

Development of a live attenuated pertussis vaccine

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RESEARCH ARTICLE

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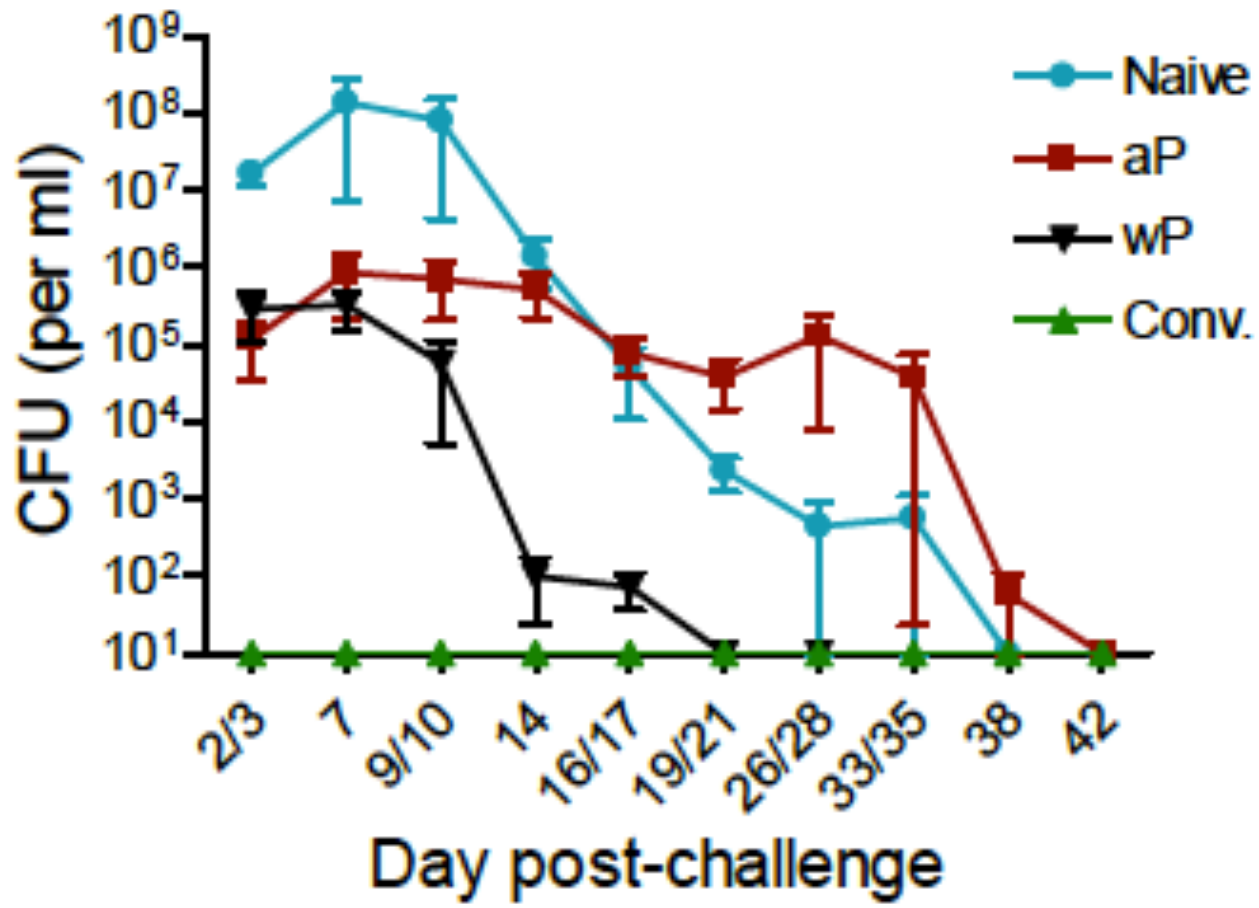
Asymptomatic transmission and the resurgence of *Bordetella pertussis*

Benjamin M. Althouse* and Samuel V. Scarpino



Interpretation Although a clear role for the previously suggested mechanisms still exists, asymptomatic transmission is the most parsimonious explanation for many of the observations surrounding the resurgence of *B. pertussis*. These results have important implications for *B. pertussis* vaccination policy and present a complicated scenario for achieving herd immunity and *B. pertussis* eradication.

