

Live attenuated pertussis vaccines Are they the future of pertussis control ?

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Sydney, August 25/26, 2011



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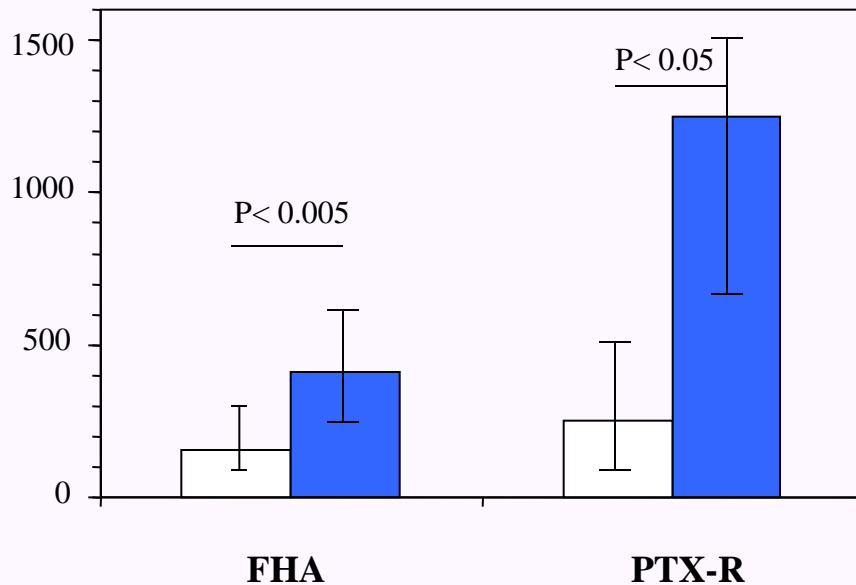
Acute *Bordetella pertussis* infection in 2 months old infants

27 one to four months-old *B. pertussis* infected children

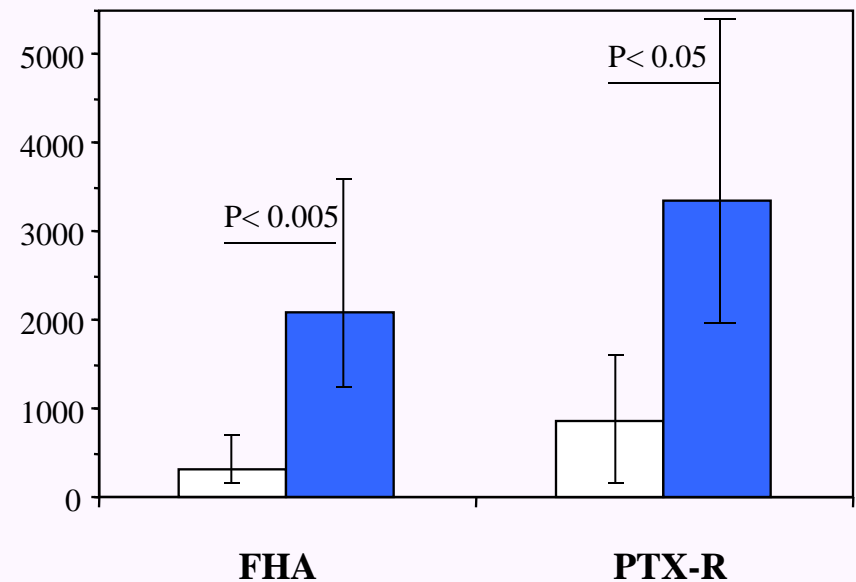
44 two months-old non-immune infants

Antigen-specific IFN- γ secretion

Nb. of IFN- γ SC / 10⁶ PBMC



IFN- γ concentration (pg/ ml)



