Center for Infection & Immunity of Lille

Developing a new live pertussis vaccine with beneficial off-target effects

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Whooping-cough or Pertussis

- 6th cause of childhood mortality due to infectious agents
- 200,000 annual pertussis-linked deaths, 16 million cases
- Prevalent in developing countries, Re-emerging in the developed world

Definition « Re-emerging infection»:

- has existed but is no more detectable or at such low-level that it is not considered a public health problem anymore
- is rapidly increasing in incidence or geographic range

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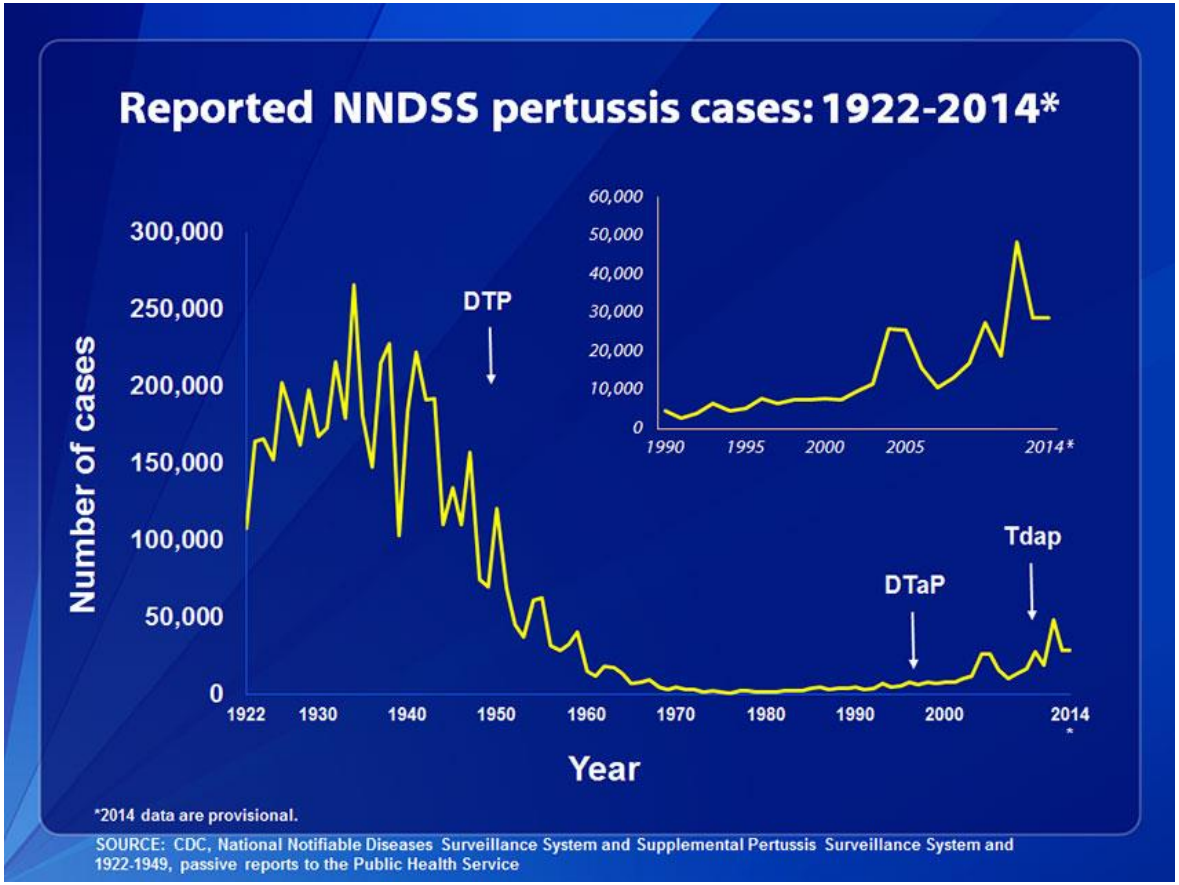
Whooping-cough or Pertussis in US



2010 > 27,000 reported cases
2012 > 48,000 reported cases , the highest number since 1955
2014 > 28,000 reported cases
2015 ?

