Rijksinstituut voor Volksgezondheid
en Milieu
Ministerie van Volksgezondheid,
Welzijn en Sport

Why do we see so much pertussis despite vaccination?

Marjolein van Gent
National Institute for Public Health
and the Environment
Bilthoven, the Netherlands

29 October 2015

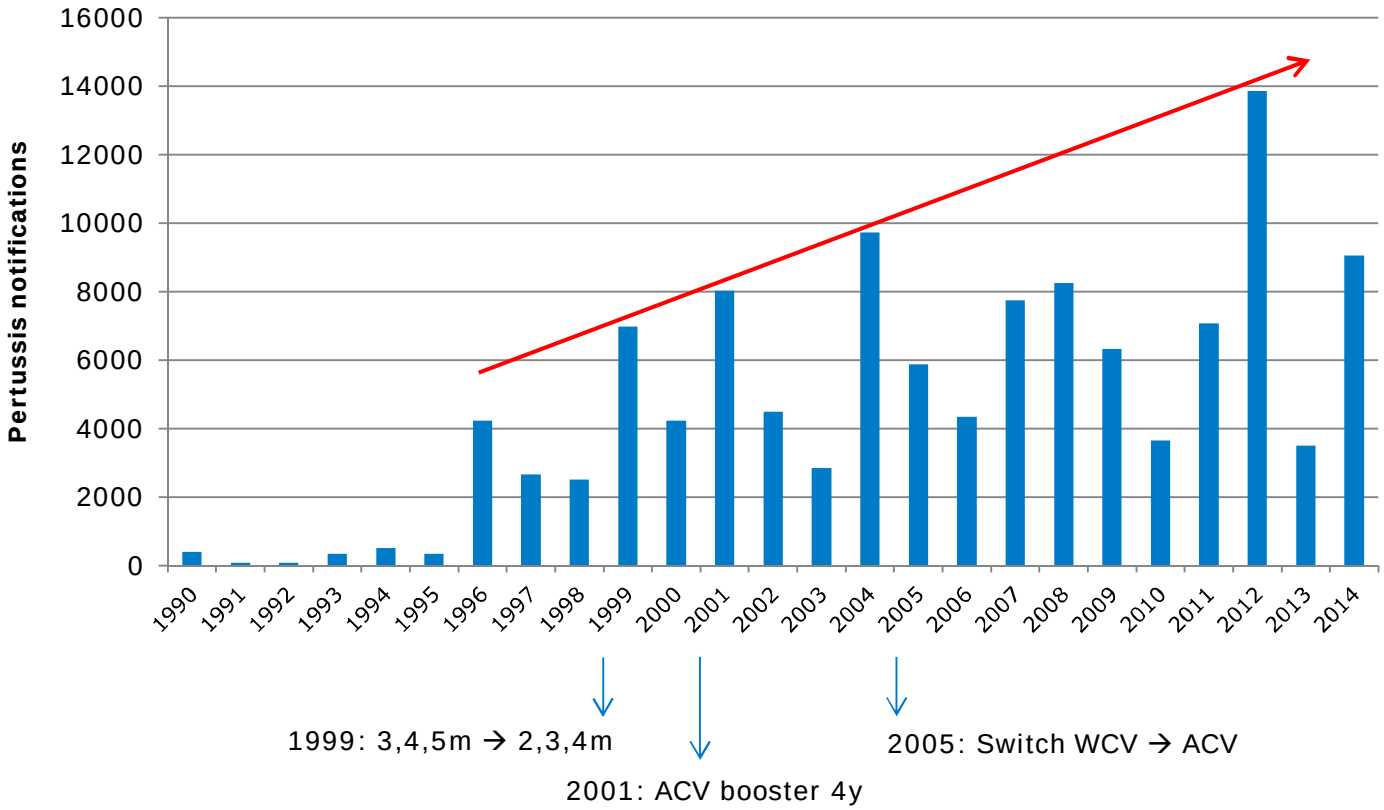
Pertussis vaccination in the Netherlands

- Pertussis vaccination in the Netherlands available since 1953
- Dutch National Immunization Program since 1957
- Pertussis is notifiable in the Netherlands since 1976

Year	Vaccination Schedule
1957	3,4 and 5 months
1962	3,4,5 and 11 months
1999	2,3,4 and 11 months
2001	2,3,4 and 11 months + acellular booster at 4 years
2005	Whole cell vaccine → acellular vaccine (due to side effects)

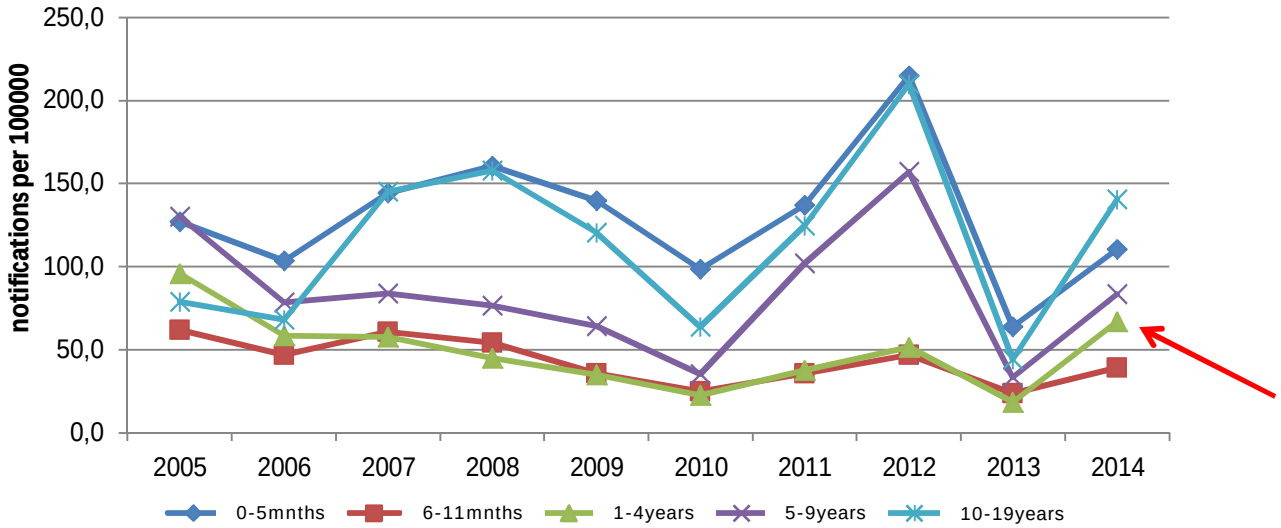
The current Dutch ACV consist of 3 purified *B. pertussis* proteins (pertactin, filamentous hemagglutinin and pertussis toxin)
Vaccination coverage in the Netherlands: >95%

Pertussis notifications in the Netherlands



Vaccination changes did not result in a decrease in notifications

Age distribution 0-19 years in 2005-2014 in NL



- Increased notifications in every age group
- Lowest incidence in age groups 6-11 months and 1-4 years
- Highest incidence in age groups 0-5 months and 10-19 years!
- Remarkable: higher incidence in 2014 in age group 1-4 years

Notifications are only the tip of the iceberg

2006-2007: Seroprevalence study, 7903 persons, > 9 years:

