Pertussis resurgence: ACV immunity and pathogen adaptation

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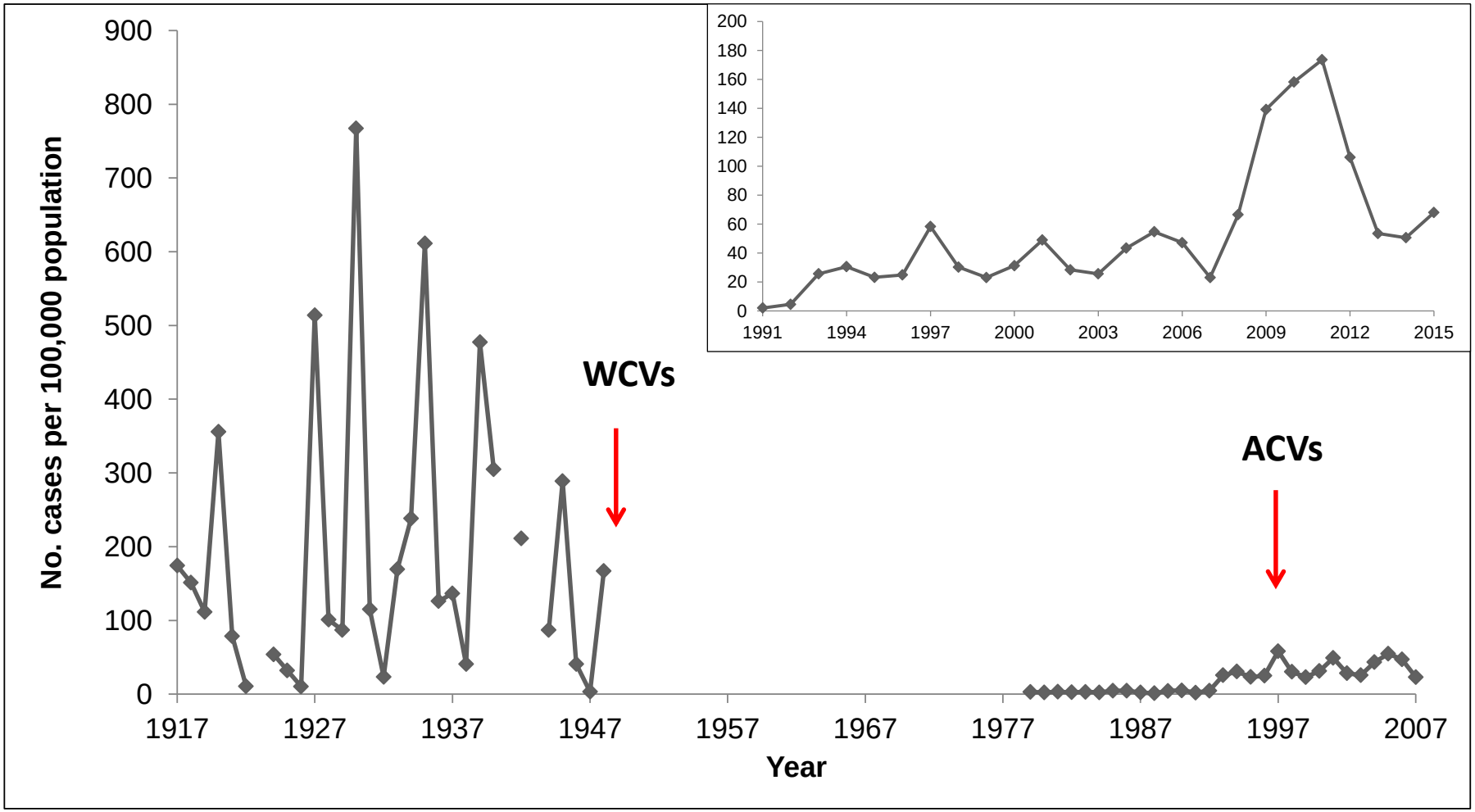
Incidence of pertussis in Australia



Hall, R. 2003. *Commun Dis Intell* 17:226-236; National Notifiable Diseases Surveillance System

Multiple factors for resurgence

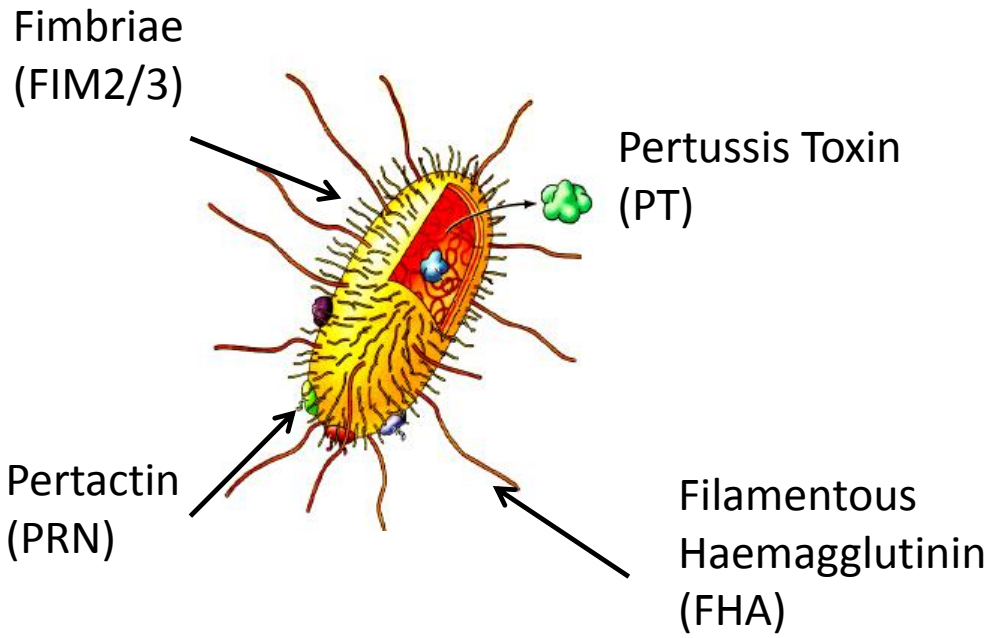
- Increased awareness/ better diagnostics

- Waning Immunity

- Adaptation of organism to acellular vaccine (ACV) selection ?

