Results of Randomized Trial of a New H1N1 LAIV Strain in US Children

February 21, 2018

Raburn Mallory, MD
Senior Director Clinical Development
MedImmune/AstraZeneca

Improved LAIV strain selection identified a new H1N1 strain that is more immunogenic in children

- LAIV is not recommended in the US as H1N1 vaccine strains used in 2013-2014 and 2015-2016 had reduced effectiveness
- A broad-based scientific investigation determined that H1N1 LAIV strains used in those seasons replicate less well compared to older more effective LAIV strains
- Assays measuring replicative fitness were incorporated into strain selection for 2017-2018 and a new H1N1 strain (A/Slovenia) selected
- A clinical trial was conducted in US children to determine if new A/Slovenia strain was more immunogenic compared to previous A/Bolivia strain used in 2015-2016
- In the study, the new A/Slovenia H1N1 strain induced antibody responses that were significantly higher than those seen with the A/Bolivia strain
  - Immune responses were similar to those seen with a highly effective pre-pandemic LAIV H1N1 strain
- Clinical study results validate improved strain selection process
- New strain selection process applied to all future LAIV strains and data reviewed by FDA/EMA annually

LAIV = Live attenuated influenza vaccine

Pediatric shedding and immunogenicity study design

Dose 1
200 subjects 2 to < 4 years randomized
Baseline immunogenicity assessed

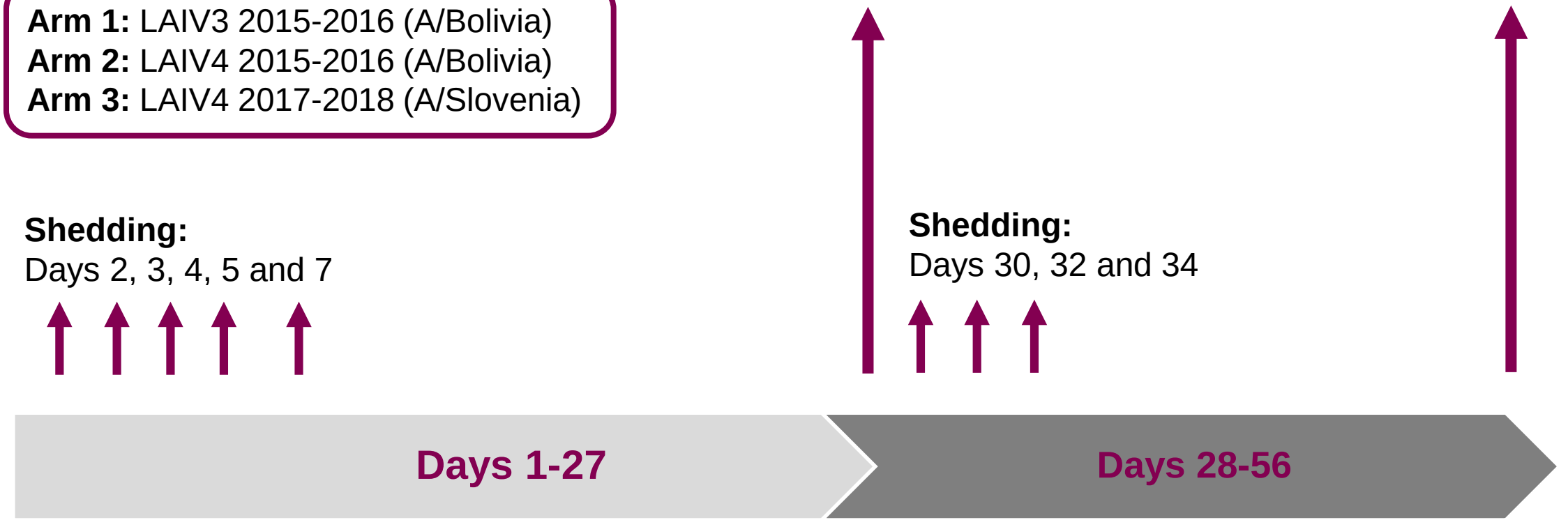
Dose 2
Immunogenicity
Assessed

Day 56
Immunogenicity
Assessed

Arm 1: LAIV3 2015-2016 (A/Bolivia)
Arm 2: LAIV4 2015-2016 (A/Bolivia)
Arm 3: LAIV4 2017-2018 (A/Slovenia)

Shedding:
Days 2, 3, 4, 5 and 7

Shedding:
Days 30, 32 and 34



LAIV3 = Trivalent live attenuated influenza vaccine; **LAIV4** = Quadrivalent live attenuated influenza vaccine

Vaccine strains by study arm

Vaccine type/subtype	Arm 1: LAIV3 2015-2016	Arm 2: LAIV4 2015-2016	Arm 3: LAIV4 2017-2018
A/H1N1	A/Bolivia	A/Bolivia	A/Slovenia
A/H3N2	A/Switzerland	A/Switzerland	A/New Caledonia/14
B/Yamagata lineage	B/Phuket	B/Phuket	B/Phuket
B/Victoria lineage	**--**	B/Brisbane	B/Brisbane

The two quadrivalent arms (Arms 2 and 3) represent the commercial vaccine that was distributed in those seasons

Study endpoints

Primary endpoint:

- The proportion of subjects with strain-specific HAI antibody seroconversion (≥ 4-fold increase) through Days 28 and 56
  - Response rate for A/H1N1 strains in LAIV4 formulations was pre-specified for significance testing*

Secondary Endpoints:

- Immunogenicity
  - Neutralizing antibody seroconversion rates (≥ 4-fold increase from baseline)
  - Nasal Immunoglobulin A (IgA) (≥ 2-fold increase from baseline; ≥ 4-fold shown)
  - The proportion of subjects with any antibody response (≥ 4-fold increase in HAI antibodies, neutralizing antibodies or IgA antibodies)
- Shedding of vaccine virus
- Safety

HAI = Hemagglutination inhibition * Testing pre-specified in Statistical Analysis Plan for study

Baseline subject demographics were balanced between the treatment groups

	LAIV3 2015-2016 (A/Bolivia) N = 67	LAIV4 2015-2016 (A/Bolivia) N = 66	LAIV4 2017-2018 (A/Slovenia) N = 67	All subjects N = 200
Median age, months	36.00	34.85	35.30	35.30
Gender				
Male	40 (60%)	34 (52%)	32 (48%)	106 (53%)
Female	27 (40%)	32 (48%)	35 (52%)	94 (47%)
Prior vaccination and serostatus				
Not previously vaccinated	29 (43%)	29 (44%)	29 (43%)	87 (44%)
Seronegative*	30 (45%)	43 (66%)	39 (58%)	112 (56%)

* Baseline HAI antibody titer ≤ 10

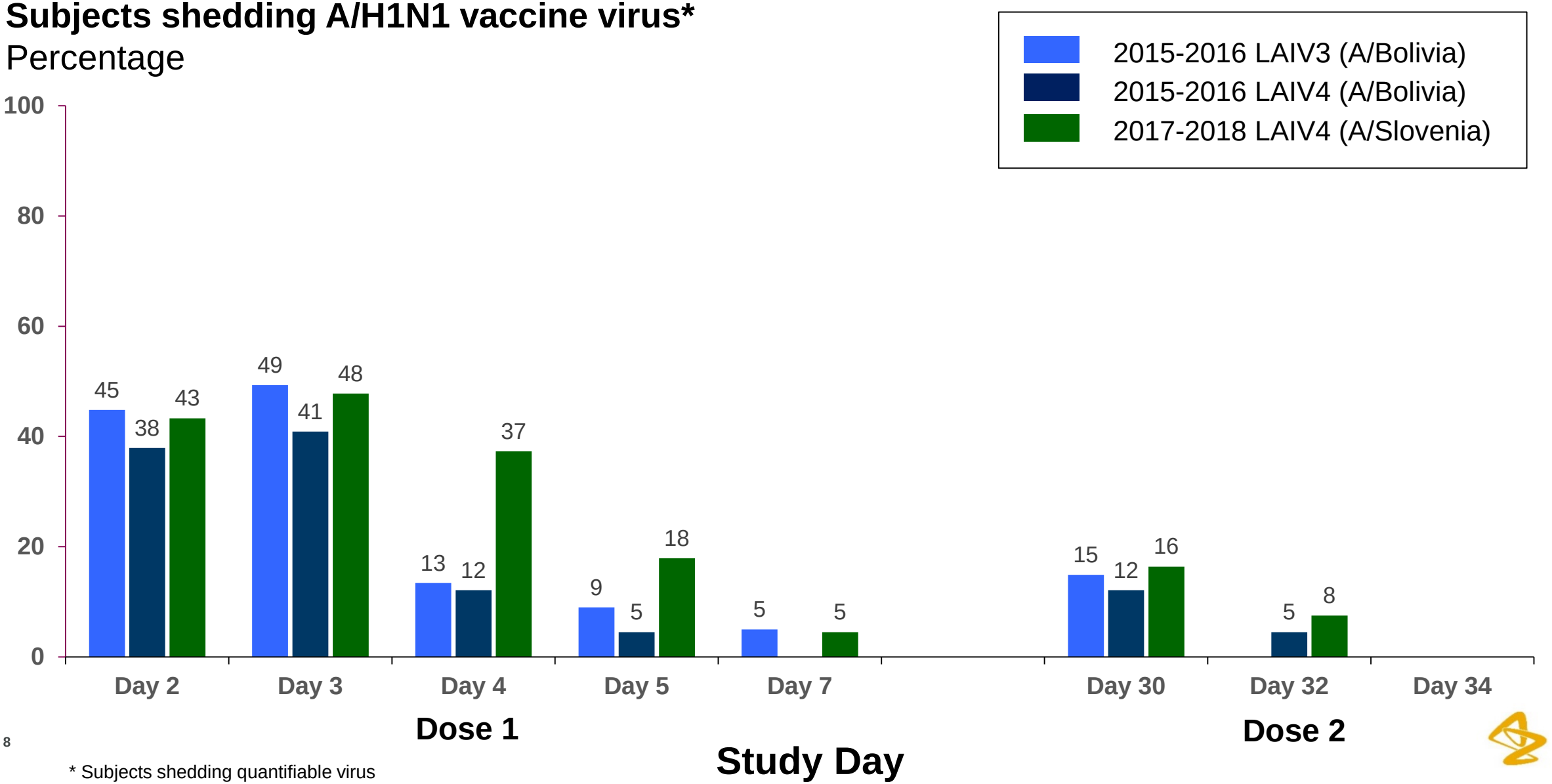
Subject disposition

	LAIV3 2015-2016 (A/Bolivia)	LAIV4 2015-2016 (A/Bolivia)	LAIV4 2017-2018 (A/Slovenia)	All subjects
Number of subjects randomized	67	66	67	200
Number of subjects completing study	65 (97.0%)	63 (95.5%)	67 (100%)	195 (97.5.0%)
Reasons for not completing study				
Withdrawal by legal guardian	0	1 (1.5%)	0	1 (0.5%)
Lost to follow-up	2 (3.0%)	2 (3.0%)	0	4 (2%)