- Infection frequency 9% (1,3 million), based on IgG titers against Ptx
- 25% had coughing symptoms
- 0,4% was notified as pertussis with typical symptoms

  >99% was not notified as pertussis

(de Greeff et al., PLoS One 2010, 5 (12): e14183)

1995-1996:

- Infection frequency 4%

(de Melker et al., Journal of Infection 2006, 53 (2), 106-113)

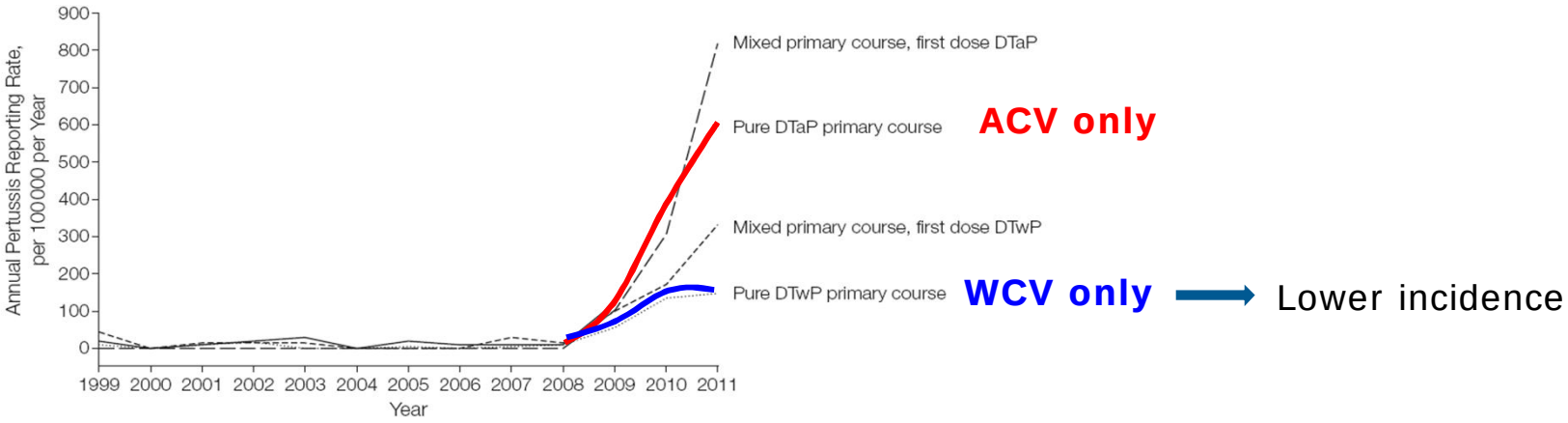
Increase mainly in adolescents and young adults who often have atypical or mild symptoms. The high circulation is a threat to young unvaccinated infants.

Possible causes for the resurgence of *B. pertussis* – 1.

- Increased awareness
- Improved and more sensitive diagnostic procedures (PCR)
- Waning immunity – shorter duration of protection by ACV compared to WCV

Australia: Incidence birth cohort from 1998:
Outbreak period 2009-2011
(Sheridan et al., JAMA, 2012)

Primary course **WCV**
Primary course **ACV**



Possible causes for the resurgence of *B. pertussis* – 2.

- **Pathogen adaptation:**

  1. Antigenic divergence between vaccine strains and circulating strains

  (Mooi et al., 1998; Fry et al, 2001; Hallander et al, 2005; van Gent et al, 2012)

  2. *ptxP3* strains that produce more pertussis toxin (more immunosuppression)

  (Mooi et al., 2009)

  3. Emergence of Vaccine Antigen Deficient (VAD) strains

  Increased frequency in Ned; 18% in 2015 so far

  High frequencies found in Japan (32%, 2005-2009), Australia (78% in 2012) and USA (85% in 2012)

  (Otsuka et al., 2012; Hegerle et al., 2012; Lam et al., 2014; Queenan et al., 2013; Zeddeman 2014)

One cause: waning immunity caused by pathogen adaptation and suboptimal vaccines

Pathogen adaptation

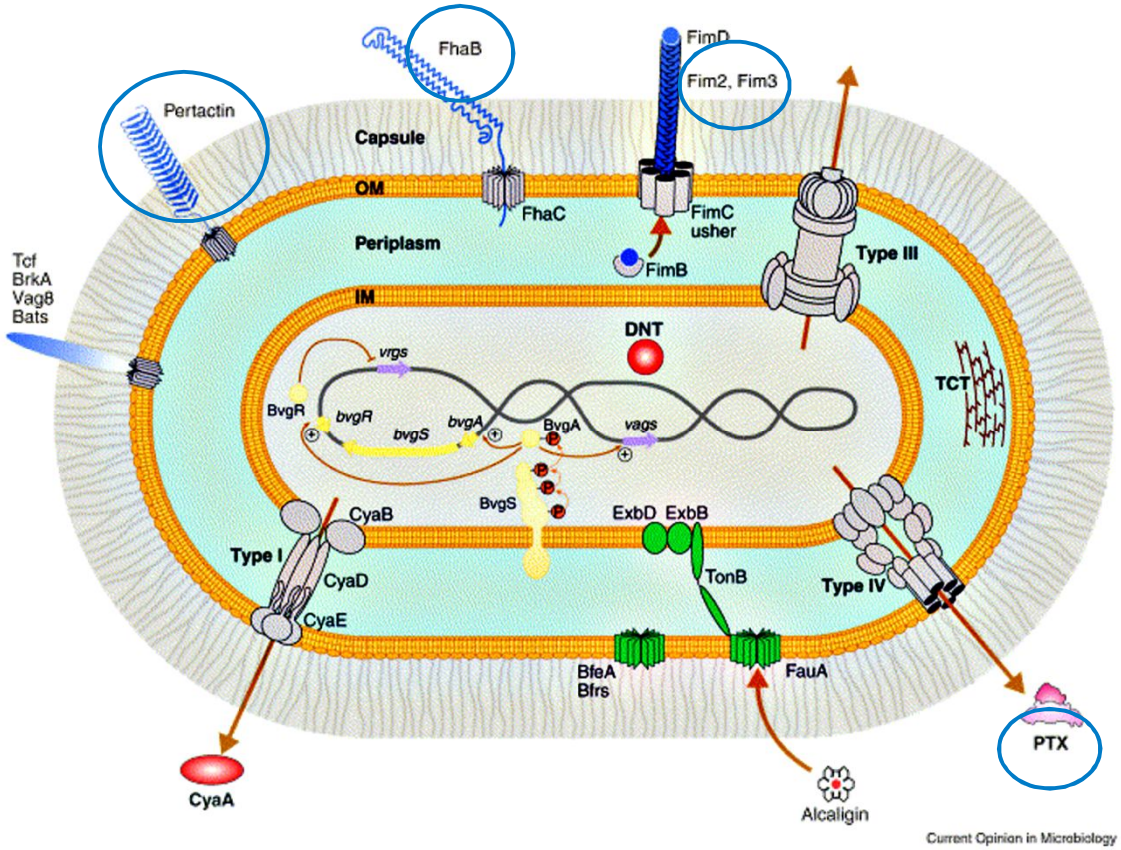
Why is strain typing important?