Baboon studies



Live attenuated *B. pertussis* for intranasal administration

- ✓ Mucosal administration

 - ↪ Induction of systemic and mucosal immune responses

- ✓ Ease of administration

- ✓ Persistence of the bacteria in the host

 - ↪ Long-lived immune responses

 - Reduced number of administrations to induce protection

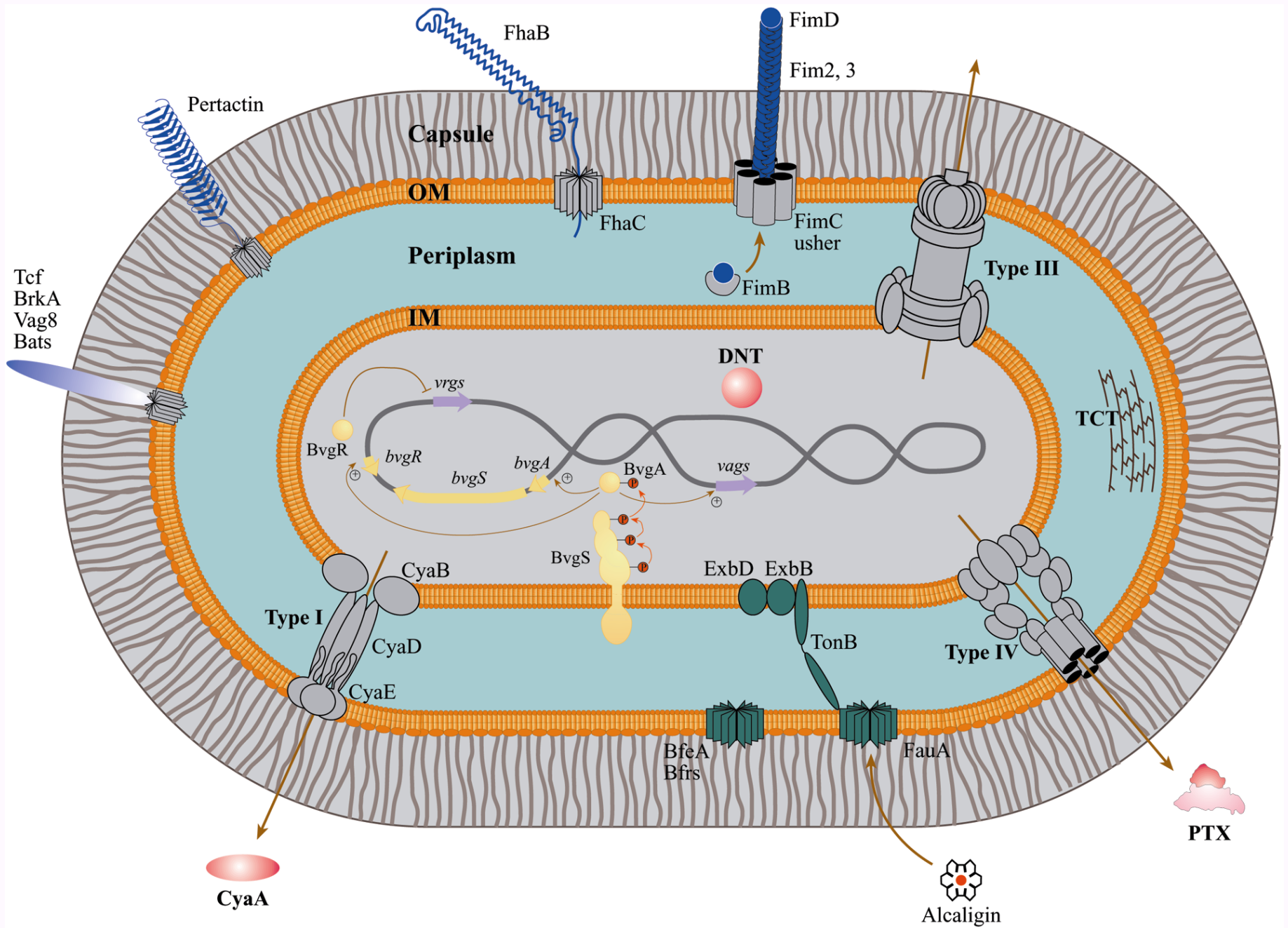
- ✓ Potential as a multivalent vaccine

Safety - natural biology of pertussis

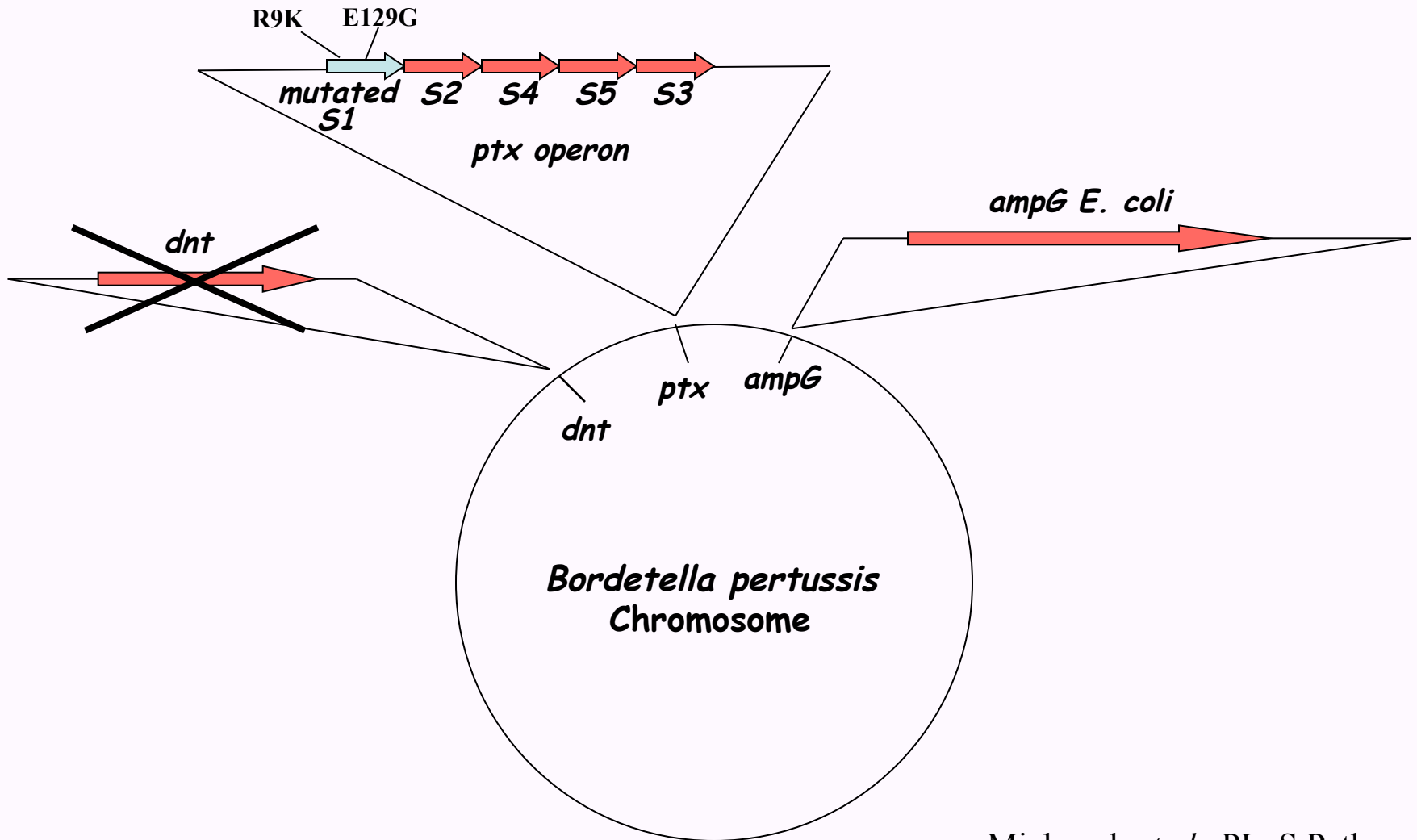
- B. pertussis* = strictly upper-respiratory pathogen
(no dissemination)
- No fever (although high fever after WCV)
- Pertussis = rare in AIDS patients (Cohn *et al.*, 1993)
(in contrast to *B. bronchiseptica*)
- B. pertussis* = extremely sensitive to erythromycin
- Very limited survival of *B. pertussis* in environment
(Porter & Wardlaw, 1993)

Feasibility

- B. bronchiseptica* in dogs and pigs (2-days old)
(Bey *et al.*, 1981; De Jong, 1987)



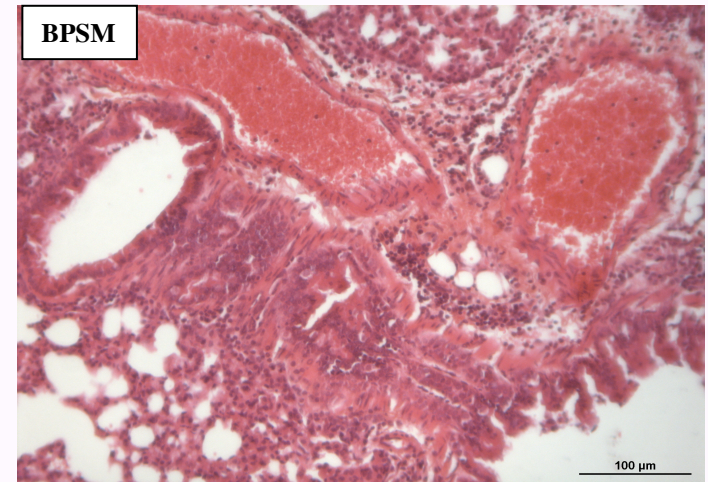
Attenuated *B. pertussis* strain BPZE1 (DNT- PTRE TCT-)



