Pediatric Influenza and Rotavirus Challenge Models

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Should challenge models be conducted in children?

- Infants and young children are the most important target groups for most vaccines because they have higher incidence, more severe outcomes and overall greatest disease burden
- For many pathogens, studies in immunologically experienced adults may not be predictive of effects in immunologically naïve children
- Human challenge models could lead to more rapid development of vaccines for important infections in children leading to overall benefit

Should challenge models be conducted in children?

- Exposure of a high-risk population to a virulent pathogen, even with careful monitoring, has the potential to cause significant harm
- Participation is unlikely to be of direct benefit to the subject
- Children are unable to give independent informed consent
- Parental consent may be vulnerable to coercion

Should challenge models be conducted in children?

- Solution!

  - Substitute an attenuated version of the pathogen for the wild-type pathogen
  - Evaluate factors that impact replication of the attenuated version of the pathogen
  - Assumes that immunologic mechanisms are the same as true for wild-type pathogen
  - Ideally, uses the same site of exposure and replication

Should challenge models be conducted in children?

- Practically, limited to situations where a live, attenuated version of the pathogen is available that replicates at the same or similar site as the wild-type version
  - Influenza
  - Rotavirus
  - Polio
  - Others

Influenza

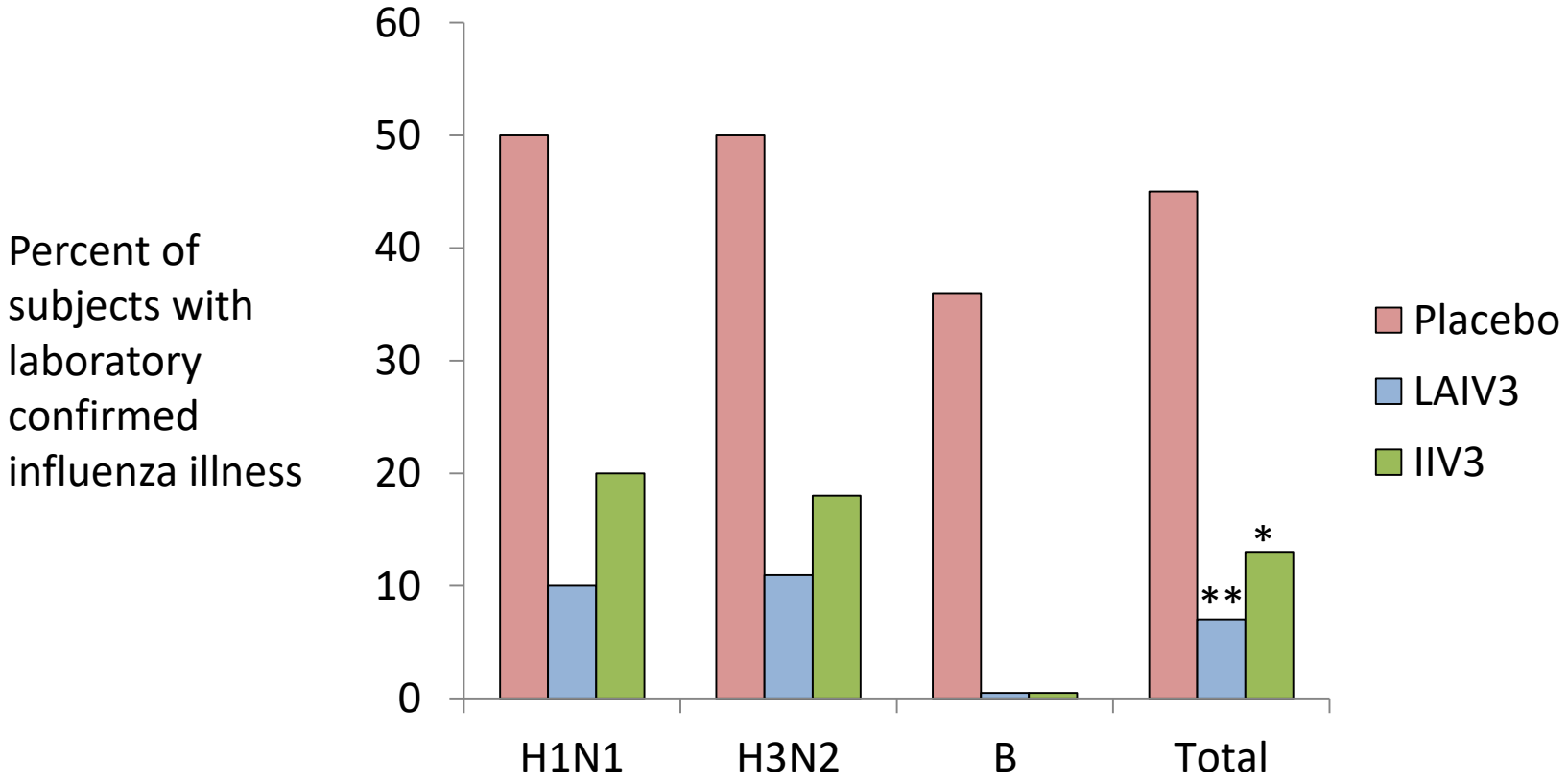
- Multiple types of attenuated vaccines have been developed and are in development
- Temperature sensitive, neuraminidase deficient, codon deoptimized, single cycle replication, avian, cold adapted, etc.
- Cold adapted influenza vaccine
  - A/AA/6/60 and B/AA/6/66 MDV
  - Reassortant viruses with target HA and NA genes extensively studied in multiple populations
  - Licensed as Flumist®