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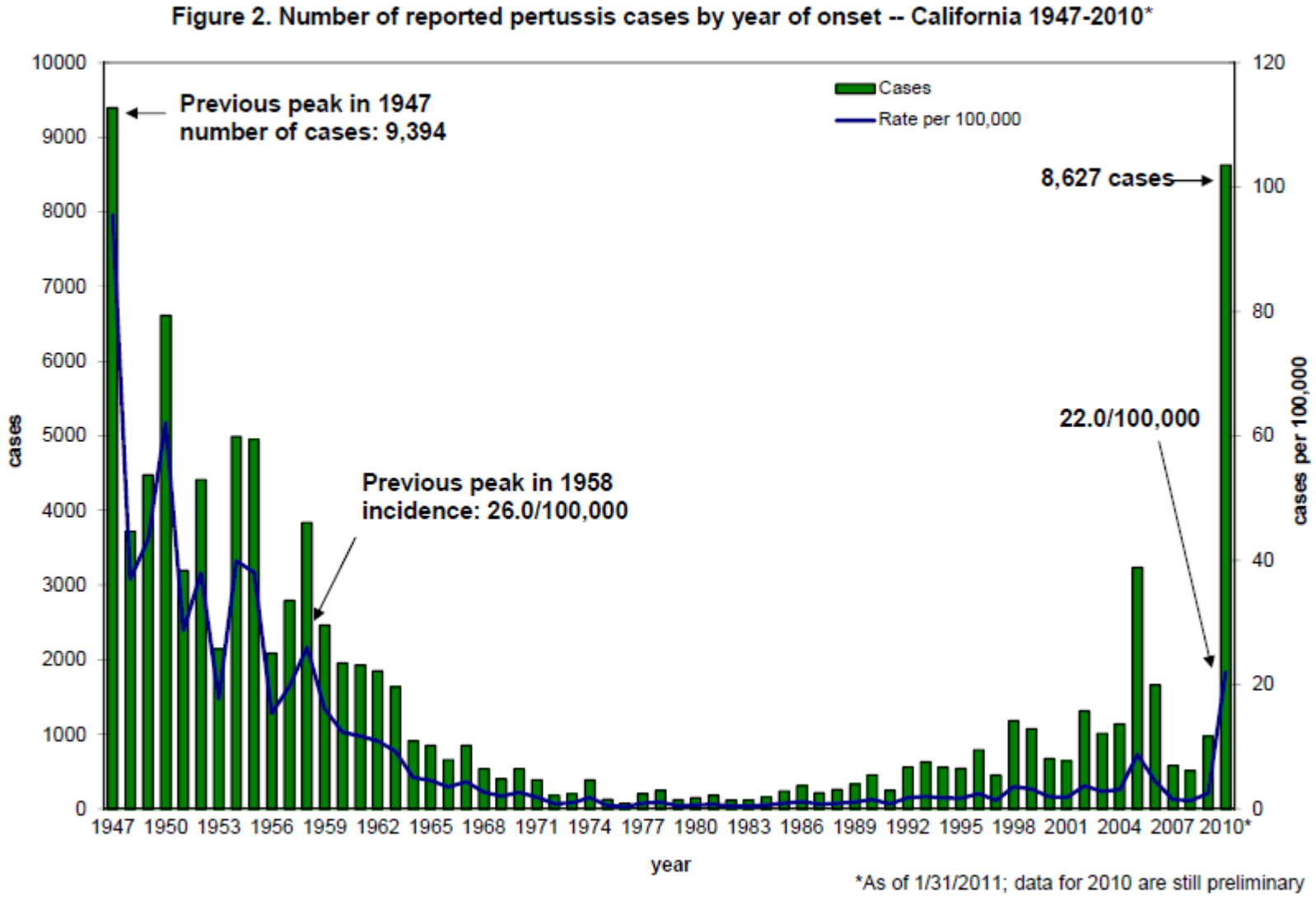
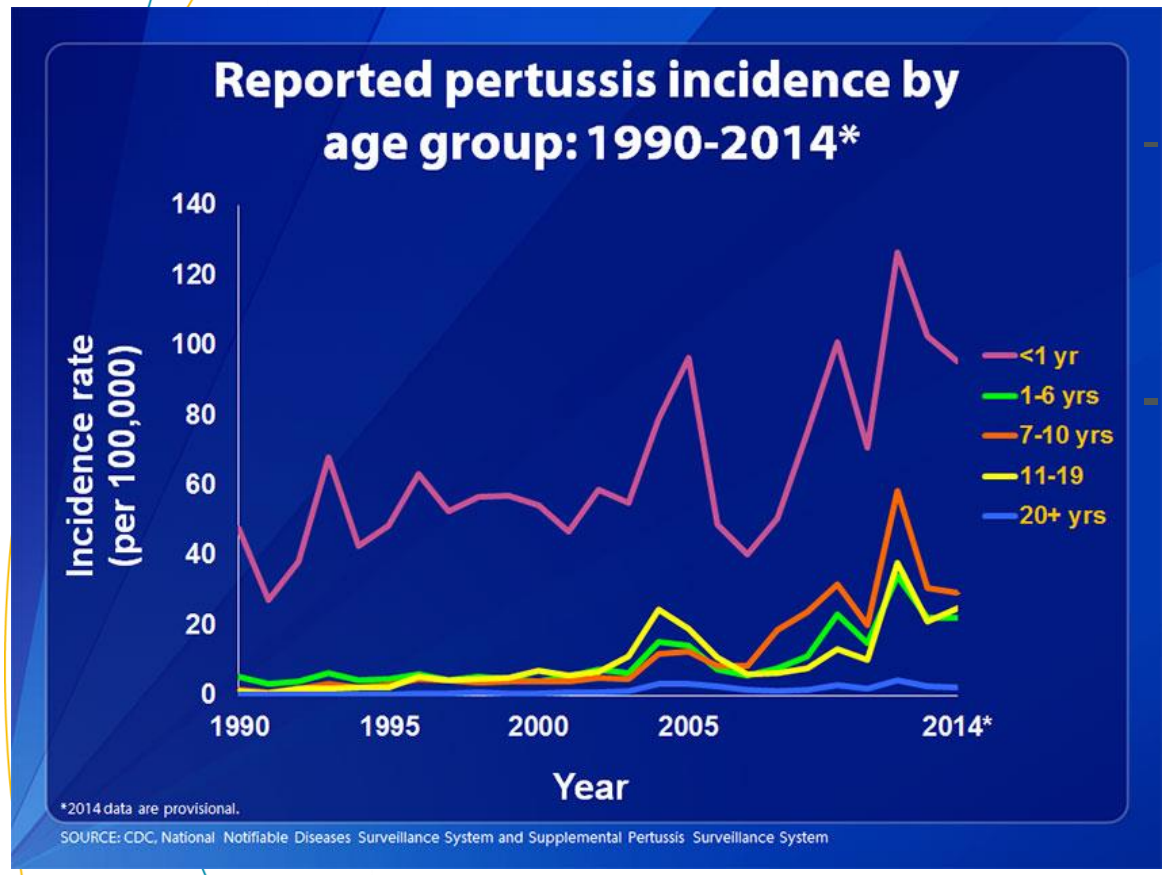
http://www.cdc.gov/pertussis/outbreaks/trends.html

Pertussis in California



Infants are particularly at risk



- Vaccination is initiated between 6 and 8 weeks of age
- 3 doses are required

Parents are the main source of transmission

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Hypotheses for re-emergence of pertussis

- Increased awareness of health professionals
- New diagnostics, more sensitive (PCR)
- Reduction of vaccine coverage
- Bacterial strain adaptation (vaccine-escape mutations)


Forbes · New Posts · Most Popular · Lists

Steven Salzberg, Contributor

Anti-Vaccine Movement Causes The Worst Whooping Cough Epidemic In 70 Years

The great northwest of the U.S. is known for its natural beauty. It's also a high-tech region with a highly educated public – not exactly the kind of place one would expect to fall for the anti-science rhetoric of the anti-vaccine movement.

=> « Not found to contribute to observed country level resurgence ». Revised guidance on the choice of pertussis vaccines: July 2014. WER. N° 30, 2014, 337-344.