Whole cell and Acellular vaccines

Whole cell vaccine (WCV) 1950s-1990s

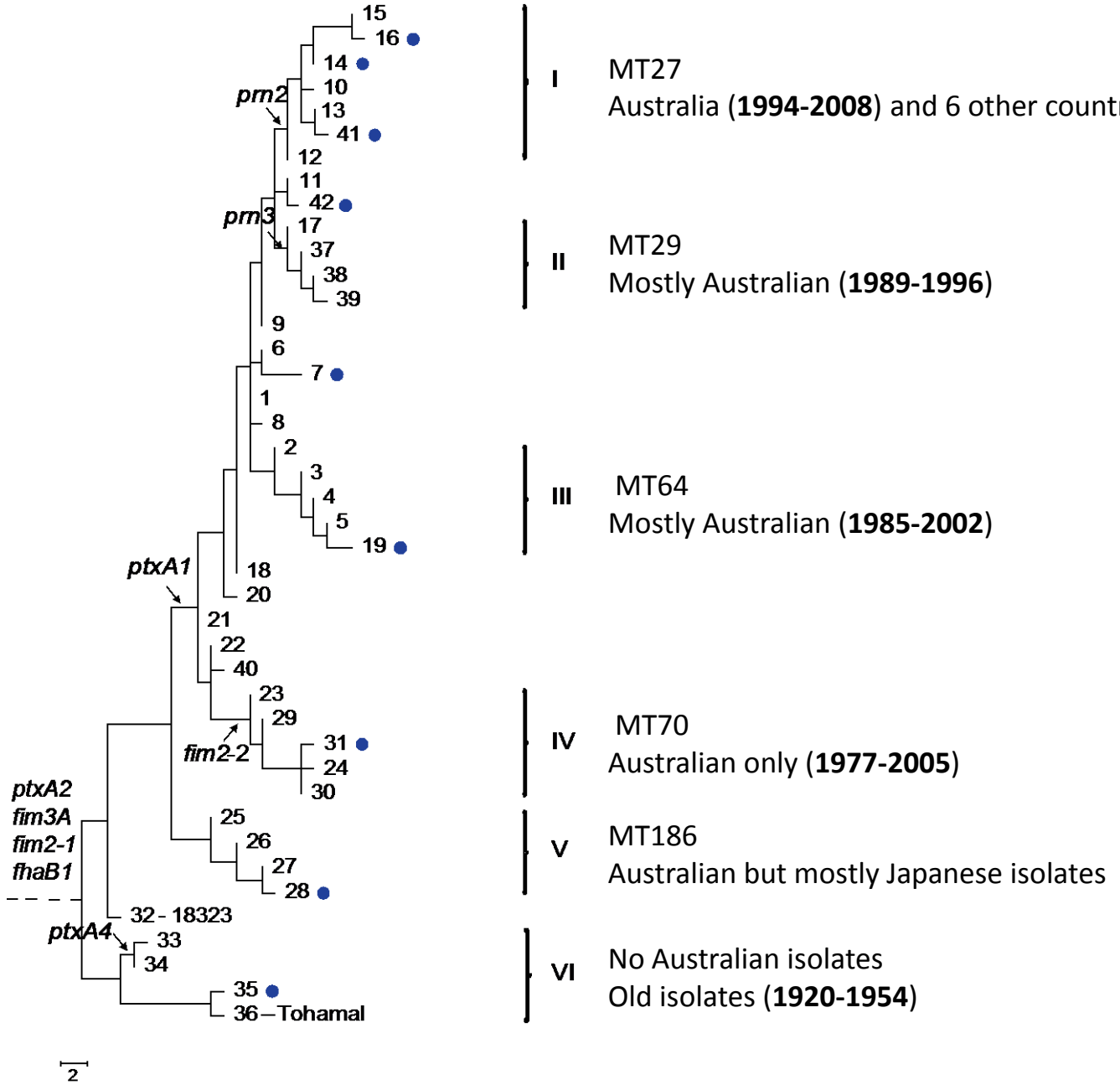


Acellular vaccine (ACV) 1997- present

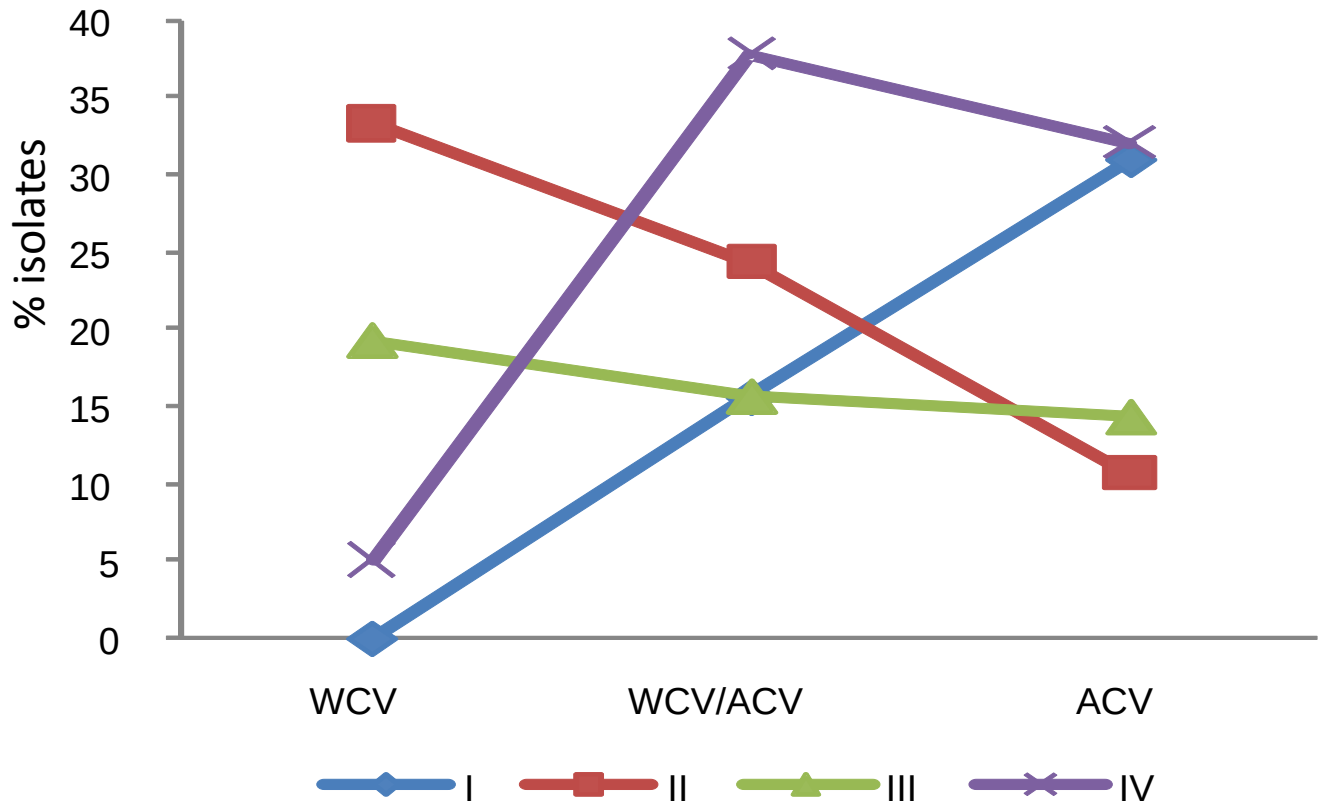