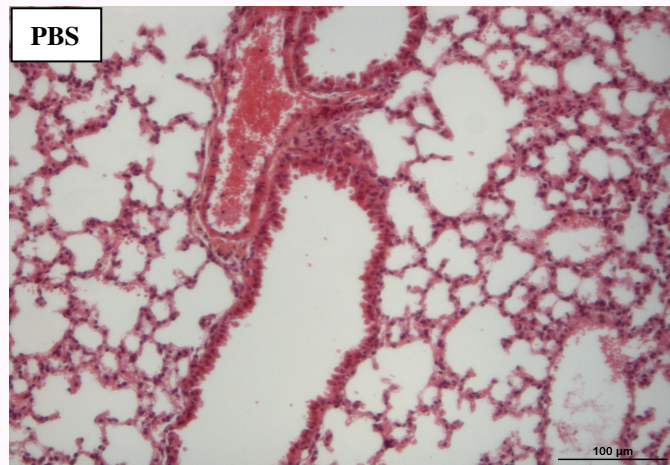
Drastic attenuation of *B. pertussis* BPZE1



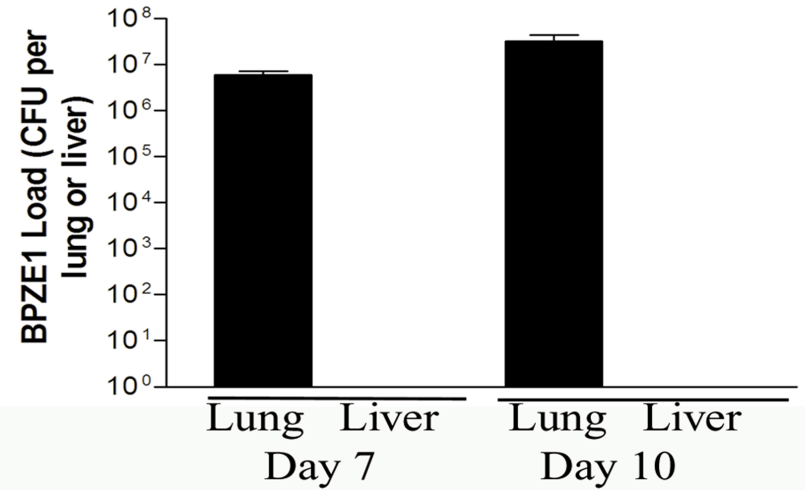
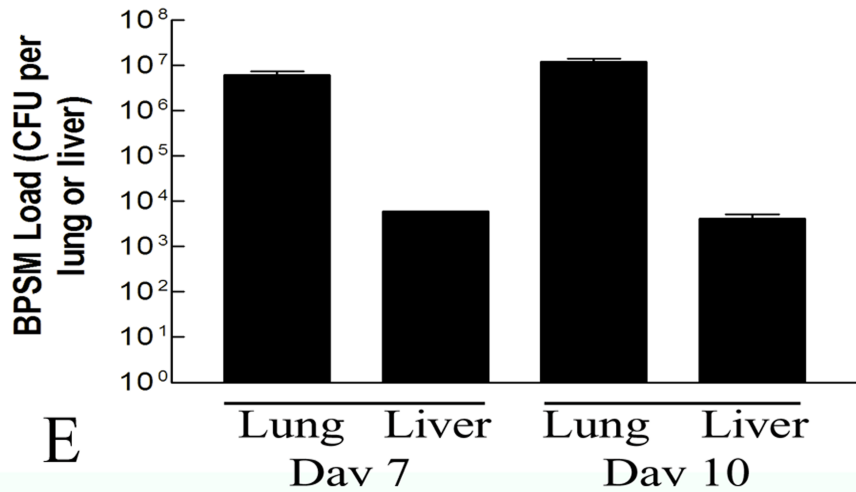
One week after i.n. infection, histology of the BPZE1-infected mice was similar to that of the control mice



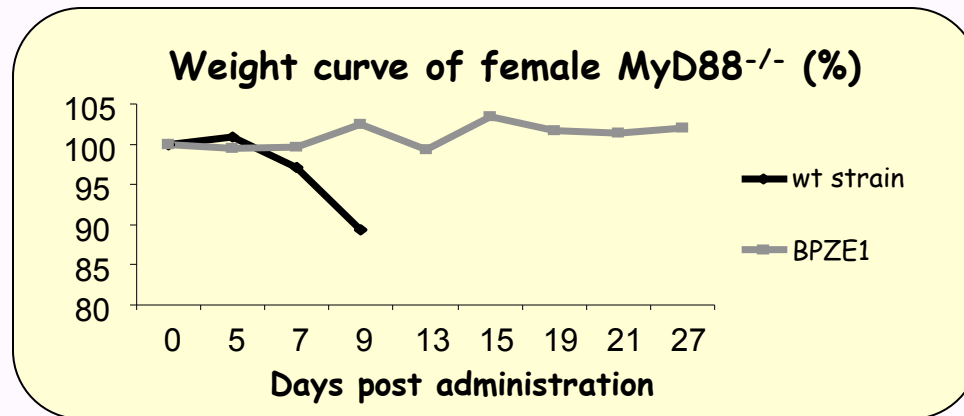
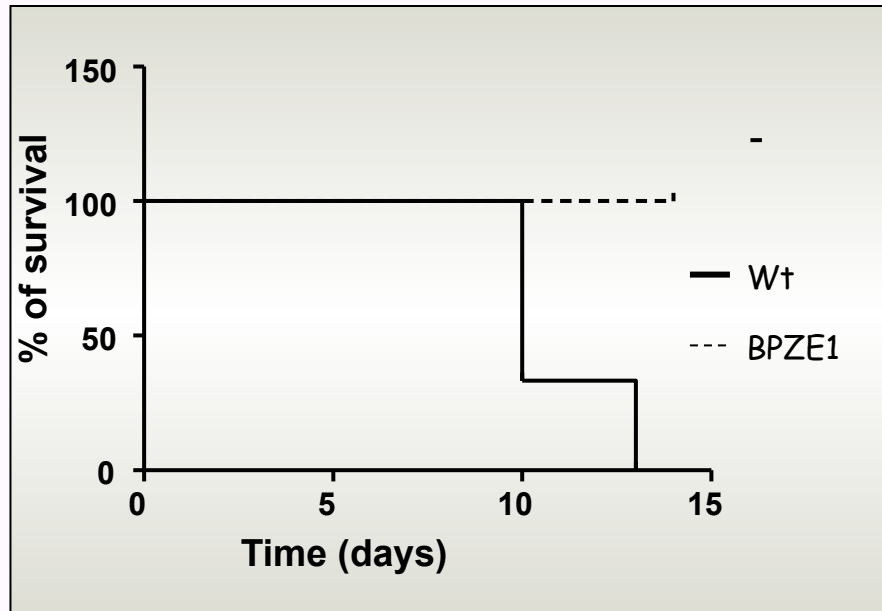
Infection with BPSM induced strong peribronchovascular infiltrates associated with hypertrophy of the bronchiolar epithelial cells