Absence of antigen-specific IL-4 and IL-13

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

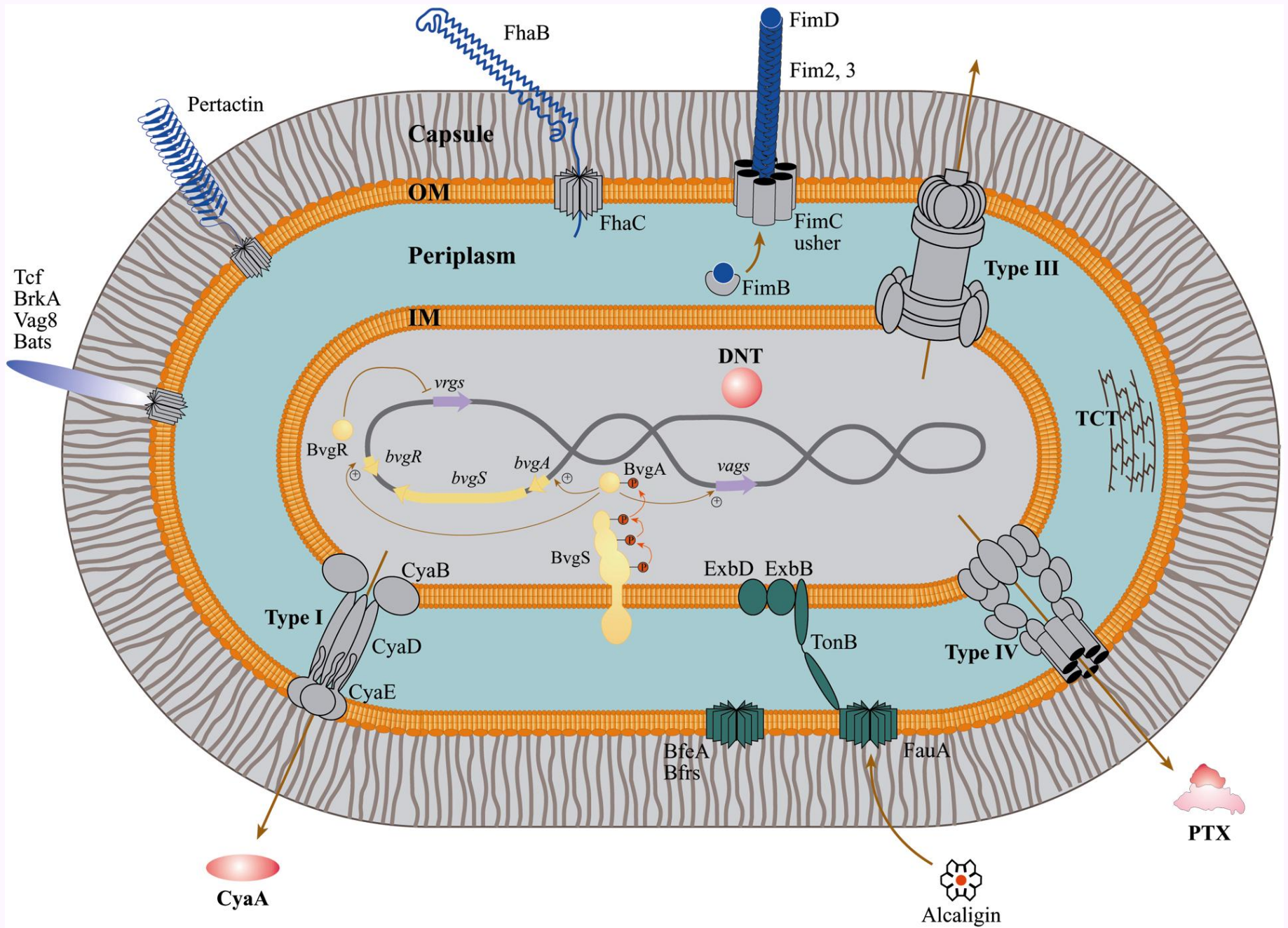
- ✓ Potential as a multivalent vaccine

Safety - natural biology of pertussis

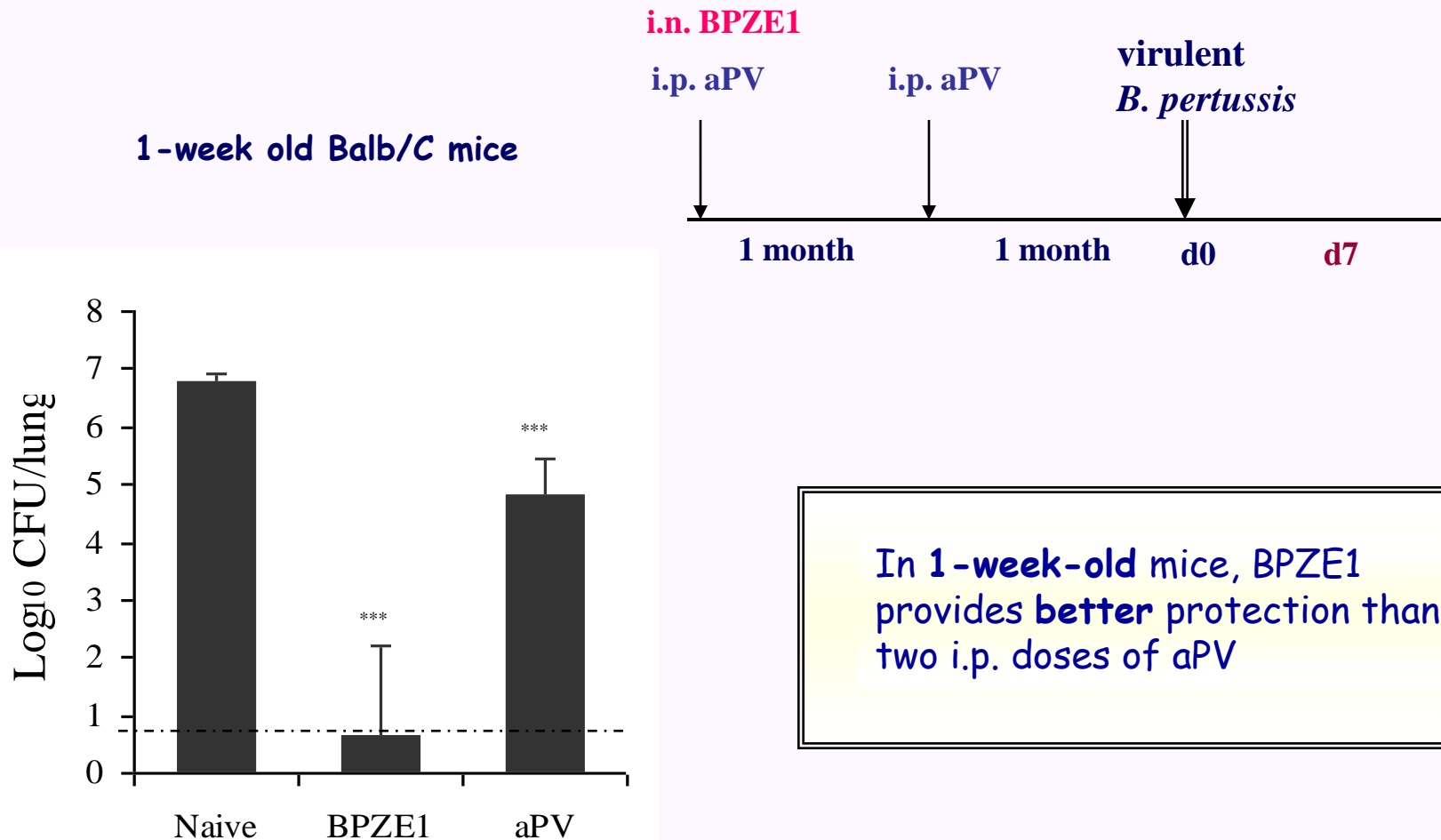
- B. pertussis* = strictly upper-respiratory pathogen
(no dissemination)
- No fever (although high fever after WCV)
- Pertussis = rare in AIDS patients (Cohn *et al.*, 1993)
(in contrast to *B. bronchiseptica*)
- B. pertussis* = extremely sensitive to erythromycin
- Very limited survival of *B. pertussis*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