Antigenic component	Boostrix	Adacel
PT (μg)	8	2.5
FHA (μg)	8	5
PRN (μg)	2.5	3
FIM 2 + 3 (μg)	–	5

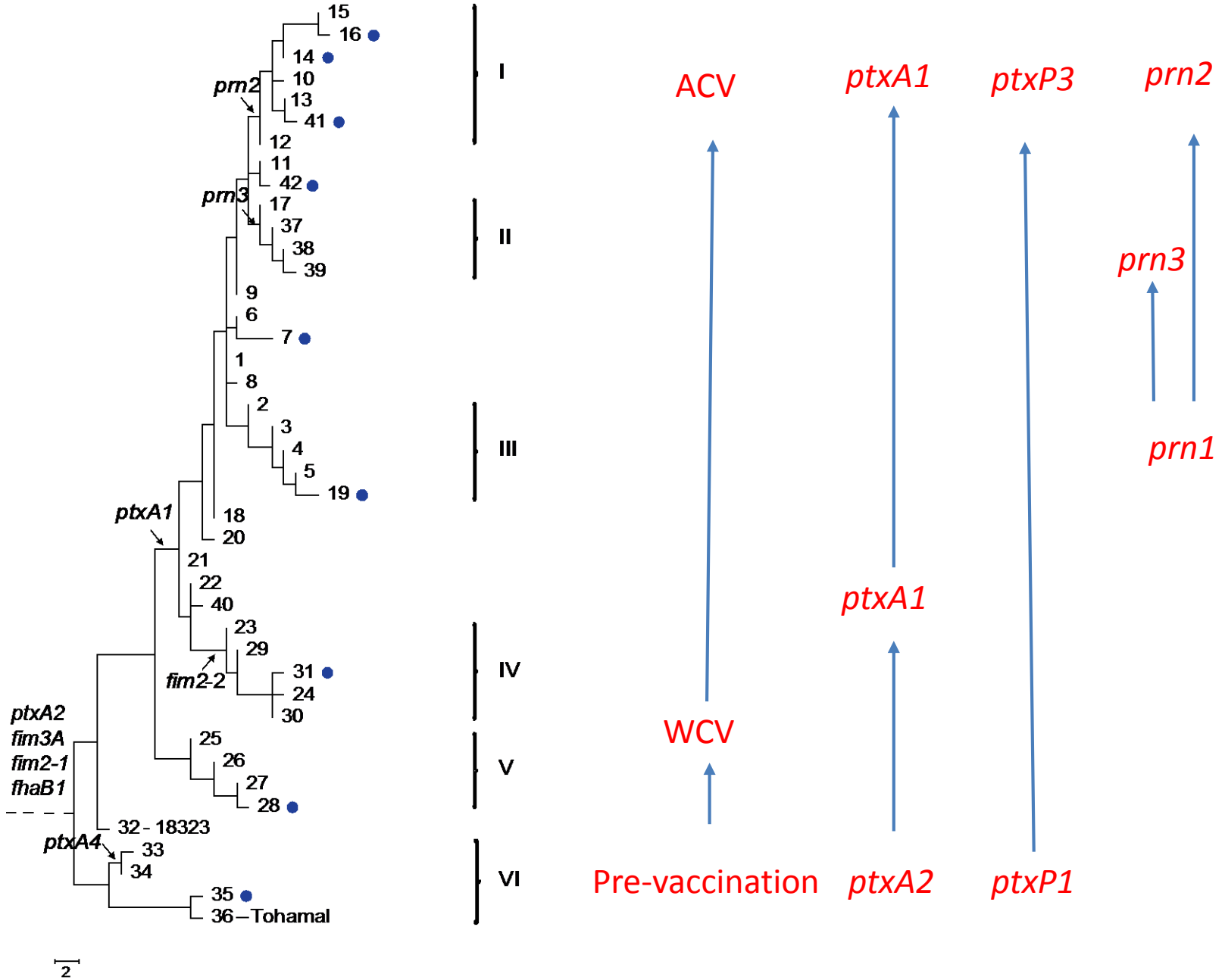
Is *B. pertussis* under ACV selection pressure

