

# Global Challenges for Pertussis Vaccines

**Scott A. Halperin, MD**

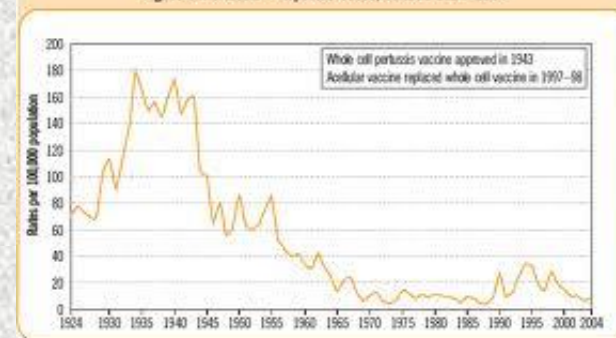
**Canadian  
Center for  
Vaccinology**



Dalhousie University  
IWK Health Centre  
Capital Health

***15<sup>th</sup> ADVAC  
15 May 2014***

Figure 9. Pertussis – Reported Cases, Canada 1924–2004



# Disclosures

- Research Funding
  - Government
    - CIHR
    - Public Health Agency of Canada
    - Nova Scotia Department of Health and Wellness
  - Institution
    - IWK Health Centre
  - Industry
    - GlaxoSmithKline
    - Novartis
    - Sanofi Pasteur
    - Pfizer
    - Merck
    - PREVENT
- Consultant/Advisory Board/Committee
  - Government
    - NACI Influenza Working Group
    - NACI MenB Working Group
    - CDC Pertussis Working Group
    - WHO SAGE Pertussis WG
    - NS, PEI, and NB Depts of Health
  - NGO
    - PATH
  - Industry
    - PREVENT
    - ImmunoVaccine
    - GlaxoSmithKline
    - Sanofi Pasteur
    - Novartis
    - Medicago

# Whooping Cough....does it matter?

- Is it really such a big deal?
  - How bad is the disease?
  - Is there much associated morbidity?
  - Does anyone die anymore
  - Is it worth the effort to try to prevent outbreaks and further reduce cases?

# Pertussis vaccine....what's the problem?

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- Didn't we solve the problems with the acellular pertussis vaccine?
- Why don't we just go back to whole cell vaccine?
- What is the likelihood of a new vaccine?
  - What else do we need to know?
  - How will we get that information?

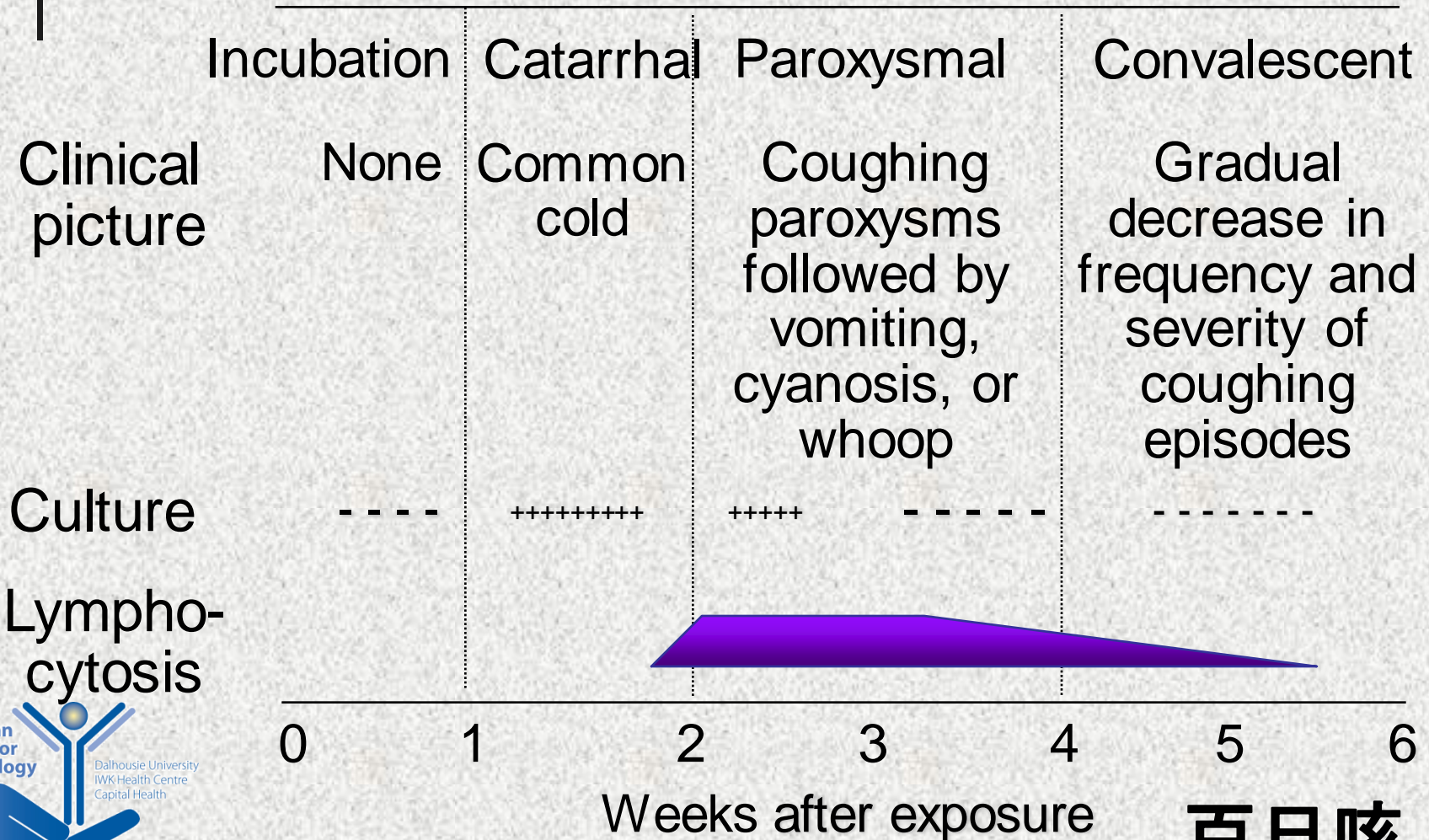


# Isn't it just a cough?



# Ok, so you cough for a while....

Stage



百日咳

# Failure of Physicians to Consider the Diagnosis of Pertussis in Children

Shelley Deeks, Gaston De Serres, Nicole Boulianne,  
Bernard Duval, Louis Rochette, Pierre Déry,  
and Scott Halperin

From the Field Epidemiology Training Program, Laboratory Centre for Disease Control, Ottawa, Ontario, Centre de recherche du Pavillon CHUL, Centre hospitalier universitaire de Québec, and the Faculty of Medicine, Laval University, Québec, Québec, and the Department of Pediatrics, Dalhousie University, and the IWK Grace Health Centre, Halifax, Nova Scotia, Canada

## Pertussis is under-diagnosed



To determine the ability of physicians to make a diagnosis of pertussis and factors associated with improved diagnosis, 8,235 children from 88 child care centers and 14 elementary schools from Quebec City, Quebec, Canada, were evaluated by using a questionnaire completed by parents and a medical record review. Children must have consulted a physician to be included in the evaluation. There were 558 children meeting the surveillance case definition and 416 meeting a modified World Health Organization case definition who consulted a physician. A diagnosis of pertussis was considered in 24%–26% of children meeting either case definition, made in 12%–14%, and reported for 6%. Pertussis diagnosis was significantly associated with having a history of pertussis exposure ( $P \leq .003$ ), four pertussis-related symptoms ( $P < .001$ ), and a cough for  $\geq 5$  weeks ( $P \leq .05$ ) and consulting in a hospital setting ( $P \leq .03$ ). The proportion of cases of pertussis diagnosed and reported is low even when children present with classical symptoms.

