A PHASE 2 CLINICAL TRIAL ASSESSING THE EFFECT OF BPZE1, A NOVEL LIVE ATTENUATED PERTUSSIS VACCINE, IN HEALTHY ADULTS

Cheryl Keech, MD/PhD, Ken Solovay, Marcel Thalen PhD, Keith Rubin MD

Cheryl Keech
Chief Medical Officer
Executive VP, ILiAD Biotechnologies

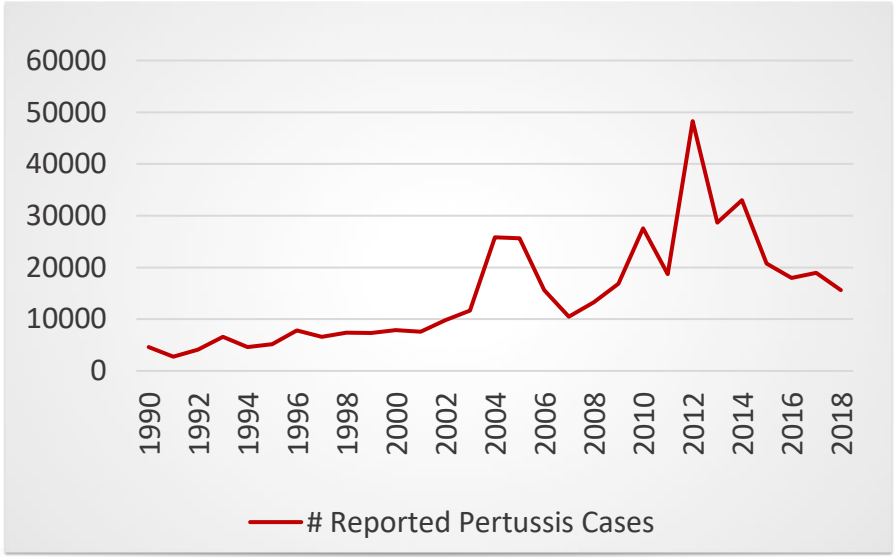
ILiAD BIOTECHNOLOGIES

The Epidemiology of Vaccination and *B. Pertussis* Transmission/Resurgence

The short duration of protection and inability to alter transmission with aP vaccines has contributed to the resurgence of pertussis in multiple countries.[1]

- Relative to other vaccines, acellular pertussis (aP) immunity wanes rapidly; requiring multiple boosters
- aP vaccine introduction is associated with pertussis resurgence (by surveillance and modeling estimates)[1]
- WHO recommends to continue wP vaccines if switching to aP has not yet occurred[1]

Pertussis Cases Reported U.S. 1990-2018[3]



Pertussis reaches worst year in 2012, since 1955[2]

ILiAD BIOTECHNOLOGIES

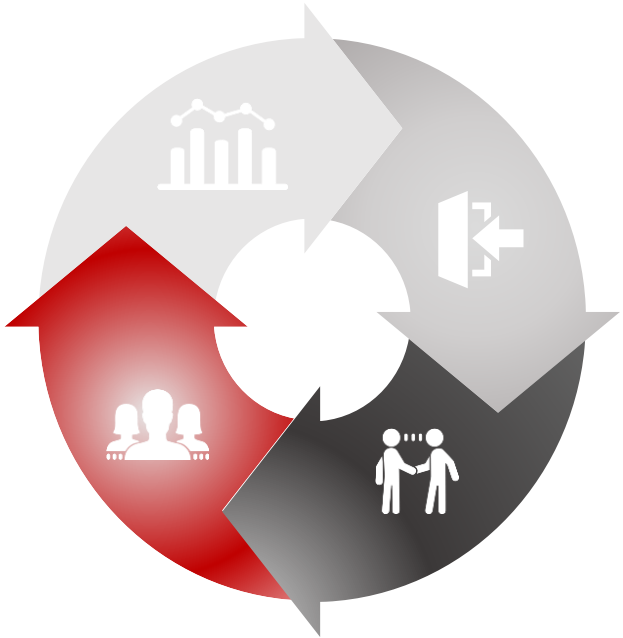
The Public Health Impact of Interrupting *B. Pertussis* Transmission

Epidemic cycle propagates

Epidemic cycles reduced/eliminated

Vulnerable population develops severe disease

Cocooning strategies and herd protection can be improved



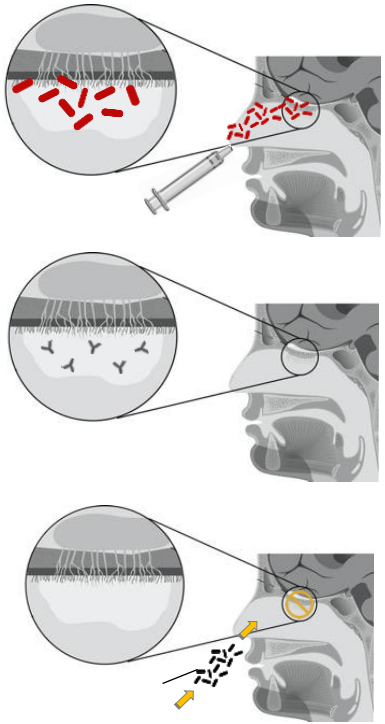
Pertussis enters a community

Humans are only known *B. Pertussis* reservoir.