Potential efficacy of cold-adapted influenza demonstrated by exposure to cold-adapted vaccine

- Protection by monovalent H1N1 against shedding of a subsequent dose in children 12-48 months of age (Belshe JID 149:735, 1984)
- Protection by monovalent H3N2 against shedding of a subsequent dose in children (Johnson JID 154:121, 1986)

Prior flu exposure	N	% Shed	Total $\log_{10}$ virus shed	Proportion of days with shedding (%)
Infection	21	48	0.25 ± 0.70	13/63 (21)
LAIV	13	46	0.66 ± 0.29	9/39 (23)
IIV	16	94	2.56 ± 0.61	24/44 (55)
None	9	100	2.66 ± 0.89	16/25 (65)

Protective efficacy of LAIV3 (Flumist®) demonstrated in adults in a challenge study

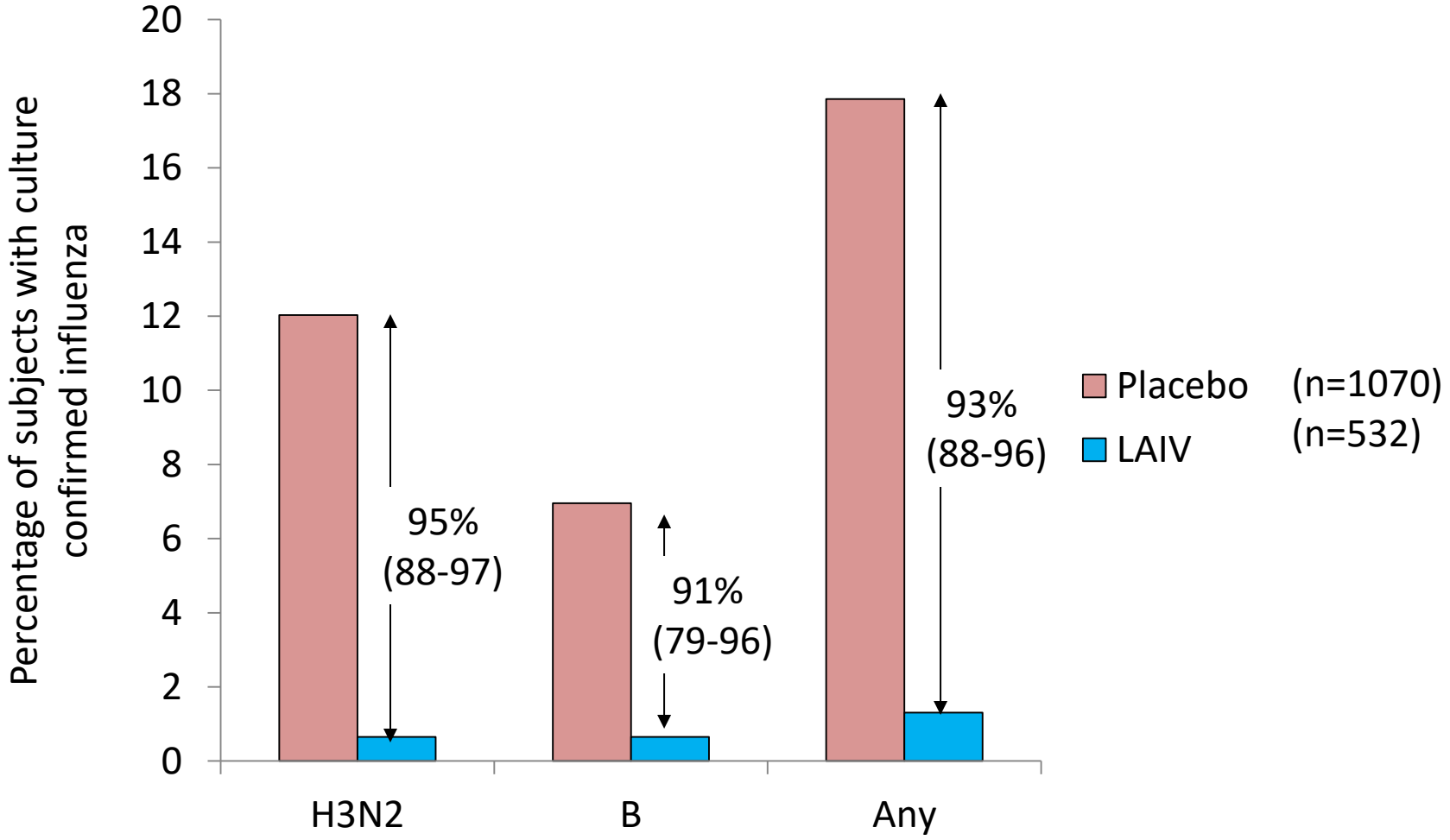


** Protective efficacy 90%, 95% CI 99%-48%

* Protective efficacy 82%, 95% CI 96%-70%

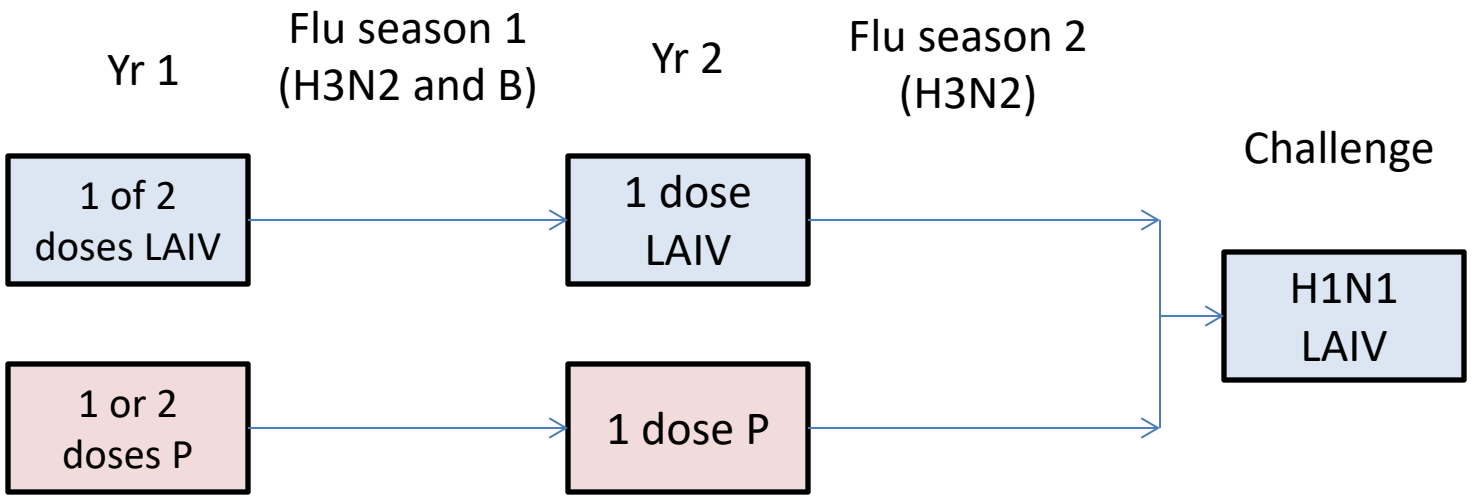
Treanor et al Vaccine 18:899, 2000

Efficacy of Flumist® demonstrated in children 15-71 mo. against H3N2 and B, but not H1N1



Belshe et al NEJM, 338:1405, 1998

Use of intranasal challenge with monovalent LAIV to demonstrate potential protective efficacy of LAIV against H1N1 influenza



- Healthy children 34 to 91 mo. of age who participated in both years of the study
- Remained blinded to vaccine assignment