*Bordetella pertussis* continues to be an important cause of morbidity in North American children [1–3]. The actual burden of illness from pertussis is greater than reflected in national statistics, because of underreporting associated with a passive reporting system, the relative insensitivity of laboratory tests, and difficulties in physician diagnosis [2–7]. In the United States, it has been estimated that only 3% to 12% of cases of pertussis in young children are reported to the Centers for Disease Control and Prevention [2, 8]. Nasopharyngeal (NP) culture, the current diagnostic gold standard for pertussis, is highly specific; however, it is relatively insensitive and labor-intensive [8–10]. Delayed specimen collection, prior immunization, and prior use of erythromycin therapy have been associated with decreased sensitivity of culture for *B. pertussis* [8, 9, 11]. The lack of a highly sensitive and specific diagnostic test reinforces the importance of adequate history taking on the part of physicians, as the diagnosis must often be made on clinical grounds.

Relatively little literature is available pertaining to physician ability to make the diagnosis of pertussis. A distinguishing feature of the disease is the paroxysmal cough and characteristic whoop. Because the child may not cough in the physician's presence, the diagnosis could easily be missed without a high index of suspicion [12]. In a study of pediatric patients with pertussis, the disease was not considered in the initial differential diagnosis in more than one-half of the cases [13]. Other

studies have also demonstrated physician difficulty with diagnosis, especially in adolescents and adults [3, 5, 6, 11].

A study was undertaken in Quebec City, Quebec, Canada, between May and June 1993. The objectives were to determine the following: the ability of physicians to make a diagnosis of pertussis, the factors associated with improved diagnosis, and the proportion of cases reported to the provincial surveillance system. This study was conducted during a period of increased incidence of disease. Between 1991 and 1993, the incidence of pertussis in the province of Quebec increased more than sixfold, reaching 59.4 reported cases per 100,000 population in 1993 [1, 14]. This increase in incidence was associated with a general increase in public and professional awareness of pertussis.

### Methods

Two retrospective cohort studies were conducted simultaneously in Quebec City between 31 May and 20 June 1993. The study methodology has been described in detail previously [15]. Briefly, the first cohort study included children attending 88 of the 91 child care centers in Quebec City, and the second included pupils attending kindergarten to grade 3 in 14 elementary schools in a suburb of Quebec City. Because the objectives of the current study were independent of the setting attended by the children, data from the two cohort studies were merged and analyzed together. Parents completed a standardized questionnaire regarding all cough-associated illness of at least 2 weeks' duration and pertussis-related symptoms (paroxysmal cough, posttussive vomiting or apnea, and whoop) in their child during the 11-month period between 1 July 1992 and 31 May 1993.

Children were classified as meeting either of two clinical case definitions for pertussis. Because neither case definition

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1058-4838/99/2804-0027\$03.00



# Classical Pertussis Epidemiology

- Pertussis a disease of infants and young children
- Peak incidence in pre-school aged children
- Most morbidity and nearly all mortality in young infants
  - One of the leading causes of infant mortality in early 19<sup>th</sup> century
- Nearly 50% of children with evidence of infection by school entry



# Children are still dying of pertussis



## How best to estimate the global burden of pertussis?

N S Crowcroft, C Stein, P Duclos, and M Birmingham

In most countries, pertussis surveillance is inadequate for accurately estimating numbers of cases or deaths. Good estimates are needed to help set priorities for vaccination programmes. We aimed to develop a simple, reliable, and explicit method for estimating pertussis cases and deaths for children under 15 years to calculate the global disease burden in 1999. We estimated the proportion of susceptible children becoming infected in countries with poor vaccination coverage (<70%) in 1999 at 30% by 1 year, 80% by 5 years, and 100% by 15 years of age and for countries with good coverage (>70%) at 10% by 1 year, 60% by 5 years, and 100% by 15 years. Vaccine efficacy was estimated at 80% for preventing infection and 95% for preventing deaths. We used UN population estimates and vaccination coverage reported to WHO (adjusted for specific survey data if available). Case fatality ratios for countries with high and low child mortality were derived from published and unpublished work. For some countries with good vital events registration we used reported deaths adjusted for underascertainment. In 1999 there were an estimated 48.5 million pertussis cases in children worldwide. Deaths from pertussis were estimated at 390 000 and at 295 000 after adjustment for local data sources. Based on this approach, disability-adjusted life years from pertussis (12.7 million) in 2000 exceeded those of other preventable diseases such as lung cancer (11.4 million) and meningitis (5.8 million). This simple approach yields estimates that can be used for setting vaccination programme priorities. Better data are needed on the public health importance of pertussis in high mortality countries, the benefits of incomplete vaccination, and the harm from delayed vaccination.

*Lancet Infect Dis* 2003; 3: 413–18

**Table 1. Method of calculation of pertussis cases and deaths**

<b>Total cases</b>	
Cases in unvaccinated	$N(1-V)p_i+C_i$
Cases in vaccinated	$NV(1-e)p_i+C_i$
<b>Total deaths</b>	
Deaths in unvaccinated	$N(1-V)p_d+C_d$
Deaths in vaccinated	$NV(1-e)p_d+C_d$

Calculations of cases and deaths for each country for population in age group  $N$ , number of birth cohorts  $C$ , vaccination coverage  $V$ , vaccine efficacy against infection  $e$ , vaccine efficacy against death  $e'$ , proportion of susceptible children infected by age group  $i$  of  $p$ , and case fatality rate of  $d$

### Methods

Our starting point for the methods was the approach taken by Galazka<sup>3</sup> for previous global estimates. The evidence base for some of the parameters used by Galazka had not been fully described, and we made use of further evidence that has accumulated since Galazka developed his method. For the Global Burden of Disease report, WHO requires numbers of pertussis cases and deaths by age and country. Relevant age groups for pertussis in children were under 1 year, 1–4 years, and 5–14 years. Reliable data are generally not available through vital-events registration or national surveillance systems for most countries. Consequently, a simple model was developed to estimate the number of cases by incorporating the effects of vaccination and known epidemiology of pertussis (tables 1 and 2).