- Worldwide standardization to investigate the effects of different vaccines and vaccination schedules on the *B. pertussis* population
- Typing can serve as an “early warning” system for *B. pertussis* epidemics

  (van Gent et al., Vaccine 2009 18;27 (13): 1898-1903)
- Possibility to identify successful strains during epidemics

  (Mooi et al., Emerg Inf Dis 2009, 15 (8): 1206-1213)

B. pertussis bacterium with virulence factors



Virulence factors are components of ACVs:

- Pertactin (PRN)
- Filamentous hemagglutinin (FHA)
- Fimbriae (Fim)
- Pertussis toxin (PTX)

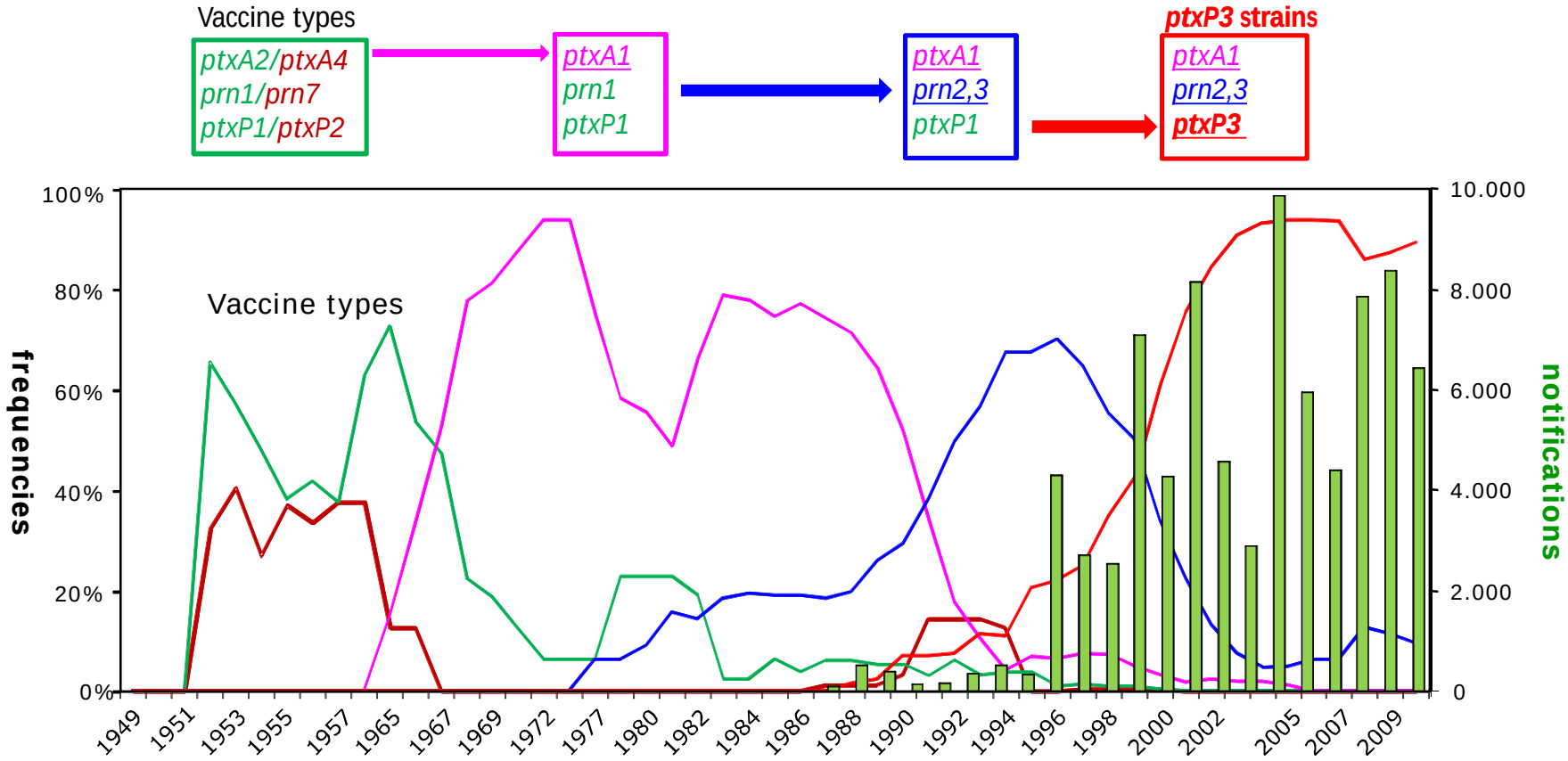
Typing of these antigens is an important part of the routine strain surveillance

Variation in the *B. pertussis* population in the last 60 years in the Netherlands

Variation in 3 genes is associated with changes in the *B. pertussis* population.
(Mooi *et al,* 1998; Mooi 2010; van Gent *et al,* 2012)

	Function:	**Vaccine types:**	**Circulating types:**
• **ptxA:**	Toxin	ptxA2 and ptxA4	→ ptxA1
• **prn:**	Adhesin	prn1 and prn7	→ prn2 and prn3
• **ptxP:**	Promoter toxin	ptxP1 and ptxP2	→ ptxP3

Variation in the *B. pertussis* population in the last 60 years in the Netherlands