Transmission occurs by close contact

Disruption of transmission will reduce/eliminate epidemics

Live Attenuated BPZE1 is Designed to Interrupt Transmission

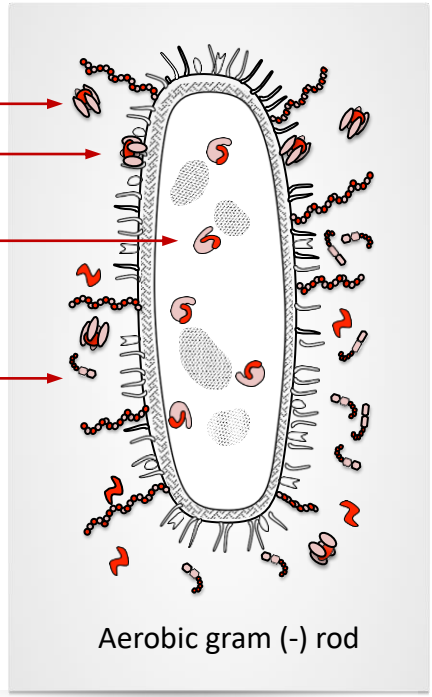


1. *Nasal vaccination with BPZE1 using VaxINator*
2. *BPZE1 stimulates mucosal and systemic immunity*
3. *B. pertussis* transmission is interrupted at mucosal barrier

PT—Pertussis Toxin
Mutation creates an enzymatically inactive PT

DNT—Dermonecrotic Toxin
Removed via allelic exchange

TCT—Tracheal Cytotoxin
Gene replaced – reduces TCT release to <1%



Aerobic gram (-) rod

Phase 2b Clinical Protocol Endpoints*

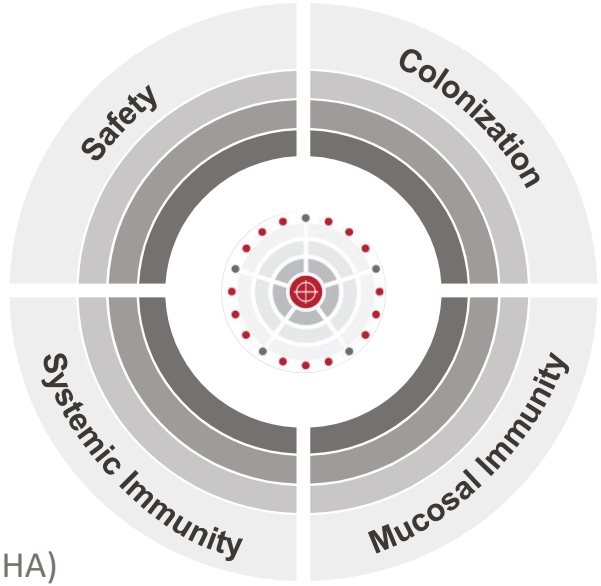
SAFETY

Reactogenicity (1°)

Safety Labs (cohort)

Vitals

Unsolicited AEs



COLONIZATION

Effect of BPZE1 Revaccination/Challenge

B. Pertussis culture and colony counts

SYSTEMIC IMMUNITY

IgG Whole cell extract (WCE)

Individual IgG antigens (PT, PRN, FHA)

Individual IgA antigens (PT, PRN, FHA)

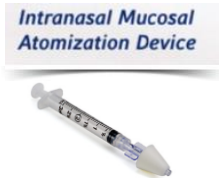
MUCOSAL IMMUNITY

IgA Whole cell extract (WCE) (1°)

Individual IgA antigens (PT, PRN, FHA)

*Descriptive only, no adjustments for multiplicity

Phase 2b Design- Randomized Control Trial (18-59 Year Old Healthy Adults)



Day 1
Vaccination
(Intranasal and IM)

BPZE1 + Placebo: N=200

10^9 CFU (full cohort n=252; safety cohort n=24)
10^7 CFU (safety lead-in n=24)

Boostrix + Placebo: N=100

BPZE1: N=100

Placebo: N=100

BPZE1: N=50

Placebo: N=50

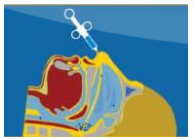
Day 85
Revaccination/
Challenge
(Intranasal)

Days	-6	1	8	29	78	85	92	96	113	169	254
Reactogenicity		—	—								
Safety Labs (subset)		◉	◉			◉	◉				
Immune Serum		●		●		●			●	●	●
Immune Mucosal	●			●	●				●	●	●
B. Pertussis Culture					●		●	●	●		
PBMC Subset		○	○				○				
Safety		All AE			AE Related to Vaccination		All AE			SAE + any newly defined AESI	

Methods

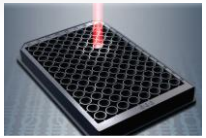
Colonization

- N-PAK nasopharyngeal aspiration
- Stored (2) in 20% glycerol -70C
- Qualitative culture on charcoal agar plates
- Confirmed Bordetella with MALDI-TOF
- (+) samples re-plated for colony counts with 2nd aliquot



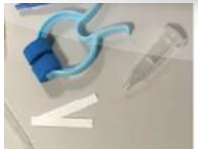
Serum Assay

- Whole cell extract and PRN assays – validated on MesoScale Diagnostic (MSD) platform
- PT and FHA assays – commercial kits (EuroImmune)