Pertussis vaccination has a limited effect on transmission of the infection<sup>4</sup> and a greater effect on more severe disease.<sup>5</sup> For this reason, epidemic cycles continue to be monitored even in countries with good vaccination coverage. Statutory notifications are biased towards typical disease and under-reporting will occur, especially during inter-epidemic

# Infant Pertussis

- In Canada, a case control study from 1991-2002
  - all 16 fatal cases of pertussis were infants 6 months of age or younger
  - 15 were 2 months of age or younger
  - mean age 6.5 weeks.
- Jan-Sept 2010: 4,017 cases, California
  - majority of infant cases <3 months of age
  - 9 deaths, all in infants <2 months of age

# Pertussis in Infants





# Complications of Pertussis

## ■ Pulmonary

- Pneumonia 9.4%
- Atelectasis 3.0%

## ■ Hernia

- Inguinal 0.4%
- Umbilical 0.4%

## ■ Neurological

- Seizures 1.9%
- Encephalopathy 0.3%

## ■ Weight Loss

1.3%

## ■ Death

0.8%



# Pertussis in Infants



# Pertussis causes morbidity in adolescents and adults

## Morbidity of Pertussis in Adolescents and Adults

Gaston De Serres,<sup>1,2</sup> Ramak Shadmani,<sup>2</sup>  
Bernard Duval,<sup>1,2</sup> Nicole Boulianne,<sup>1,2</sup> Pierre Déry,<sup>3</sup>  
Monique Douville Fradet,<sup>4</sup> Louis Rochette,<sup>2</sup>  
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<sup>1</sup>Institut National de Santé Publique du Québec, <sup>2</sup>Laval University, Department of Social and Preventive Medicine, Public Health Research Unit, CHUL Research Center, <sup>3</sup>Department of Pediatrics, Centre Hospitalier Universitaire de Québec and Laval University, and <sup>4</sup>Ministère de la Santé et des Services Sociaux du Québec, Québec, and <sup>5</sup>IKW-Grace Health Centre and Dalhousie University, Halifax, Canada

The effect of age on the clinical presentation of pertussis was assessed in 664 adolescent and adult cases. Complications were more frequent in adults than in adolescents (28% vs. 16%). Pneumonia occurred in 2% of patients <30 years old but in 5%–9% of older patients. Urinary incontinence occurred in 34% of women ≥50 years old. Duration of cough, risk of sinusitis, and number of nights with disturbed sleep increased with smoking and asthma. The secondary attack rate in other household members ≥12 years was 11%. Pertussis in secondary case patients was less severe than in index case patients but presented with classic symptoms. The main source of infection in adolescents was schoolmates or friends; in adults it was workplace or their children. Teachers and health care workers had a greater risk of pertussis than did the general population. The burden of disease appears to increase with age, with smoking, and with asthma.

Pertussis was long considered a childhood illness; however, in the last 2 decades, there has been increasing evidence that pertussis affects not only children but adolescents and adults [1–14]. Although the morbidity of pertussis and the frequency of complications are well-known in children, there are fewer data about the changes that occur with increasing age. The 2 largest published pertussis adult case series included 64 and 79 persons ≥18 years old (mean, 31 and 36 years, respectively), which were insufficient to compare the morbidity by age [6, 7]. This study documents the morbidity of pertussis in 280 adolescent (12–17 years old) and 384 adult (≥18 years old) case patients and the susceptibility of their adolescent and adult household contacts.

### Methods

**Setting and outbreak.** In Quebec, the second largest Canadian province (7 million people), universal vaccination against pertussis was introduced in 1946. Thereafter, the number of cases steadily decreased and stabilized between 1970 and 1989, when a mean of 318 cases was reported annually. Since 1990, there has been a re-

surge of pertussis, with numerous epidemic years (figure 1). During 1998, 4881 cases were reported, the highest number since 1950, and 26% occurred among adolescents or adults. These cases were either culture-positive or met the Canadian surveillance case definition for pertussis: cough ≥2 weeks with ≥1 pertussis-related symptom (paroxysms, posttussive vomiting, posttussive apnea, or whoop) and no other apparent cause [15].

Case patients were recruited in 5 of the 18 public health units where 68% (3302) of all reported cases occurred. In these regions, among the 718 eligible patients ≥12 years old and whose disease began between 1 July and 30 December 1998, we were unable to contact 51 patients, despite multiple attempts, and 3 refused to participate. We thus evaluated 280 adolescent and 384 adult cases.

Trained nurses of the public health units where the cases were reported completed a standardized questionnaire, first by using data collected as part of the routine investigation for reportable disease immediately after the case was reported. These data included age, sex, immunization history, date of onset of cough, presence of fever, coryza, other classic pertussis symptoms (paroxysmal cough, posttussive vomiting, posttussive apnea, or whoop), medication, hospital admission, and the use of chemoprophylaxis by household contacts. Nurses also called all patients in February, March, and April 1999 to collect more data on immunization history, total duration of cough, duration of paroxysmal cough, other clinical symptoms (pharyngeal pain, fatigue, or sweating episode), complications, previous health conditions, occupation, smoking history, number of medical visits in clinic or at the emergency room, laboratory and radiologic investigations, medication, hospitalization and its duration, number of workdays lost by patients or their relatives, the presence of other case patients in the family and their symptoms, and the use of chemoprophylaxis by household contacts. Medical records were not consulted to verify this information. Information on patient treatment and house-



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0022-1899/2000/18201-0022\$02.00

# Pertussis in Adults





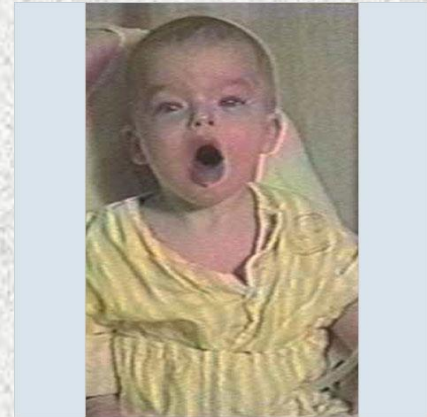
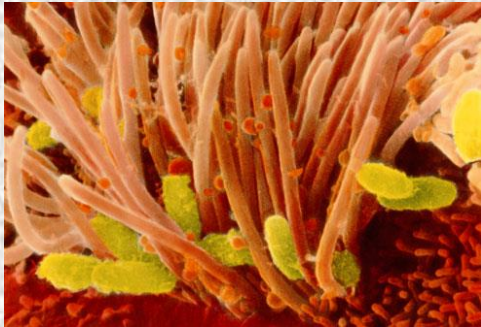
# Morbidity of Pertussis in Adolescents and Adults in Quebec

## Percent Reporting Complication

	<u>12-17</u>	<u>30-39</u>	<u>&gt;50</u>
	n=280	n=129	n=53
pneumonia	2	5	9
urinary			
incontinence	0	2	34



# What's the Global Situation



# 2010 Pertussis Oubreak: California

- Population 37.6 million
  - 9,477 cases (24.2/100,000)
    - Highest rate in infants <6 months of age
    - 10 deaths, all in infants <2 months of age



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Waning Protection after Fifth Dose of Acellular Pertussis Vaccine in Children

Nicola P. Klein, M.D., Ph.D., Joan Bartlett, M.P.H., M.P.P.,  
Ali Rowhani-Rahbar, M.D., M.P.H., Ph.D., Bruce Fireman, M.A.,  
and Roger Baxter, M.D.

ABSTRACT

### BACKGROUND

In the United States, children receive five doses of diphtheria, tetanus, and acellular pertussis (DTaP) vaccine before 7 years of age. The duration of protection after five doses of DTaP is unknown.