- Rapid waning immunity after immunization with acellular pertussis vaccine (aPv)

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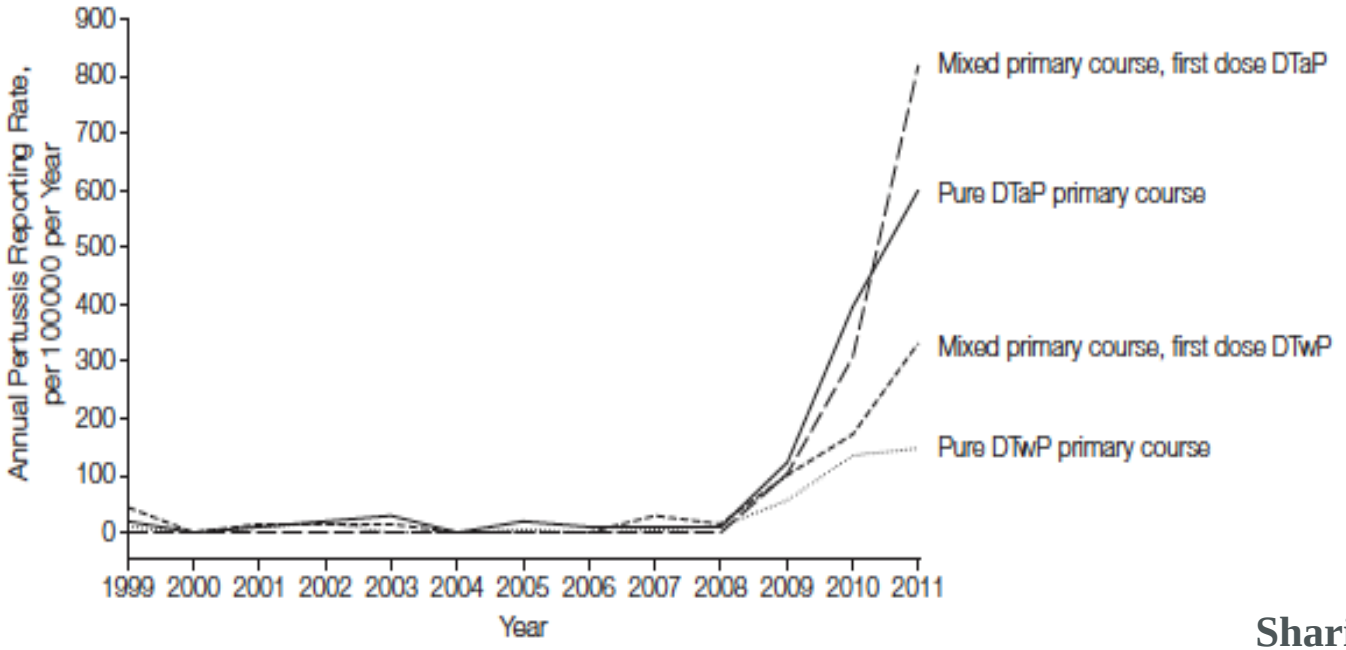
Waning of vaccine-induced protection



Queensland, Australie

Sharidan *et al.* JAMA 2012

Conclusion of SAGE

« the shorter duration of protection and likely reduced impact on infection and transmission conferred by aP vaccines play critical roles in the resurgence of pertussis ».

Revised guidance on the choice of pertussis vaccines: July 2014. WER. N30, 2014, 337-344.

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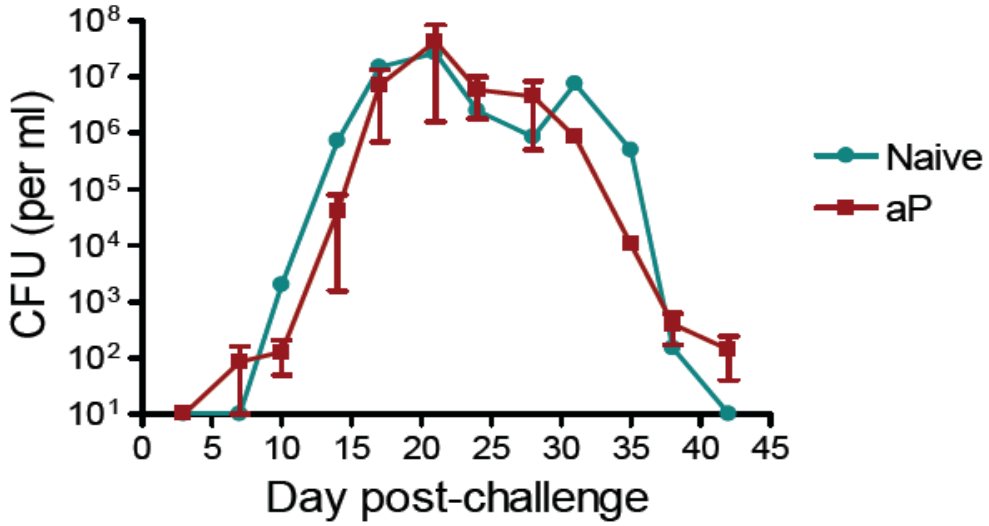
Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model

Jason M. Warfel, Lindsey I. Zimmerman, and Tod J. Merkel. PNAS. 2014



All aP-vaccinated and unvaccinated animals became colonized 7–10 d after cohousing with the infected animal

"…that aP…fails to prevent colonization or transmission provides a plausible explanation for the resurgence of pertussis and suggests that optimal control of pertussis will require the development of improved vaccines"

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An original vaccine strategy
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 doses to induce protection**
- ✓ **Potential as a multivalent vaccine**