- SNP cluster I (the *ptxP3* strains)
- The Prn deficient strains



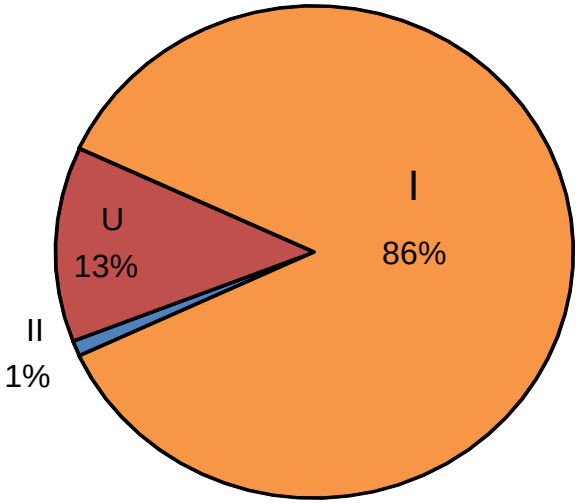
Octavia *et al.* (2011) Mol Biol Evol 48: 3504

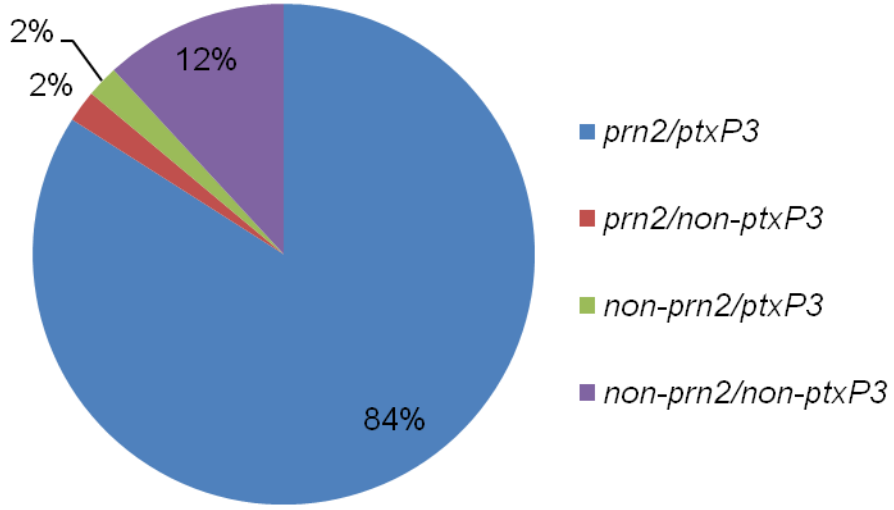

40
35
30
25
20
15
10
5
0
% isolates
WCV
WCV/ACV
ACV
I
II
III
IV



Octavia et al. (2011) Mol Biol Evol 48: 3504; Lam *et al.* (2012) Infect Genet Evol 12:492