### METHODS

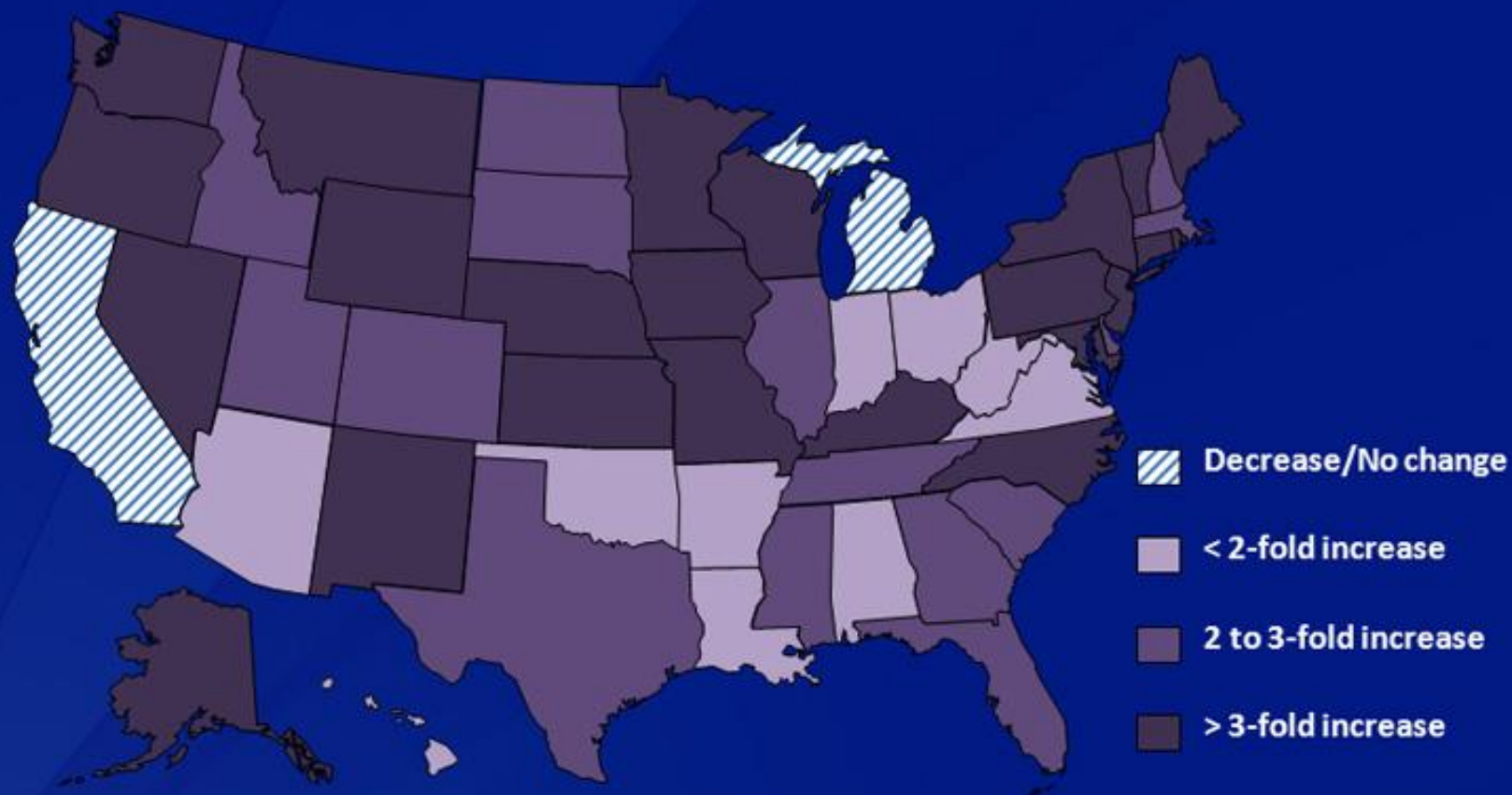
We assessed the risk of pertussis in children in California relative to the time since the fifth dose of DTaP from 2006 to 2011. This period included a large outbreak in 2010. We conducted a case-control study involving members of Kaiser Permanente Northern California who were vaccinated with DTaP at 47 to 84 months of age. We compared children with pertussis confirmed by a positive polymerase-chain-reaction (PCR) assay with two sets of controls: those who were PCR-negative for pertussis and closely matched controls from the general population of health-plan members. We used logistic regression to examine the risk of pertussis in relation to the duration of time since the fifth DTaP dose. Children who received whole-cell pertussis vaccine during infancy or who received any pertussis-containing vaccine after their fifth dose of DTaP were excluded.

From the Kaiser Permanente Vaccine Study Center, Oakland, CA. Address reprint requests to Dr. Klein at the Kaiser Permanente Vaccine Study Center, 1 Kaiser Plaza, 16th Fl., Oakland, CA 94612, or at nicola.klein@kp.org.

N Engl J Med 2012;367:1012-9.  
DOI: 10.1056/NEJMoa1200850  
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# Changes in Pertussis Reporting by State from 2011 to 2012\* †



\*Data for 2012 are provisional and subject to change.

†Cases reported through Week 37 in 2011 were compared with cases reported through Week 37 in 2012; fold-changes were calculated for each state.





# Washington State population 6.8 million

## Current Situation in Washington State

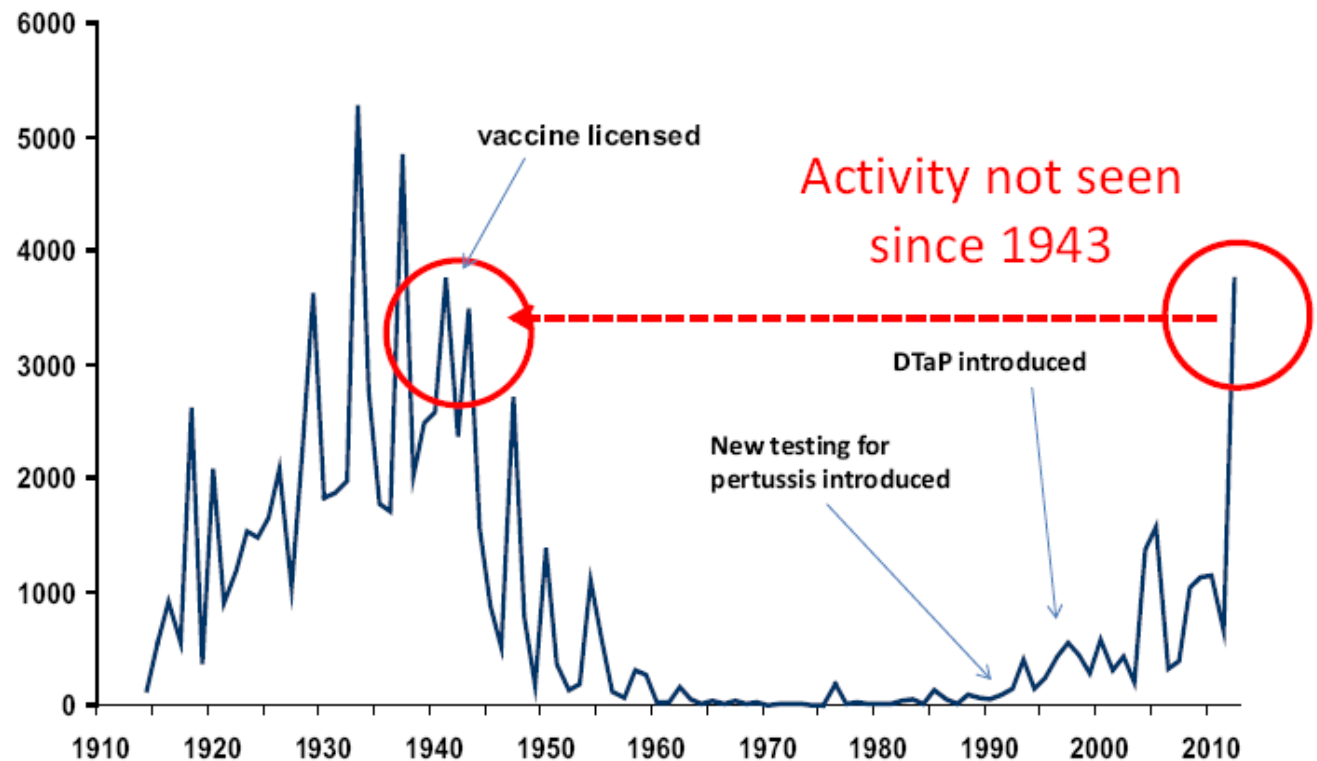
Published every Tuesday afternoon. Data through 10/06/2012