- Given $10^{7.0}$ $TCID_{50}$ of monovalent A/Shenzhen/227/95-like H1N1 vaccine intranasally approximately 8 months after second vaccine dose

LAIV was associated with decreased rates of shedding of a subsequent challenge with monovalent H1N1 LAIV

	N	No. with fever	No. with nasal congestion	No. shedding	Vaccine "efficacy"
Vaccine	144	2 (1%)	19 (13%)	6 (4%)	83% (60-93)
Placebo	78	0	7 (9%)	19 (24%)	

Belshe et al JID 181:1133, 2000

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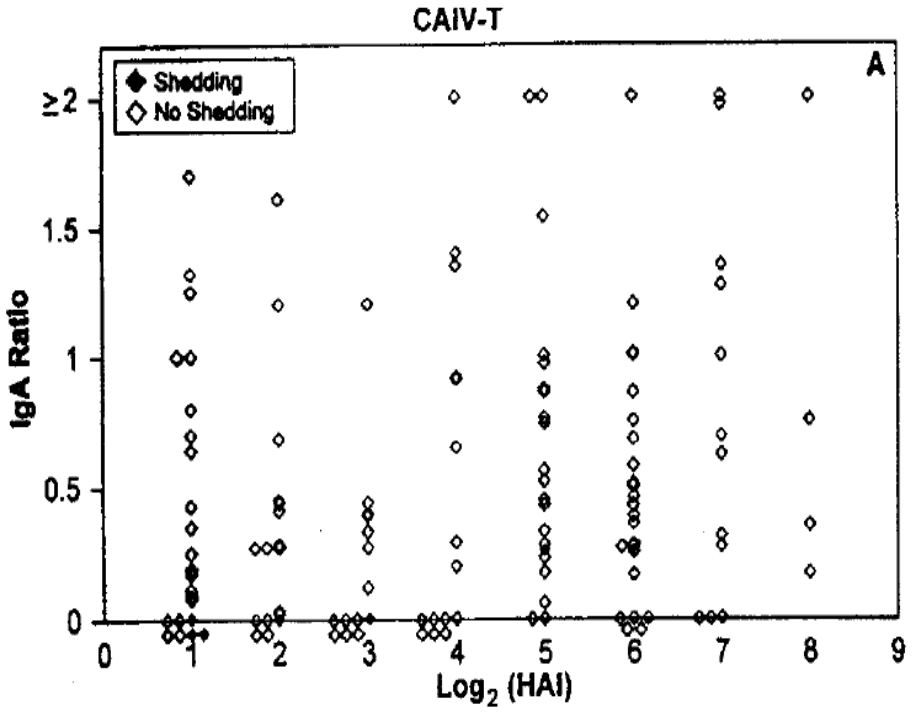
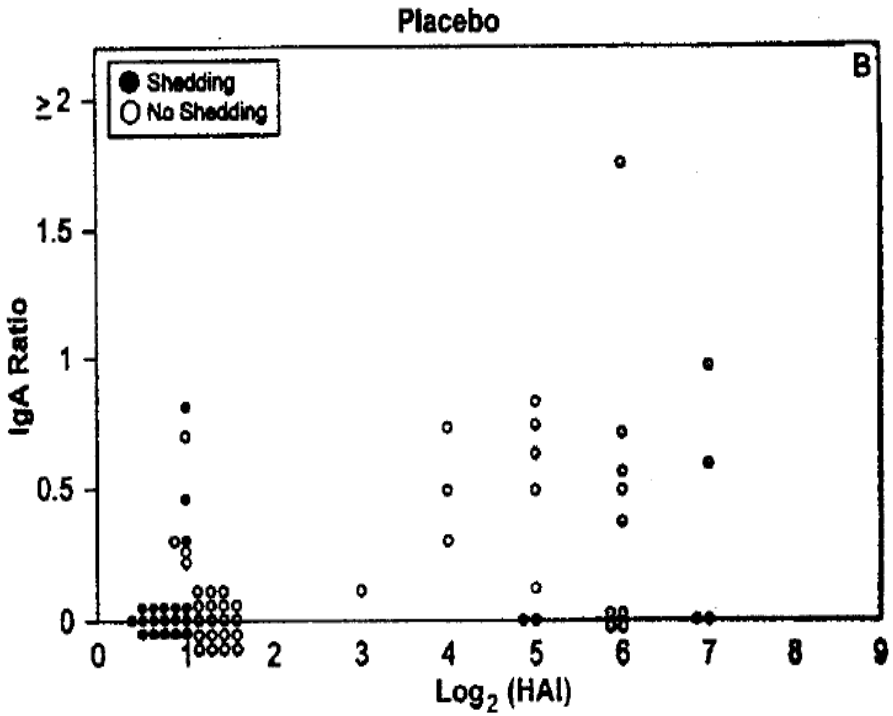
Protection against shedding was observed even in subjects with low titers of pre-exposure HAI and HA-specific nasal IgA antibody