Feasibility

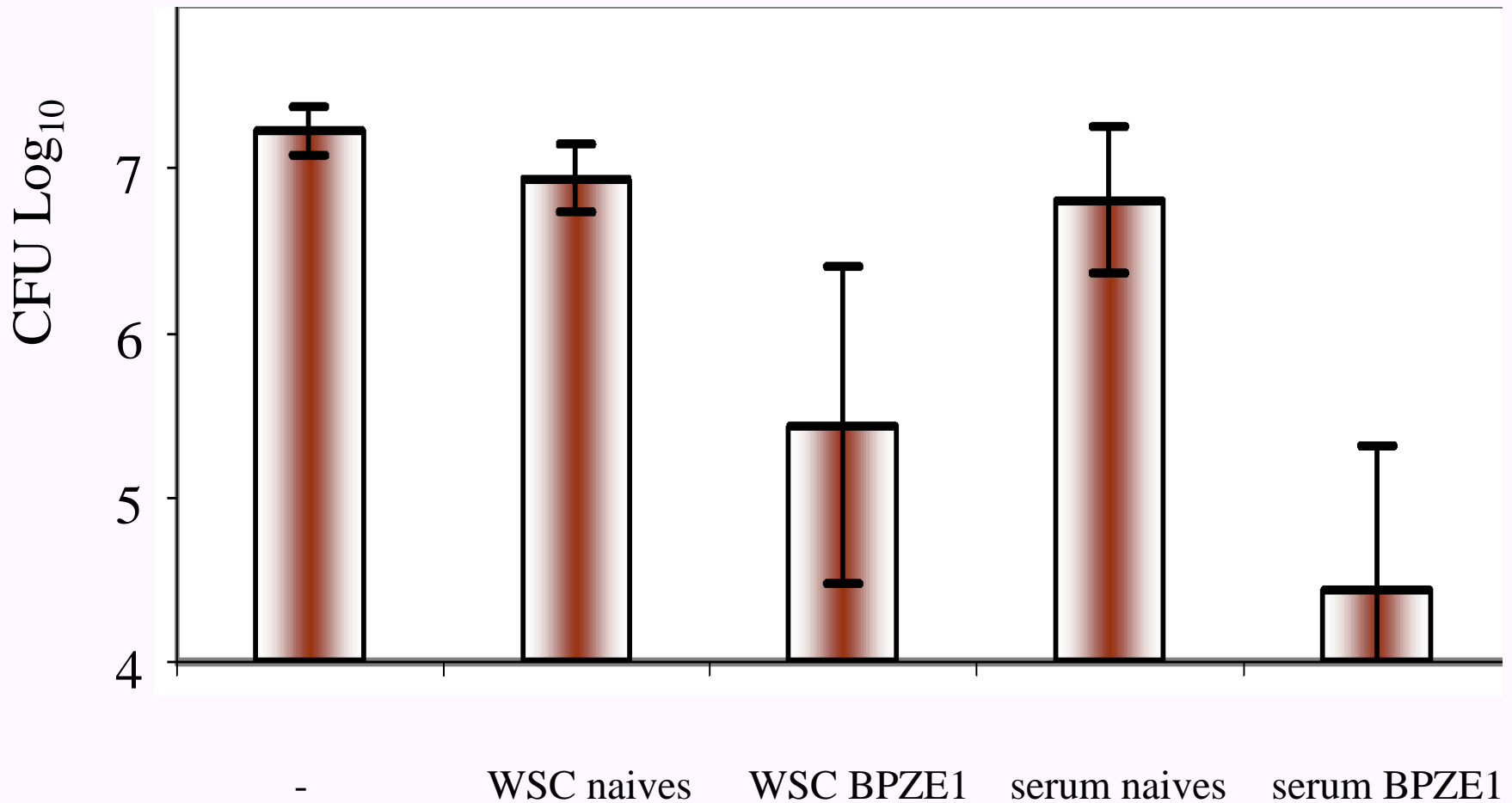
- B. bronchiseptica* in dogs and pigs (2-days old)
(Bey *et al.*, 1981; De Jong, 1987)