Shedding of A/H1N1 strains: All subjects

Subjects shedding A/H1N1 vaccine virus*

Percentage

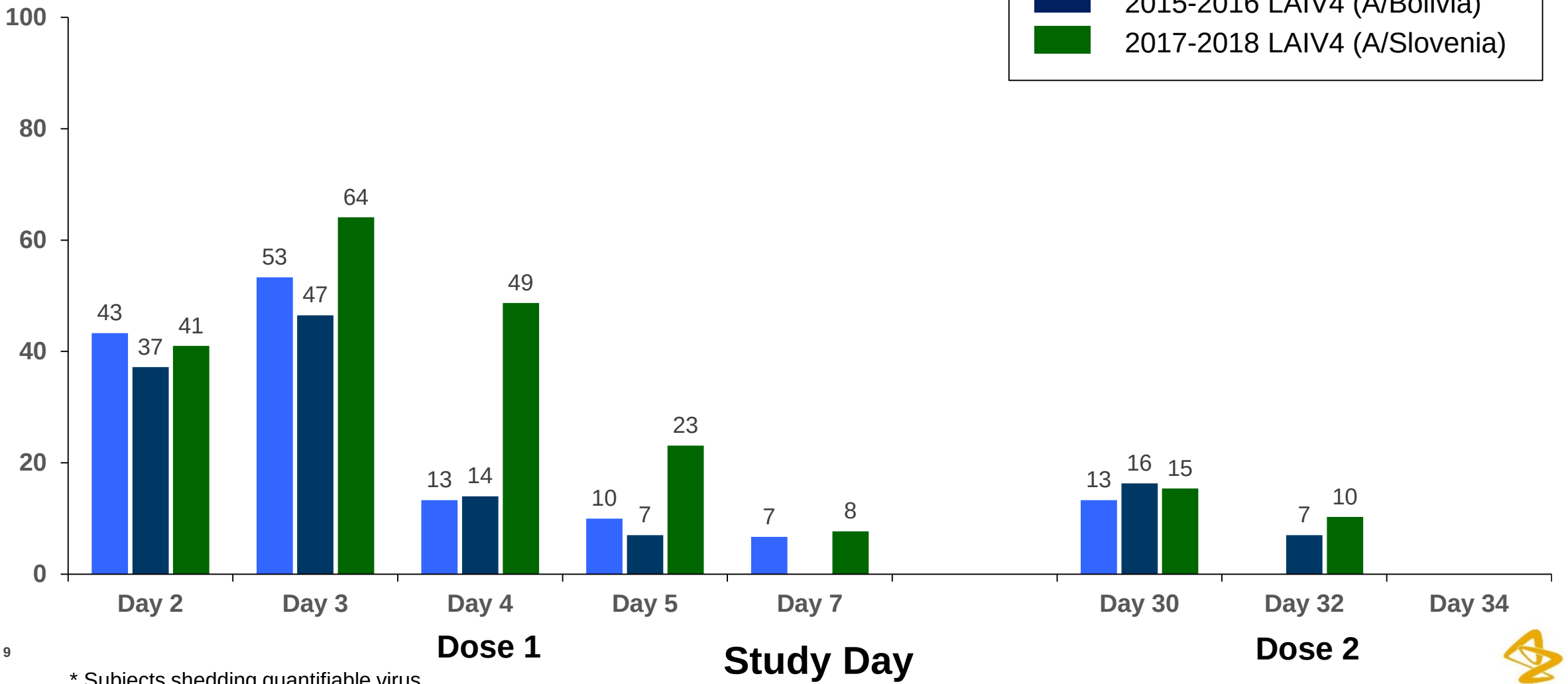


* Subjects shedding quantifiable virus

Shedding of A/H1N1 strains: Seronegative subjects

Subjects shedding A/H1N1 vaccine virus*

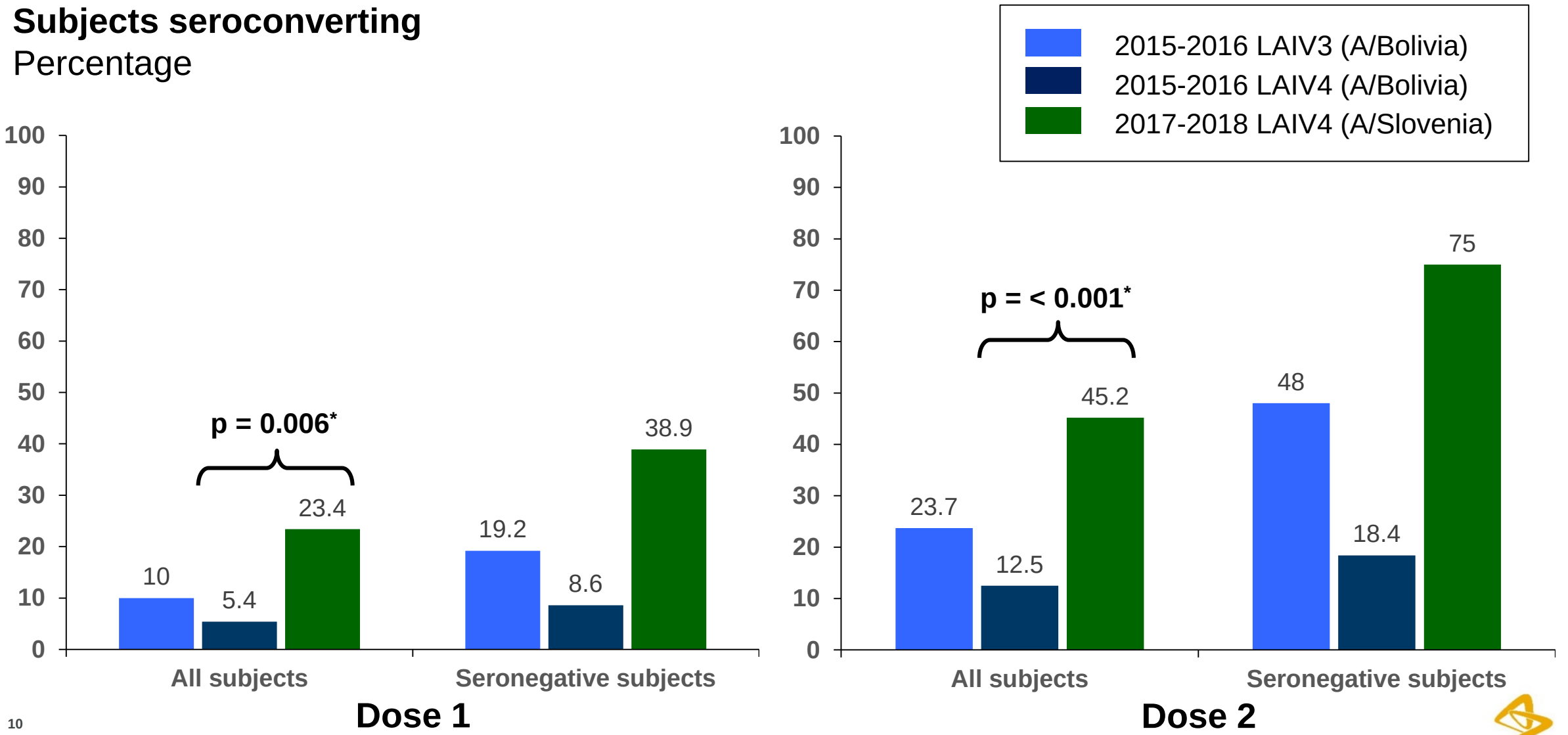
Percentage



* Subjects shedding quantifiable virus

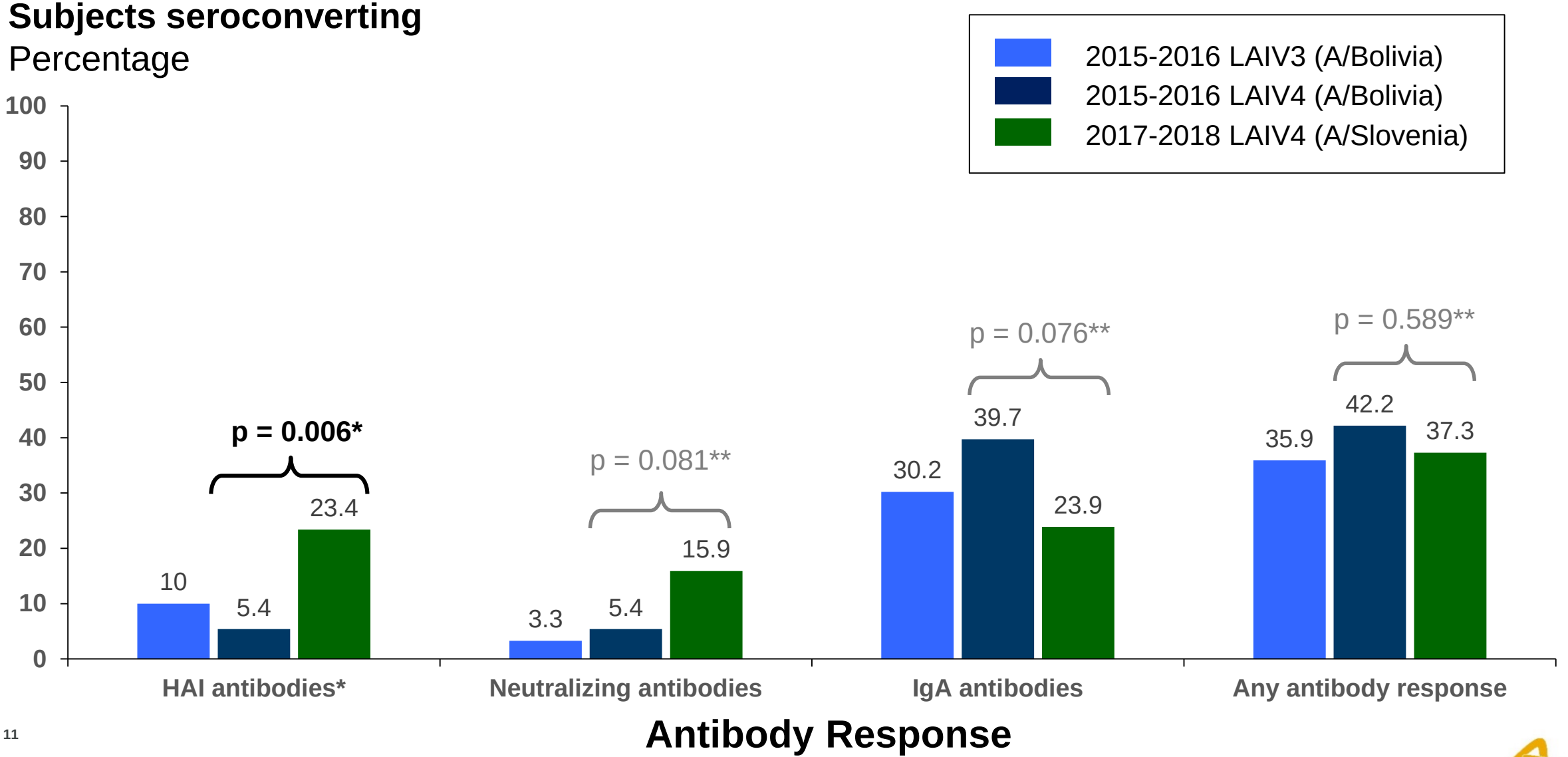
Study Primary Endpoint:
A/H1N1 HAI antibody seroconversion rates after Dose 1 and 2