		No. (%) shedding by pre-challenge HAI titer		No. (%) shedding by pre-challenge nasal IgA status	
	N	HAI ≤ 4	HAI ≥8	Neg	Pos
Vaccine	144	4/46 (9%)	2/97 (2%)	5/41 (12%)	1/90 (1%)
Placebo	78	19/51 (37%)	0/25	16/45 (36%)	3/23 (13%)

Belshe et al JID 181:1133, 2000

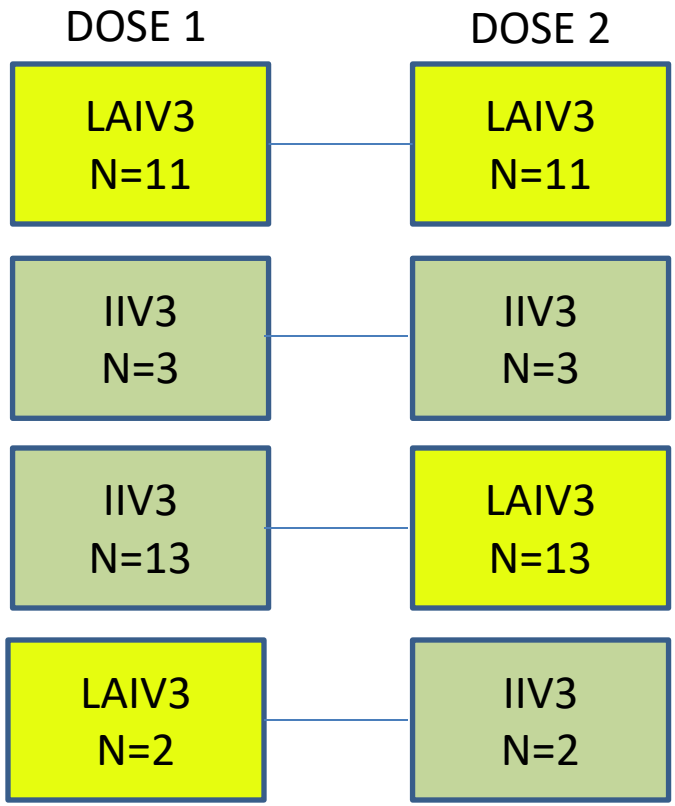
In placebo recipients, shedding of the monovalent vaccine was only seen in those with undetectable prevaccination HAI antibody