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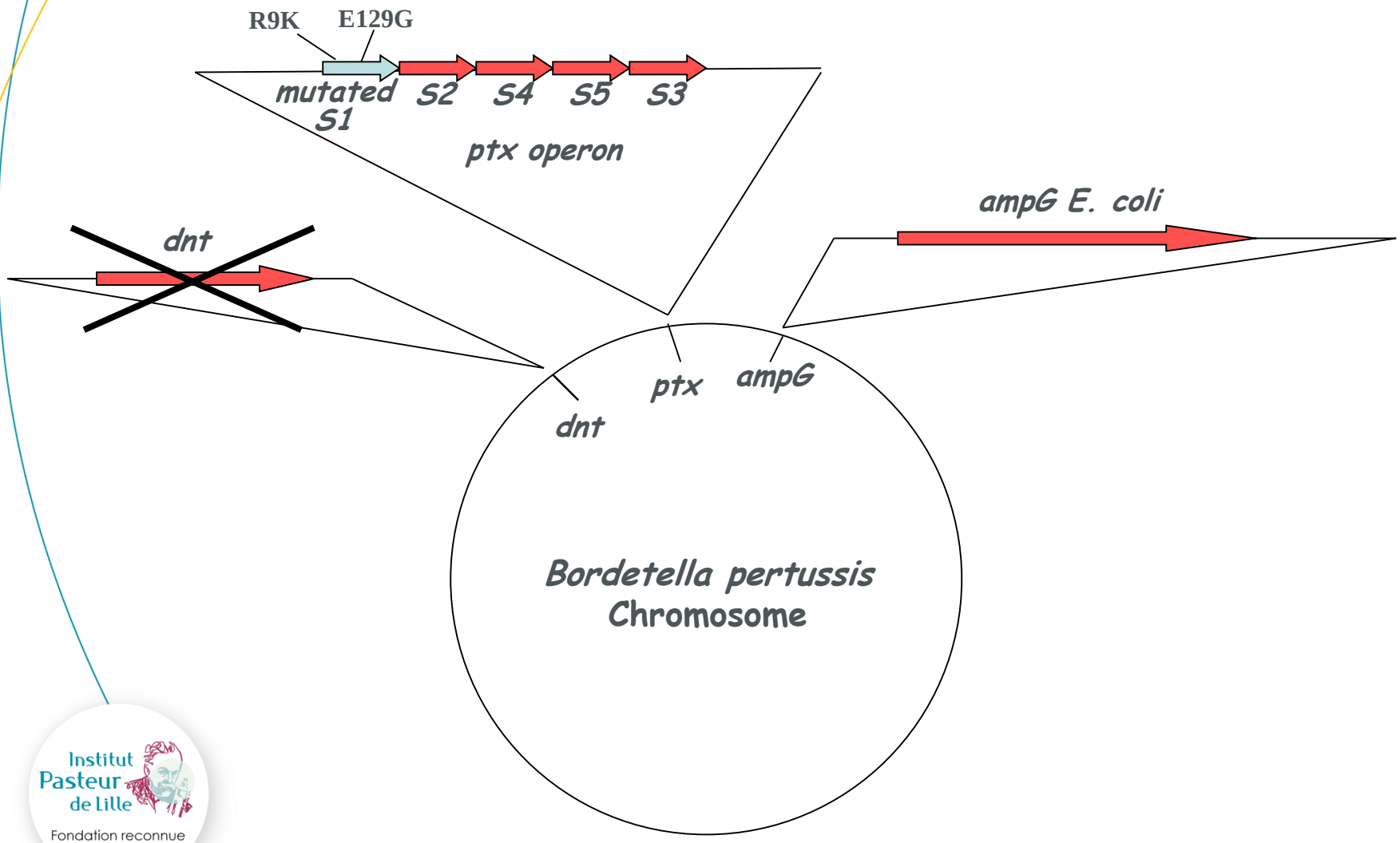
Attenuated *B. pertussis* strain BPZE1 (DNT⁻ PTRE TCT⁻)



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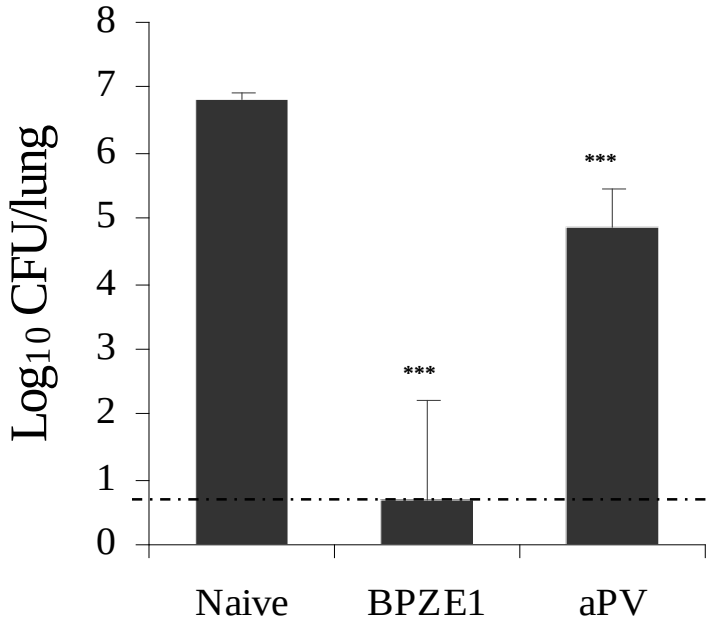
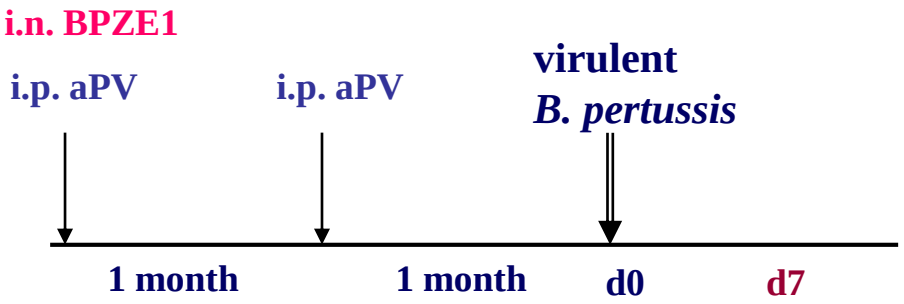
Mielcarek *et al.*, PLoS Pathog, 2006

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





1-week old Balb/C mice

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

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Feunou *et al.*, Vaccine, 2010