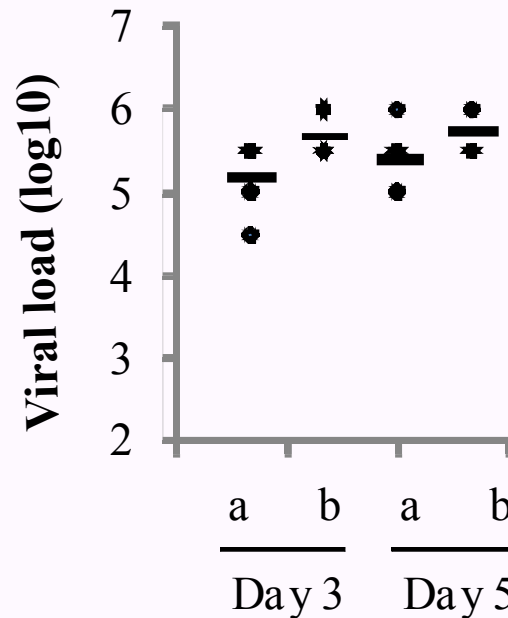
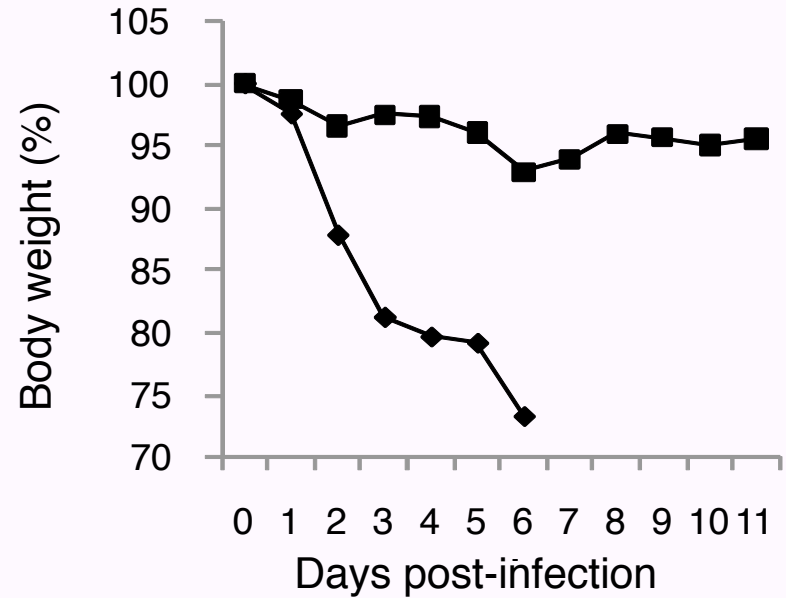
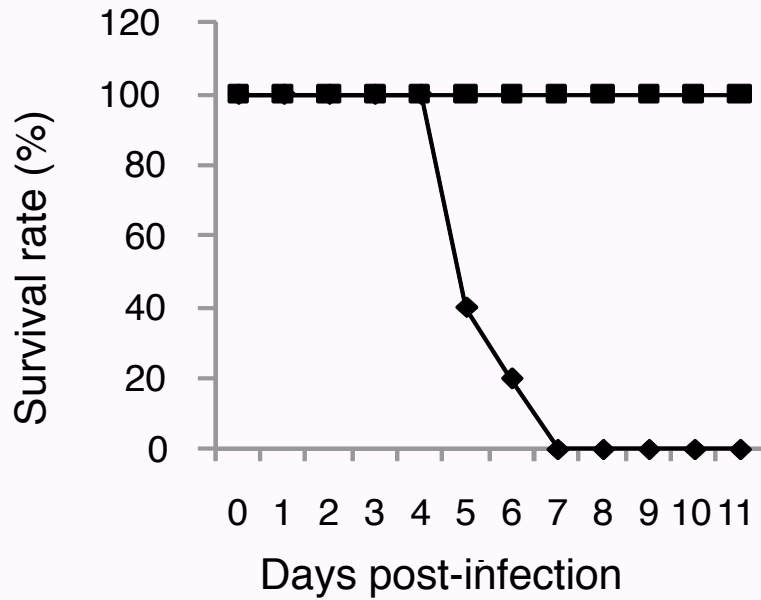
IFN- γ R KO mice