Pertussis cases in Washington, 2012	
Pertussis cases reported in 2012	4,307
Cases reported for the same period in 2011	495
New cases reported September 30-October 6, 2012	39
Age groups with highest rate	Children under age 1 Children ages 10 to 13
Cases in babies under age one in 2012	314
County with highest rate	Skagit
Counties with reported pertussis cases	38
Counties with no reported pertussis cases	1



# Minnesota Population 5.3 million

Reported Cases of Pertussis,  
Minnesota, 1914 - 9/20/2012



# Pertussis in the UK

## REVIEW ARTICLES

### Pertussis immunisation and control in England and Wales, 1957 to 2012: a historical review

G Amirthalingam (Gayatri.Amirthalingam@phe.gov.uk)<sup>1</sup>, S Gupta<sup>1</sup>, H Campbell<sup>1</sup>

1. Immunisation, Hepatitis and Blood Safety department, Public Health England, London, United Kingdom

#### Citation style for this article:

Amirthalingam G, Gupta S, Campbell H. Pertussis immunisation and control in England and Wales, 1957 to 2012: a historical review. *Euro Surveill.* 2013;18(38):pii=20587. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20587>

Article submitted on 19 September 2012 / published on 19 September 2013



This review summarises the epidemiology and control of pertussis in England and Wales since the introduction of routine immunisation and considers the implications for future control. Routine infant immunisation with a whole-cell pertussis (wP) vaccine was introduced in 1957 and had a marked impact on the overall disease burden. Following a fall in vaccine coverage during the 1970s and 80s linked to a safety scare with wP vaccine, there was an extended period of high coverage and pertussis incidence fell dramatically. Incidence continued to decrease with the introduction of an acellular pertussis vaccine in the pre-school booster in November 2001 and in the primary United Kingdom (UK) schedule in September 2004 but has increased since July 2011. In response to a high rate of pertussis in infants, a temporary vaccination programme for pregnant women was introduced in October 2012. The key aim of the programme is to protect vulnerable infants from birth in the first months of life, before they can be fully protected by routine infant immunisation. A review of the UK adolescent immunisation programme is currently ongoing and the inclusion of a pertussis booster is being considered.

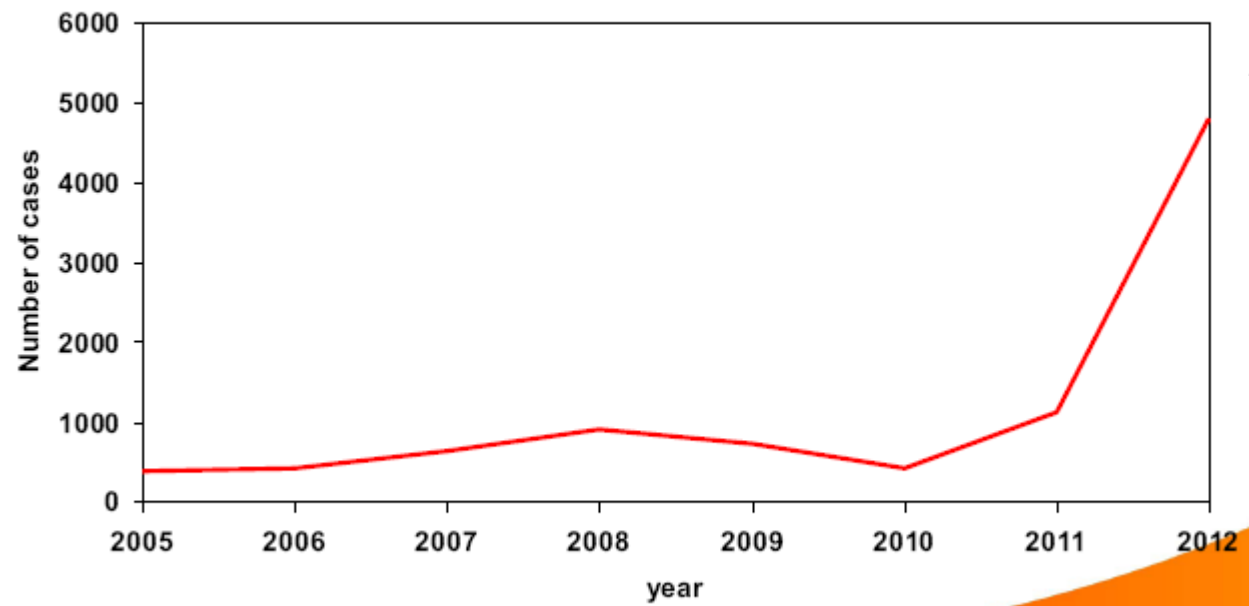
every three to five years, affecting up to 150,000 people and contributing to approximately 300 deaths each year [2]. Although England and Wales have experienced an extended period of high vaccine coverage and disease incidence has fallen dramatically, pertussis remains the most common vaccine-preventable cause of hospitalisation and death in infants [3].