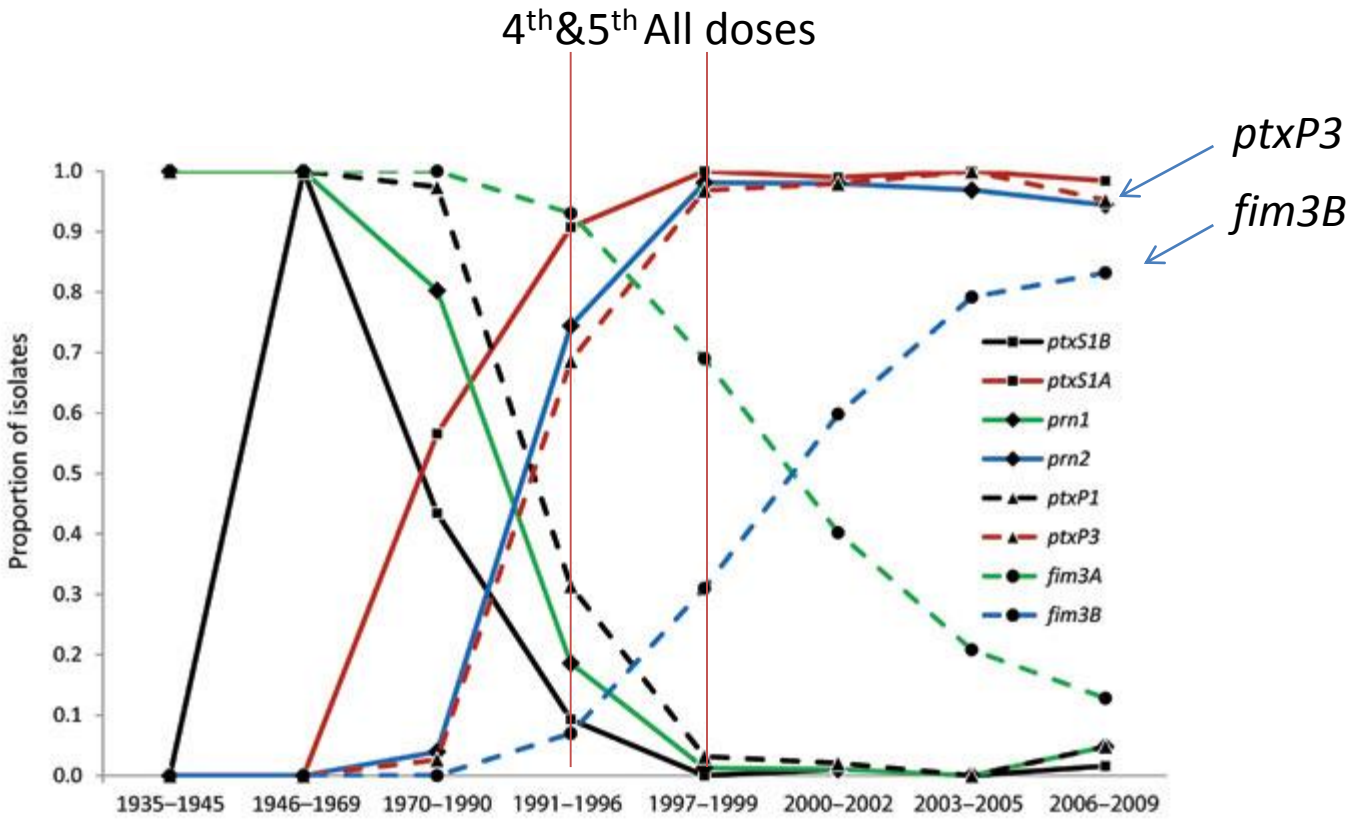
2008-2012 epidemic



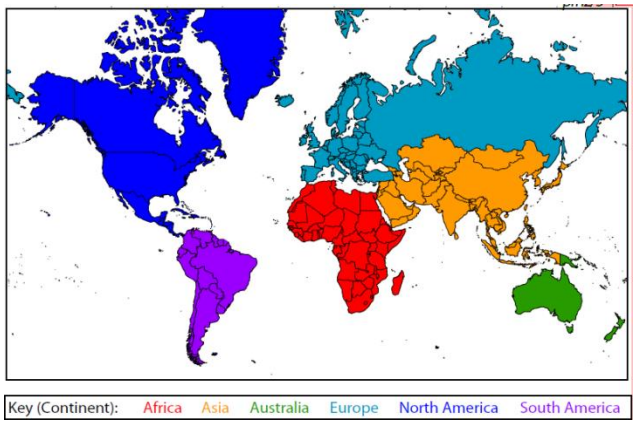


Octavia et al. JID 2012

ptxP3 strains not correlated with ACV selection in the US

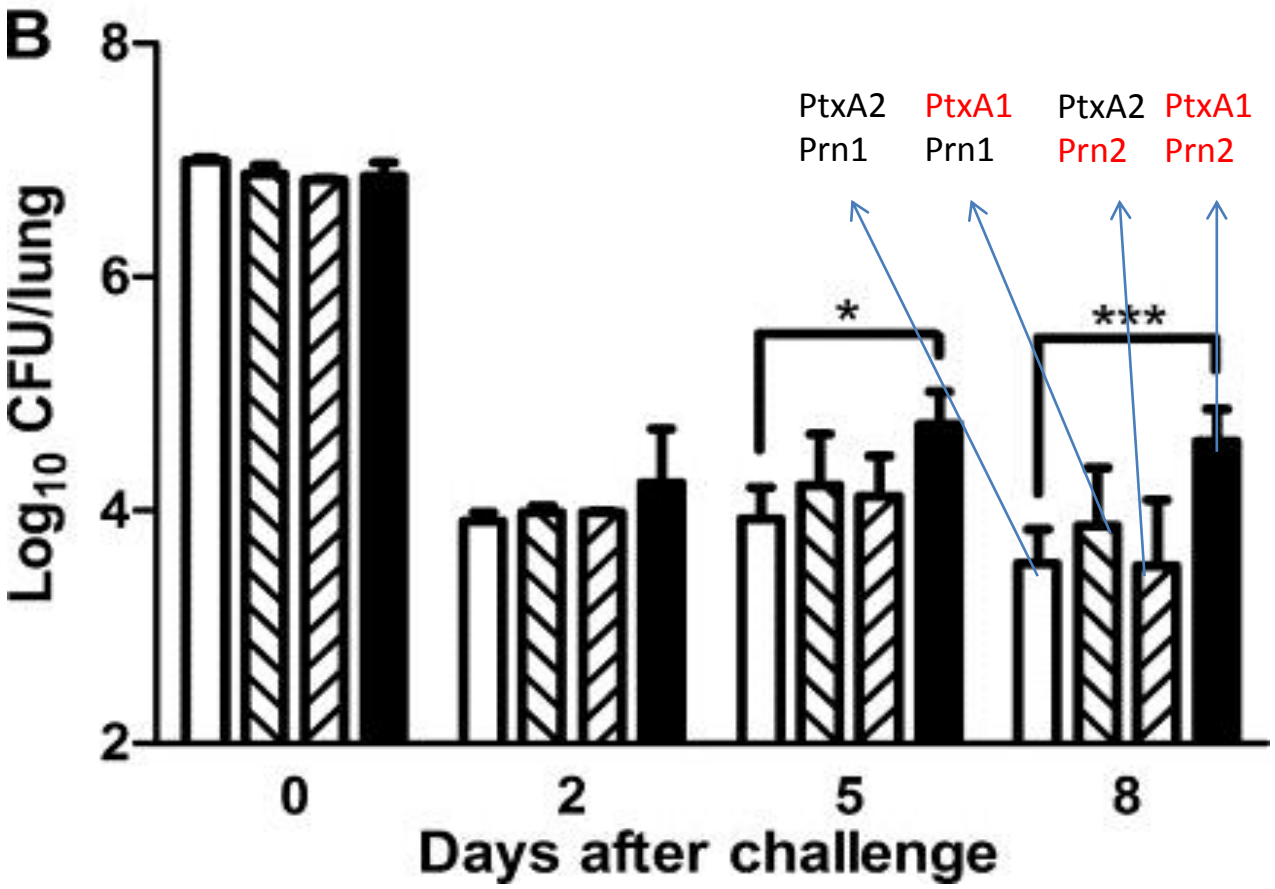


Schmidtke et al. EID 2012



Bart et al. mBio 2014

Advantage of double *ptxA1-prn2* Tohama I mutants



Komatsu *et al.* Clin Vaccine Immunol 2010 **17**: 807

Are cluster I (*ptxP3)* strains also advantageous against WCV?