Subjects seroconverting
Percentage



* A/H1N1 HAI antibody responses in LAIV4 formulations for all subjects assessed for statistical significance per Statistical Analysis Plan

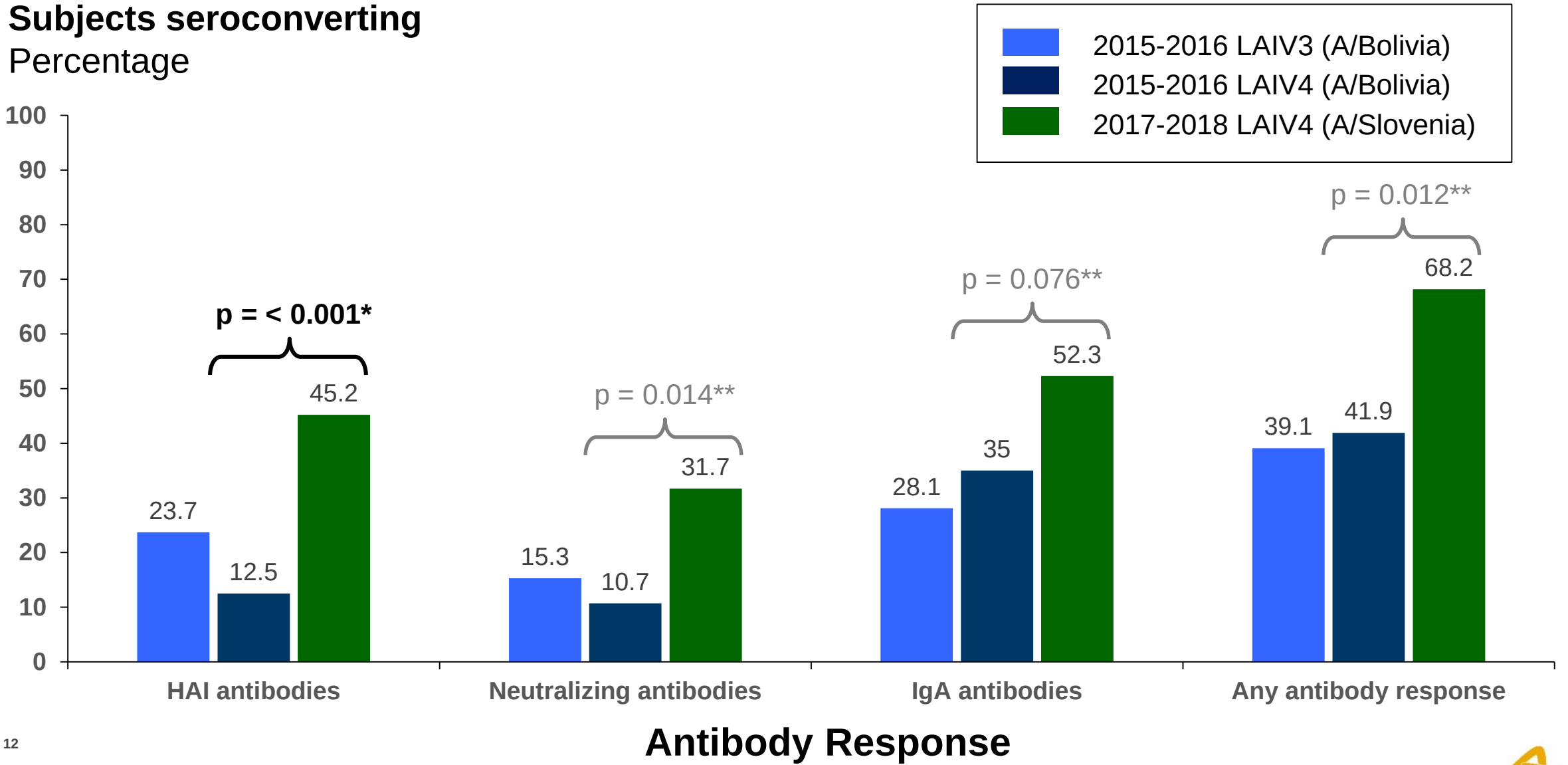
Antibody seroconversion rates after Dose 1



* A/H1N1 HAI responses in LAIV4 formulations assessed for statistical significance per Statistical Analysis Plan

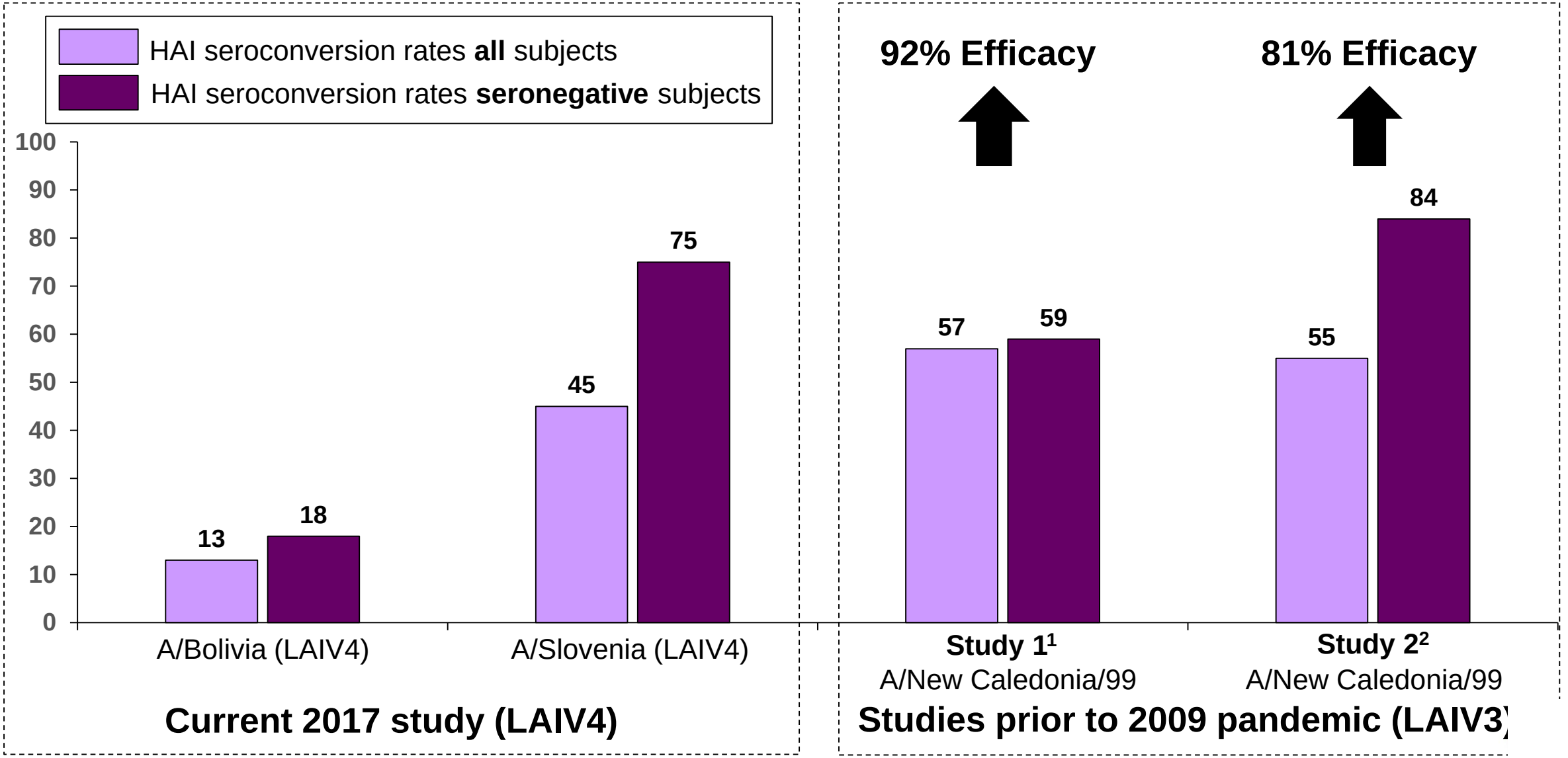
** Post hoc analyses adjusted for multiple comparisons using Benjamini-Hochberg procedure

Antibody seroconversion rates after Dose 2



* Only A/H1N1 HAI responses in LAIV4 formulations assessed for statistical significance per Statistical Analysis Plan
** Post hoc analyses adjusted for multiple comparisons using Benjamini-Hochberg procedure

A/Slovenia HAI seroconversion rates similar to those seen for previous H1N1 strain (A/New Caledonia/99) with high levels of efficacy