Non-specific effects of BPZE1

Against viral infections

Against bacterial infections

Against asthma

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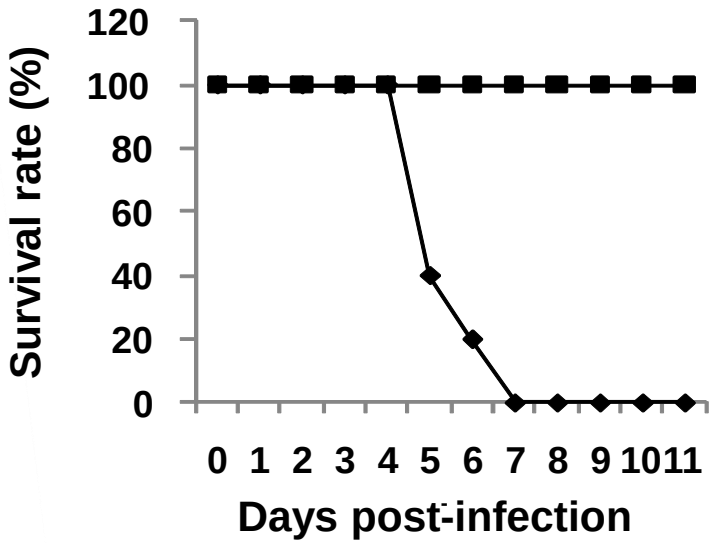
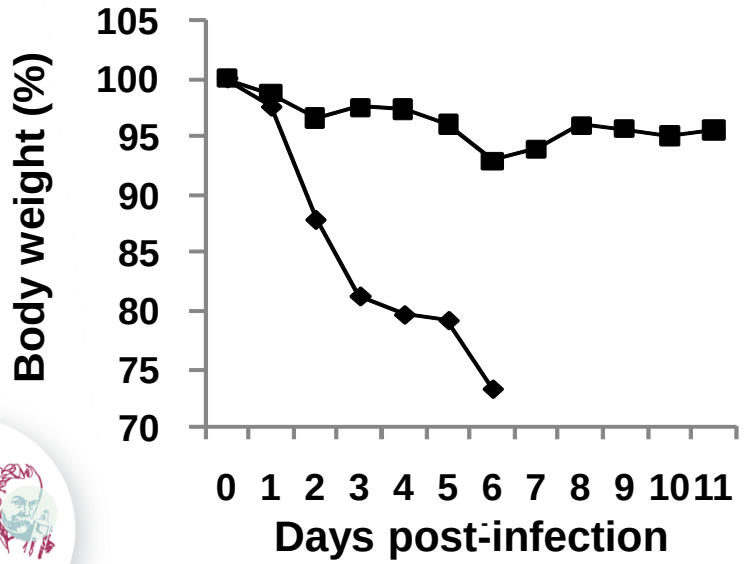
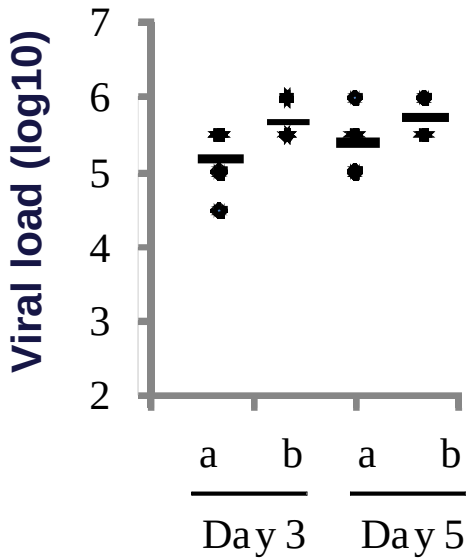
Protection against H3N2 influenza viruses



2 administrations at a 4-weeks interval with $5x10^6$ cfu of live BPZE1

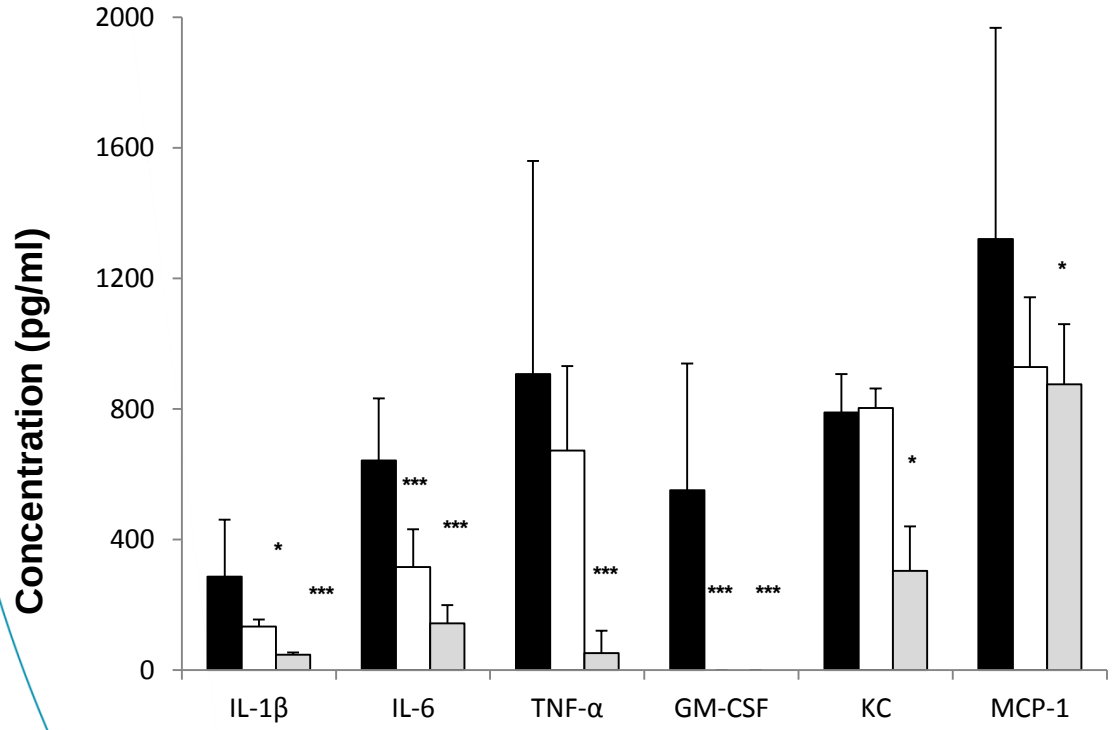
Challenge 2 weeks after the last administration with H3N2 virus (2LD50)