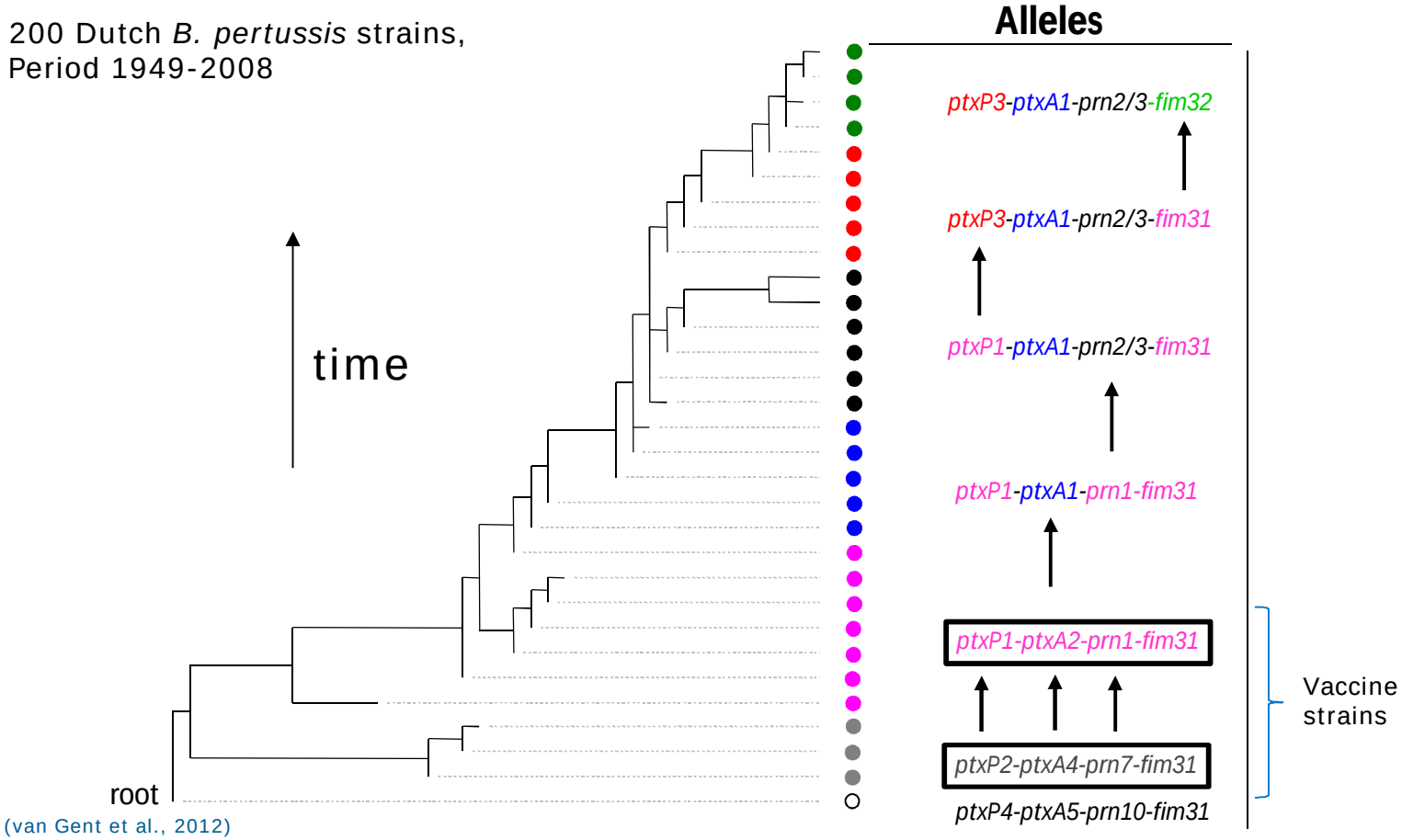


Mutations are associated with clonal sweeps suggesting they confer increased fitness (van Gent *et al.*, 2012).

The ptxP3 mutation seems to be the most important variation in the *B. pertussis* population

Evolutionary relationship between Dutch *B. pertussis* strains

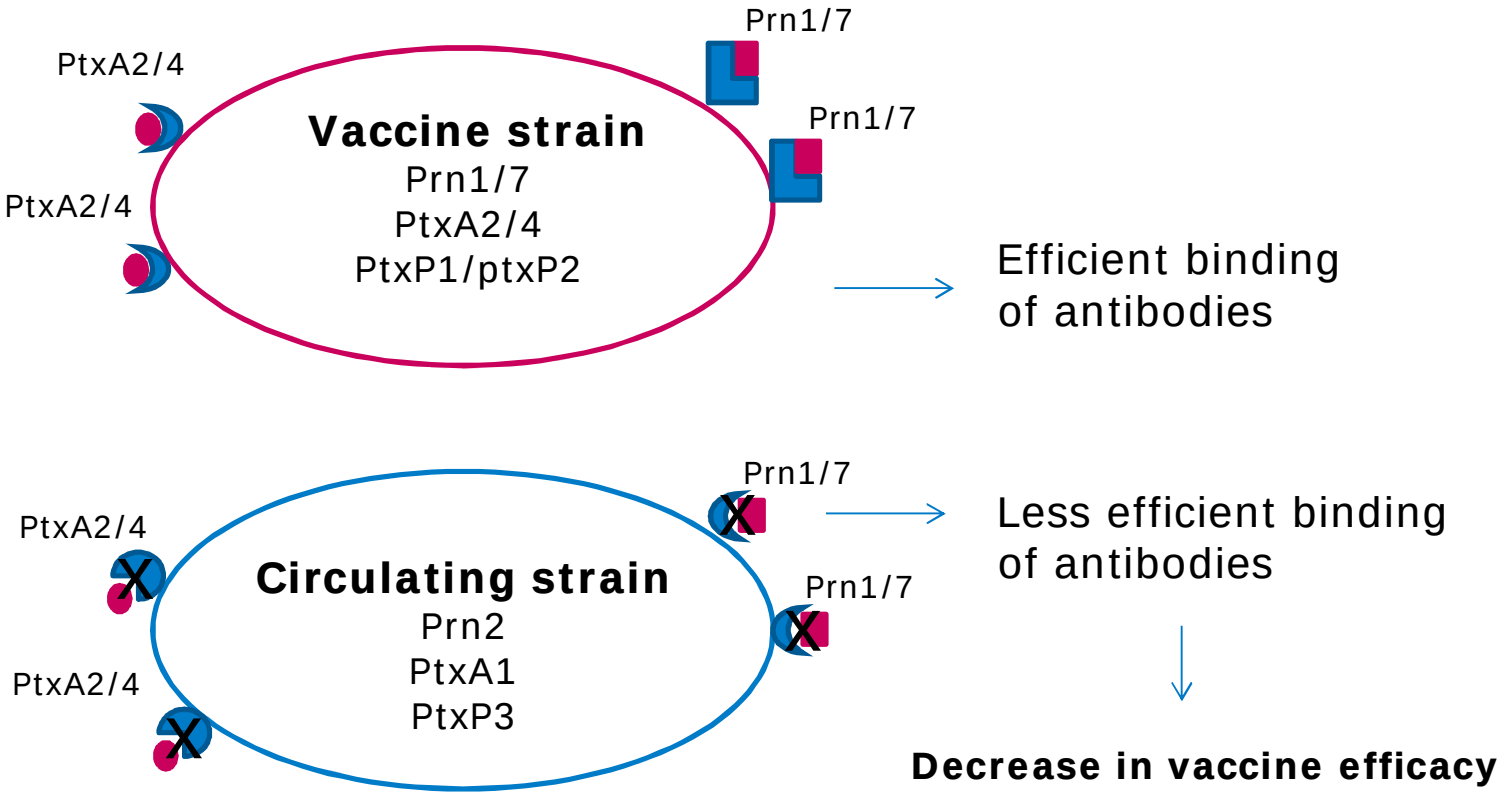
200 Dutch *B. pertussis* strains,
Period 1949-2008