[1] Vesikari *Pediatrics* 2006 and [2] Tam *PIDJ* 2007

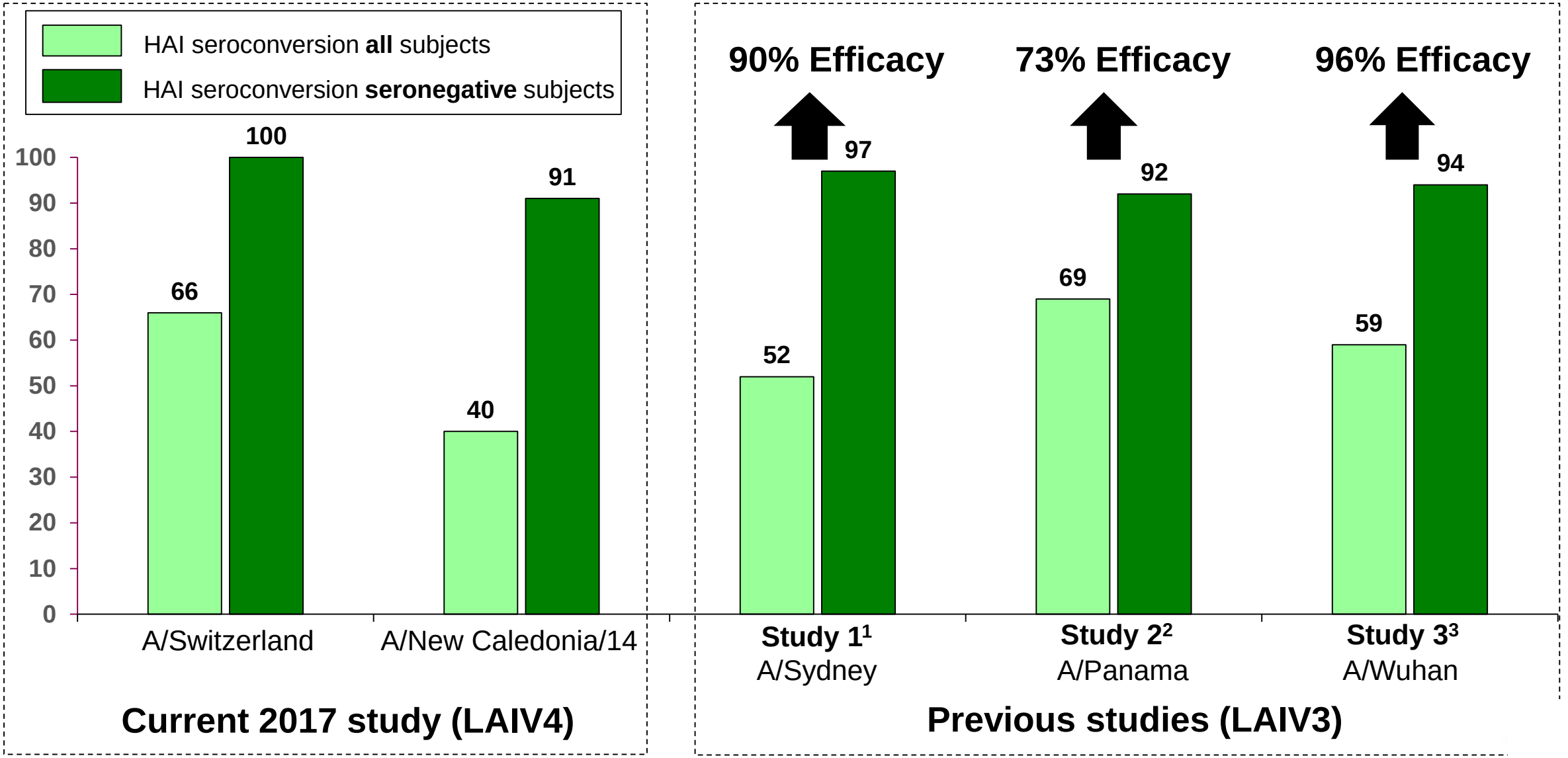
A/H1N1 strain summary

- The A/Slovenia strain was shed by a higher proportion of children from Day 4 through Day 7, after Dose 1 of the vaccine

- The study met its primary endpoint: HAI seroconversion rates were significantly higher for the A/Slovenia strain than for the A/Bolivia strain
  - Similar results seen for neutralizing antibodies and for nasal IgA

- A/Slovenia HAI seroconversion rates were similar to those seen in children the same age vaccinated with a highly efficacious pre-pandemic H1N1strain

A/H3N2 HAI seroconversion rates similar to those seen for three previous H3N2 strains with high levels of efficacy



[1] Tam *PIDJ* 2007; [2] Neto *PIDJ* 2009 and [3] Belshe *NEJM* 1998

Key changes made in the way LAIV strains are selected annually

- Human nasal epithelial cell culture now used to assess the replicative fitness of new LAIV strains
  - Previous strains were assessed for fitness in MDCK (dog kidney) cells and eggs
  - For post-pandemic H1N1 strains results were not predictive of human nasal cell replication
- $TCID_{50}$ assay added to quantify new LAIV strains
  - FFA measures infectivity of vaccine viruses through expression of antigen on the cell surface
  - $TCID_{50}$ measures spread of vaccine virus between cells following multiple rounds of replication
  - For post-pandemic H1N1 strains $TCID_{50}$ values were up to 3 logs lower than FFA results
  - As a result, post-pandemic H1N1 strains with reduced effectiveness may not have sustained intranasal replication to the level needed for optimal effectiveness
- All future strains now only selected if they have high levels of replication in human nasal epithelial cells and when the FFA and $TCID_{50}$ assays give similar results*

* $TCID_{50}$ and FFA results to be submitted and reviewed by FDA and EMA as part of annual strain change process

Summary

- A broad-based scientific investigation determined that H1N1 LAIV strains used in 2013-2014 and 2015-2016 had reduced replicative fitness compared to older more effective vaccine strains
- New assays measuring how well strains replicate were incorporated into strain selection for 2017-2018 and a new H1N1 strain (A/Slovenia) was selected
- In a randomized trial in US children, the new A/Slovenia strain induced antibody responses that were significantly higher than those seen with the 2015-16 H1N1 strain
  - Immune responses similar to those seen with a highly effective pre-pandemic LAIV H1N1 strain
- Clinical study results validate improved strain selection process
- New strain selection process applied to all future LAIV strains and data reviewed by FDA/EMA on an annual basis
- LAIV is an important vaccine option for providers, patients, and parents in the US and other countries where it continues to be recommended

LAIV = Live attenuated influenza vaccine

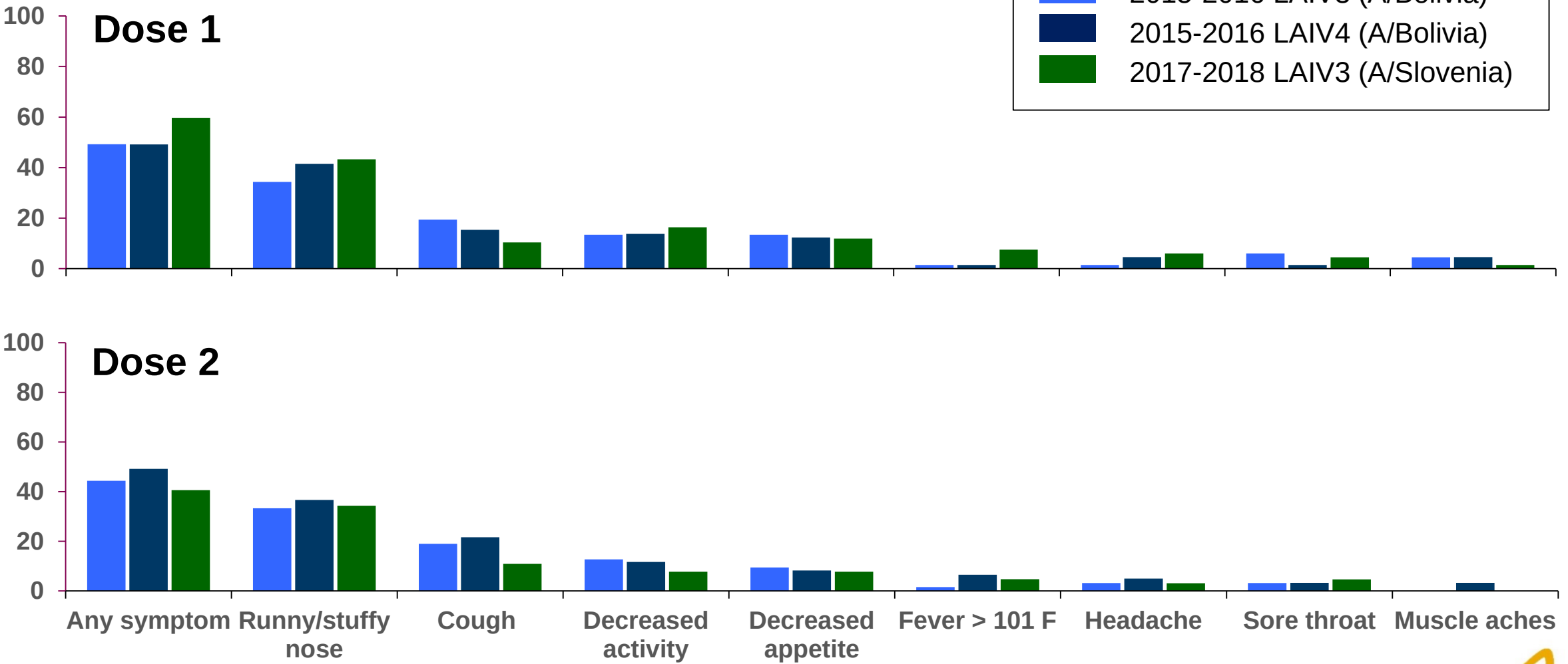
Thank you!

Safety data

Solicited symptoms following vaccination

Subjects with solicited symptoms

Percentage



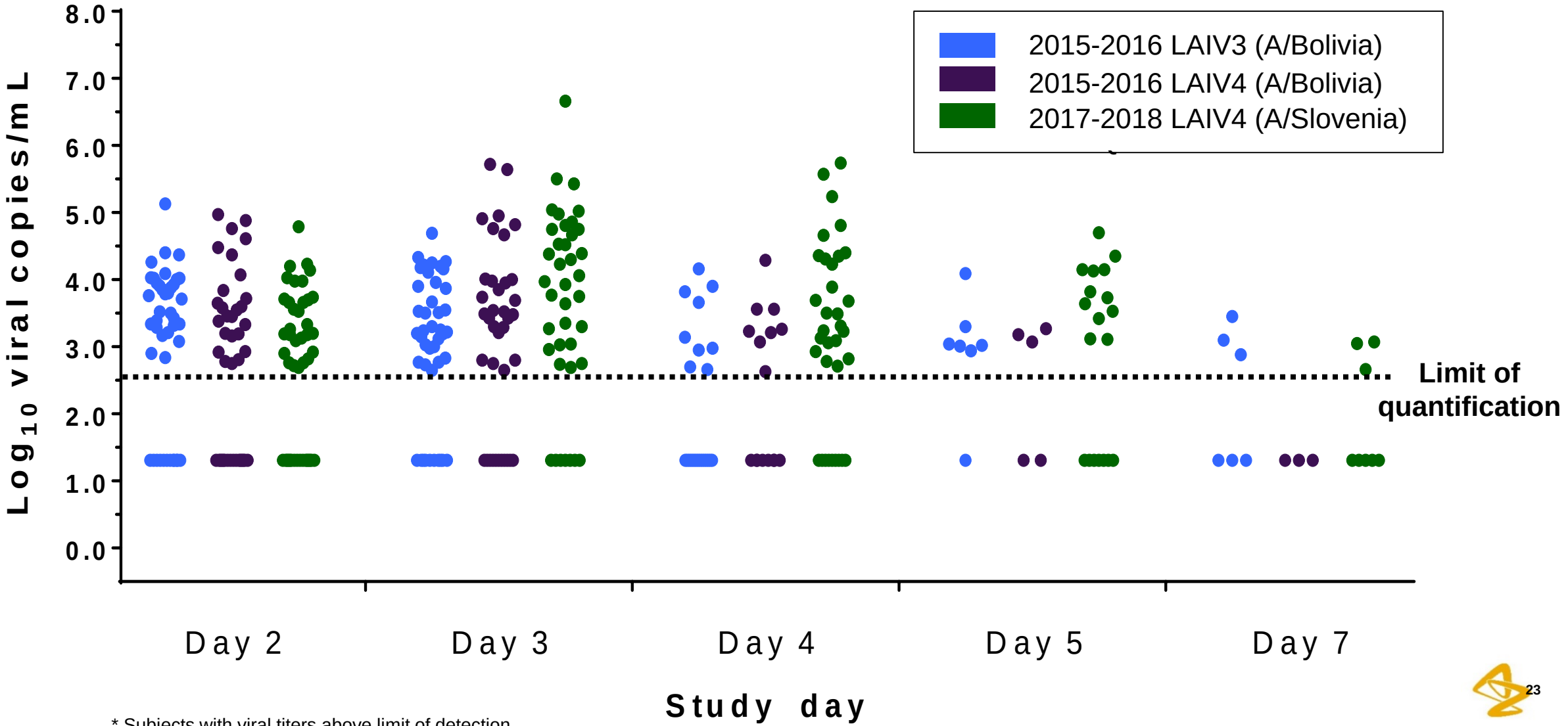
Adverse events occurred at similar rates across the arms