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

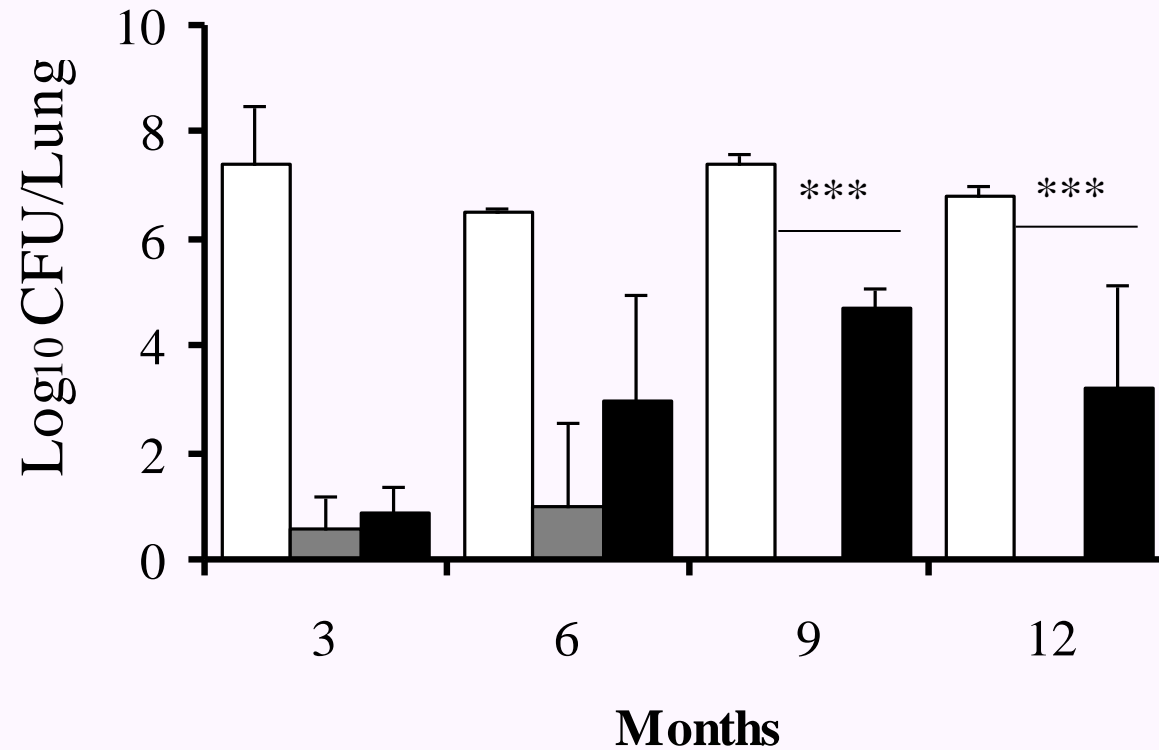


Passive transfer to SCID mice (200 μ l/50.10⁶ WSC)

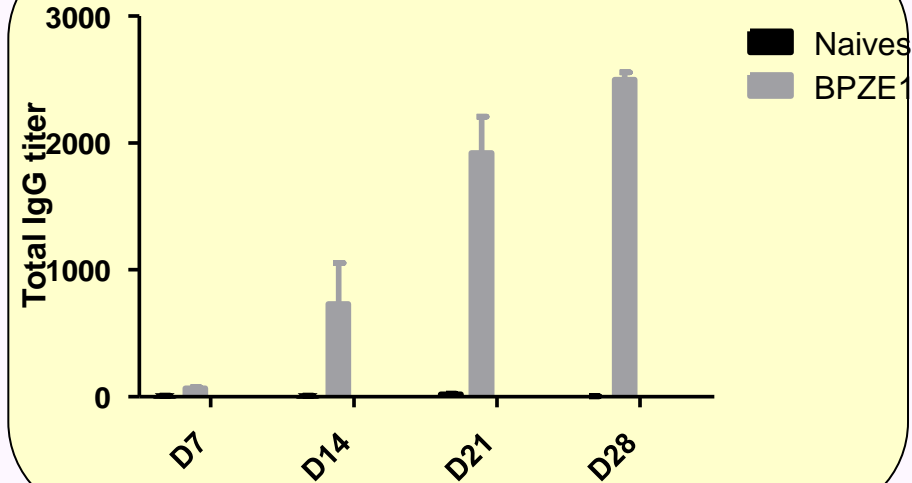
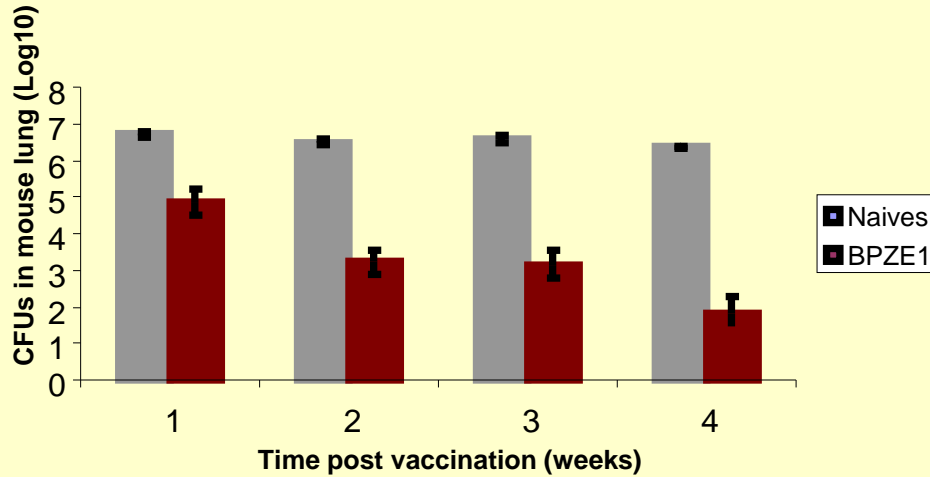
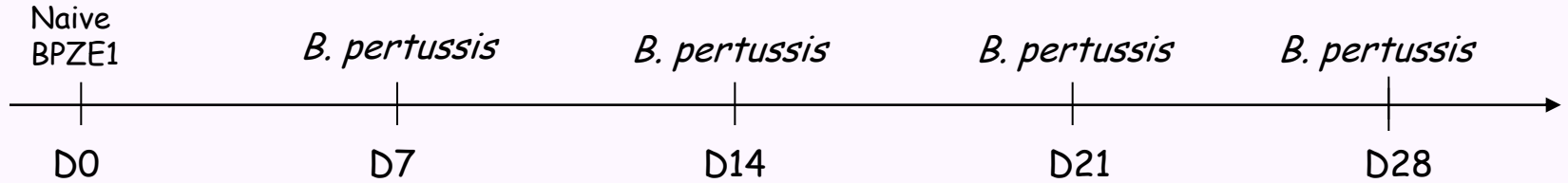