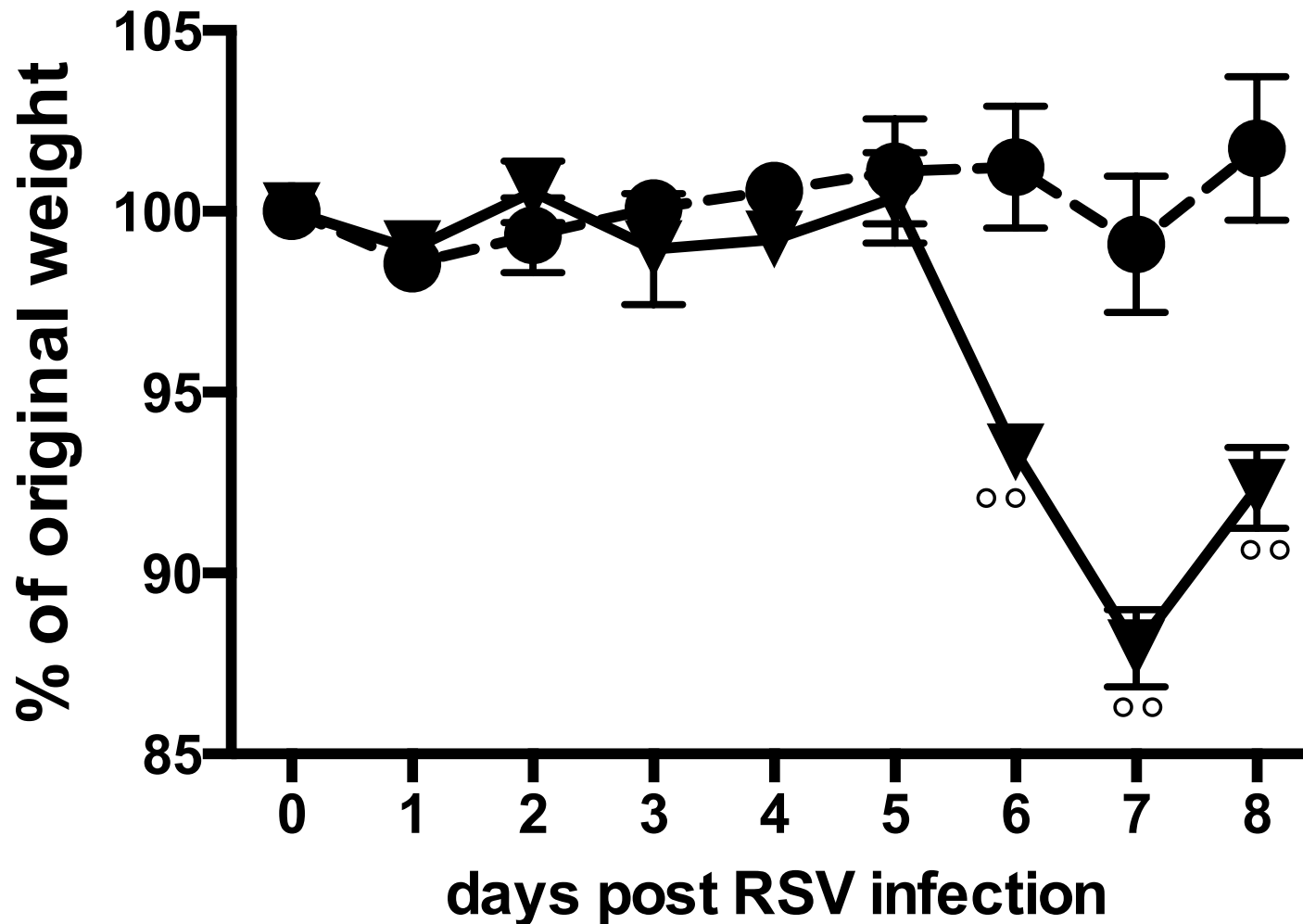
Infection of MyD88 KO mice



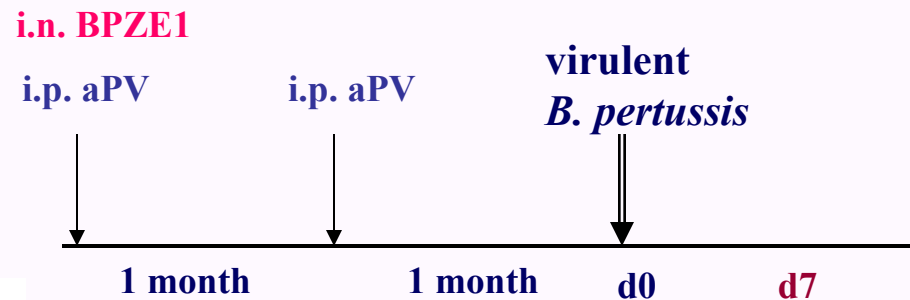
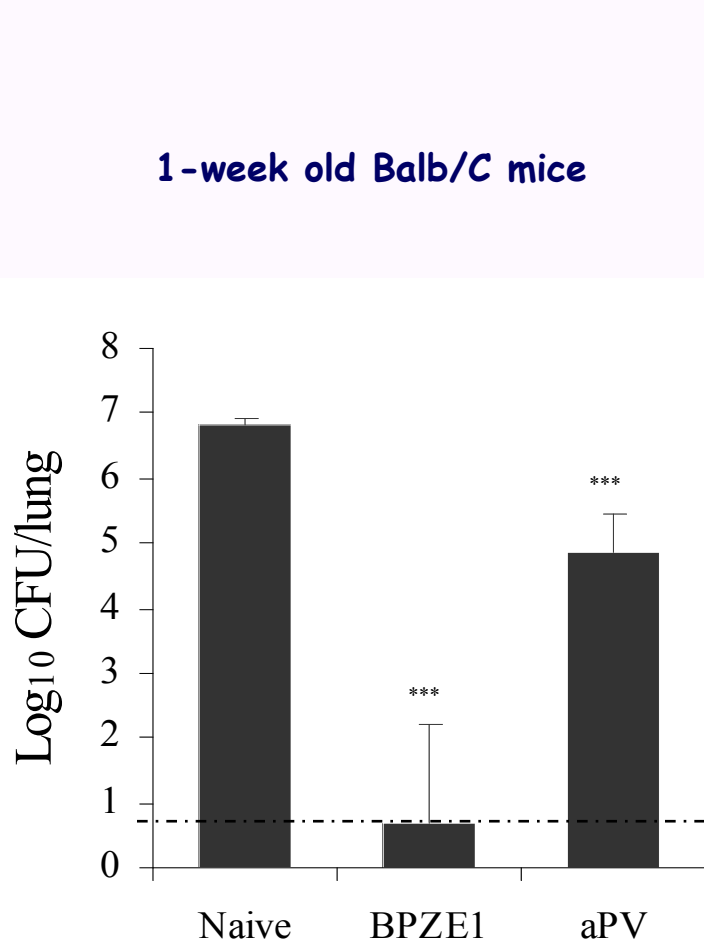
Booster effect in protection against H3N2



Protection against RSV disease



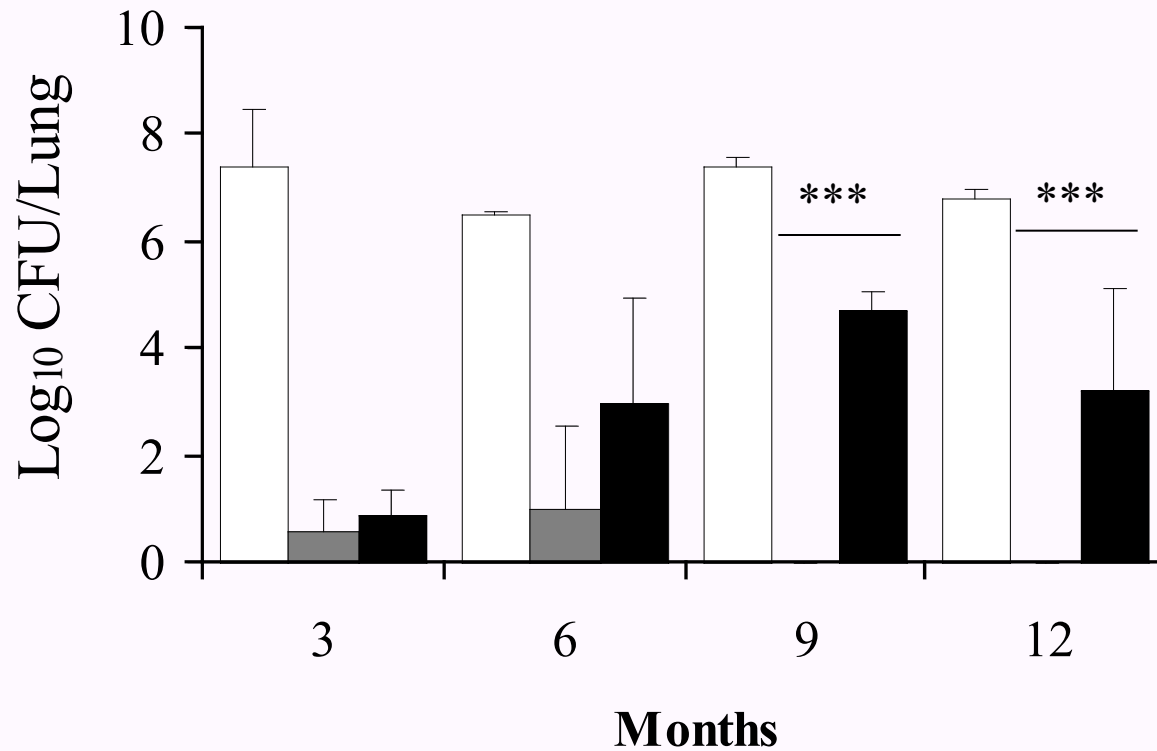
Protection against *B. pertussis* challenge after i.n. vaccination of infant mice with BPZE1