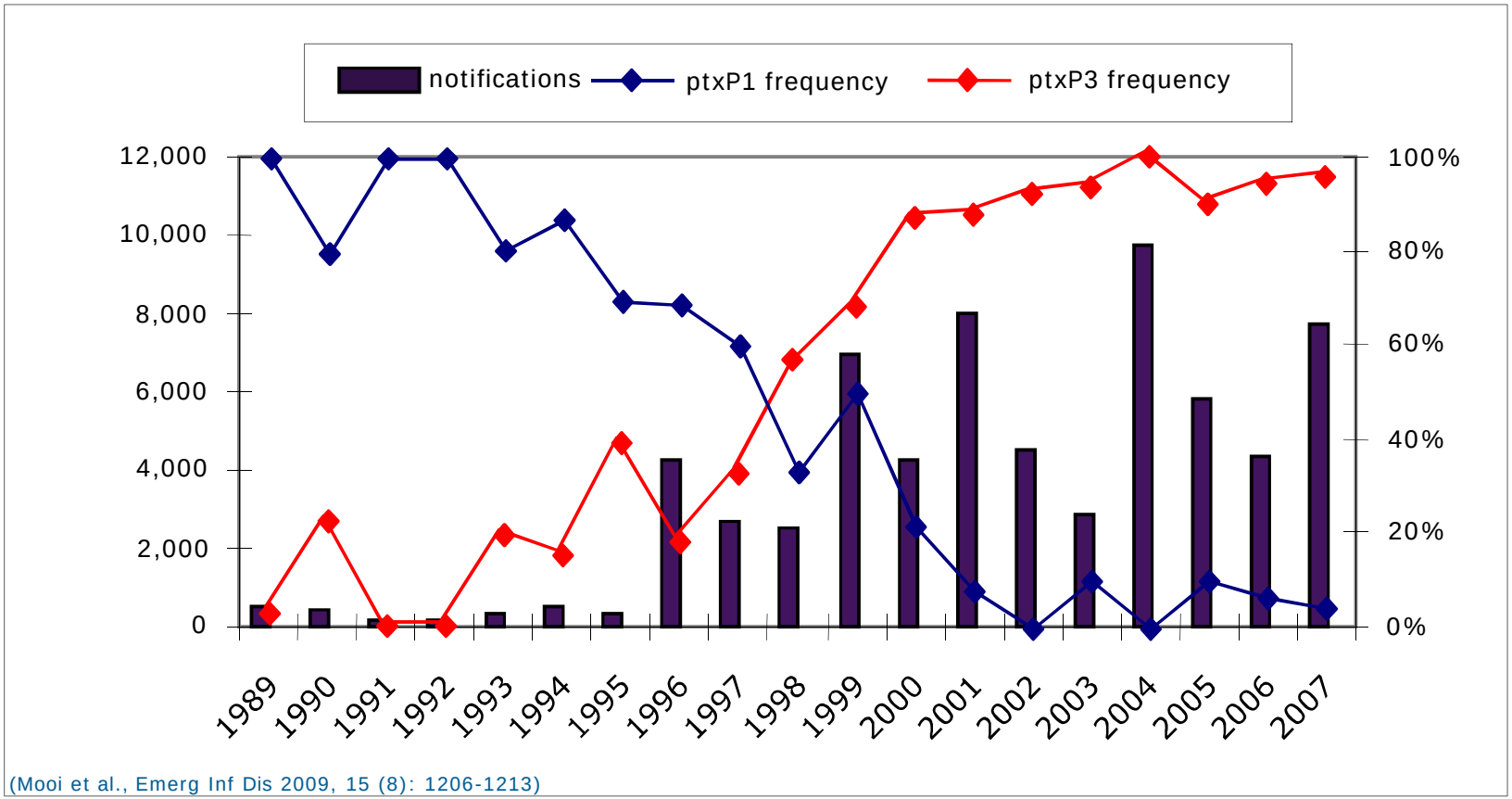
(van Gent et al., 2012)

B. pertussis reveals a stepwise adaptation with an accumulation of mutations in vaccine antigens

The effect of these mismatches on vaccine efficacy



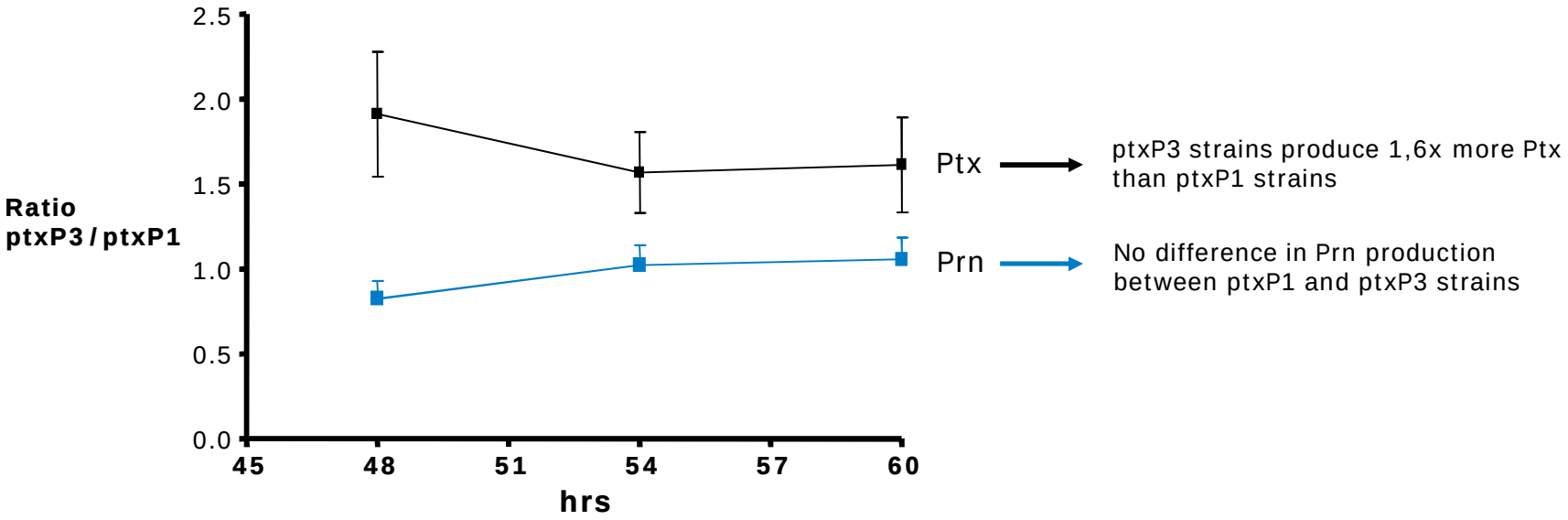
The increase in ptxP3 strains is associated with the increased notifications



(Mooi et al., Emerg Inf Dis 2009, 15 (8): 1206-1213)

- The ptxP3 strain has replaced the old ptxP1 strain almost completely
- The ptxP3 strain appeared before the epidemic started, an example of “early warning”

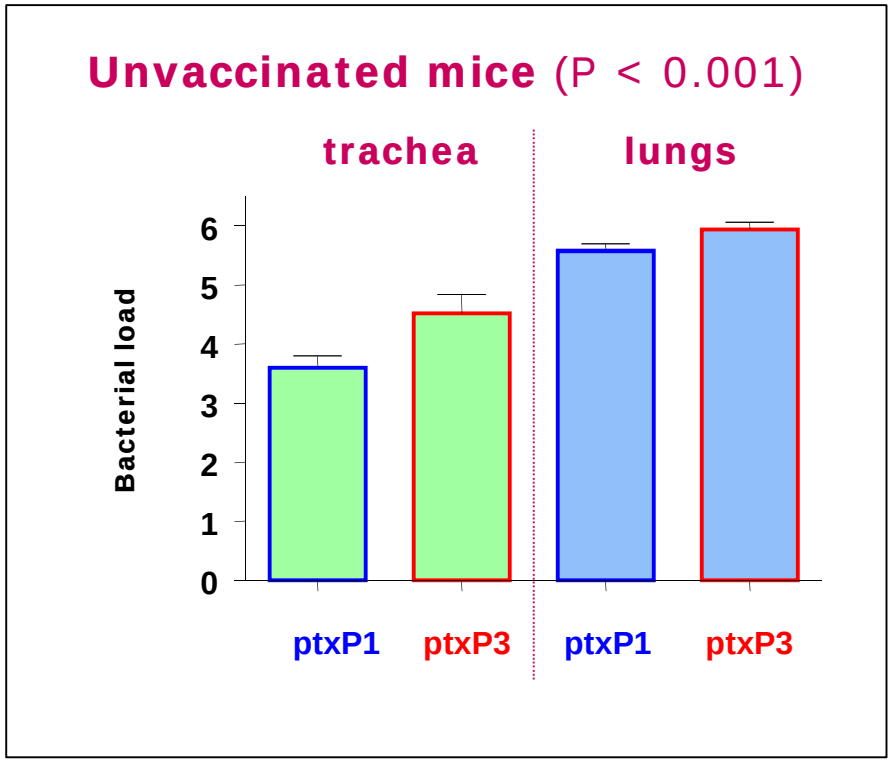
Why is the ptxP3 strain so successful?