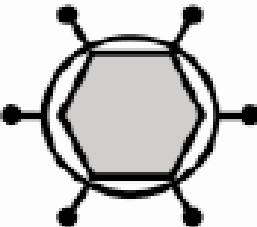


Longevity of BPZE1-induced immunity

3 weeks

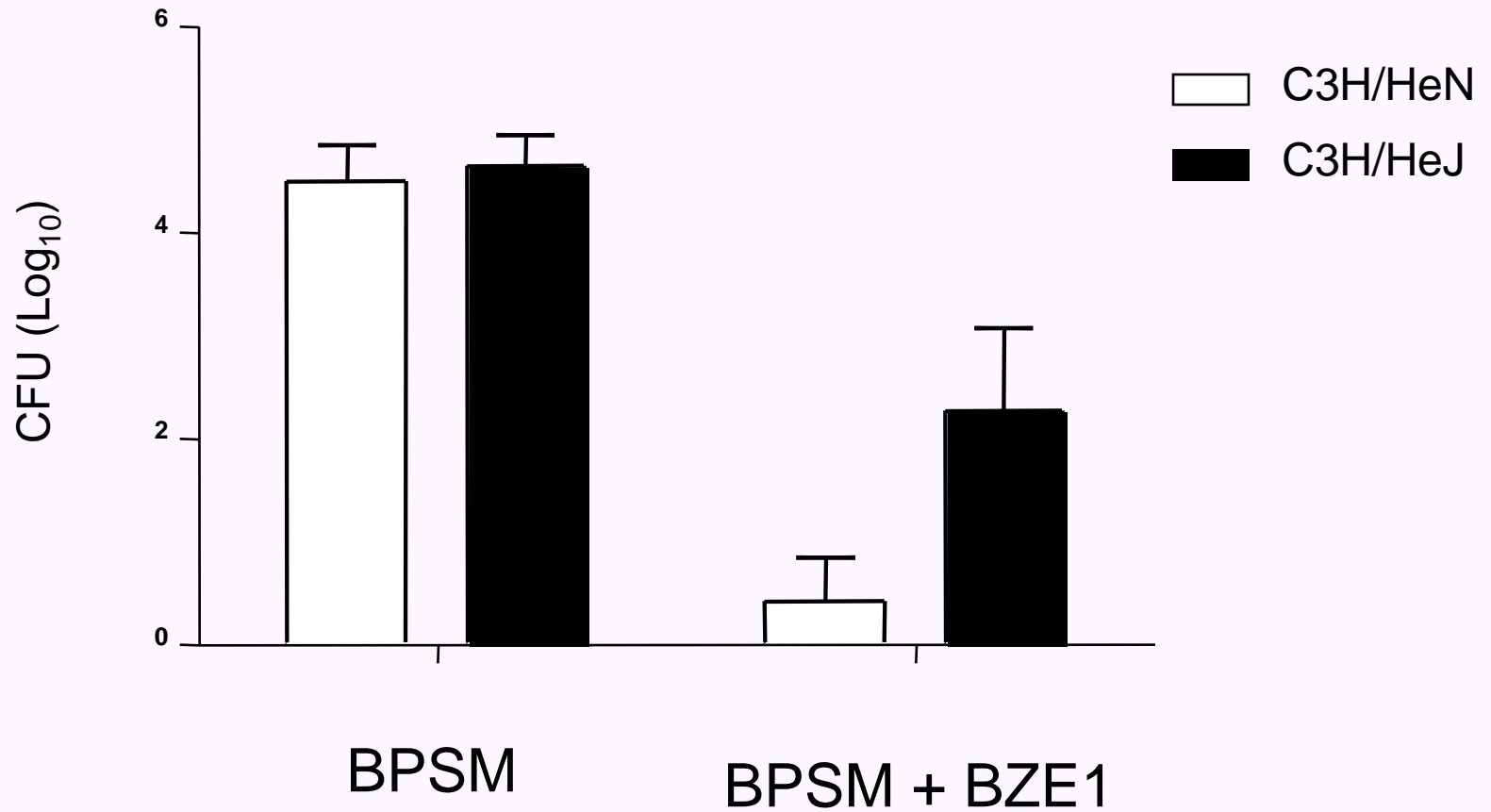


Early protection induced by BPZE1 vaccination

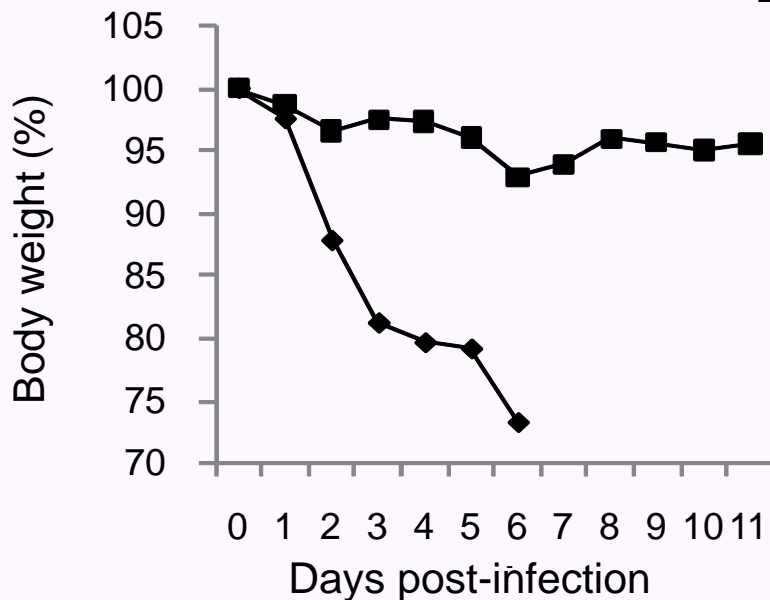
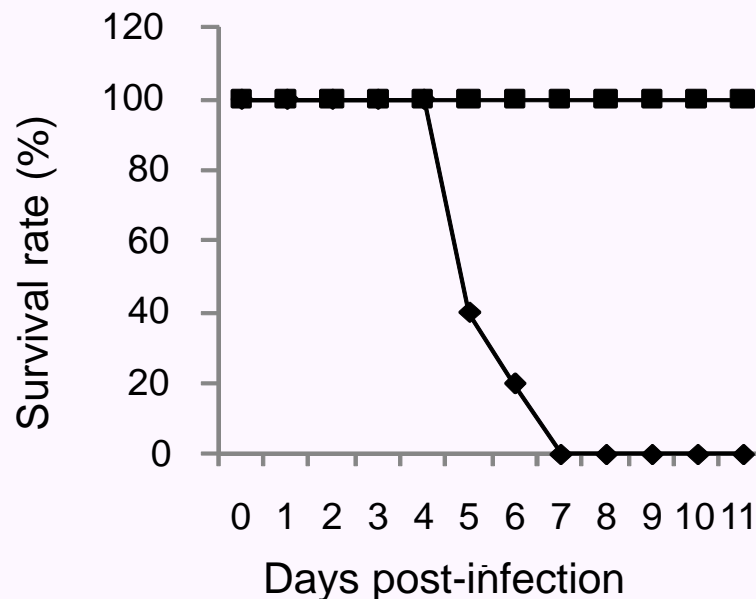
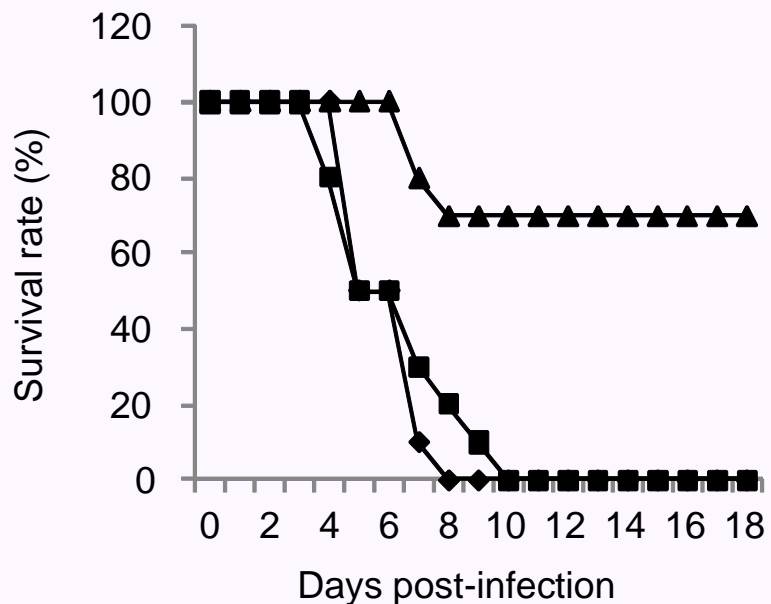


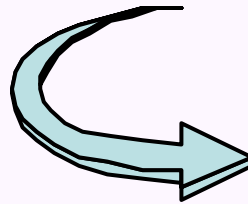
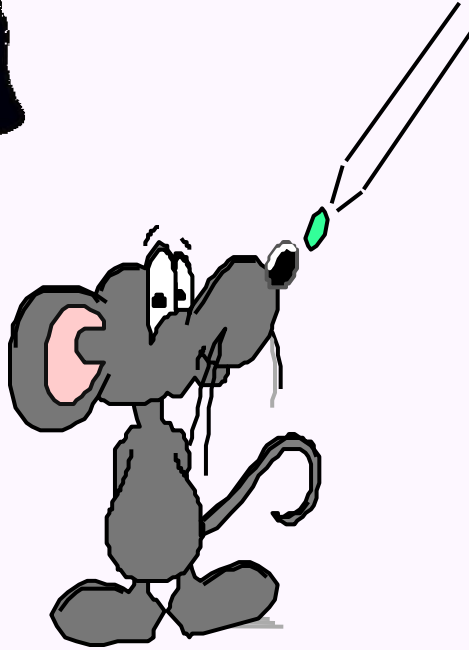
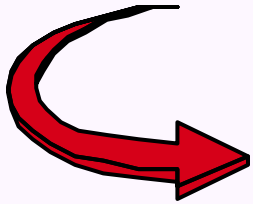
Microbe	PAMP	PRR	Site of recognition
 <p>Virus</p>	Glycoproteins 5'PPP RNA ss RNA dsRNA Genomic DNA	TLR2, TLR4 RIG-I TLR7, TLR8 TLR3, MDA5, RIG-I TLR9, DAI	Cell surface Cytoplasm Endosomes Endosomes/cytoplasm Endosomes/cytoplasm
 <p>Bacteria</p>	Lipopeptides Lipoteichoic acid	TLR2 TLR2	Cell surface Cell surface
	Peptidoglycan LPS	TLR2 TLR4	Cell surface Cell surface
	Flagellin CpG DNA B-form DNA Diaminopimelic acid Muramyl dipeptide	TLR5 TLR9 DAI NOD1 NOD2	Cell surface Endosome Cytoplasm Cytoplasm Cytoplasm
 <p>Protozoa</p>	GPI anchors dsRNA CPG DNA Haemozoin Profilin-like protein	TLR2, TLR4 TLR3 TLR9 TLR9 TLR11	Cell surface Endosomes Endosomes Endosomes Cell surface