Li *et al.*, J. Virol., 2010

BPZE1 reduces virus-induced cytokine storm after influenza infection

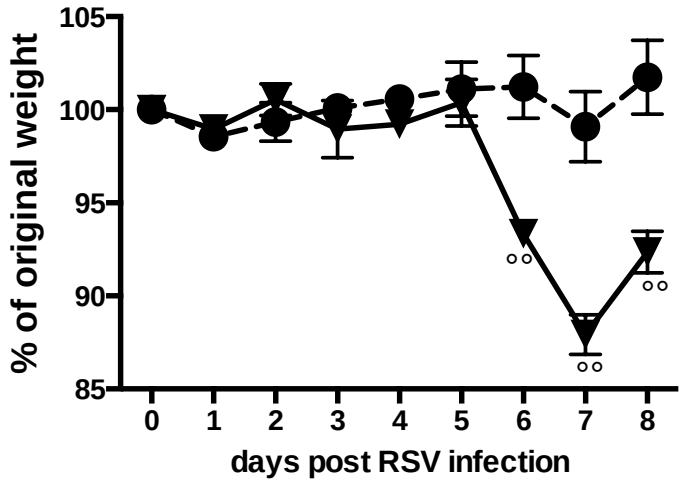


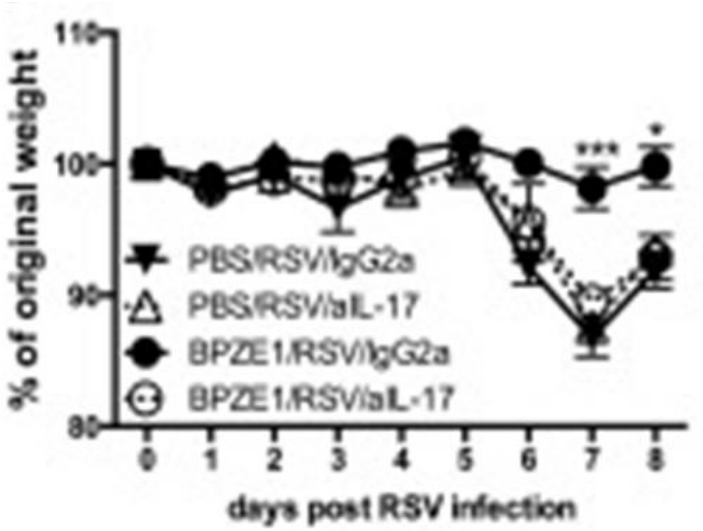
Cytokines and chemokines levels in BALFs 3 days post-viral challenge (n=5)
Naïve
1 x BPZE1
2 x BPZE1

Similar level of IFNg and IL12a

Li *et al.*, J. Virol., 2010

Protection against RSV disease is IL-17 dependent





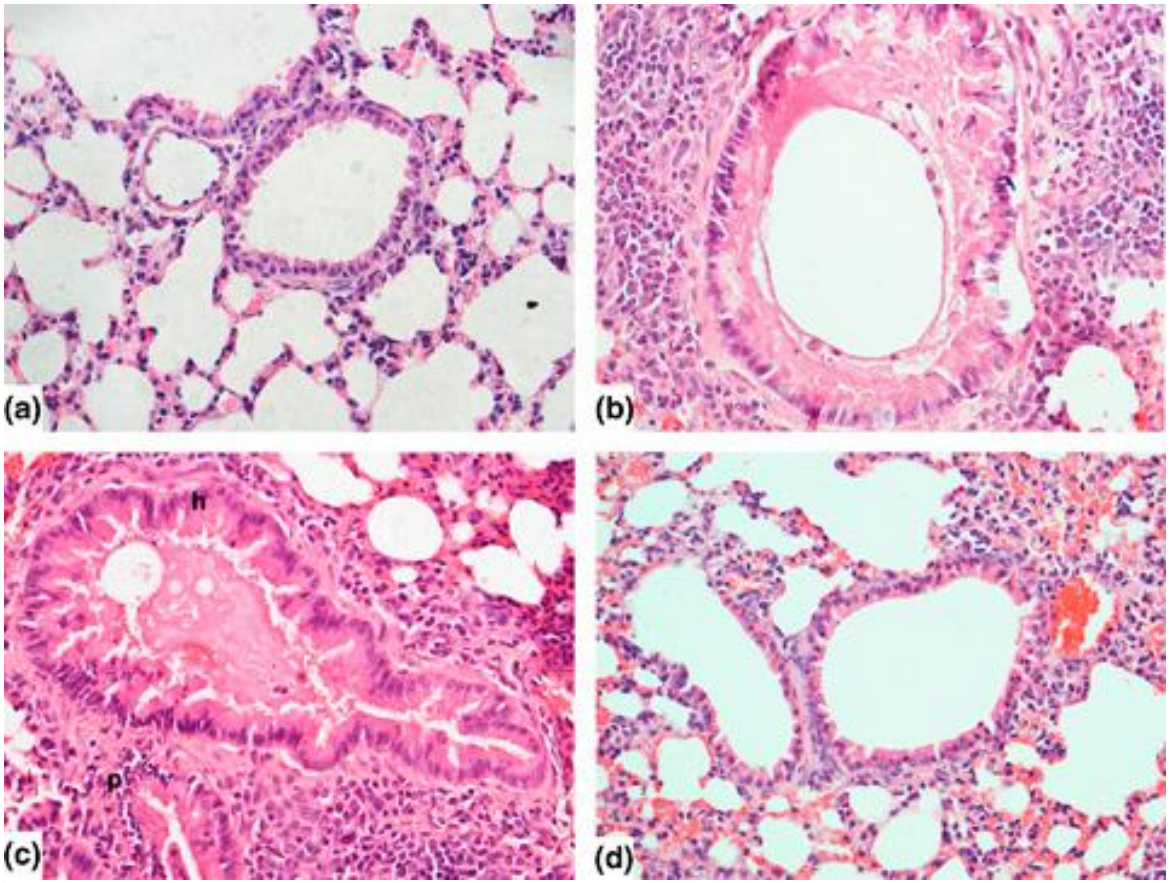
Neonatal (2-5d) priming with BPZE1 ($1x10^6$ cfu)
Challenge of adult mice (8 wks) with $5x10^5$ pfu of RSV

Schnoeller *et al.*, AJRCCM, 2014

BPZE1 against allergy?