In 1-week-old mice, BPZE1 provides better protection than two i.p. doses of aPV

Longevity of BPZE1-induced immunity

3 weeks



First-in-man clinical trial

Study Objectives

✓ First-in-man, dose-escalating, placebo-controlled, double blind, safety trial

✓ Primary Objective

Assess general safety and local tolerability in the respiratory tract after single ascending dose of BPZE1

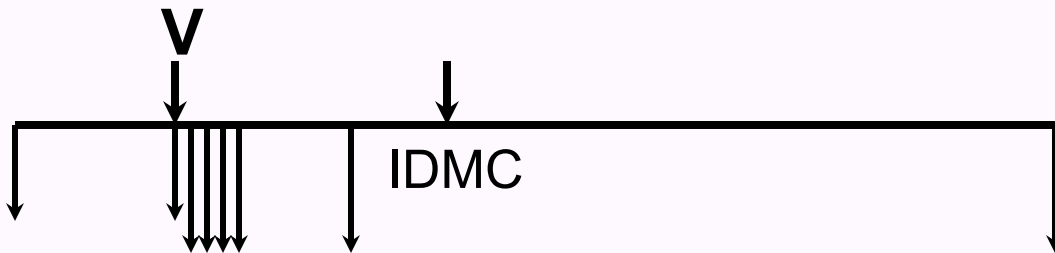
✓ Secondary Objectives

- Evaluate colonization of the human respiratory tract after a single ascending dose of BPZE1

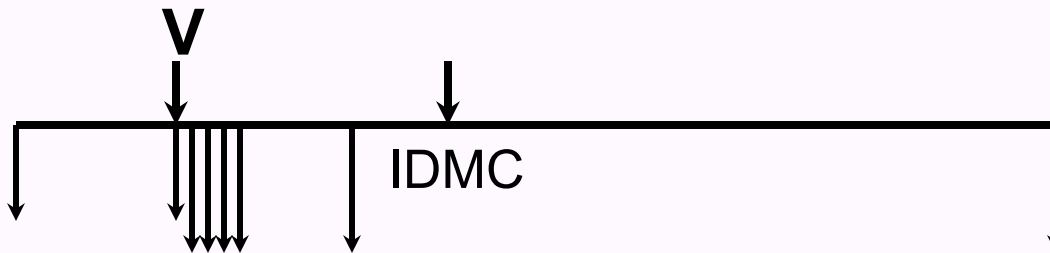
- Evaluate immune responses to *B. pertussis* after a single ascending dose of BPZE1

Phase I Trial Design

2010
Aug Sept Oct Nov Dec 2011
Jan Feb March Apr May June July

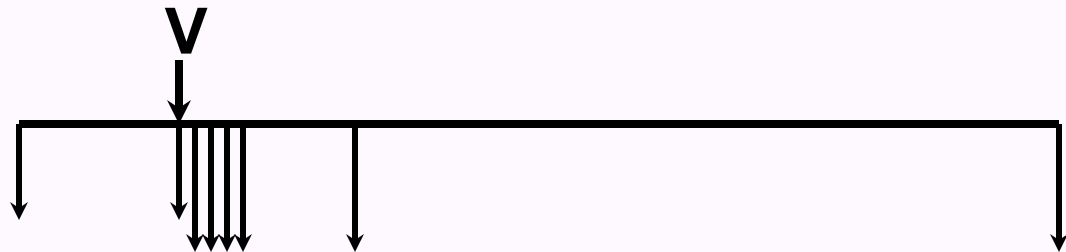


Low dose 10^3



Medium dose 10^5

High dose 10^7



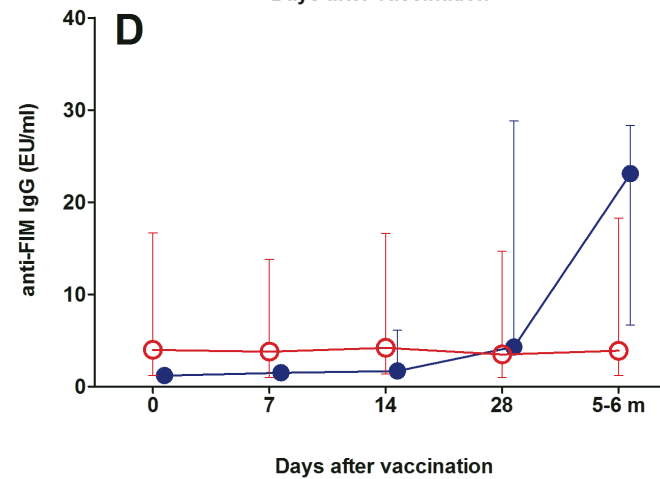
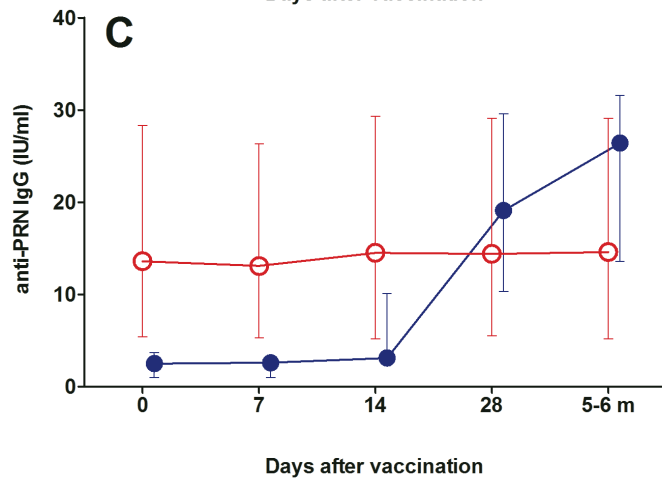
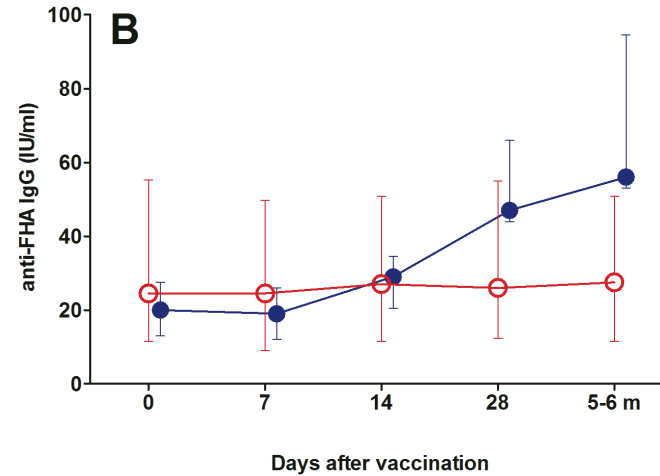
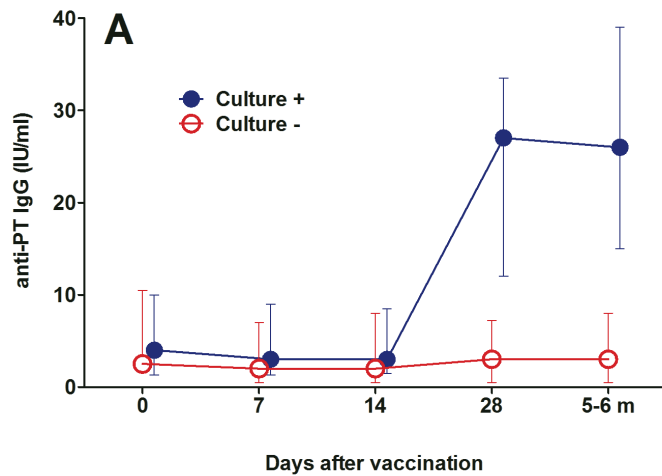
Solicited AE at two-week visit