Role of TL4 in early protection



Protection against Influenza A virus-induced mortality





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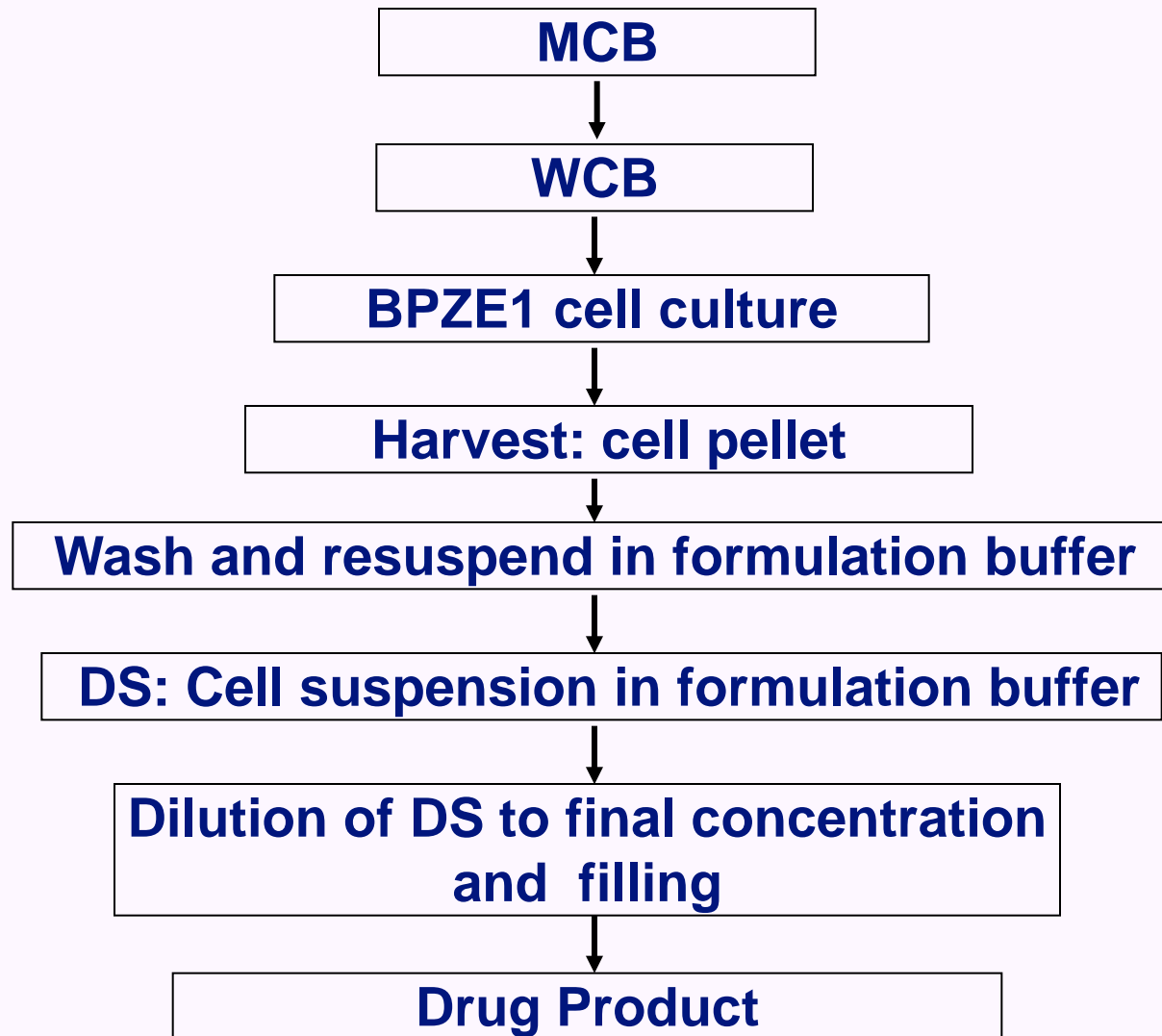
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www.child-innovac.org

C Ausiello
AM Buisman
C Locht
B Mahon
F Mascart
P Openshaw
R Thorstensson
A van Broekhoven
C van Els
J Weinbach



Manufacturing Process of BPZE1 DP



Release Parameters and Characterization

Parameter	Assay	MCB	WCB	DS	DP
Description Quantity	Visual aspect				+
	pH				+
	Osmolarity				+
	cfu – assay	#	#	#	Δ/+
	OD-measurement	#	#	#	
	Delivered dose uniformity (EP2.9.40)				+
	Endotoxin				#
Identity (attenuated BPZE1)	Colony morphology	+	+	+	+
	Genetic tests (PT, DNT, <i>ampG</i>)	+		+	
Safety*	Microbial purity	+	+	+	+
	Absence of revertant <i>B. pertussis</i>	+		+	
	Absence of active PTX: in vitro CHO clustering test			#	
Stability plan	cfu/ml in function of storage time	+	+		+

Δ: must have for Tox; +: must have for Phase I; # In Process Control, internal test for information only

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 T and B cell immune responses to *B. pertussis* after a single ascending dose of BPZE1

Inclusion Criteria

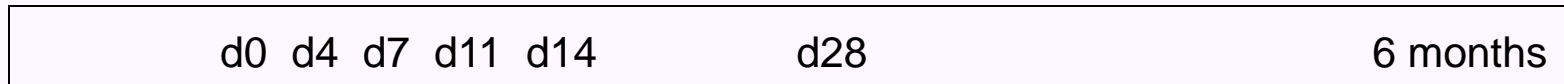
- Healthy male volunteer born between 1979 and 1991, who has not experienced pertussis during the last 10 years and has not been vaccinated with any pertussis vaccine
- Informed consent form signed by subject
- Subject able to attend all scheduled visits and to understand and comply with the study procedures (able to read and write Swedish)