ptxP3 strains produce more pertussis toxin than ptxP1 strains

(Mooi et al., Emerg Inf Dis 2009, 15 (8): 1206-1213)

Colonization of ptxP1 and ptxP3 strains in unvaccinated mice



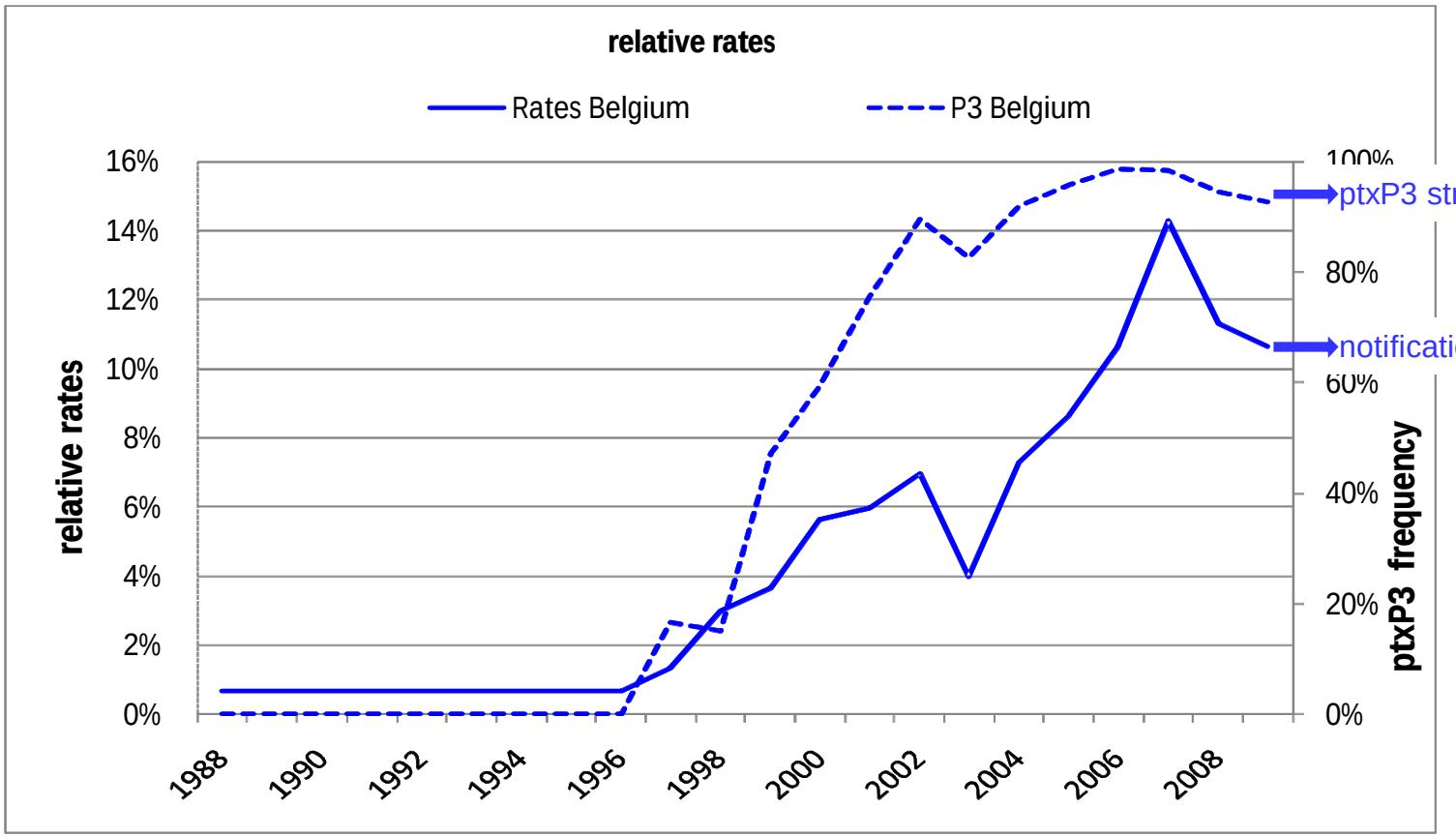
ptxP3 strains are more efficient colonizers of unvaccinated mice than ptxP1 strains

Is the ptxP3 strain more virulent than the ptxP1 strain?

The increase of ptxP3 strains is associated with increase of notifications, hospitalizations and lethality
(Mooi et al., Emerg Inf Dis 2009, 15 (8): 1206-1213)

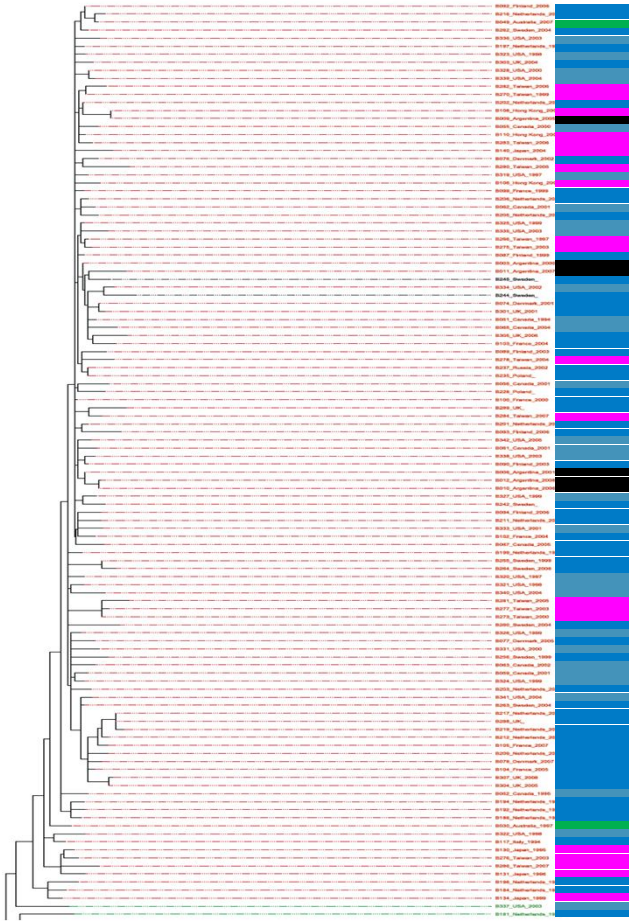
Infections with ptxP3 strains were associated with a longer duration of hospital stay in Sweden
(Advani et al., APMIS 2007; 115 (6): 736-742)