Use of a second dose of LAIV to probe potential correlates of immunity

34 healthy children aged 2-9 yrs
Two doses separated 28-42 days, randomized to order



After each dose:

- Viral shedding
- Serum antibody
- CMI
- Mucosal Ab
- Luminex

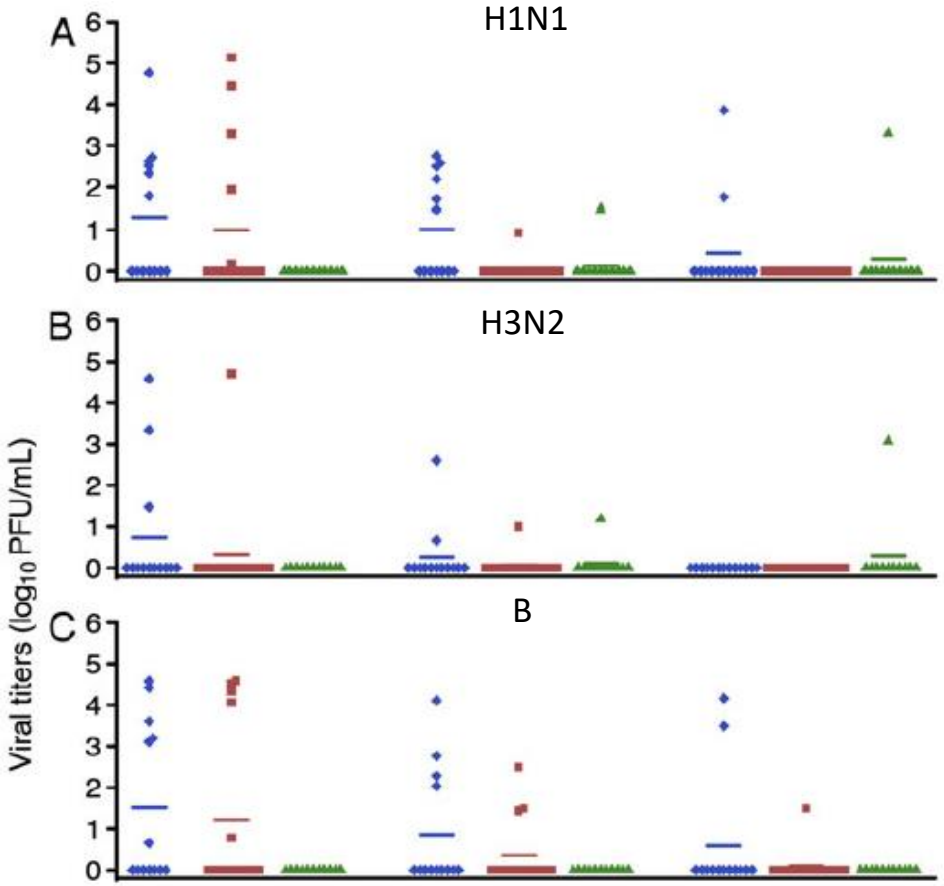
Ilushina et al JID 211:352, 2015

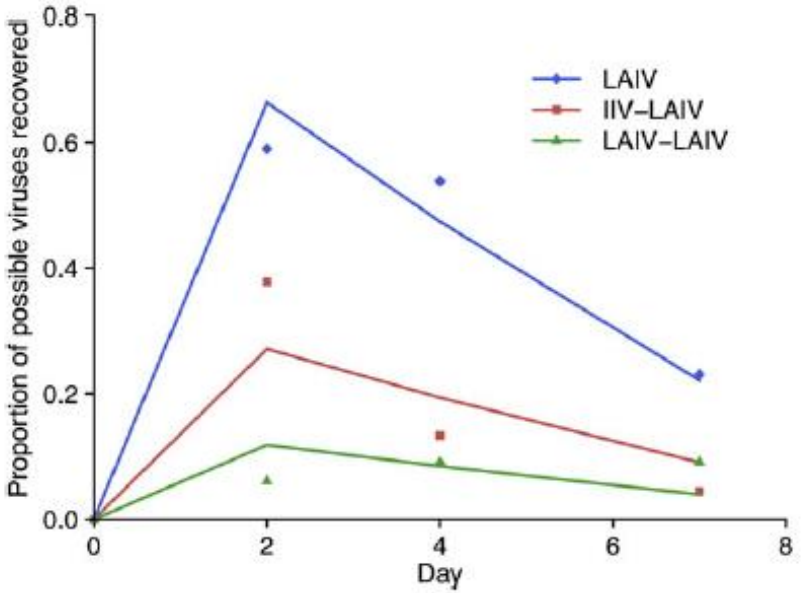
Previous LAIV, but not IIV, was associated with decreased shedding of a subsequent LAIV dose

Prior Vaccine	N	No. shedding (mean peak log10 titer among shedders)			No. viruses shed/no possible viruses
		H1	H3	B	
None	13	8 (2.9)	3 (3.1)	6 (3.7)	17/39 (44%)
LAIV	11	1 (3.3)	1 (3.1)	0	2/33 (6%)
TIV	15	4 (3.7)	1 (4.7)	5 (4.0)	8/45 (18%)