Exclusion Criteria

1. Pertussis toxin serum IgG ≥ 20 units/mL
2. Blood pressure after resting $\geq 150/90$ mmHg
3. Heart rate after resting ≥ 80 bpm
4. Respiratory rate after resting ≥ 20 /min
5. Unwillingness to refrain from nicotine from screening to day 28
6. Donated blood or blood loss (≥ 450 ml) within 60 days prior to screening
7. Receipt of Ig/blood products/immunosuppressive drugs within the previous 3 ms
8. Receipt of corticosteroids in respiratory tract 30 days prior to day 0
9. Use of herbal medications or dietary suppl. 7 days prior to day 0 and for 30 days
10. Any vaccine within the last 30 days and 30 days after day 0
11. Evolving encephalopathy within 7 days of a previous vaccination
12. Known hypersensitivity to any component of the study vaccine
13. Participation in other trials in the previous 3 months
14. Inability to adhere to the protocol
15. Family history of congenital or hereditary immunodeficiency
16. Infection with HIV, HCV, HBV
17. Any medical condition which, in the opinion of the investigator, might interfere with evaluation of the study objectives
18. Clinically significant abnormal lab. Values
19. Frequent contact with children < 1 year of age

Phase I Trial Primary Objective

V
↓



Serious AE
Non-sol.AE

X X X X X

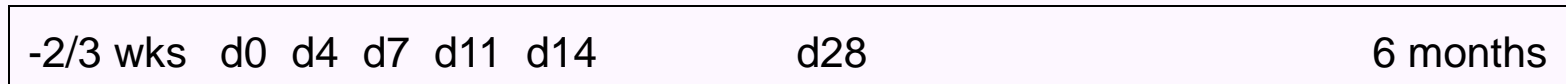
X

X

Solicited AE
Severity
Duration
Outcome

- Local, systemic, haematologic
- Classified in diary
- Any cough (Start, duration, severity, outcome)

Phase I Trial Secondary Objective



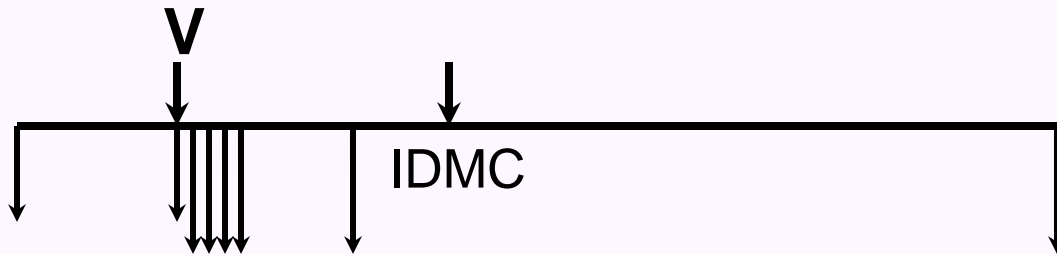
		X	X	X	X		X		X	Culture
										Serology
X	X	X	X	X	X		X		X	(FHA, PT, Prn, Fim, WCL)
										Saliva
X	X	X	X	X	X		X		X	(FHA, PT, Prn, Fim, WCL)
										B/T Elispot
	X				X		X		X	(FHA, PT, Prn, Fim, WCL)

Phase I Trial Study Design (I)

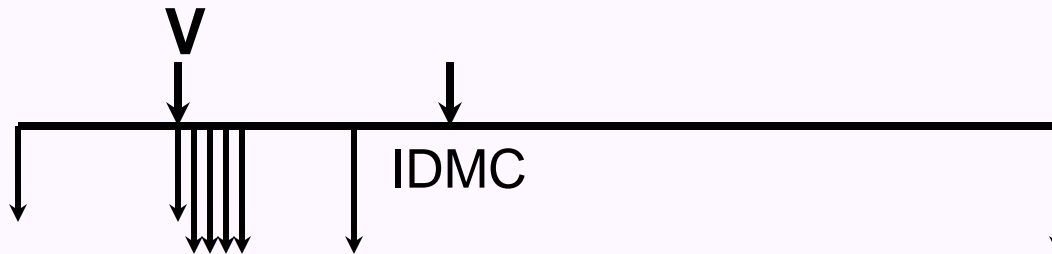
Thursday, September 9, 2010		1 V
Friday, September 10, 2010		1 V
Monday, September 12, 2010		2 V/P
Tuesday, September 13, 2010	3 V/P	
Wednesday, September 14, 2010		4 V/P
Thursday, September 15, 2010		5 V/P
TOTAL		12 V + 4 P

Phase I Trial Design (II)

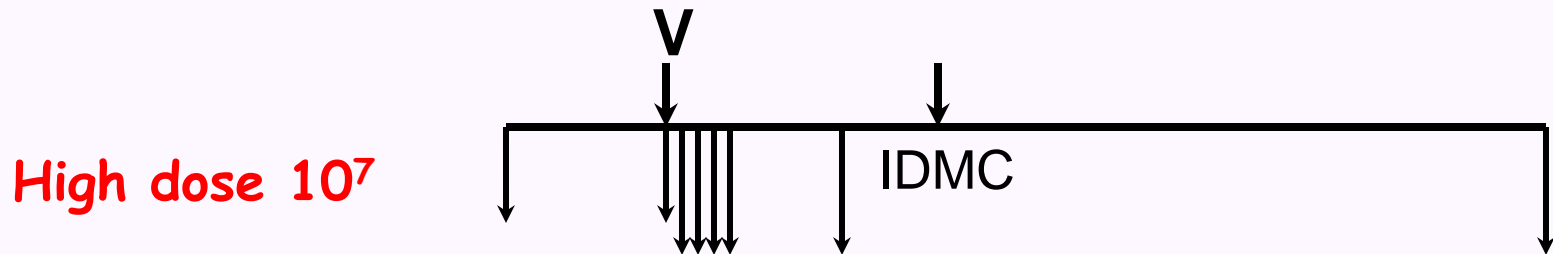
2010
Aug Sept Oct Nov Dec 2011
Jan Feb March Apr May June July



Low dose 10^3



Medium dose 10^5



High dose 10^7



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