Invasion of ptxP3 strains is also associated with increased notifications in Belgium



Belgium: data from Denis Pierard, Universitair Ziekenhuis Brussel

Geographic distribution of the ptxP3 strain



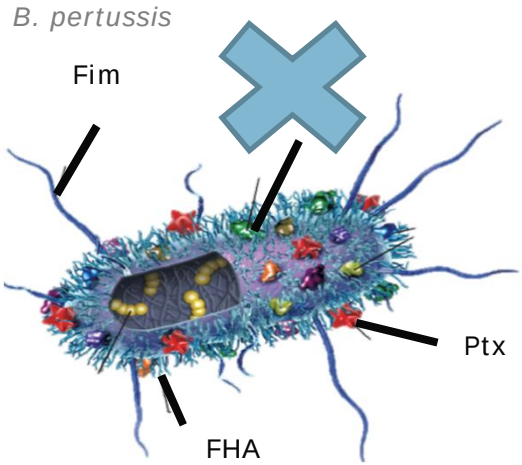
- Europe
- Asia
- Australia
- North America
- South America

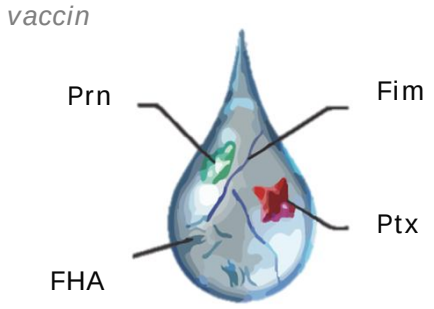
- ptxP3 strains found in all continents, except Africa
- No geographic clustering: rapid transmission of ptxP3 strains worldwide

Emergence of Vaccine Antigen Deficient strains, PRN-

Acellular pertussis vaccines

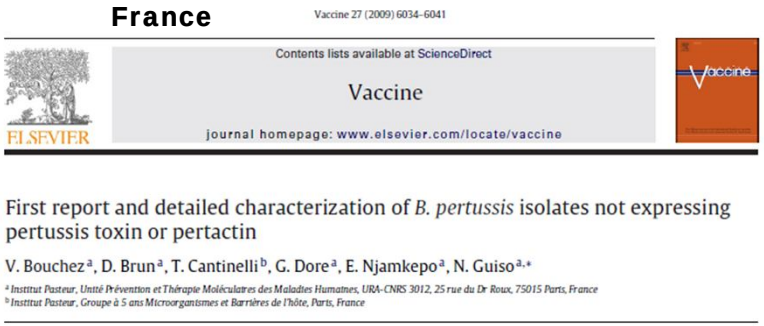
		NL	
ACV1	ACV2	ACV3	ACV5
Ptx	**Ptx**	**Ptx**	**Ptx**
	FHA	**FHA**	**FHA**
		Prn	~~**Prn**~~
			Fim2
			Fim3





Emergence of Vaccine Antigen Deficient strains, PRN-

France


Vaccine 27 (2009) 6034–6041

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

First report and detailed characterization of *B. pertussis* isolates not expressing pertussis toxin or pertactin

V. Bouchez[a], D. Brun[a], T. Cantinelli[b], G. Dore[a], E. Njamkepo[a], N. Guiso[a,*]

[a] Institut Pasteur, Unité Prévention et Thérapie Moléculaires des Maladies Humaines, URA-CNRS 3012, 25 rue du Dr Roux, 75015 Paris, France
[b] Institut Pasteur, Groupe à 5 ans Microorganismes et Barrières de l'hôte, Paris, France

Australia


RESEARCH

Rapid Increase in Pertactin-deficient *Bordetella pertussis* Isolates, Australia

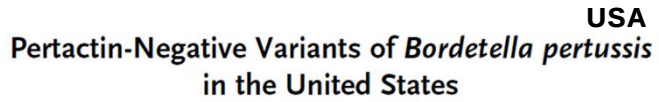
Connie Lam, Sophie Octavia, Lawrence Ricafort, Vitali Sintchenko, Gwendolyn L. Gilbert, Nicholas Wood, Peter McIntyre, Helen Marshall, Nicole Guiso, Anthony D. Keil, Andrew Lawrence, Jenny Robson, Geoff Hogg, and Ruiting Lan

Finland

LETTER TO THE EDITOR

Appearance of *Bordetella pertussis* Strains Not Expressing the Vaccine Antigen Pertactin in Finland

USA


CORRESPONDENCE

Pertactin-Negative Variants of *Bordetella pertussis* in the United States

The Netherlands


RESEARCH ARTICLES

Investigations into the emergence of pertactin-deficient *Bordetella pertussis* isolates in six European countries, 1996 to 2012

A Zeddeman[1], M van Gent[1], C J Heuvelman[1], H G van der Heide[1], M J Bart[1], A Advani[2], H O Hallander[2], C H Wirsing von König[3], Marion Riffelman[3], J Storsaeter[4], D F Vestrheim[4], T Dalby[5], K A Krogfelt[5], N K Fry[6], A M Barkoff[7], J Mertsola[8], Q He[7], F Mooi (frits.mooi@rivm.nl)[1]

Canada


International Journal of Infectious Diseases 28 (2014) 65–69

Contents lists available at ScienceDirect

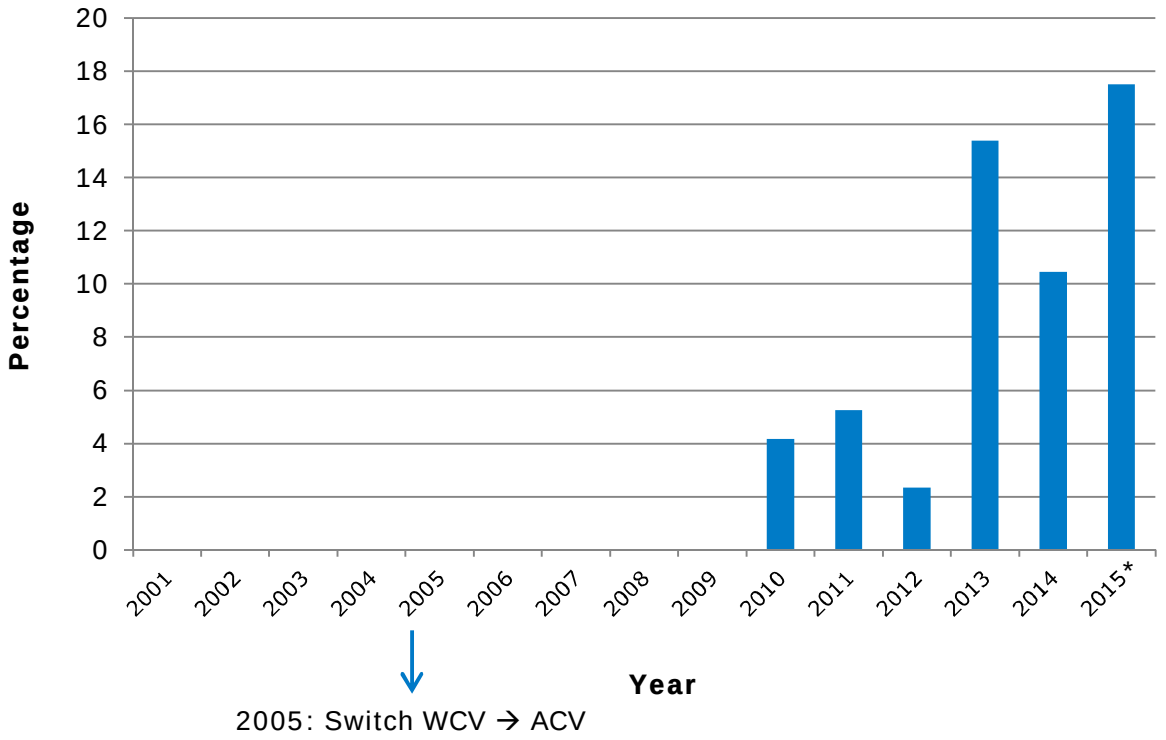
International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Pertactin-negative *Bordetella pertussis* strains in Canada: characterization of a dozen isolates based on a survey of 224 samples collected in different parts of the country over the last 20 years