	LAIV3 2015-2016 (A/Bolivia) N = 67	LAIV4 2015-2016 (A/Bolivia) N = 66	LAIV4 2017-2018 (A/Slovenia) N = 67	All subjects N = 200
At least one event	29 (43.3%)	31 (47.0%)	34 (50.7%)	94 (47.0%)
At least one related event	5 (7.5%)	2 (3.0%)	3 (4.5%)	10 (5.0%)
At least one ≥ Grade 3 event	0	0	1 (1.5%)	1 (0.5%)
Death	0	0	0	0
At least one serious event	0	0	0	0

Grade 3 event was strep throat: this occurred in a male subject 16 days after the second dose of vaccine and was considered not related to vaccination

H1N1 data

Viral titers of shed A/H1N1 strains after Dose 1*



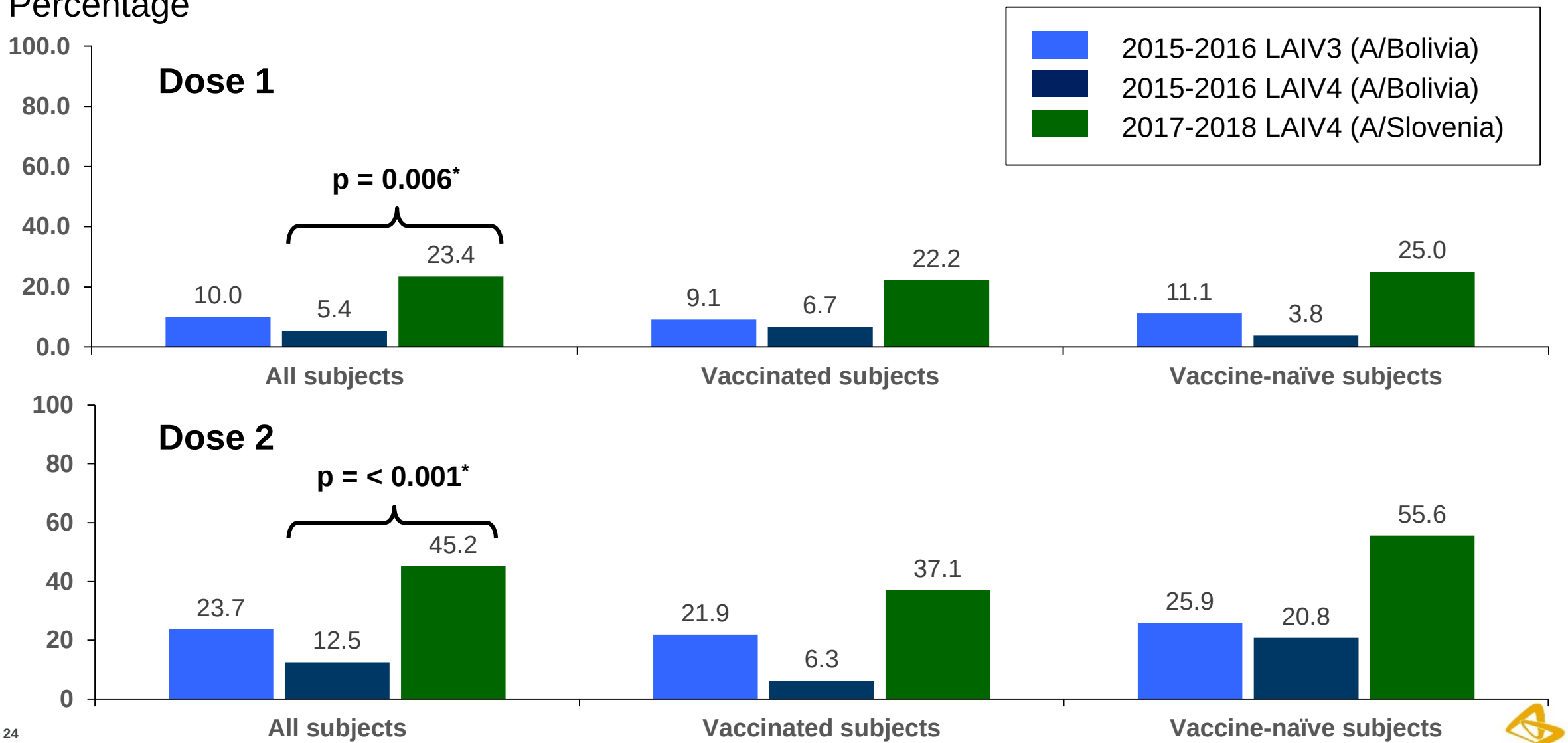
* Subjects with viral titers above limit of detection

23

A/H1N1 HAI seroconversion rates, by vaccination status

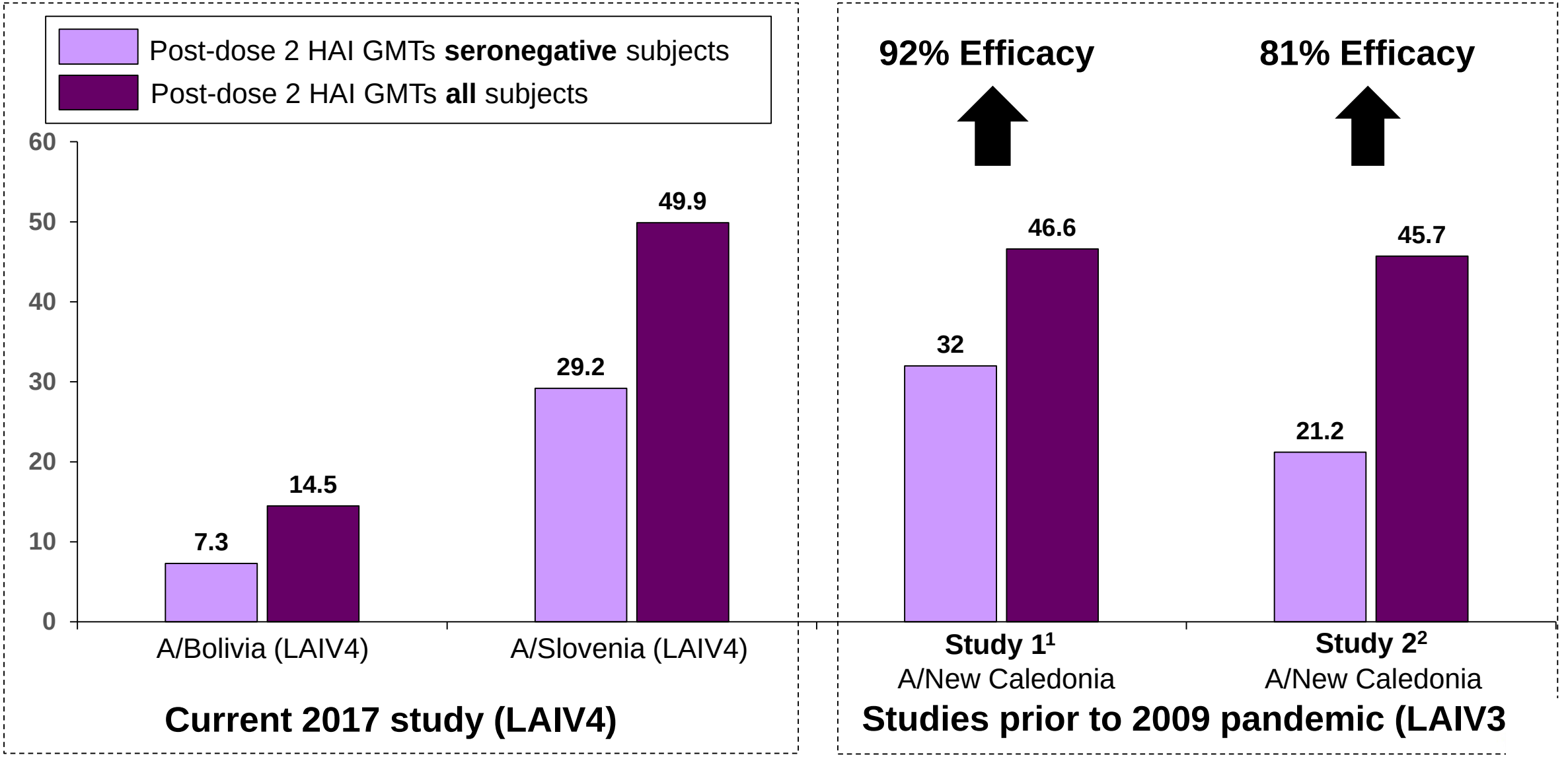
Subjects seroconverting

Percentage



* A/H1N1 HAI antibody responses in LAIV4 formulations for all subjects assessed for statistical significance per Statistical Analysis Plan

A/Slovenia post-dose 2 GMTs similar to those seen for previous H1N1 strain (A/New Caledonia) with high levels of efficacy