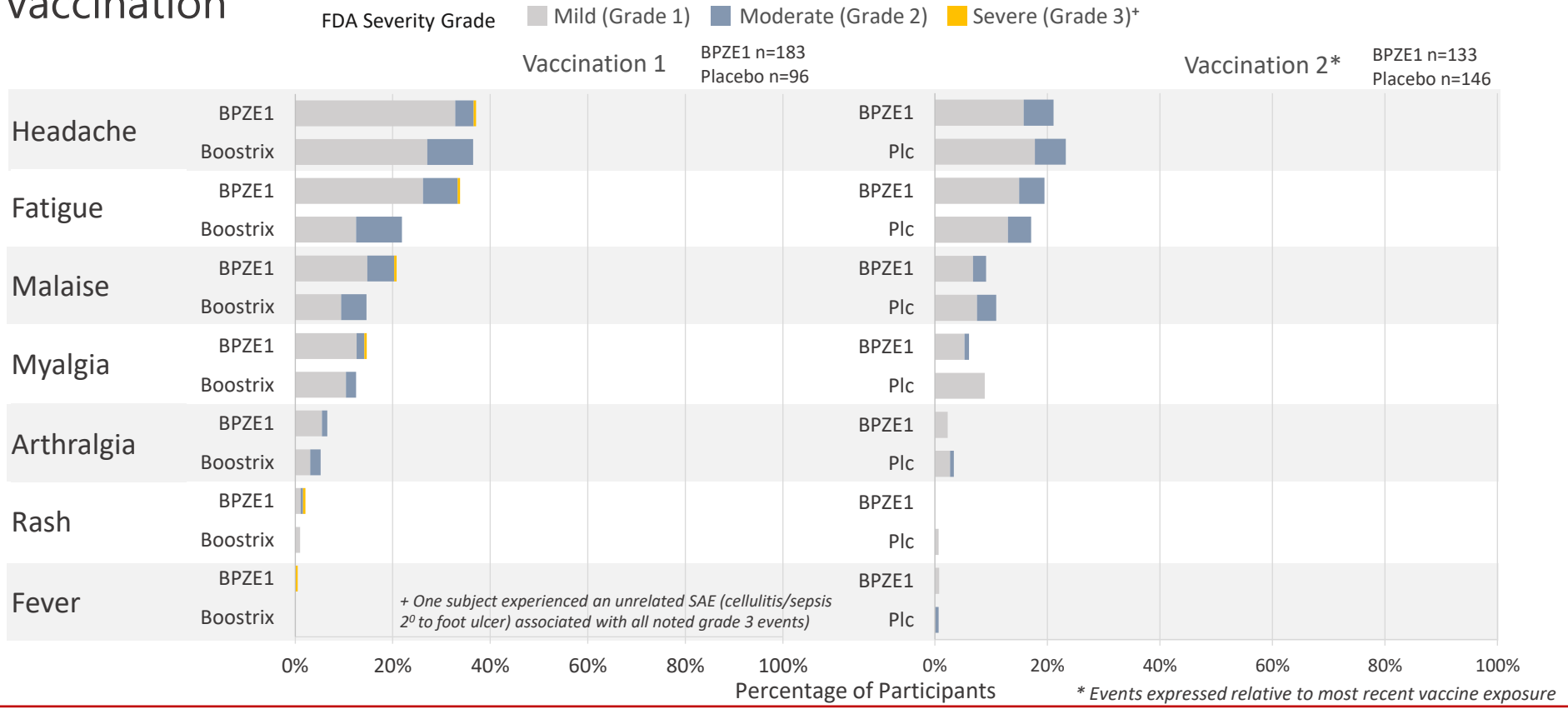


Mucosal Sample and Assay

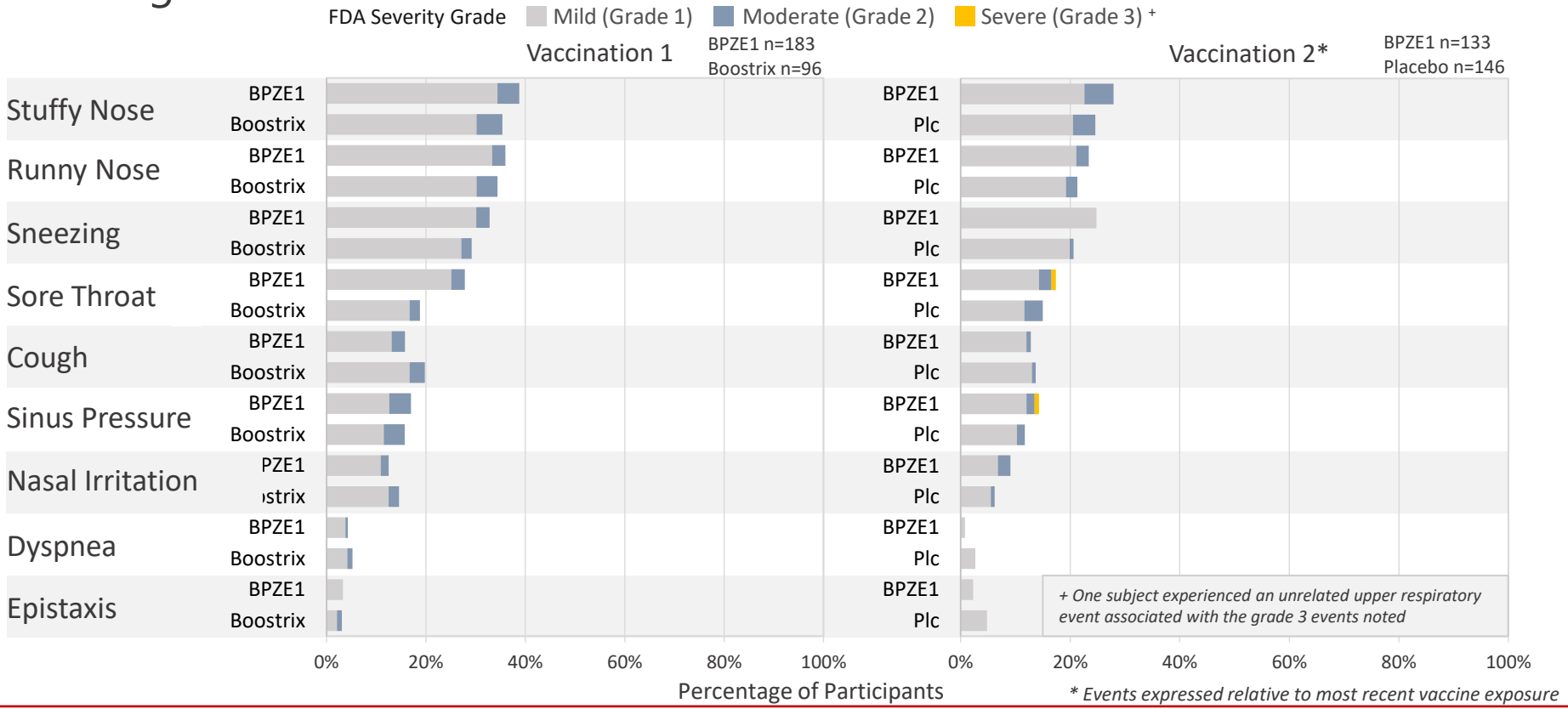
- Synthetic Absorptive Matrix (SAM) Leukosorb strips
- 2 min Nasal absorption
- Centrifuged with diluent and stored at -20C
- Same assay platforms as for serum testing (validated)