Raymond S.W. Tsang[a,*], Michelle Shuel[a], Frances B. Jamieson[b,c], Steven Drews[d,e], Linda Hoang[f], Greg Horsman[g], Brigitte Lefebvre[h], Shalini Desai[i], Monique St-Laurent[i]

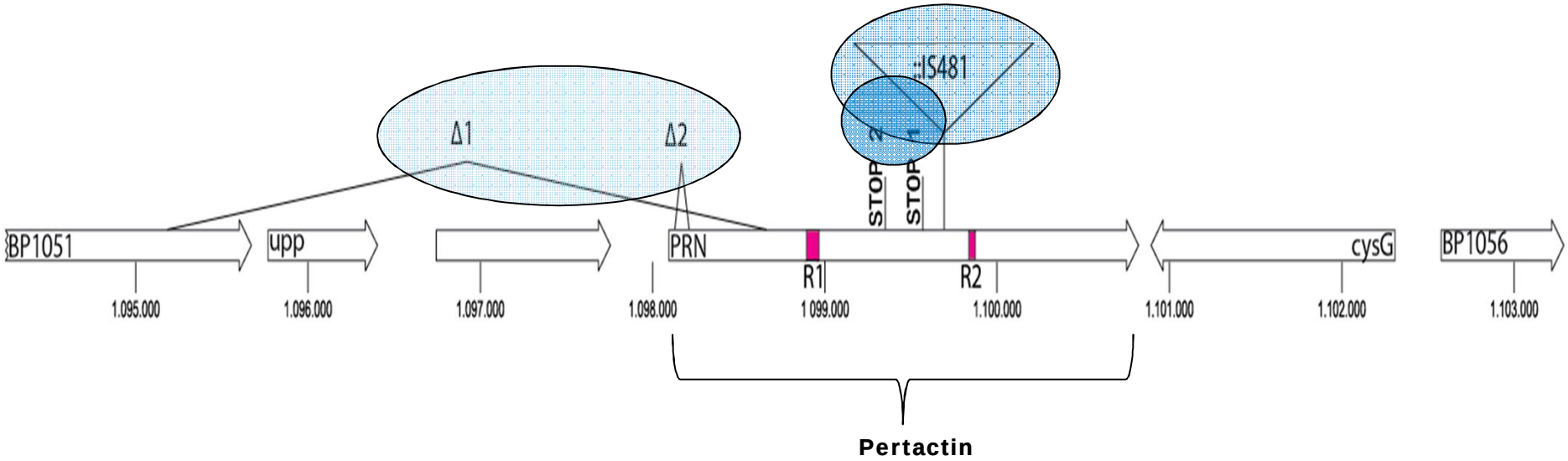
Percentage PRN-strains in the Netherlands



Is this one clone that spread worldwide?

* 40 strains were analyzed in 2015 so far

Emergence of Vaccine Antigen Deficient strains, PRN-



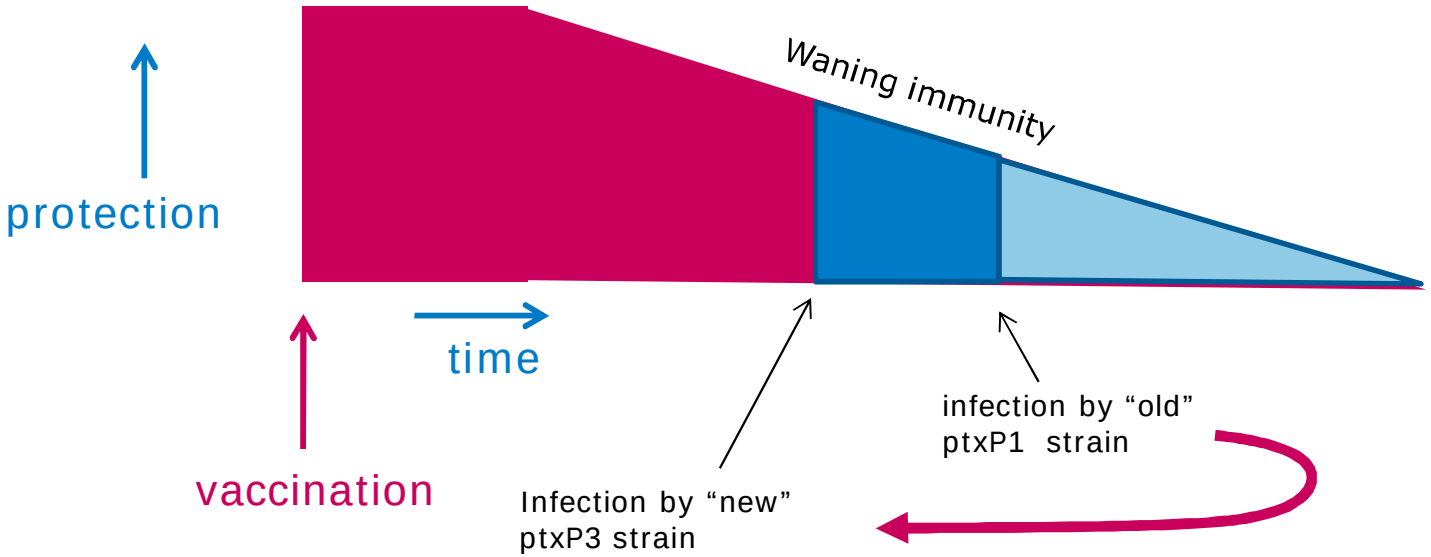
Different mutations are responsible for Prn deficiency:

- Insertion of a transposon
- SNP that causes a stop codon (premature termination of translation)
- Deletions

(Zeddeman et al. 2014)

Why do we see so much pertussis despite vaccination?

The combined effect of waning immunity and adaptation of the bacterium



When immunity wanes after ACV, ptxP3 strains can infect earlier:

- Antigenic divergence with vaccine strain
- More pertussis toxin production
- **Deletions of vaccine antigens (PRN-)**
- Other unknown mutations → what will follow?? FHA-??