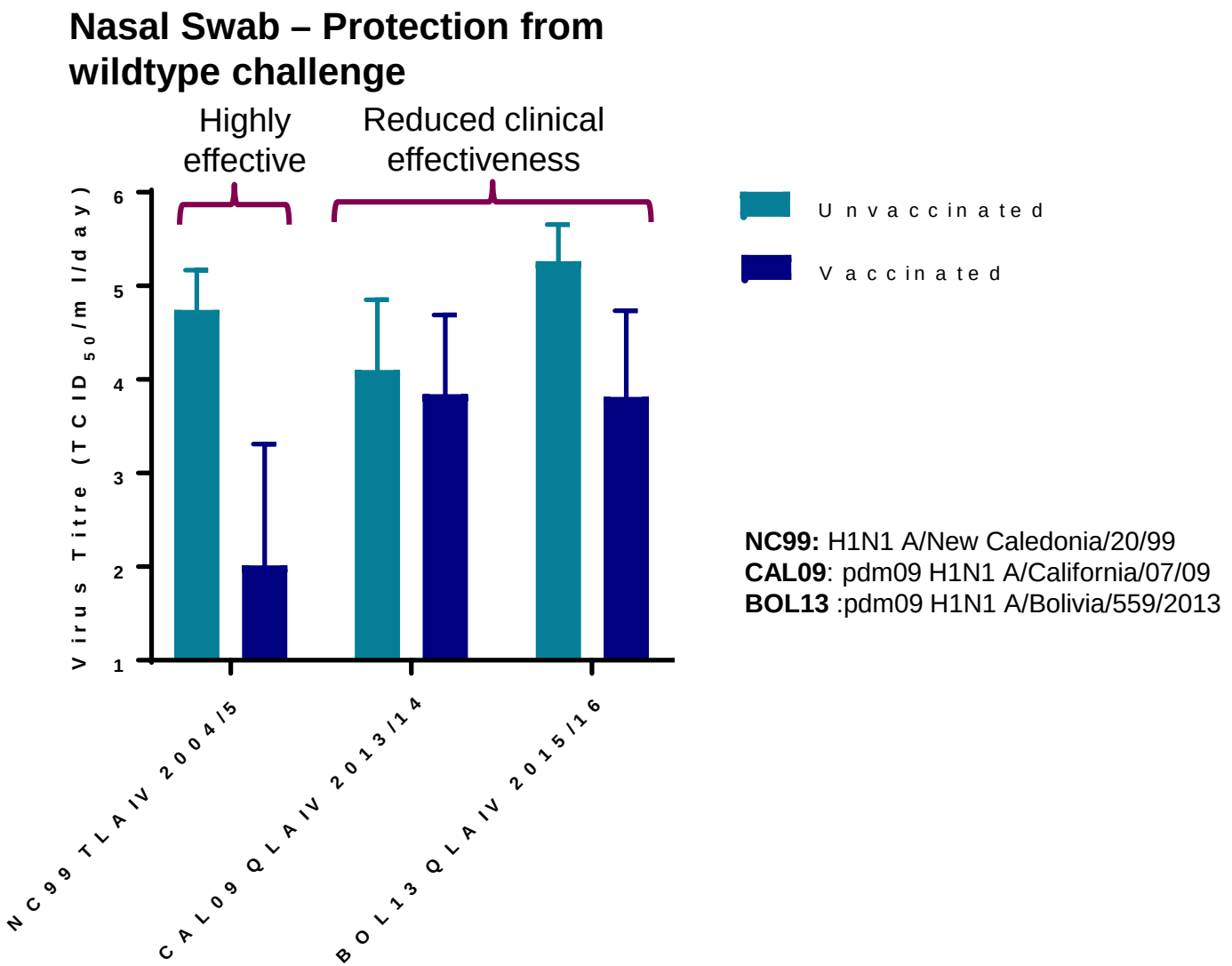


[1] Estimate for all strains regardless of match to vaccine, except where noted; LAIV estimate not available for US and IIV estimate not available for UK. [2] Estimate for matched strains [3] Presented at Japan Ministry of Health 25 Aug 2017; test-negative study conducted in children < 6 years of age given two doses of vaccine. [4] Efficacy estimates for A strains; >90% of A strains were H3N2 strains. [5] Unadjusted estimate.