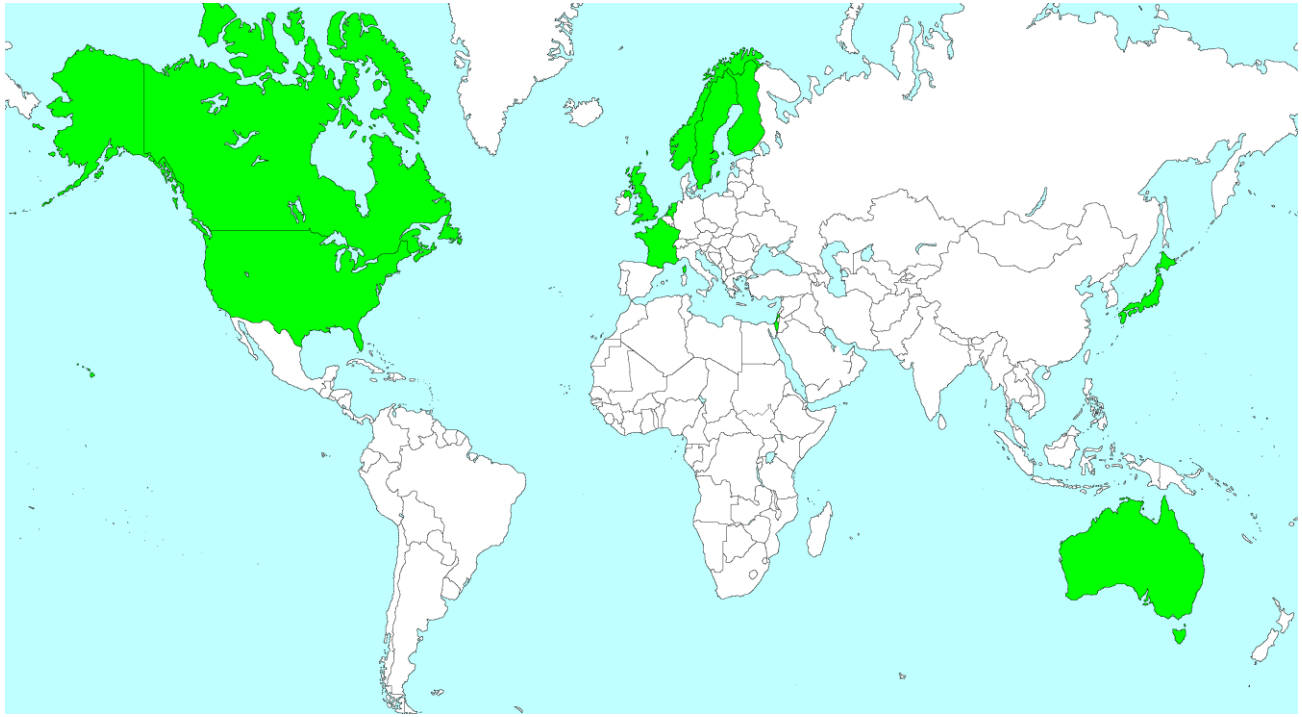
- Non-*ptxP3* strains are more prevalent in countries where WCV is in use or have just been phased out
  - China: Yang *et al.* (2015) PLoS ONE, 10: e0138941.
  - Poland: Mosiej *et al.* (2011) JCM 49:1452