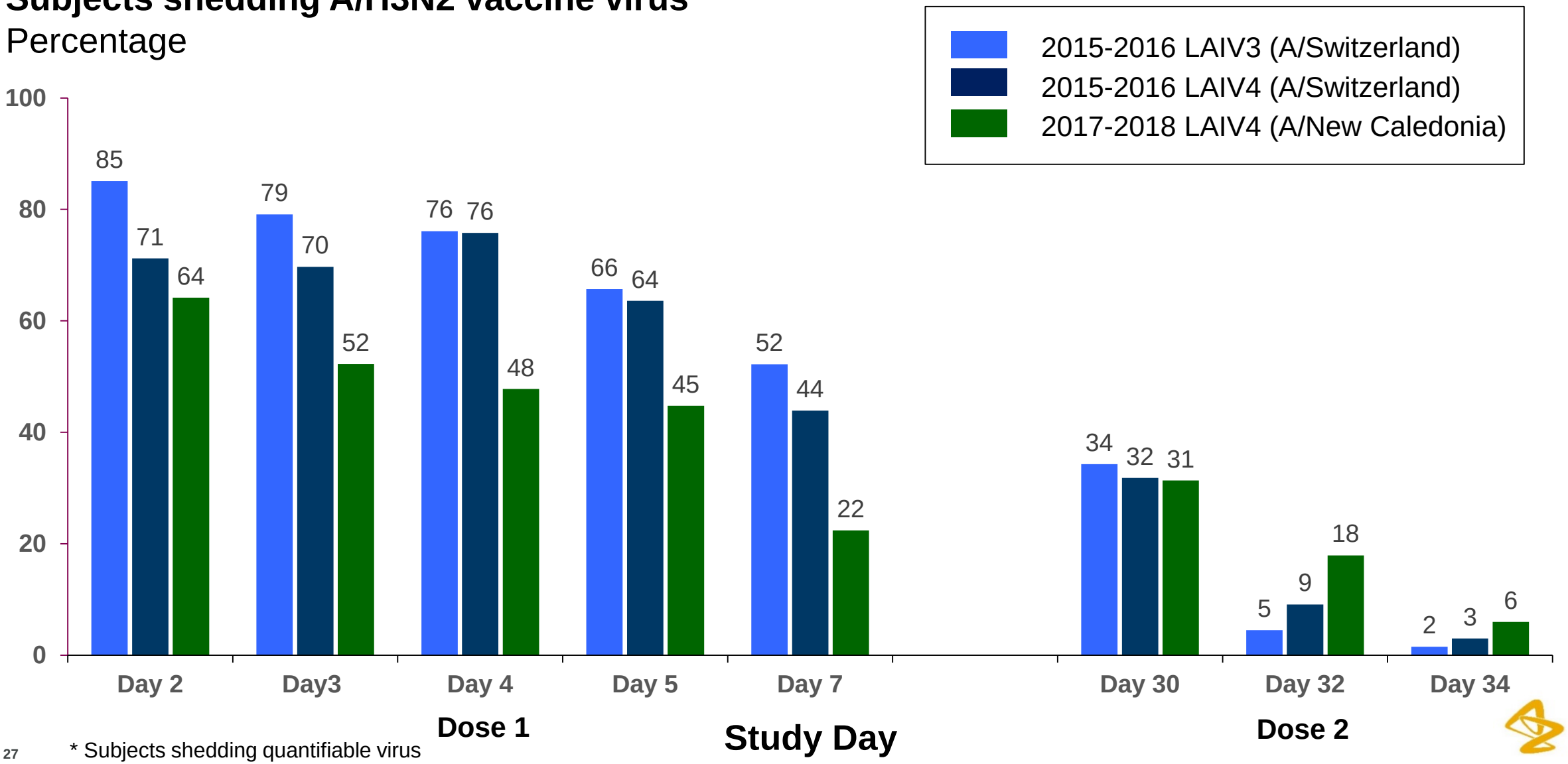
GMT = Geometric mean titer

[1] Vesikari *Pediatrics* 2006 and [2] Tam *PIDJ* 2007

H3N2 data

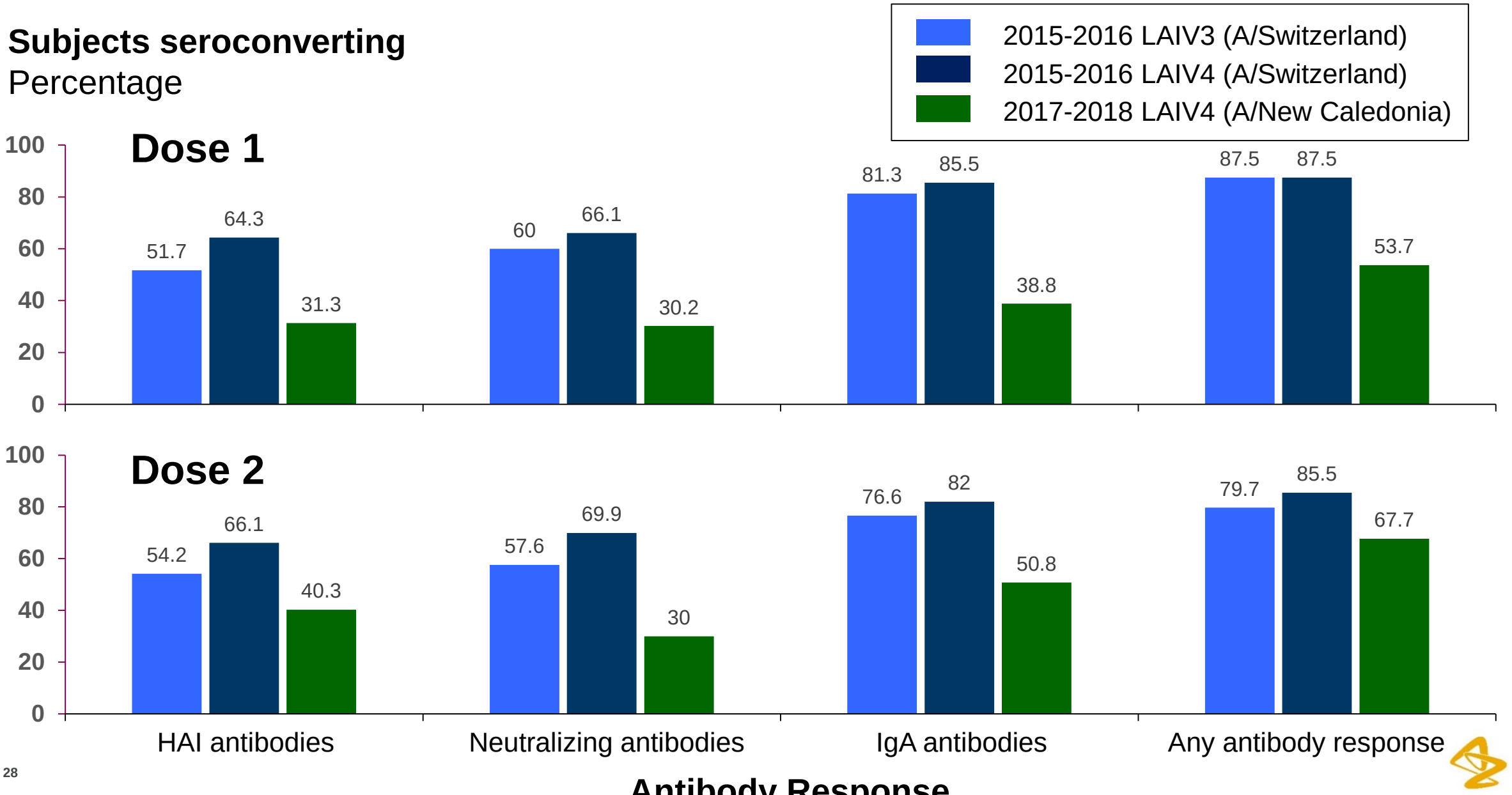
Shedding of H3N2 strains

Subjects shedding A/H3N2 vaccine virus*
Percentage

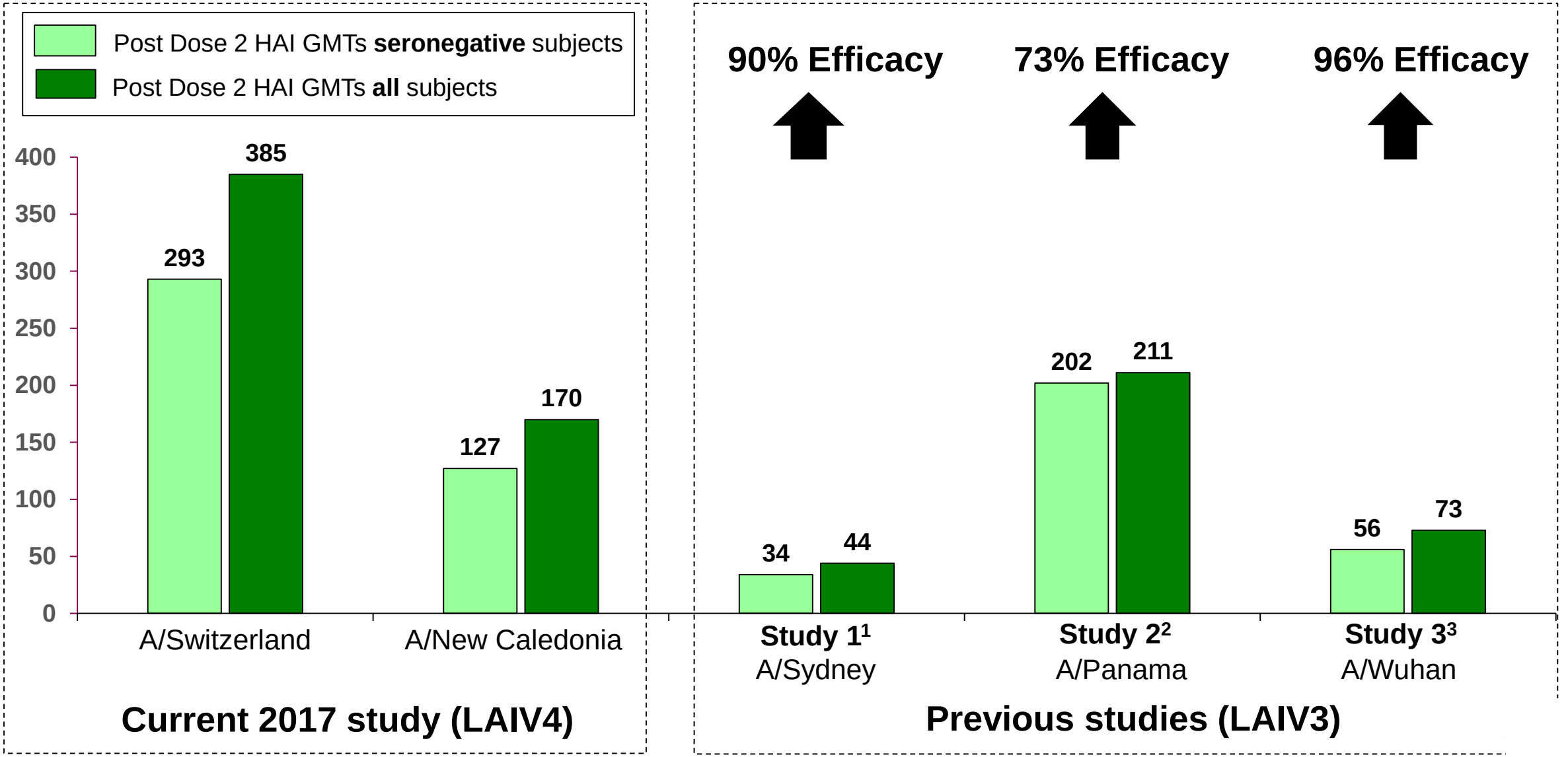


* Subjects shedding quantifiable virus

A/H3N2 antibody seroconversion rates after Dose 1 and Dose 2



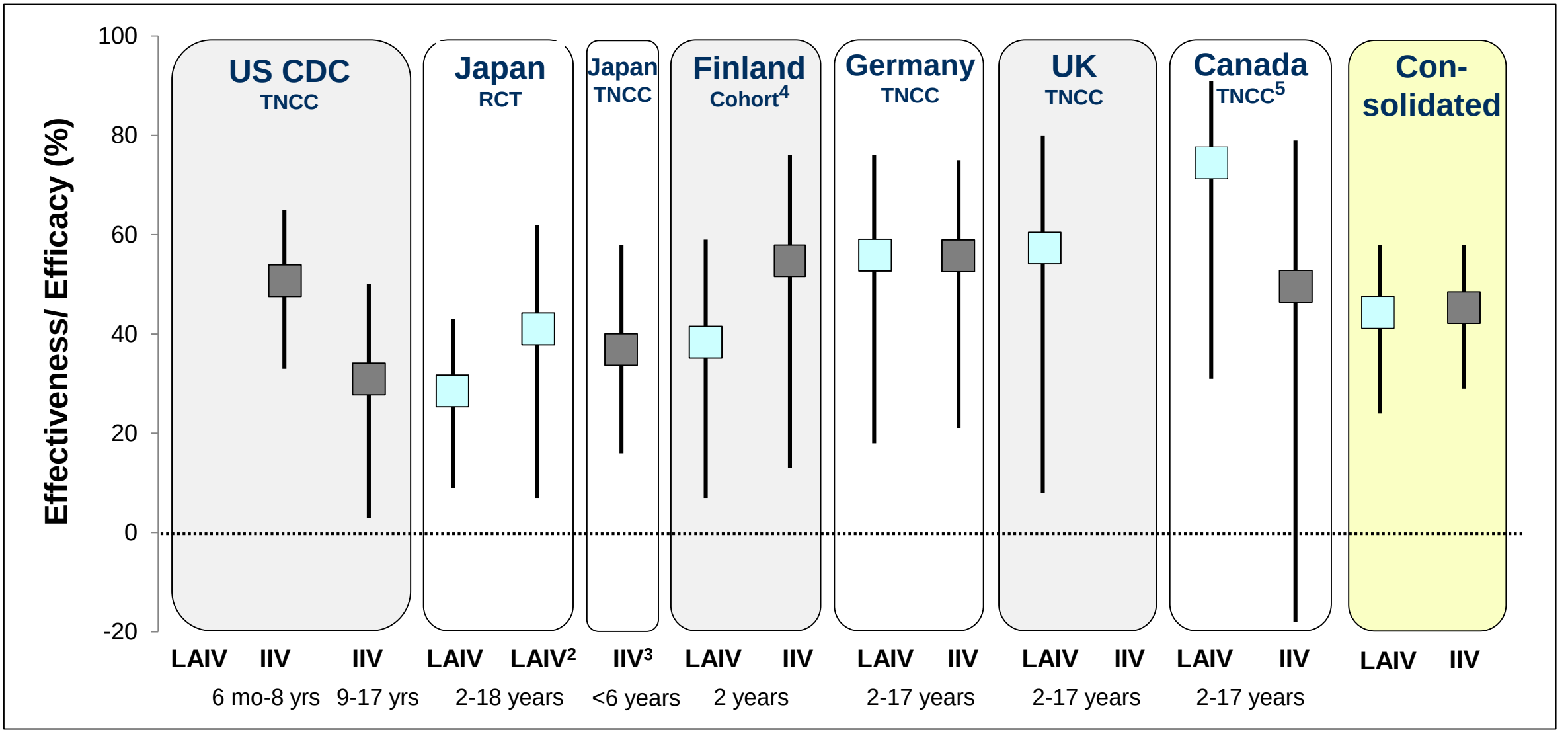
A/H3N2 post-dose 2 GMTs similar to those seen for three previous H3N2 strains with high levels of efficacy



GMT = Geometric mean titer

[1] Tam *PIDJ* 2007; [2] Neto *PIDJ* 2009 and [3] Belshe *NEJM* 1998