Improved ferret model of vaccine virus fitness

- Ferrets are the most well-established animal model of human influenza virus replication and vaccine immunogenicity
- Improved previous ferret model of LAIV efficacy on multiple parameters
  - Tested H1N1 strains with known efficacy/effectiveness in human
  - Evaluated quadrivalent formulation
  - Reduced dose from 10^7 (human dose) to 10^4 virus particles (ferret appropriate dose)
- Clinically relevant endpoints
  - Virus replication: pediatric absorbent swab and nasal turbinate recovery
  - Immunogenicity: HAI and neutralizing antibody
  - Clinical symptoms: fever by telemetry (every 15mins)

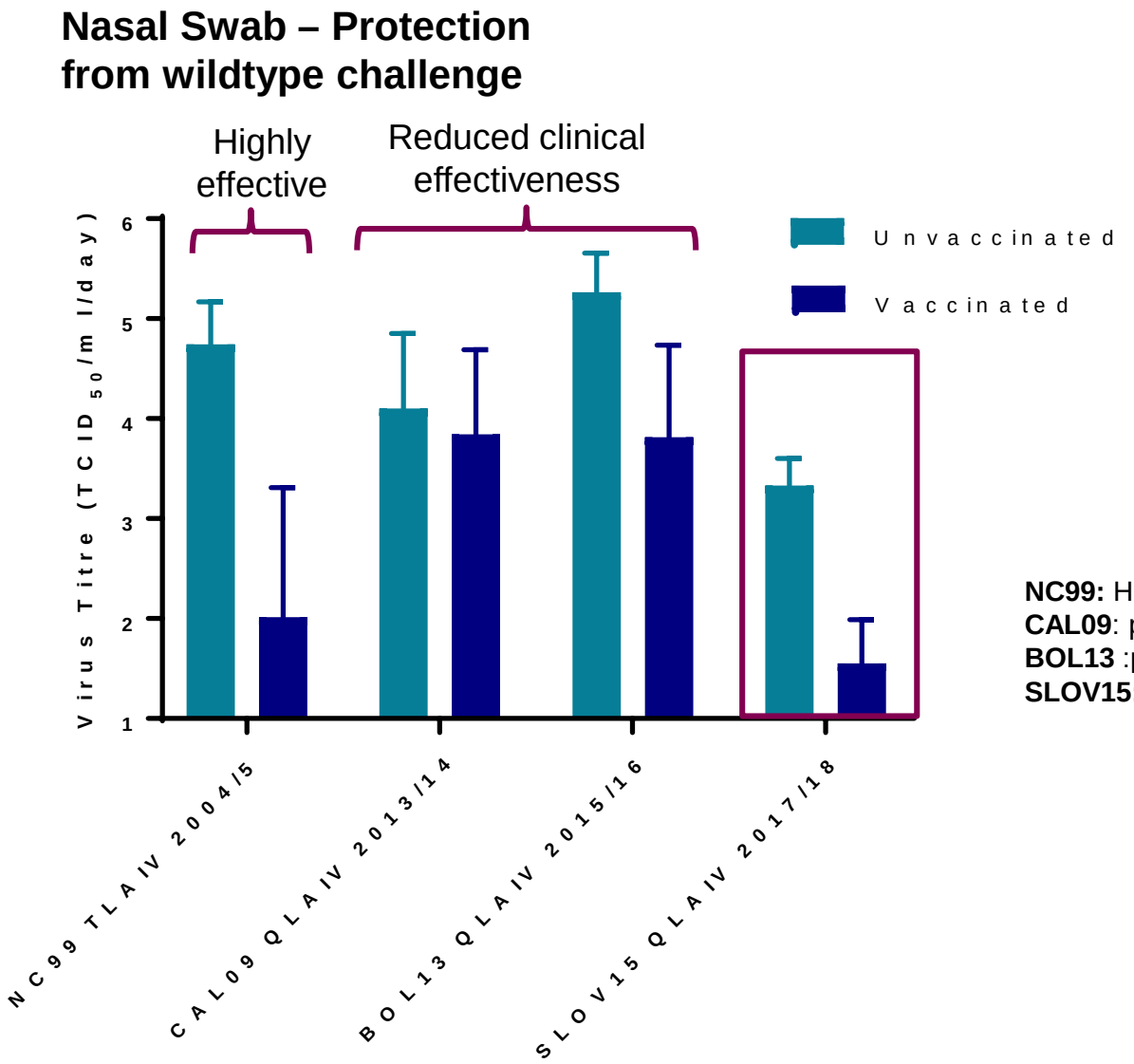
Reduced challenge virus shedding in vaccinated ferrets correlates with observed effectiveness in children