Conclusion 1

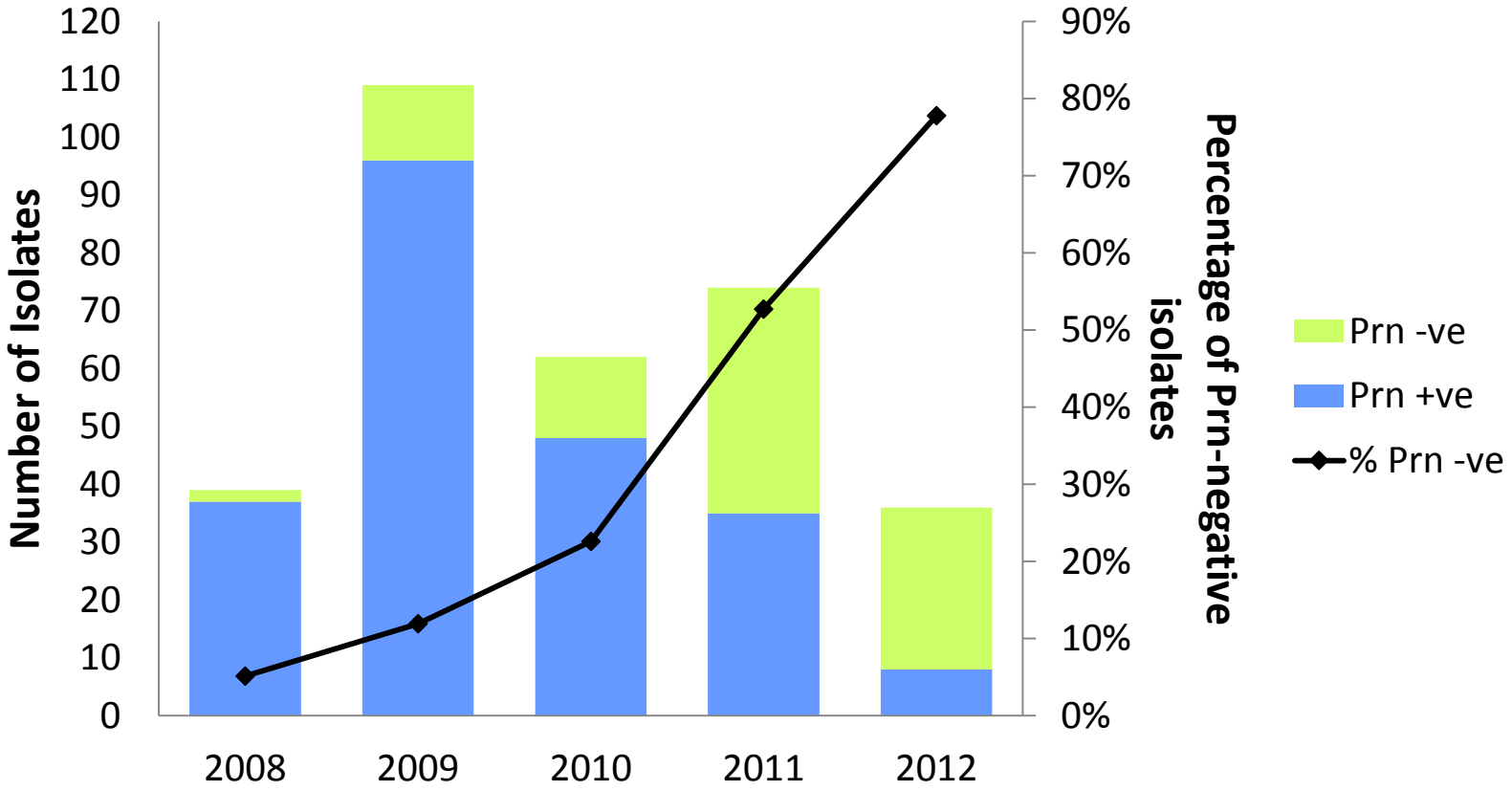
- Cluster I (*ptxP3)* strains are fitter than cluster II strains in both ACV and naive environment
- The emergence of *ptxP3* strains may not be due to ACV selection pressure
- The increase of *ptxP3* strains may be associated with ACV

Emergence and expansion of Prn-strains

- Prn deficient strains first reported by Guiso *et al.* in 2012 from France
- Now reported in many countries



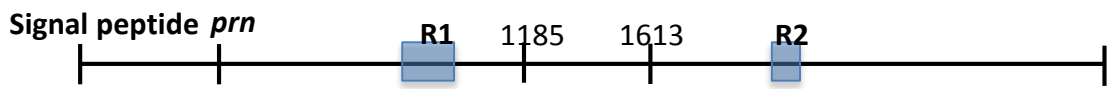
Epidemiology of Prn– strains in Australia



Phase variation

Prn+: GCTGACCGGG GG-CGCCGAT GCGCAGGGCG

Prn-: GCTGACCGGG GGGCGCCGAT GCGCAGGGCG (n=1)



prn deletion (n= 2)

No damage (n=16)

....ACTAGG CAGCGCGGCG ....

IS disruptions

IS*481*F

ACTAGG tgtgaagatt ----//----attgacagtt cacaactagg CAGCGCGGCG (n= 13)

IS*481*R

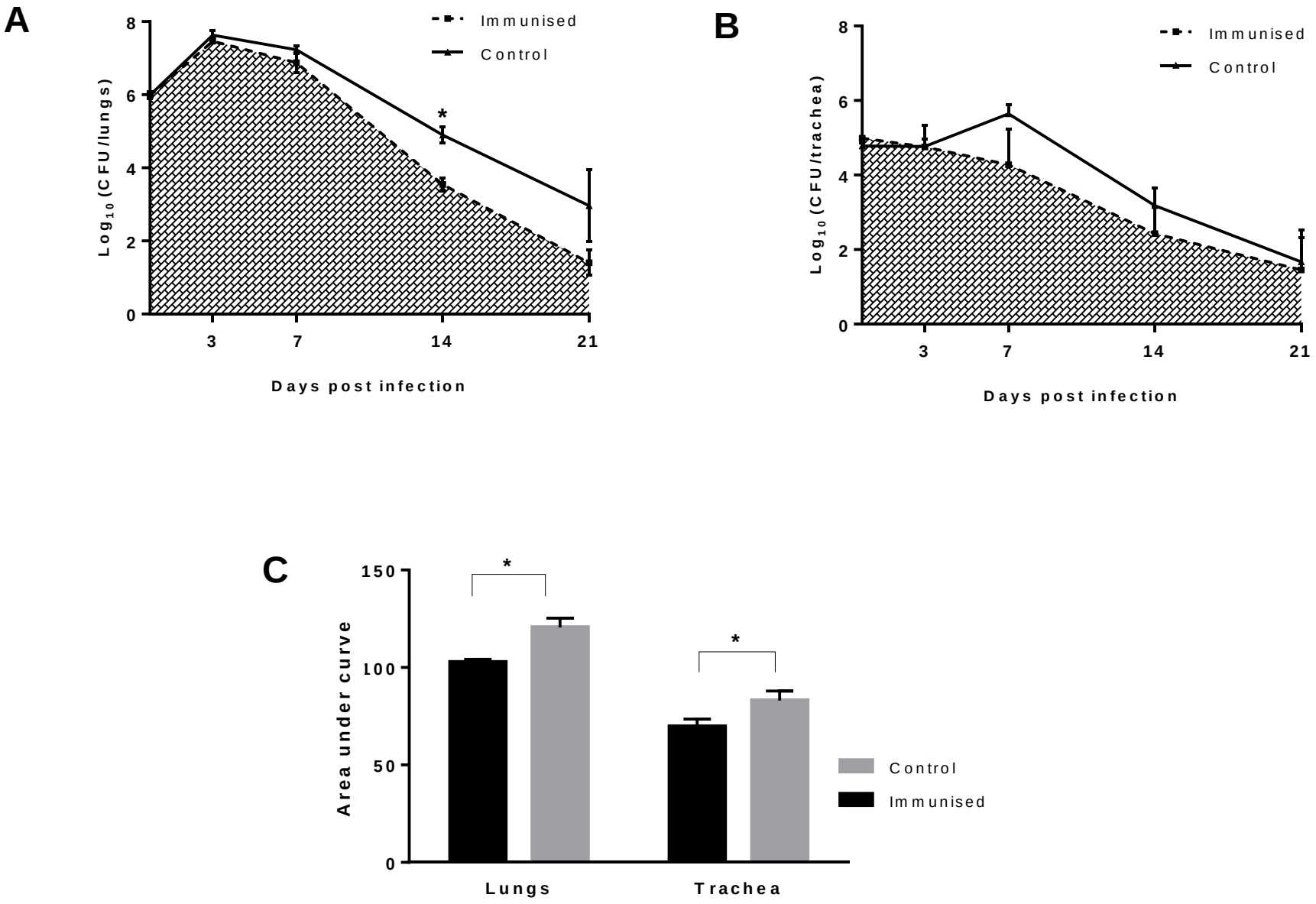
ACTAGG tgtgaactgt ----//----attgaatctt cacaactagg CAGCGCGGCG (n= 58)