A/New Caledonia H3N2 strain was effective in 2016-2017, comparable to IIV[1]



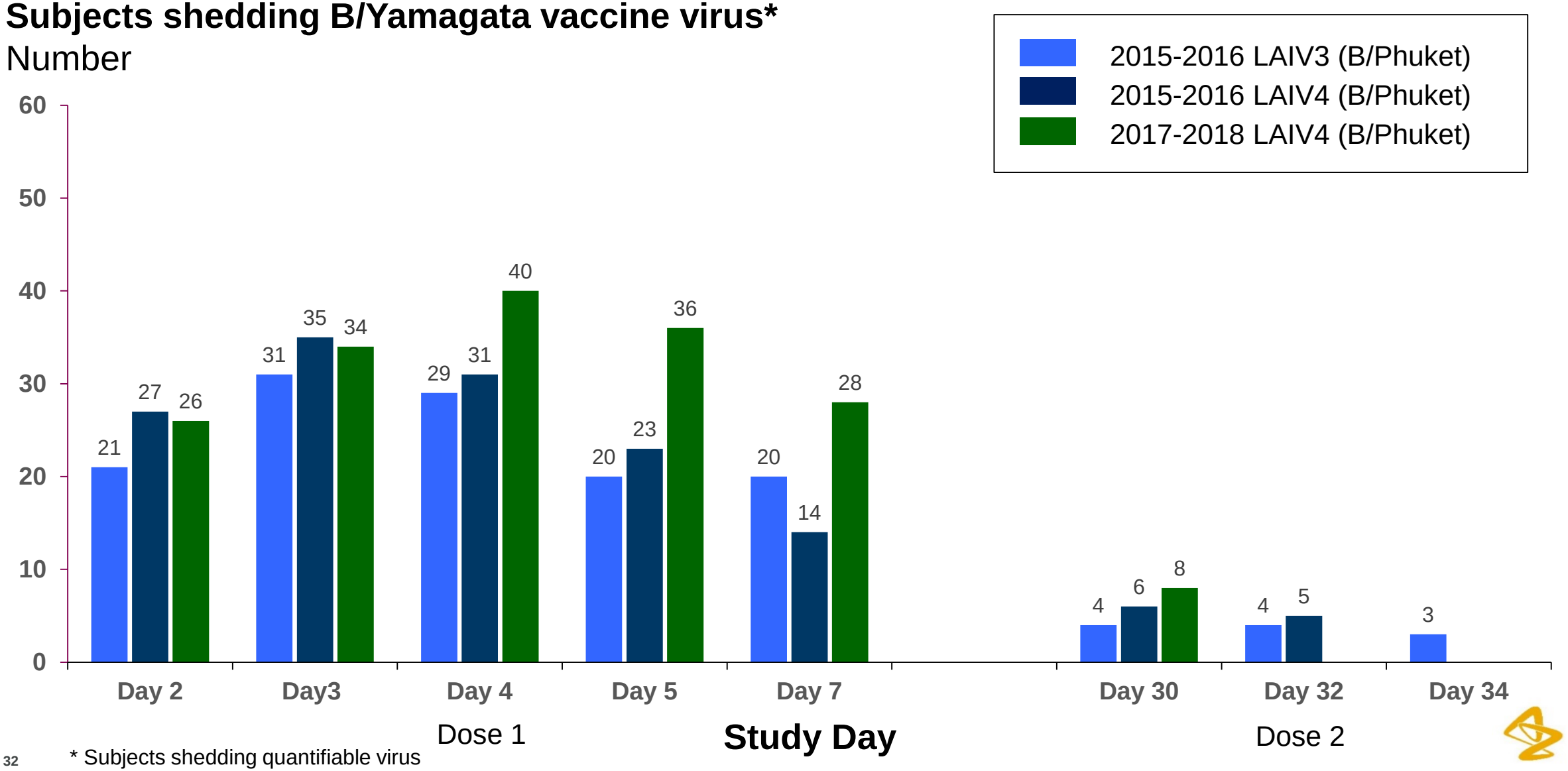
[1] Estimate for all strains regardless of match to vaccine, except where noted; LAIV estimate not available for US and IIV estimate not available for UK. [2] Estimate for matched strains
[3] Presented at Japan Ministry of Health 25 Aug 2017; test-negative study conducted in children < 6 years of age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

B strain data

Shedding of B/Yamagata strain

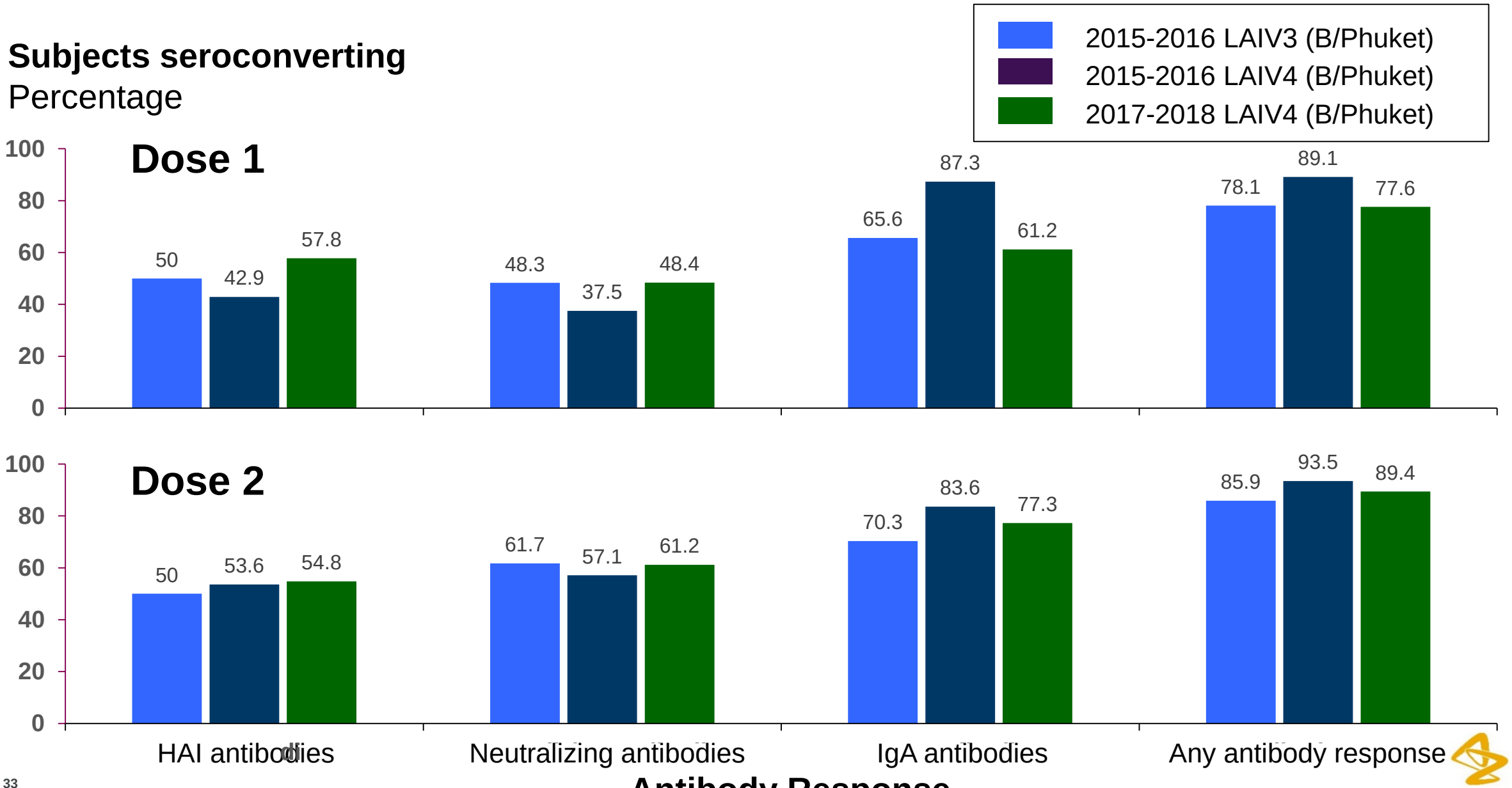
Subjects shedding B/Yamagata vaccine virus*