NC99: H1N1 A/New Caledonia/20/99
CAL09: pdm09 H1N1 A/California/07/09
BOL13 :pdm09 H1N1 A/Bolivia/559/2013

Internal Data, MedImmune. Speke UK, Sep 2017.

A/Slovenia demonstrates improved protection in ferret model



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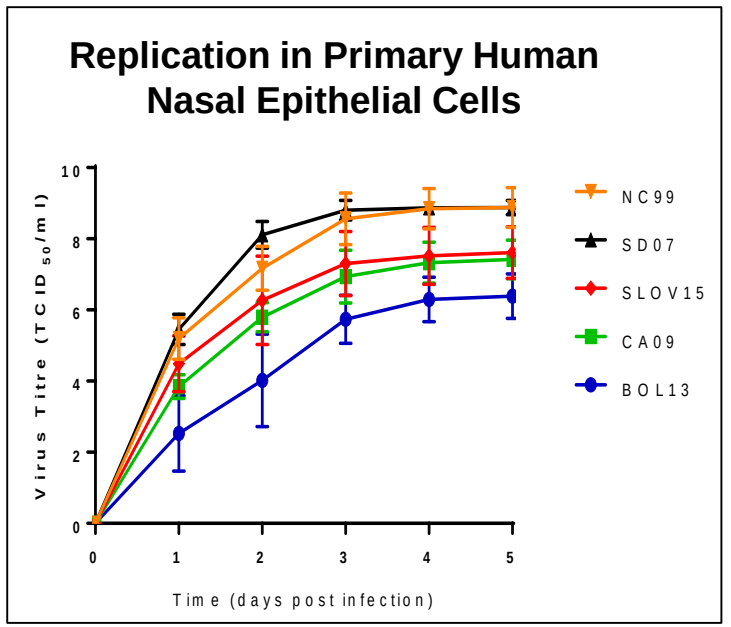
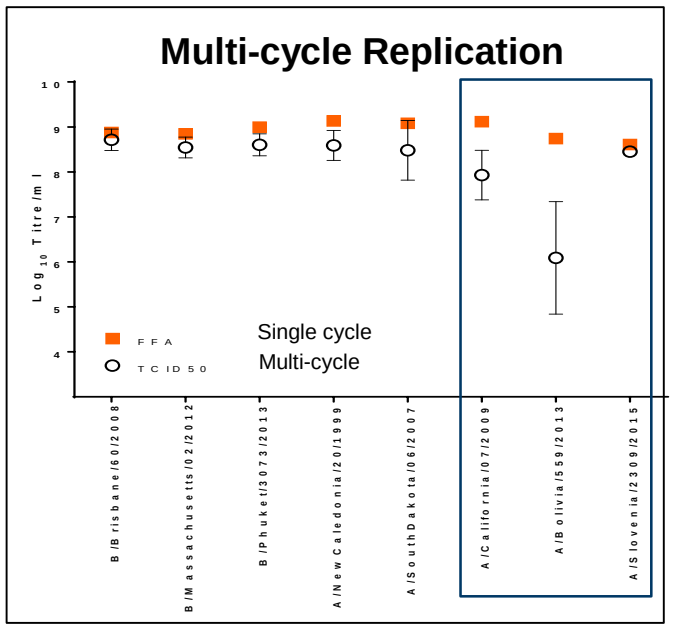
SLOV15: pdm09 H1N1 A/Slovenia/2903/15