IS*1002*

ACTAGG tgtcgattct ----//---- gacat cacacctagg CAGCGCGGCG (n= 6)

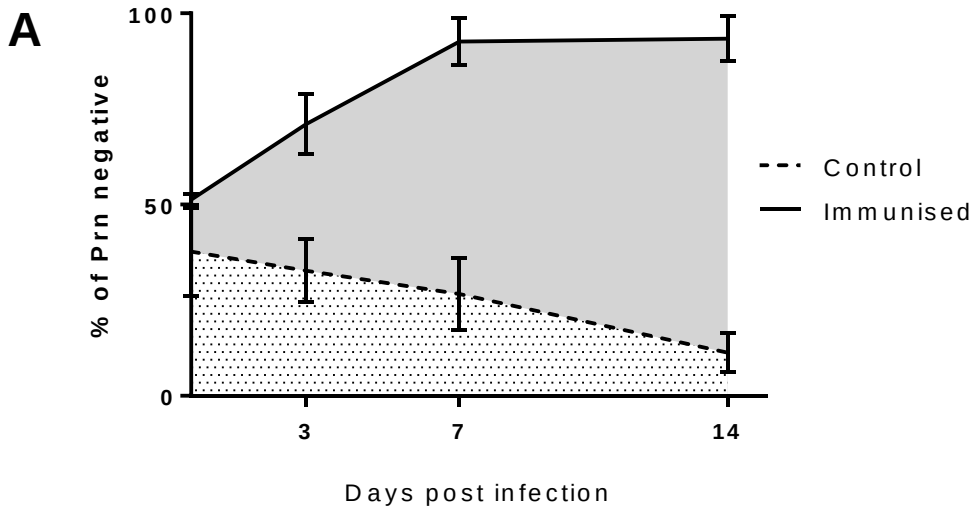
Competitive fitness of Prn- versus Prn+ strains

- Mixed infection
  - Cluster I strain (*ptxP3,* Prn-)
  - Cluster I strain (*ptxP3,* Prn+)
- 1/50 human dose, immunisation 2x
- 3 component vaccine (Ptx, Prn and Fha)
- NGS sequencing to distinguish the 2 strains in the mixed infection

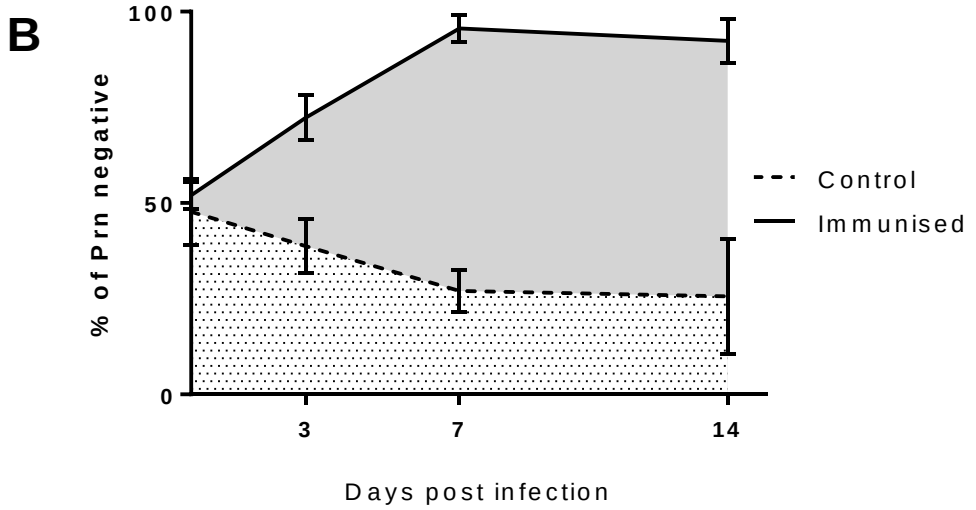


Safarchi *et al.* Vaccine 2015

Lung



Trachea



Safarchi *et al.* Vaccine 2015

Conclusion 2

- Prn- strains arose numerous times and likely independently in different countries
- Prn- strains are fitter in the ACV environment
- Emergence and expansion of Prn- strains are likely to be associated with ACV selection
- However, disadvantageous in non-immunised hosts

Overall conclusion

- Both epidemiological data and animal models suggest pathogen adaptation in response to vaccine selection pressure

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