naive

Ova-sensitized



Virulent B. pertussis –infected and ova-sensitized

BPZE1-immunized and ova-sensitized

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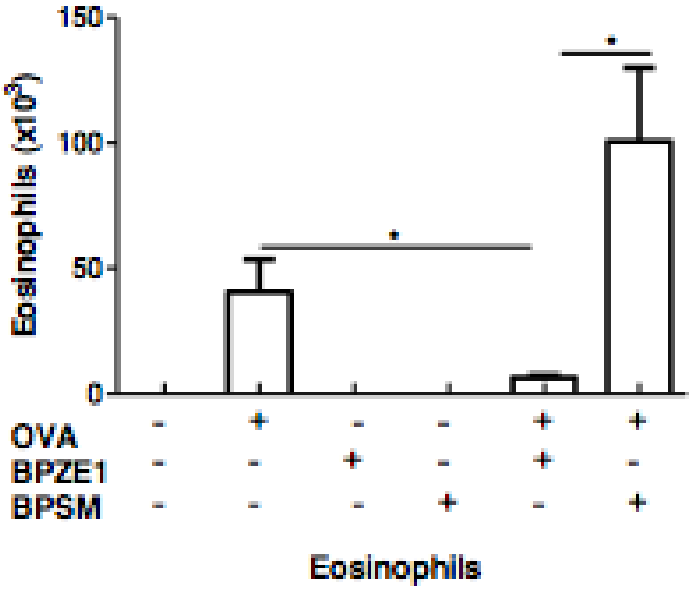
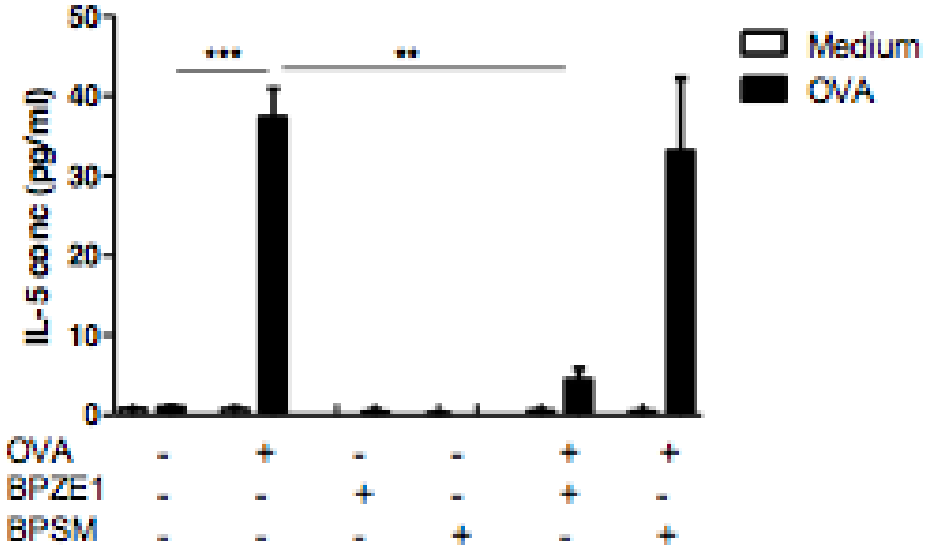
Kavanagh *et al.*, Clin. Exp. Allergy, 2010





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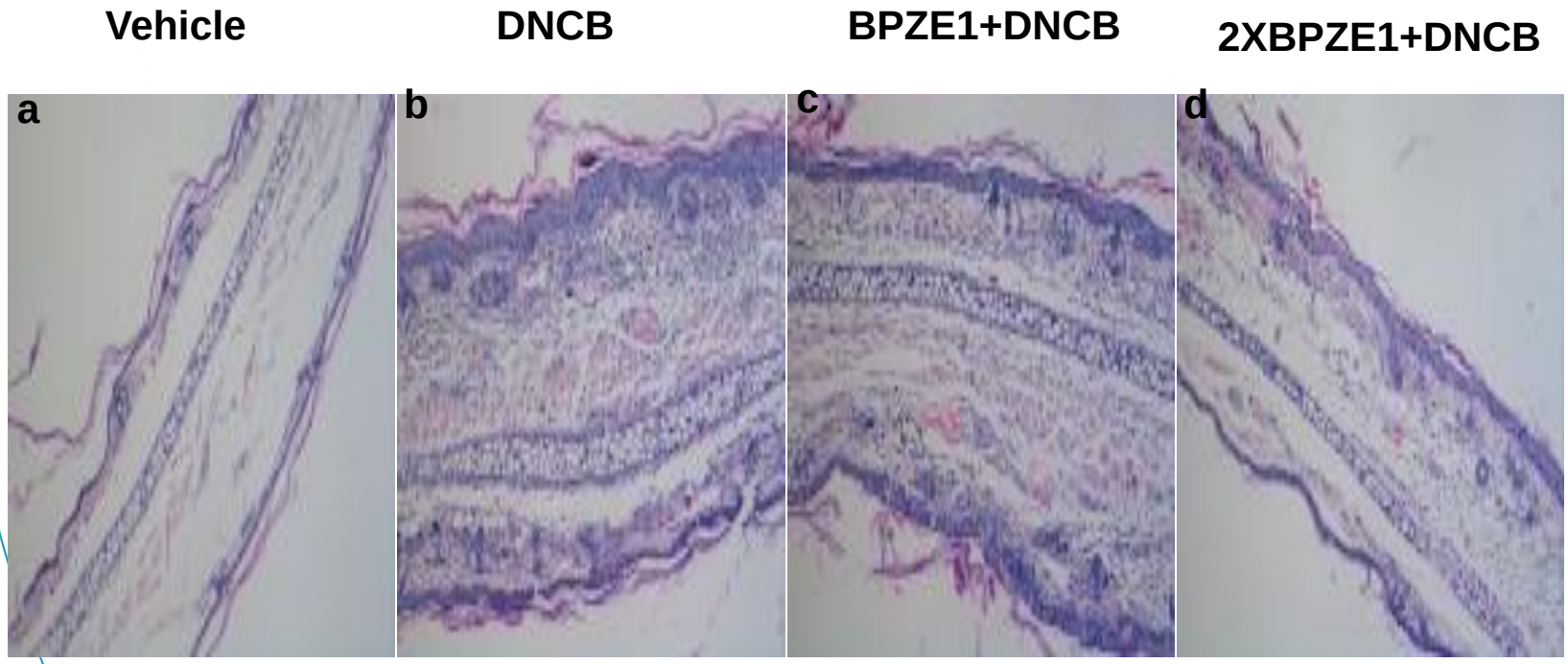
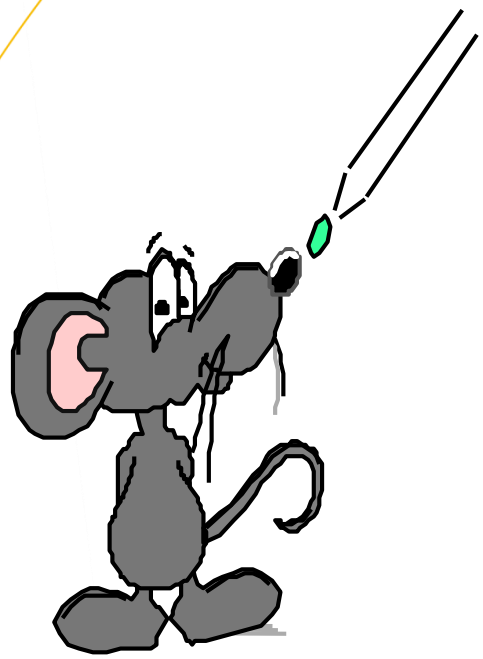
Kavanagh *et al.*, Clin. Exp. Allergy, 2010