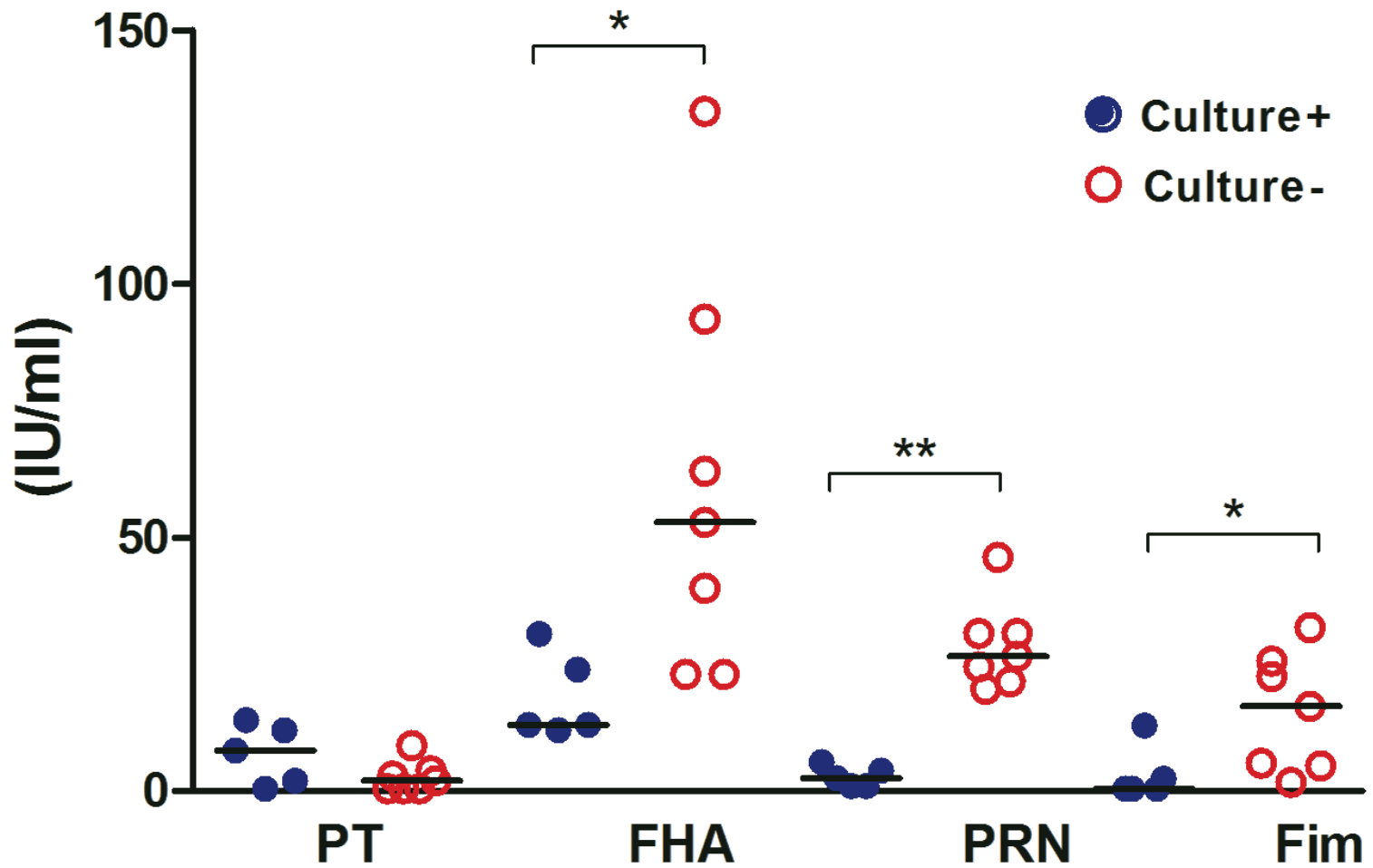
	Placebo	Low dose	Medium Dose	High dose
Cough	1	3	2	0
Nasal congestion	1	4	3	2
Epistaxis	0	0	0	0
Rhinnorhoea	2	5	1	2
Sneezing	3	2	3	1
Ear pain	0	1	0	1
Eye pain	0	0	0	0
Dyspnoea	0	0	0	0