Pertussis persists as an infection of global public health importance. Many countries with long-standing vaccination programmes have reported a resurgence of pertussis, particularly in adolescents and adults [4-6] and young infants less than 6 months of age [7-9], despite sustained high vaccine coverage. This has led to a growing international debate on the potential strategies to optimise global pertussis control. A 2010 review by the Strategic Group of Experts in Immunisation (SAGE) on pertussis control strategies recommended a booster dose for children aged 1-6 years, preferably during the second year of life, following completion of the primary infant schedule [10]. Although a number of countries, including France, the United States (US) and Australia, have recommended

# Pertussis, United Kingdom

population 62.6 million

Laboratory confirmed cases of pertussis 2005 to end August 2012

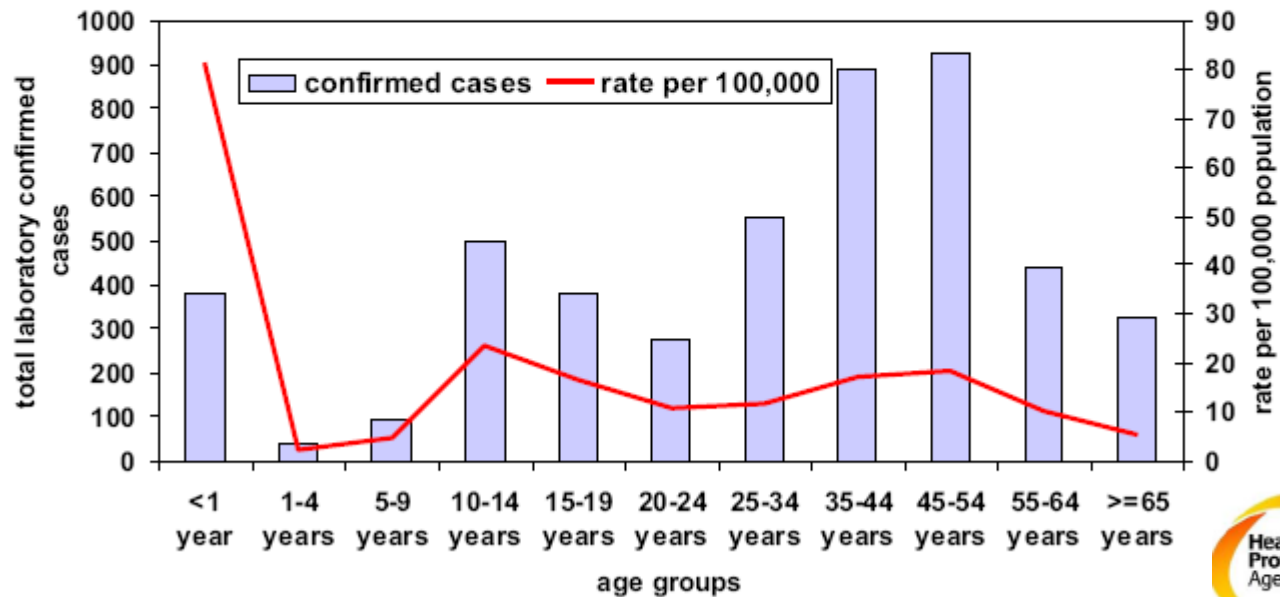




# Pertussis in England and Wales

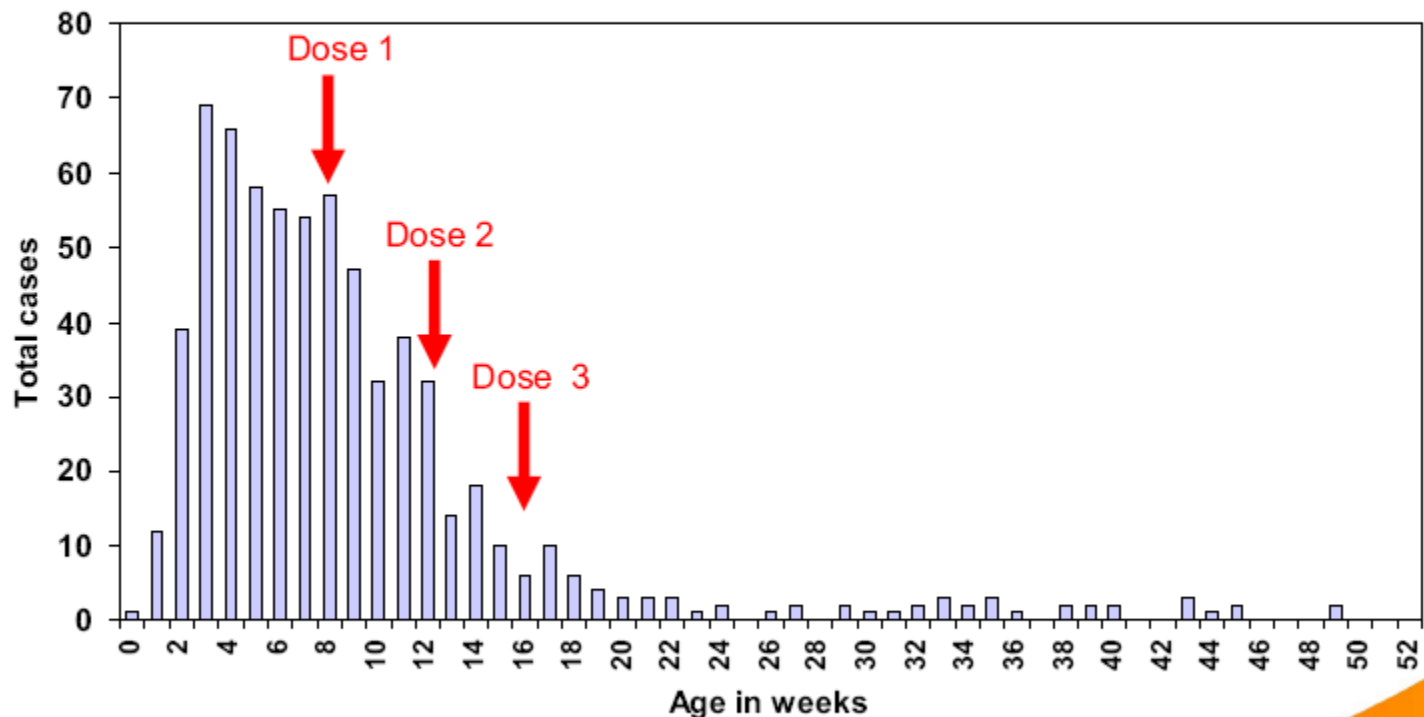
## Current epidemiology of pertussis in England and Wales

Age distribution of laboratory confirmed cases of pertussis in 2012 (to end August) and rate per 100,000 (extrapolated from data to end August 2012)



# Pertussis in Infants, England and Wales

Confirmed cases in infants under 1 year, by week of age at onset\* (2011-end August 2012), England and Wales