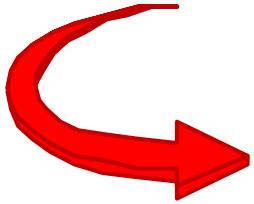
Contact dermatitis model in mice



DNCB: dinitrochlorobenzene

Li *et al.*, Allergy, 2012





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Phase 1 clinical trial

- ☑ 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, after a single ascending dose of BPZE1:

- colonization of the human respiratory tract
- immune responses to *B. pertussis*

Solicited AE at two-week visit

	Placebo	Low dose 10^3 CFU	Medium Dose 10^5 CFU	High dose 10^7 CFU
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

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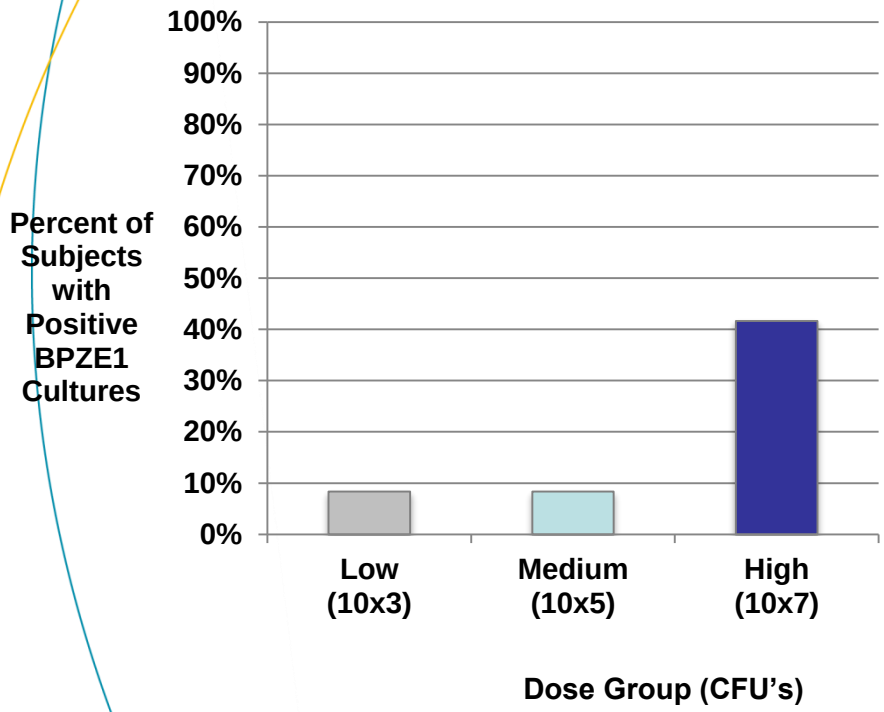
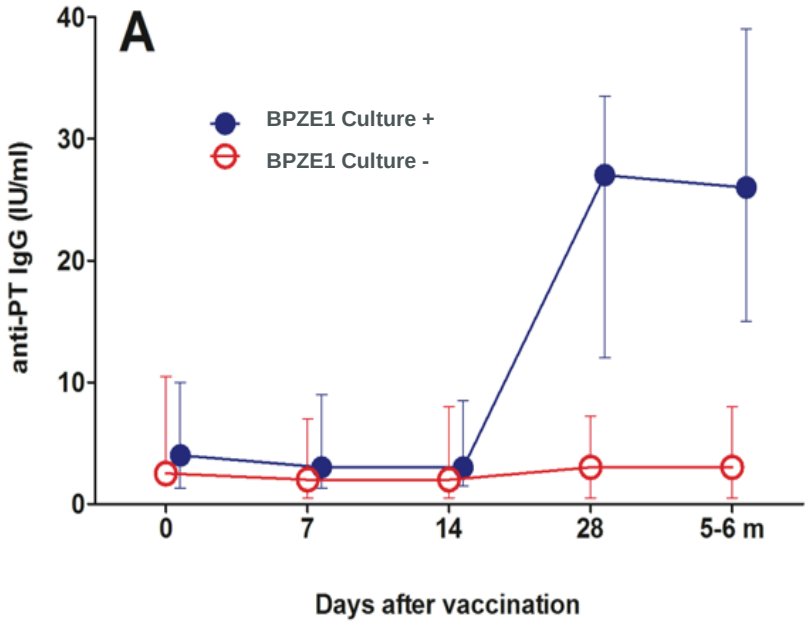
Colonization rate and antibody response in human volunteers





All BPZE1 colonized subjects (Culture +) developed a specific immune response to *B. pertussis* antigens

Next step Phase 1b: higher volume and dose

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ILiAD BIOTECHNOLOGIES

Summary

- ✓ Single nasal BPZE1 vaccination induces long-term protection in mice against *B. pertussis*
- ✓ BPZE1 expresses potent anti-inflammatory properties without immunosuppression
- ✓ Anti-inflammatory properties of BPZE1 are boostable (trained innate immunity)
- ✓ BPZE1 is safe in humans
- ✓ BPZE1 is able to colonize human nasopharynx
- ✓ BPZE1 induces immune responses in all colonized human subjects

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