Systemic Reactogenicity - Maximum Symptoms Through 7 Days Following Vaccination



Nasal/Respiratory Reactogenicity - Maximum Symptoms Through 7 Days Following Vaccination



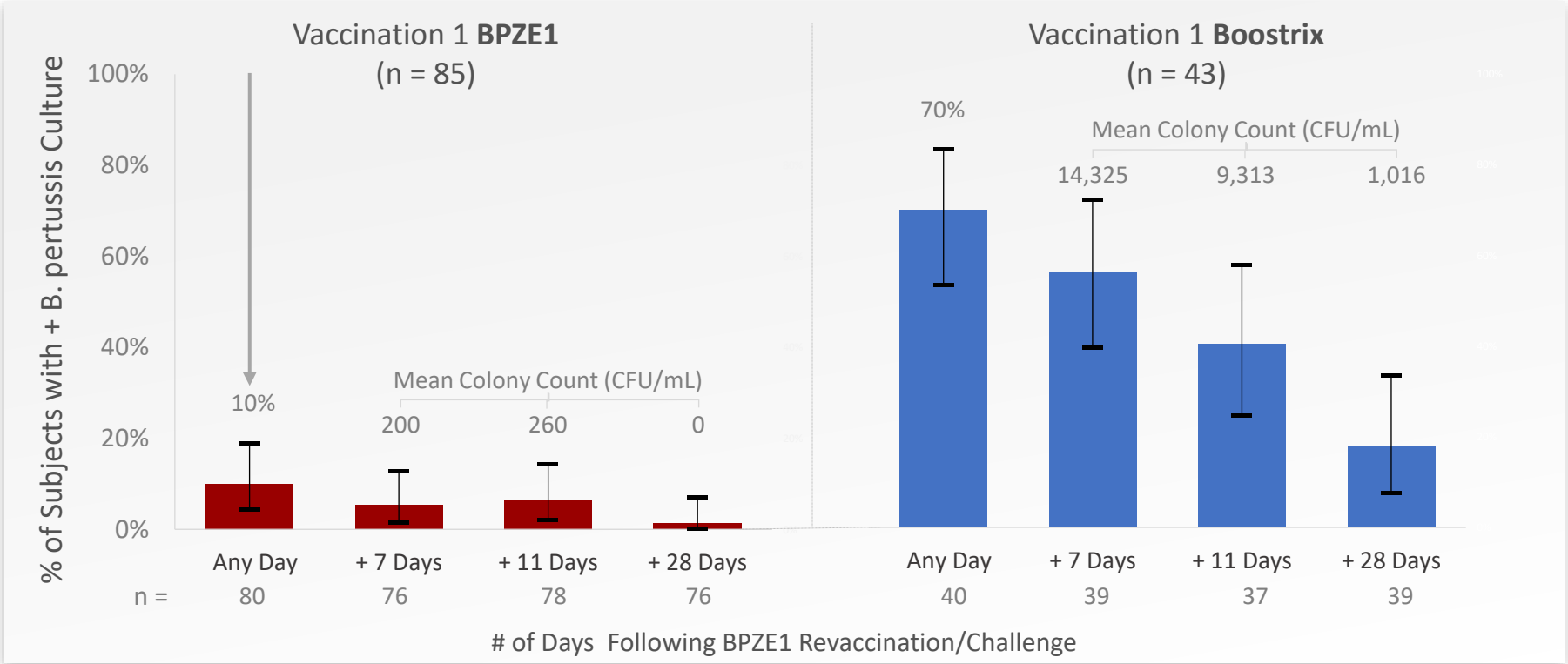
Treatment Emergent Adverse Events (% Incidence)

- Majority of vaccination-related events were respiratory classification; with similar incidence between treatment groups (7.7% vs 6.3%, BPZE1 and Boostrix, respectively Days 1-84)
- Second vaccination was withheld in 2 subjects due to concurrent workup/ ongoing adverse event
- No SAEs were related to vaccination