\* Where provided; specimen date used when onset not available

# Is Australia the World Capital of pertussis?



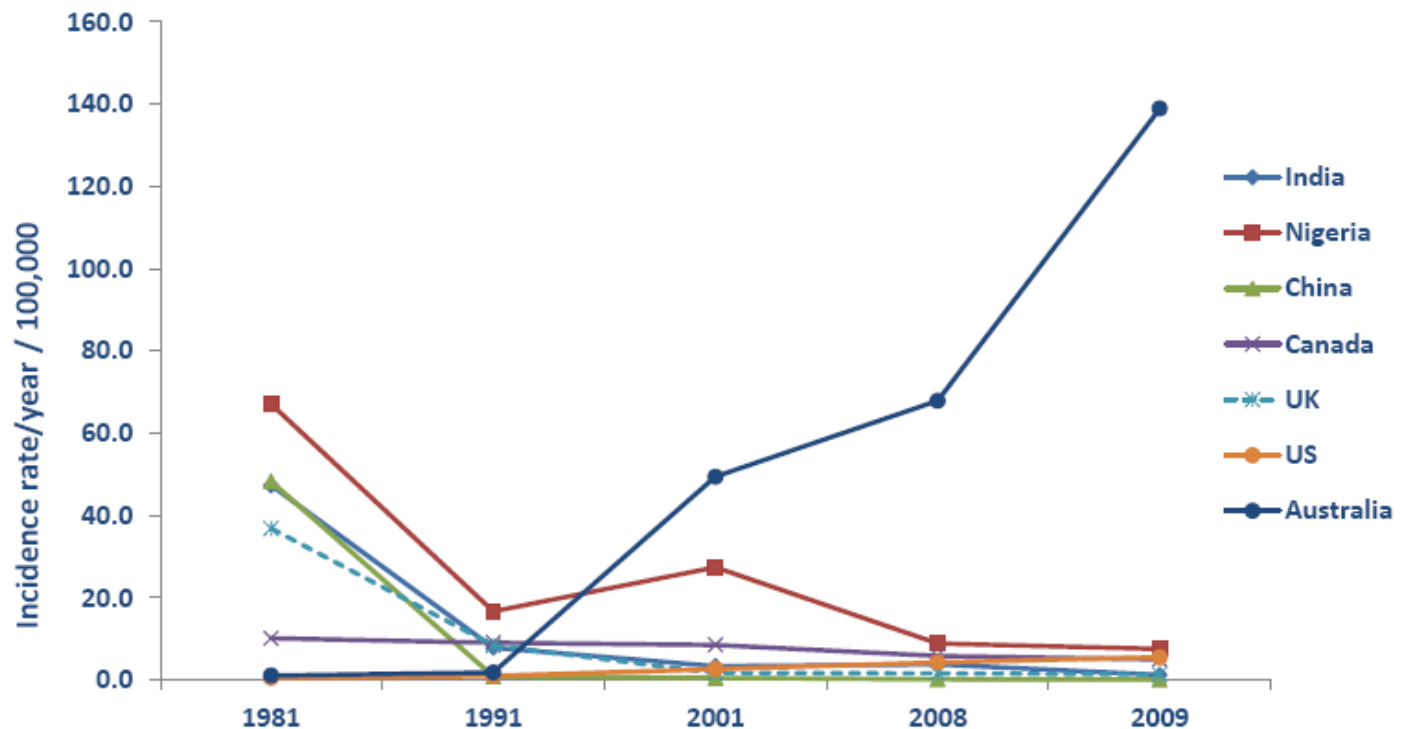
**Peter McIntyre**

**National Centre for Immunisation Research and  
Surveillance, Sydney, Australia**



# Pertussis in Australia

## Pertussis incidence rate by WHO region



# Pertussis

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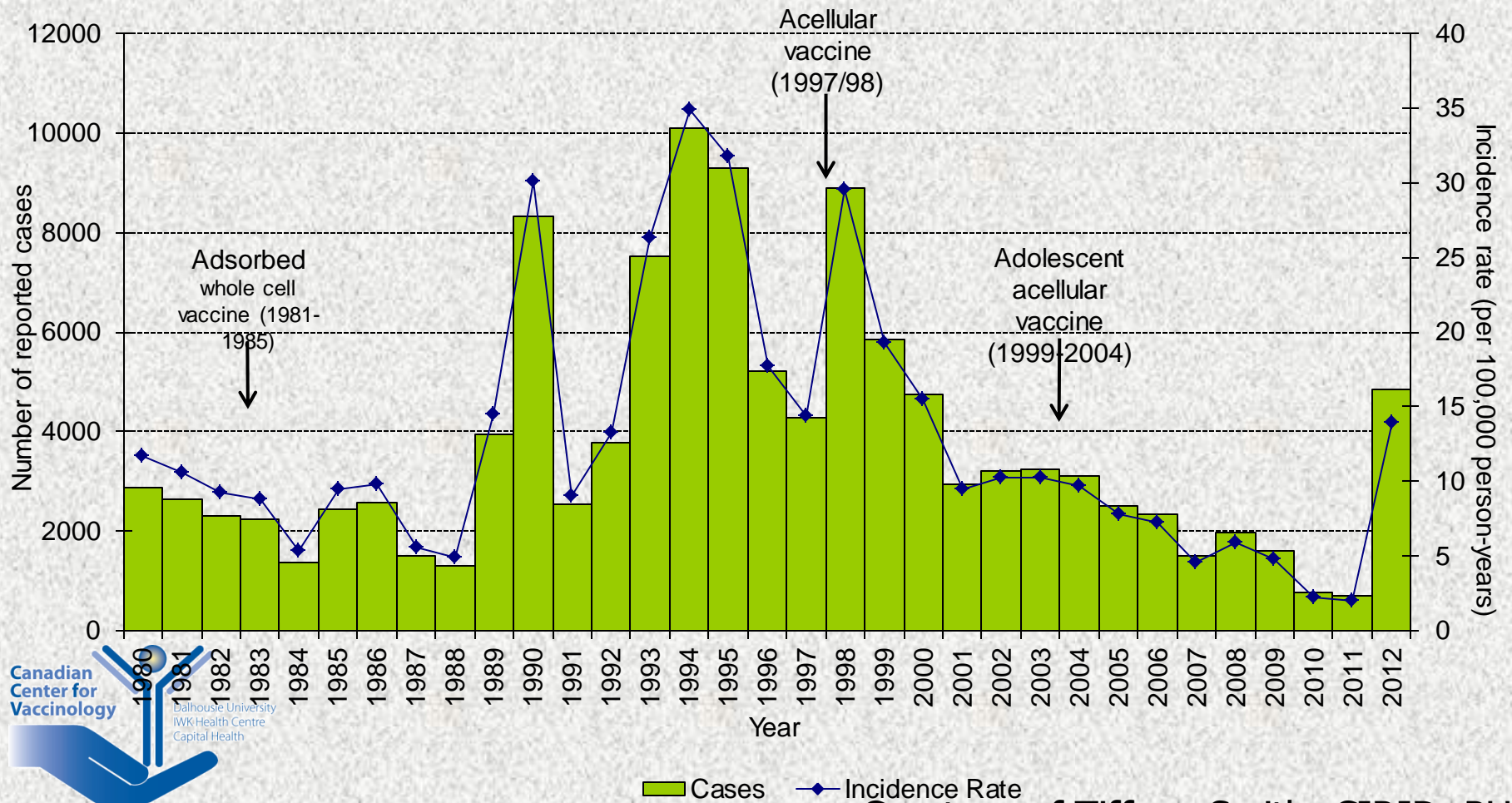
## **Increase observed**