Ilushina et al JID 211:352, 2015

Greater reduction of vaccine virus shedding in children who had received a first dose of LAIV





Ilushina et al JID 211:352, 2015

- All of the immune responses measured correlated with all of the other immune correlates but the patterns induced by IIV and LAIV were distinct
- After corrections for multiple comparisons, there was no statistically significant correlation with shedding of LAIV on re-exposure

Wright et all Open Forum ID 2016

Rotavirus

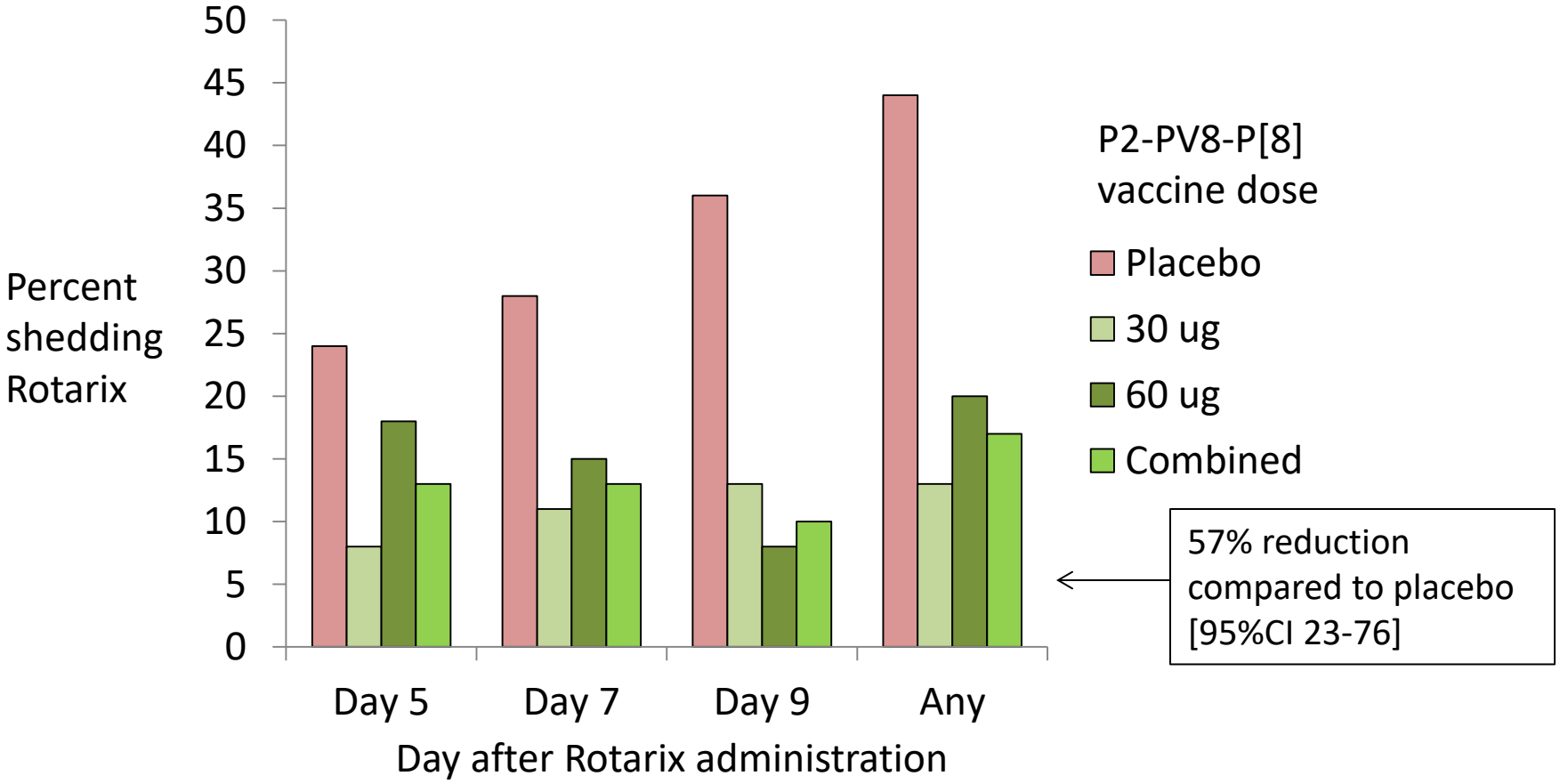
- Multiple attenuated rotavirus vaccines
  - Rhesus rotavirus
  - Bovine rotavirus
  - Culture passaged human rotavirus