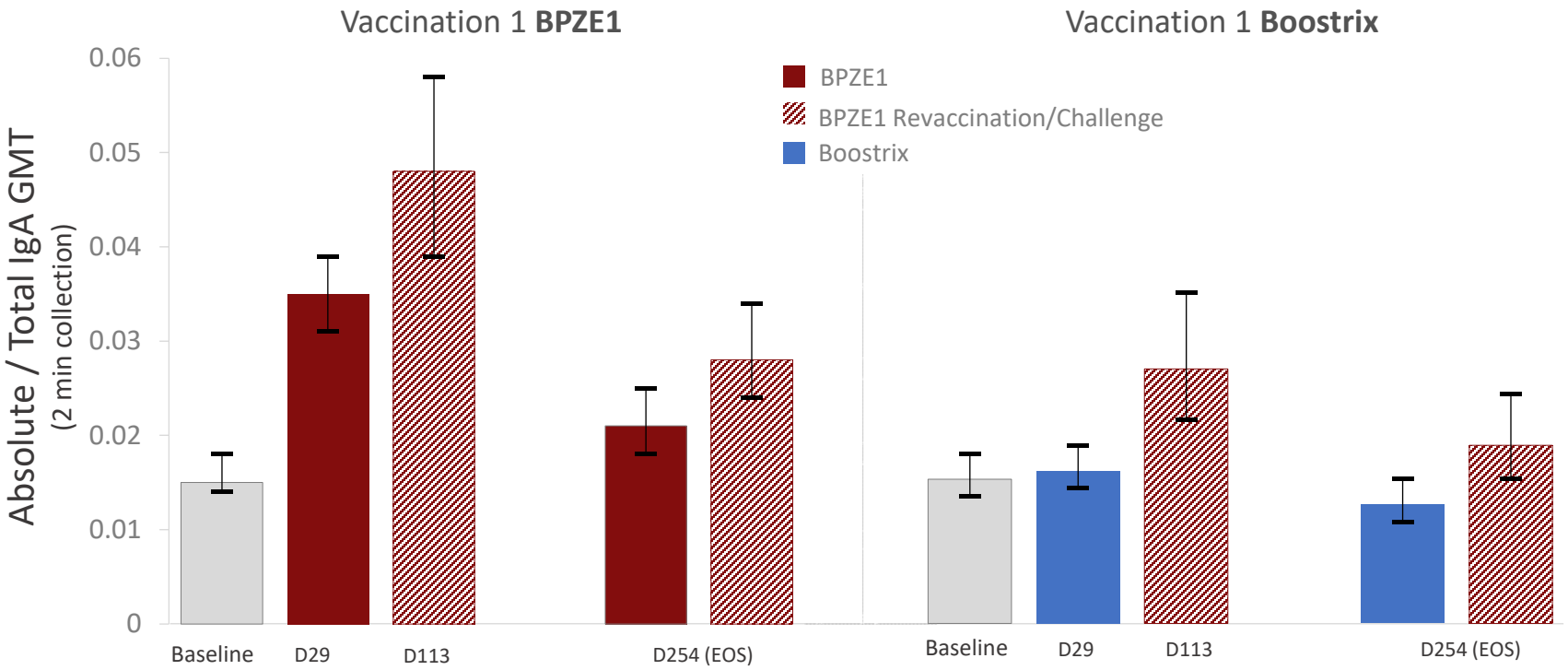
	Vaccination 1 (Day 1 - 84)		**Vaccination 2** (Day 85 - 113)	
	BPZE1 (n=183)	**Boostrix** (n=96)	**BPZE1** (n=133)	**Plc** (n=146)
Any TEAE* (%)	29.5	31.	16.5	25.3
Mild (Grade 1)	*20.8*	*20.8*	*13.5*	*20.5*
Moderate (Grade 2)	*6.6*	*5.2*	*3*	*4.1*
Severe (Grade 3)	*0.5*	*1.0*	*0*	*0.7*
Vaccination-Related (%)	11.5	11.5	3.8	8.2
Severe (%)	1.1	1.0	0	0.7
Serious (%)	1.6	0	0	0.7
2nd Vaccination Withheld (%)	1.1	0	n/a	n/a
Leading to Study Discontinuation (%)	0	0	0	0
Death (%)	0	0	0	0

**Severity graded through 28 days following vaccination*

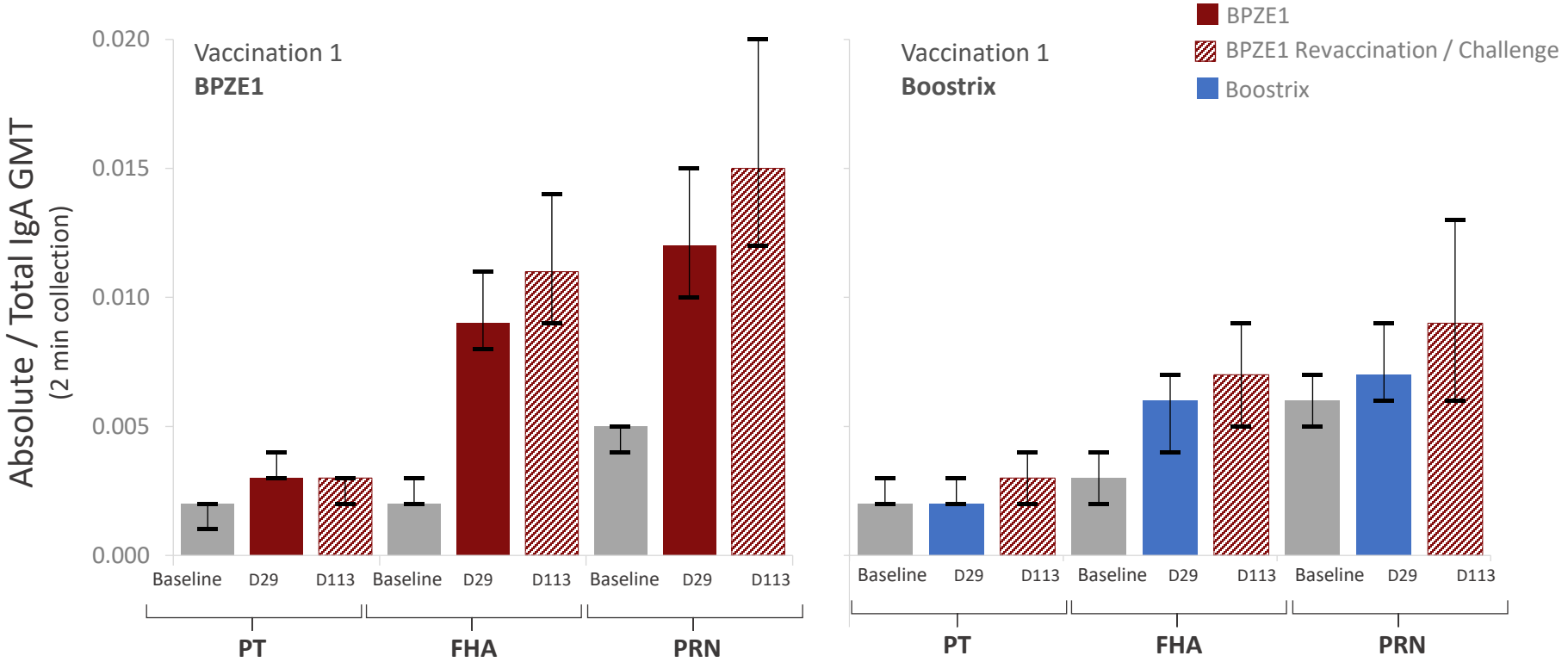
Effect of BPZE1 Revaccination/Challenge on Nasopharyngeal Colonization