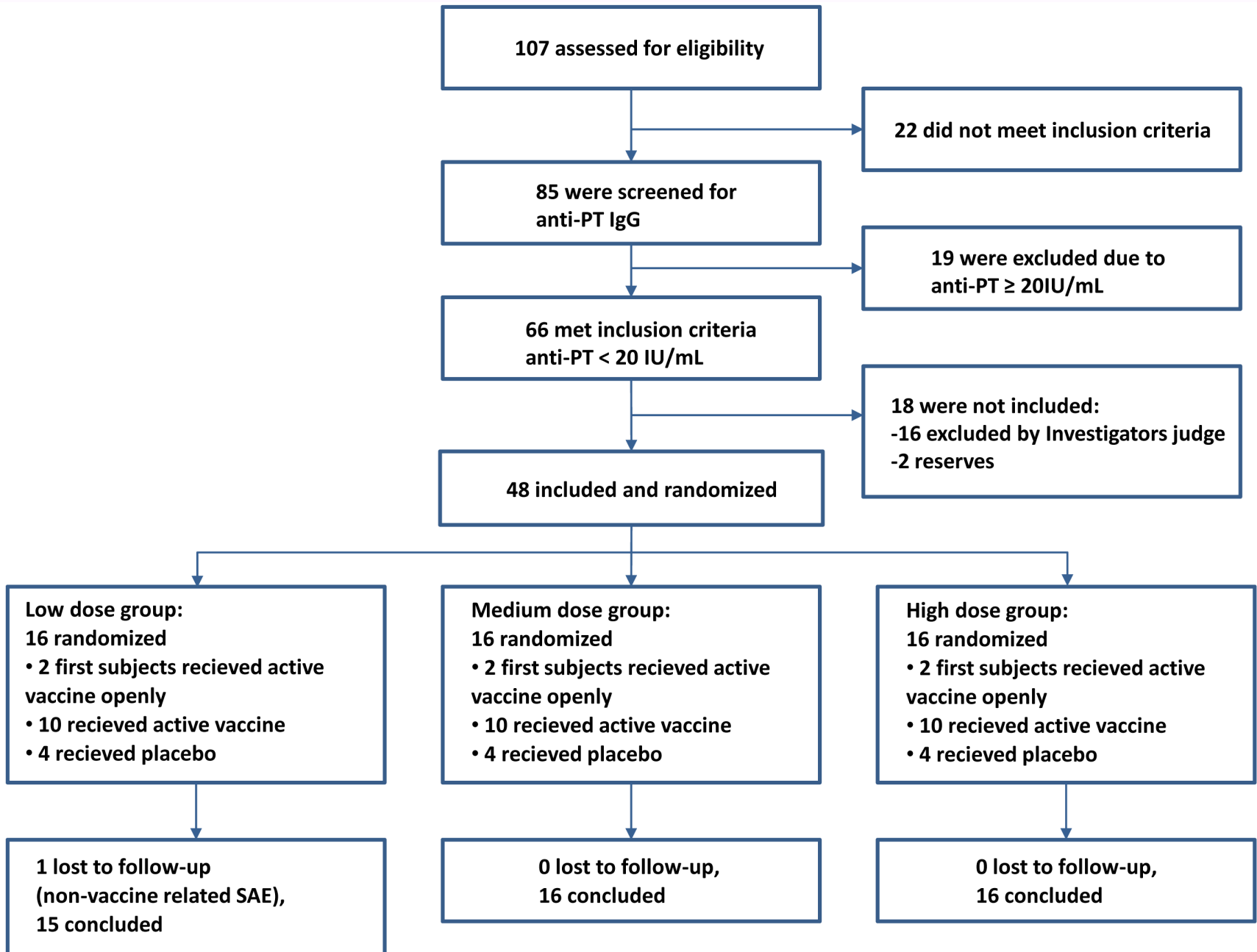
Colonization by BPZE1

Culture positive subjects						
Dose	Subject ID	Day 4	Day 7	Day 11	Day 14	Day 28
Low	110					
Medium	228					
High	334					
	343					
	344					
	345					
	346					

Antibody responses







Conclusions

- ✓ BPZE1 is safe in all pre-clinical models
- ✓ BPZE1 is safe in adult male volunteers
- ✓ BPZE1 induces strong protection against infection in mice & baboons
- ✓ BPZE1 can colonize human respiratory tract
- ✓ BPZE1 induces immune responses in all colonized human volunteers
- ✓ BPZE1 has off-target beneficial effects in mice

Future directions

- ✓ Phase Ib trial with higher dose/larger volume
- ✓ Further analysis of immune responses
- ✓ Development of a new formulation (e.g. freeze-dried)
- ✓ Evaluation of other methods for application
- ✓ Construction of recombinant BPZE1 derivatives

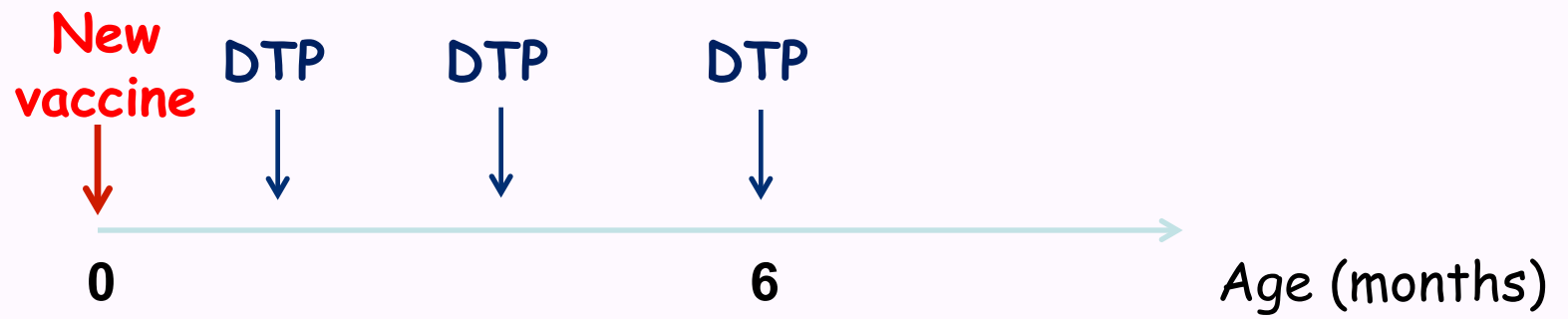
Main differences in phase Ib compared to phase Ia

- ✓ Higher vaccine doses (10^7 , 10^8 , 10^9 vs. 10^3 , 10^5 , 10^7)
- ✓ Larger vaccine volume (0.4 ml per nostril vs. 0.1 ml)
- ✓ Inclusion of both males and females
- ✓ Exclusion of subjects with either anti-PT or anti-PRN IgG
- ✓ One group with low anti-PT but high anti-PRN IgG levels
- ✓ Specific exclusion criterion regarding history of depression or suicidal attempt
- ✓ Quantification of bacteria in nasopharyngeal specimen

Secondary Objectives

- 1- To assess the colonization of the human respiratory tract by BPZE1
- 2 - To assess the B and T cell immune responses to PT, FHA, PRN and fimbriae 2/3 :
IgG and IgA in serum and in nasopharyngeal aspirate;
cytokines after stimulation with *B.pertussis* antigens and unrelated antigens.
+ cytokine levels in nasopharyngeal aspirate.
- 3 - To collect data on #1 and #2 in a small group of subjects with high PRN antibody levels (only highest vaccine dose).





Art is long, and time is fleeting

Longfellow, *Voices of the night*, 1839



BPZE1

Lost In Translation

Times will come

“when the unthinkable becomes the thinkable
and
the impossible actually happens”

Arundhati Roy

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THANK YOU VERY MUCH

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