Rotarix

- Monovalent attenuated human G1P1a[8] strain
- Derived by serial cell culture passage of human strain 89-12
- Shed by approximately 50% (range 35-80%) of naïve infants with first dose of ~ $10^{6.0}$ $CCID_{50}$
- Shedding is typically less after a second dose

E J Anderson Lancet Infect Dis 2008; 8:642-49

Reduction in shedding of the live rotavirus vaccine Rotarix administered 4 weeks after 3 IM doses of P2-PV8-P[8] subunit rotavirus vaccine



Groome et al, 2017, Lancet Infect Dis 17:843-53

Use of attenuated pathogens as a surrogate for wild-type challenge

- Pros
  - Timing and dose are under control
  - Provides possibly supportive evidence of efficacy
  - Provides opportunities to explore correlates of protection and other measures that would be difficult to do in the field
- Cons
  - Limited to available attenuated agents
  - Protection against vaccine infection is not necessarily evidence of protection against wild type
  - Endpoints are generally limited to replication of the attenuated pathogen

An ethical framework for considering challenge studies

	WT in adults	WT in children	Att in children
Is the scientific rationale for using the human infection model acceptable	√	√	±
Are the discomforts for the infection-inducing study acceptable	√	✗	√
Are the risks of the infection-inducing study acceptable	√	✗	√
Does the experiment enroll subjects from a vulnerable population	√	✗	±
Does the informed consent adequately inform subjects about risks and discomforts	√	✗	√
Does the financial compensation constitute undue inducement	√	±	√
Is the conduct compatible with the rights of subjects to withdraw without penalty	±	±	√

Miller and Grady 2001, Clin Infect Dis 33:1028-1033

Conclusions

- If an appropriate agent is available, “challenge” with an attenuated vaccine virus or similar agent may provide useful information regarding efficacy or immunity.
- Results should probably be interpreted as hypothesis generating rather than definitive.
- Particularly for infectious agents with high incidence rates, other approaches such as small field efficacy trials, may be feasible and have greater value.