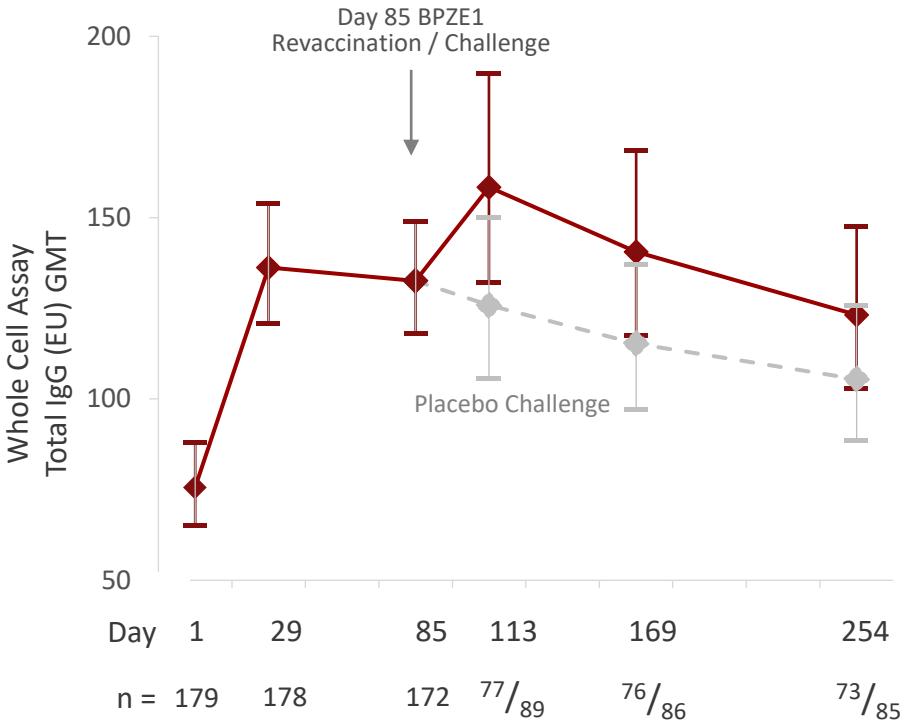
Mucosal (S-IgA) Whole Cell Pertussis Antibody Responses 28 Days Following Any Vaccination & End of Study (GMT)

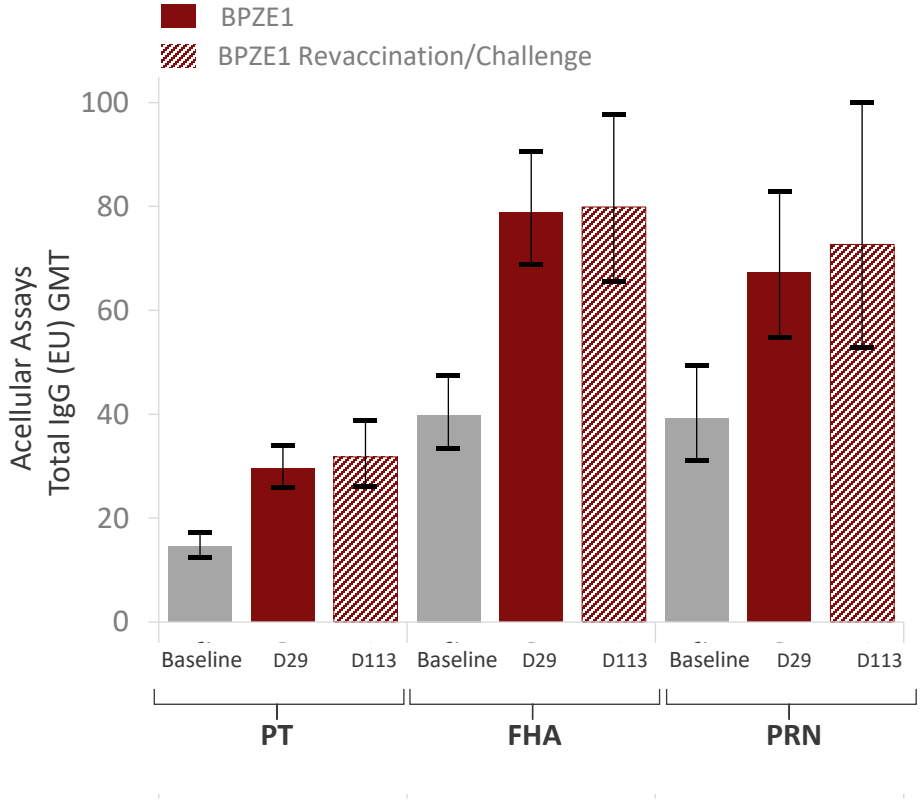


Mucosal (S-IgA) Acellular Pertussis Antibody Responses 28 Days Following Any Vaccination (GMT)