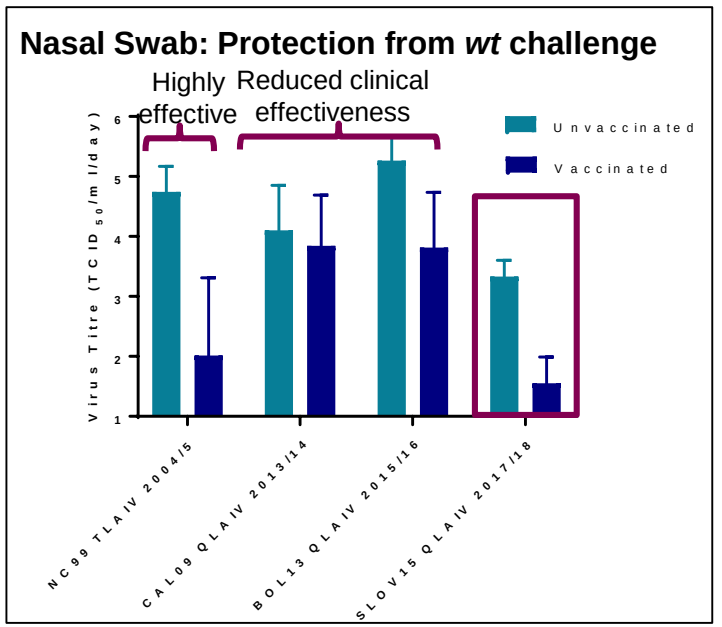
 Internal Data, MedImmune. Speke UK, Sep 2017.

In vitro and *in vivo* investigations confirm A/Slovenia has improved fitness

- A/Slovenia has improved replication in primary human nasal epithelium cells
- A/Slovenia has improved ability to sustain multiple cycles of viral replication
- A/Slovenia shows improved protection in ferrets that may correlate with clinical effectiveness







- An ongoing clinical study in US children is evaluating how the *in vitro* and *in vivo lab* findings correspond with shedding and immune responses to the strain

A pediatric study is underway to compare new A/Slovenia strain with previous A/Bolivia strain

Design

- Randomized, double-blind, study enrolled 200 children 24 to <48 months of age
  - Age group selected to maximize shedding/immune responses and ability to differentiate between strains
- Subjects 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

Pediatric study objectives and limitations

Objective:

- Primary objective is to compare shedding and immunogenicity of A/Slovenia and A/Bolivia H1N1 strains in LAIV4 formulations
  - Evaluating H1N1pdm09 strain performance in 2015-16 and 2017-18 LAIV4 formulations

Limitations:

- Study is powered to detect 20–25% differences in percentage of subjects with seroconversion and shedding vaccine virus
- LAIV formulations chosen based on those with real-world effectiveness data
  - Designed to compare different H1N1 strains, however also have different H3N2 strains
- In seropositive subjects, shedding and seroconversion are insensitive measures of LAIV efficacy

Summary

- Data from five clinical studies indicate that LAIV was effective for H3N2 strains, with a consolidated estimate of 45%, and that effectiveness was comparable to that seen for IIV
- *In vitro* investigations identified reduced replicative fitness of post-pandemic H1N1 strains as the likely root cause of reduced effectiveness (presented at Feb 2017 ACIP meeting)
- A/Slovenia strain with improved replicative fitness selected for 2017-18 LAIV formulation
- Improved ferret efficacy model supports inclusion of A/Slovenia strain in the vaccine
  - A/Slovenia provided greater protection than recent H1N1pdm09 LAIV strains, similar to previous clinically efficacious H1N1 strain
- Data available in December from randomized study in US children comparing A/Slovenia and 2015-16 H1N1 LAIV strain, A/Bolivia
  - Anticipated that study results, combined with improvements made to strain selection process, will help inform ACIP recommendation on future use of LAIV in US within the next 4 months

Thank you!