Number



* Subjects shedding quantifiable virus

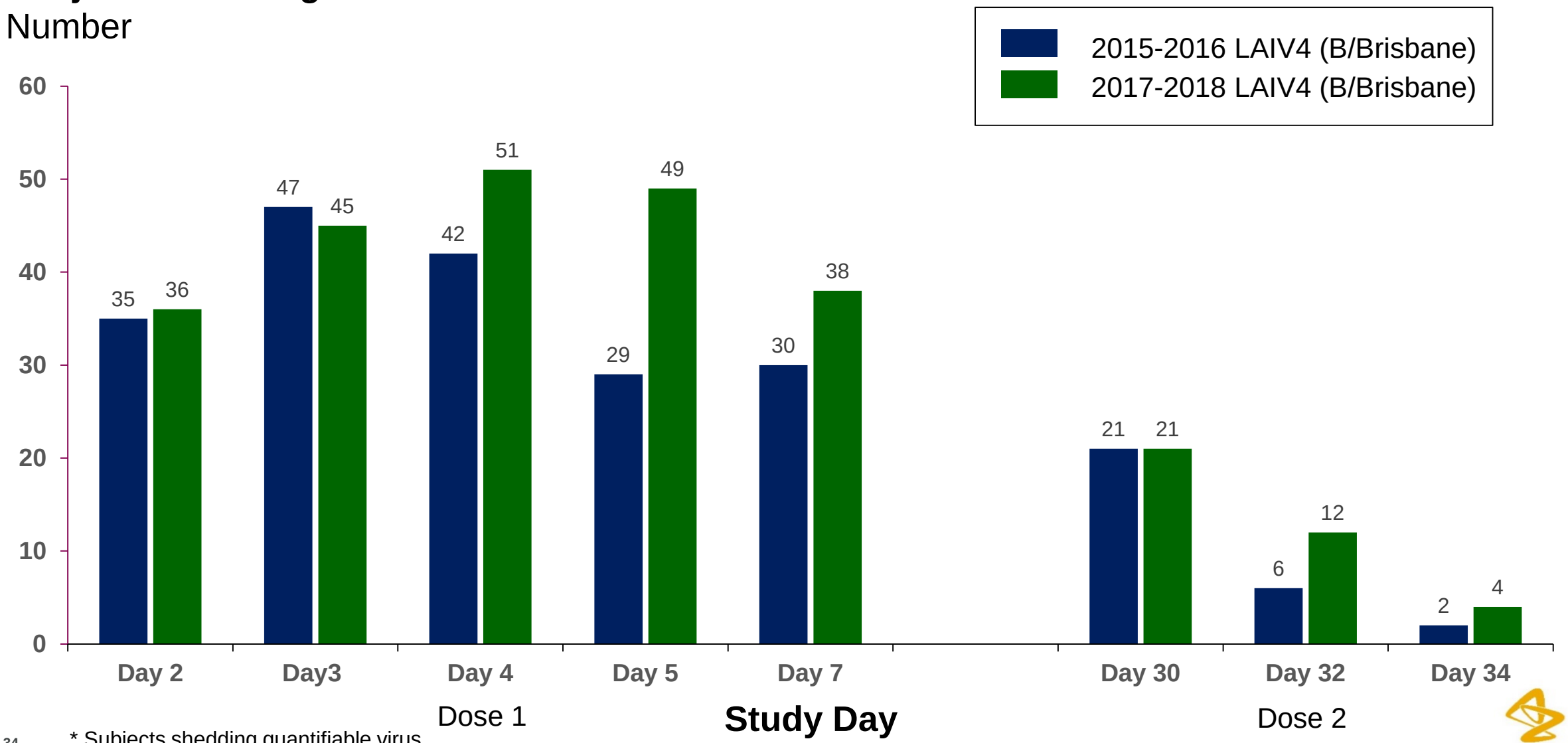
B/Yamagata seroconversion rates after Dose 1 and Dose 2



Shedding of B/Victoria strain

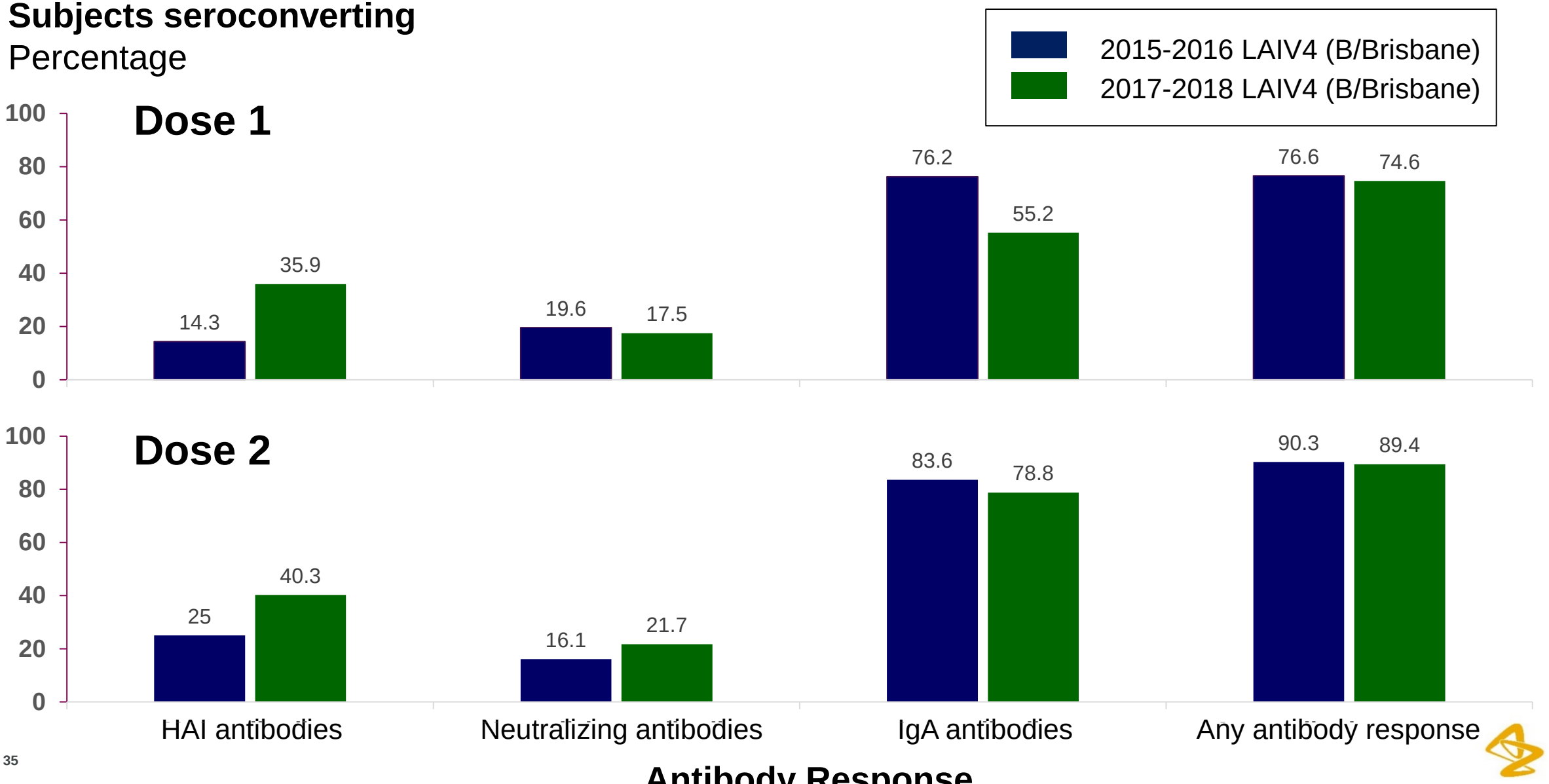
Subjects shedding B/Victoria vaccine virus*

Number



* Subjects shedding quantifiable virus

B/Victoria seroconversion rates after Dose 1 and Dose 2



Root cause investigation

LAIV effectiveness investigation: Root Causes

- Likely root cause = Reduced replicative fitness of H1N1pdm09 LAIV strains
- No support for the following as likely root causes:
  - Pre-existing immunity from prior vaccination
  - Quadrivalent-specific vaccine virus interference
  - Vaccine virus temperature stability and heat exposure during shipping
  - Manufacturing
  - Stability at 2-8 ºC

Unlikely Root Cause:
Pre-existing immunity among vaccinated children

LAIV3 demonstrated low to no vaccine effectiveness against post-pandemic strains in 2010-2011 season 1,2

Given observations of reduced effectiveness with LAIV3, quadrivalent-specific interference considered an unlikely root cause of the reduced VE

Interference could be a contributing factor to the low effectiveness in context of reduced replicative fitness of post-pandemic LAIV strains

However, A/Slovenia strain in the quadrivalent formulation was more immunogenic than the A/Bolivia strain in the trivalent or quadrivalent formulations

Immunogenicity of A/Slovenia was similar to a highly effective pre-pandemic strain in the trivalent formulation

1. Chung JR, Flannery B, Thompson MG, et. al. Pediatrics 2016, 2. Helmeke et al. PLoS One. 2015., 3. Victor J, Lewis K, Diallo A, et. al. Lancet Glob Health. 2016.

Unlikely Root Cause:
Vaccine virus interference from quadrivalent formulation

- LAIV3 demonstrated low to no vaccine effectiveness against post-pandemic strains in 2010-2011 season [1,2]
- Given observations of reduced effectiveness with LAIV3, quadrivalent-specific interference considered an unlikely root cause of the reduced VE
- Interference could be a contributing factor to the low effectiveness in context of reduced replicative fitness of post-pandemic LAIV strains
- However, A/Slovenia strain in the quadrivalent formulation was more immunogenic than the A/Bolivia strain in the trivalent or quadrivalent formulations
- Immunogenicity of A/Slovenia was similar to a highly effective pre-pandemic strain in the trivalent formulation

1. Chung JR, Flannery B, Thompson MG, et. al. Pediatrics 2016, 2. Helmeke et al. PLoS One. 2015., 3. Victor J, Lewis K, Diallo A, et. al. Lancet Glob Health. 2016.