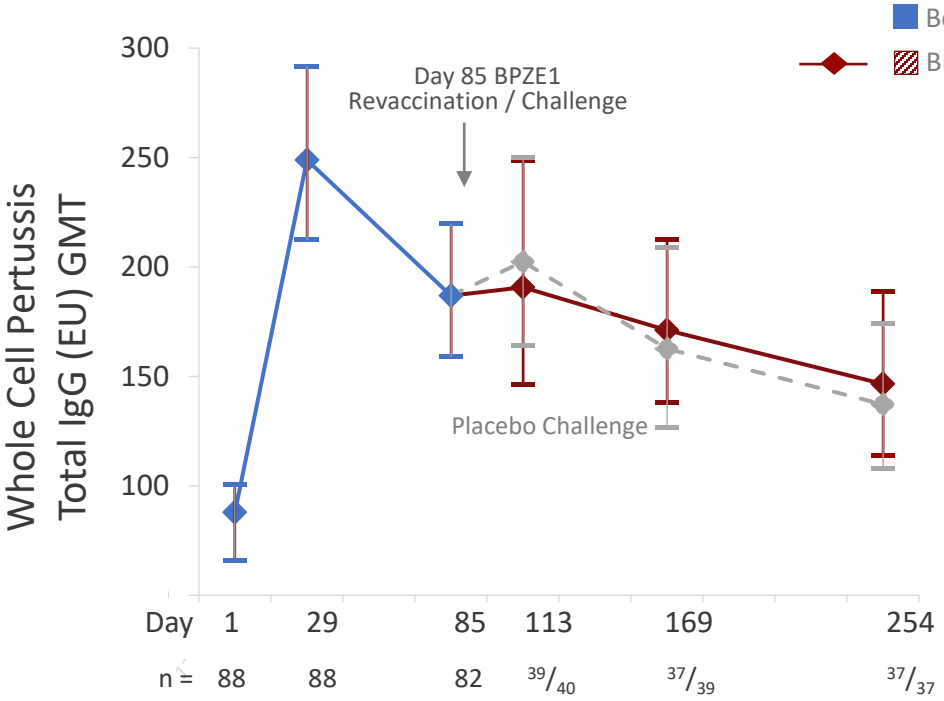


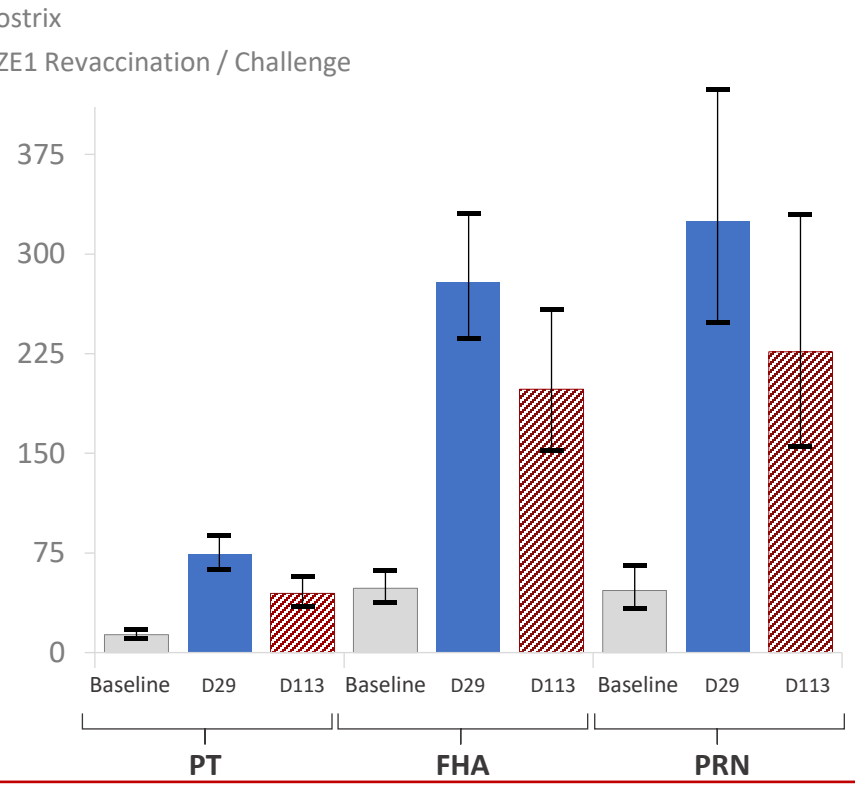
BPZE1 Induction of Serum IgG Whole Cell and Acellular Pertussis Antibody Responses Over Time (GMT)



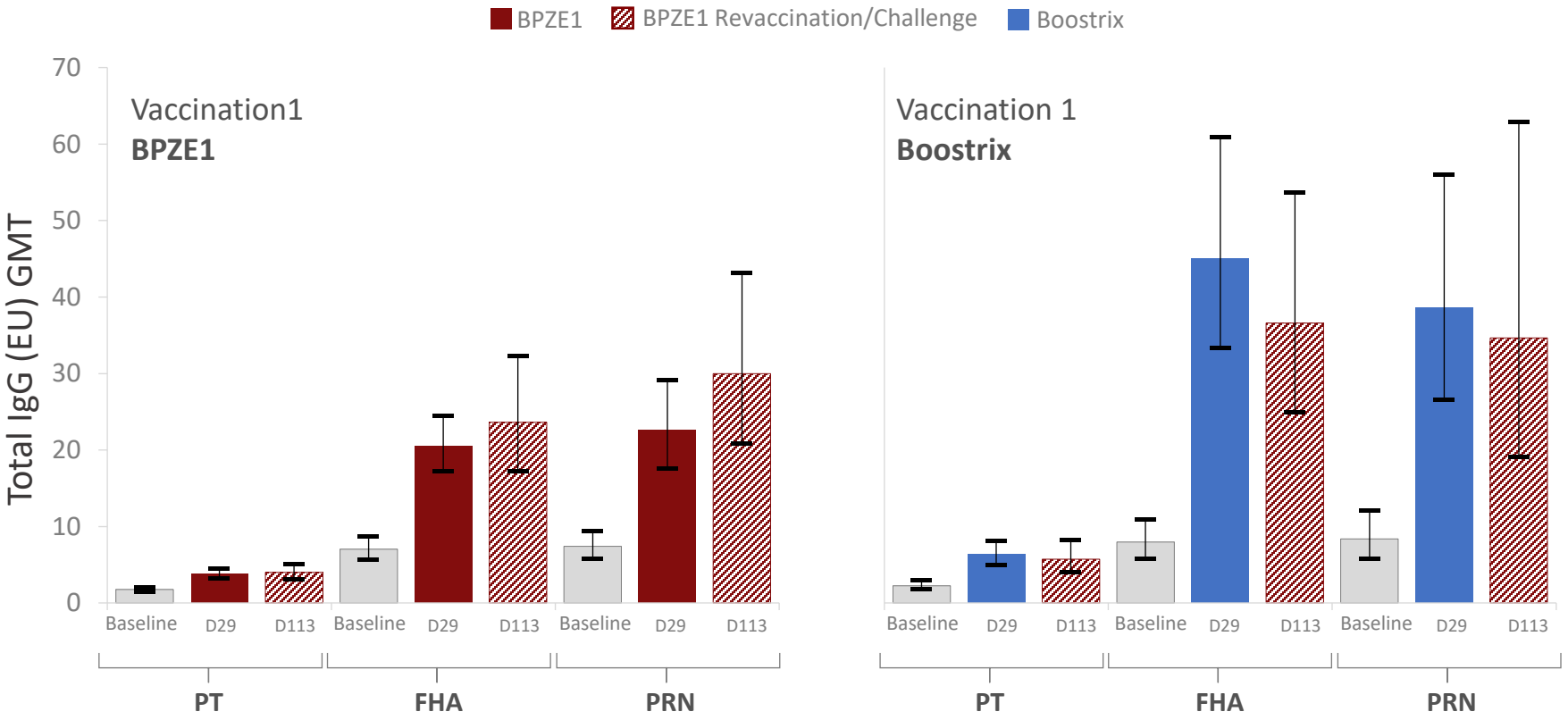


Boostrix Induction of Serum IgG Whole Cell and Acellular Pertussis Antibody Responses Over Time (GMT)





Serum IgA Acellular Pertussis Antibody Responses 28 Days Following Any Vaccination (GMT)



Conclusions – BPZE1, A Live Attenuated Pertussis Vaccine

- Nasal vaccination was well tolerated with mostly no/mild reactogenicity of short duration (similar to Boostrix and inert buffer)

- Re-vaccination/challenge at 3 month reduced colonization 90%
  - BPZE1 has the potential to disrupt pertussis transmission
  - In contrast, Boostrix vaccination reduced colonization by only 30%

- Broad mucosal immunity was induced - whole cell and acellular pertussis S-IgA antibodies
  - Responses remained above baseline through the end of the study (9 months)
  - Re-vaccination/challenge increased levels transiently. But by end of study (EOS), antibody levels were similar

- Broad serum immunity was induced - whole cell and acellular pertussis IgG and acellular pertussis IgA antibodies
  - Responses remained above baseline through the end of the study (9 months)

- In contrast, Boostrix was unable to induce a similar degree of broad mucosal immunity
  - As expected, Boostrix induce serum acellular pertussis antibodies which were observed to decay over time, resulting in antibody levels of similar magnitude at EOS.

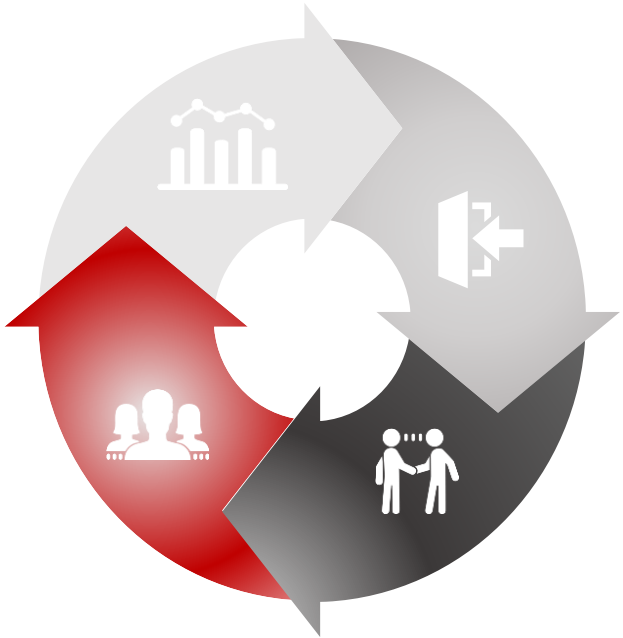
BPZE1 May Successfully Disrupt Human to Human *B. Pertussis* Transmission

Epidemic cycle propagates

Epidemic cycles reduced/eliminated

Vulnerable population develops severe disease

Cocooning strategies and herd protection can be improved



Pertussis enters a community

Humans are only known *B. Pertussis* reservoir.

Transmission occurs by close contact

Disruption of transmission will reduce/eliminate epidemics

Acknowledgements

We thank the subjects (and their families) for participating in this trial
Thank you to the members of the Independent Safety Monitoring Committee for their involvement and expertise
We recognize the Institut Pasteur de Lille for the development work on BPZE1