- United States
- United Kingdom
- Australia
- Chile
- Brazil

## **No increase observed**

- France
- Denmark
- Sweden
- Germany
- Finland

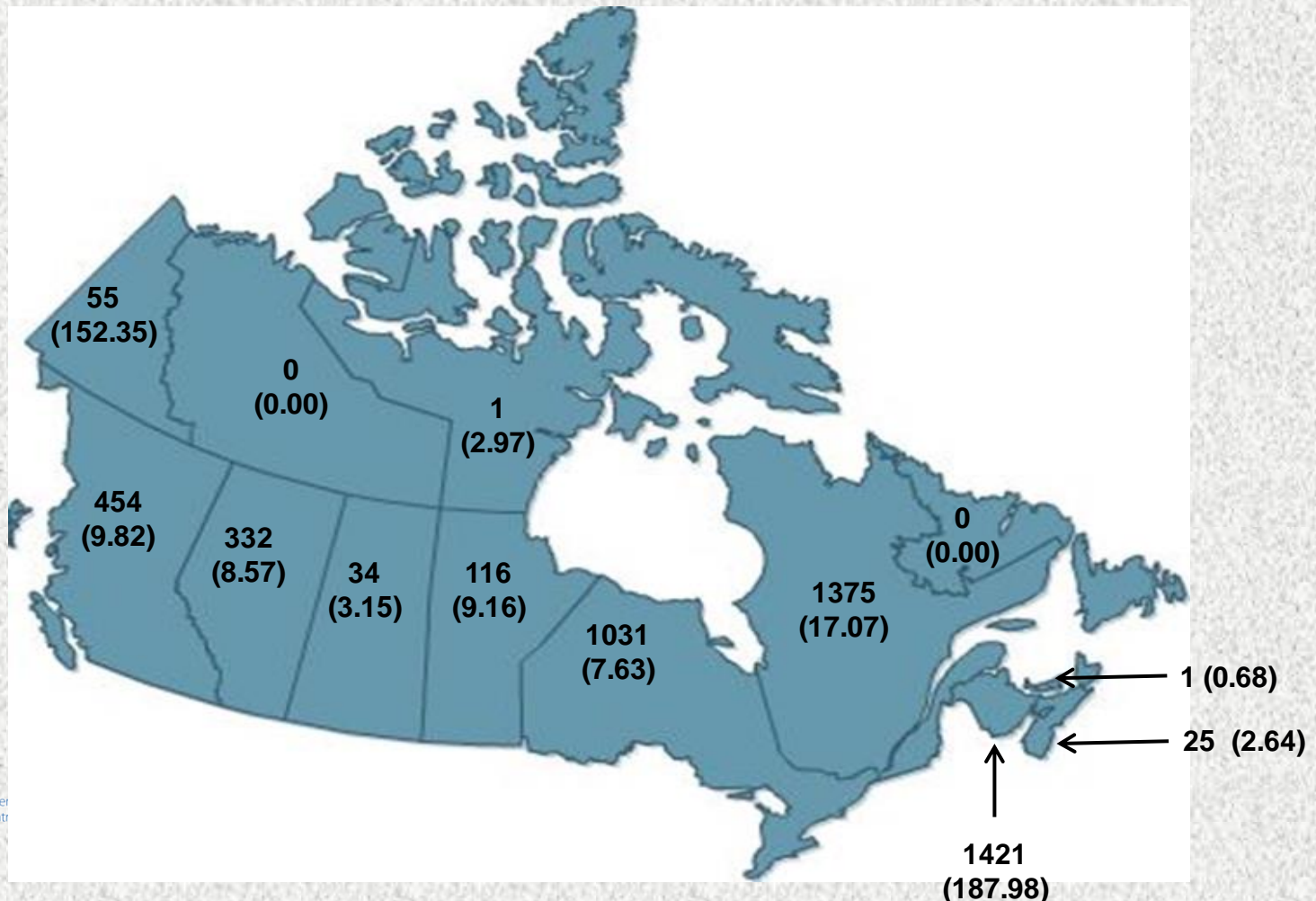
# Reported cases and incidence (per 100,000) of pertussis in Canada by year, 1980 to 2012.



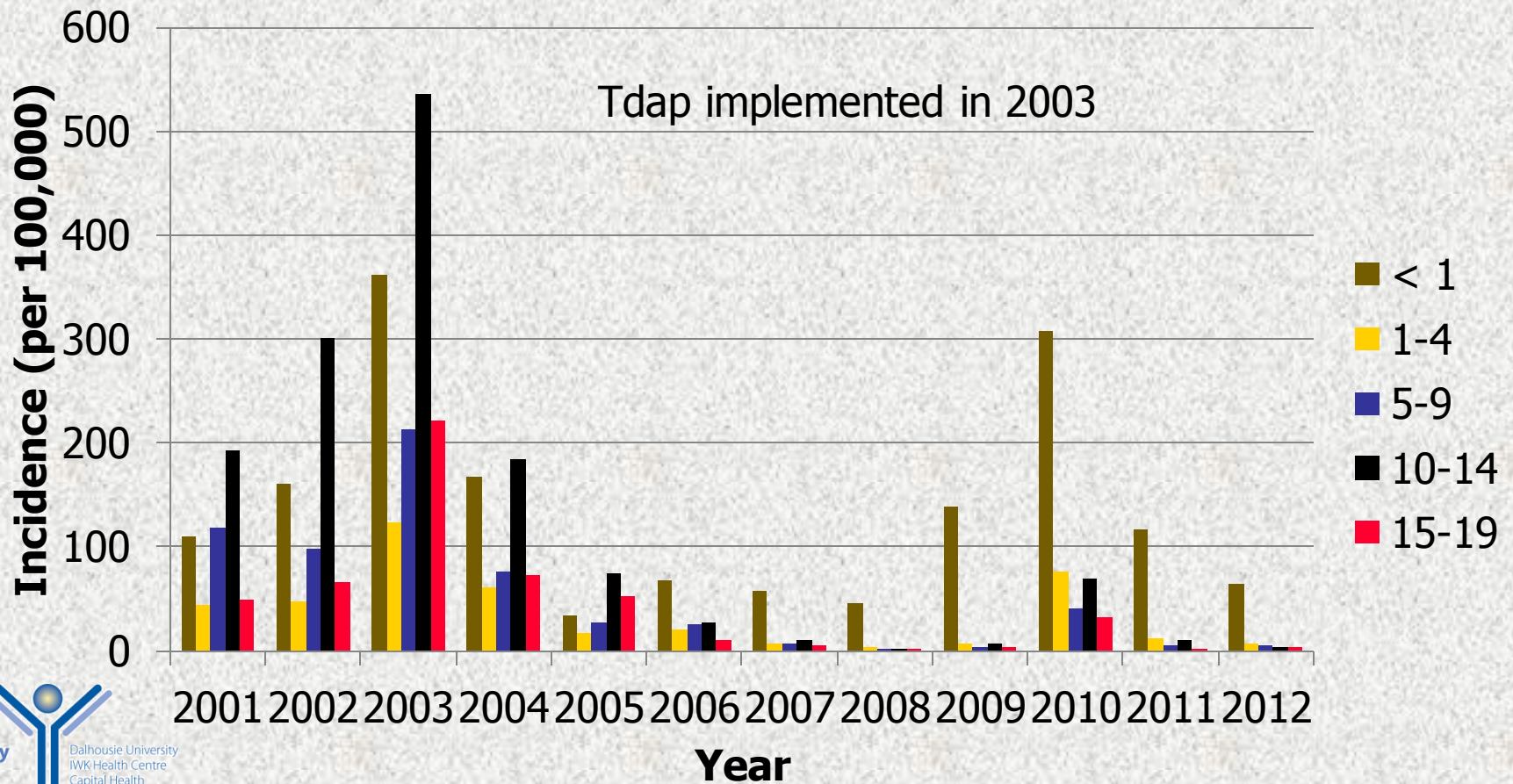
Courtesy of Tiffany Smith, CIRID, PHAC



# Reported pertussis cases and crude annualized incidence rates (per 100,000 population) in Canada, 2012.



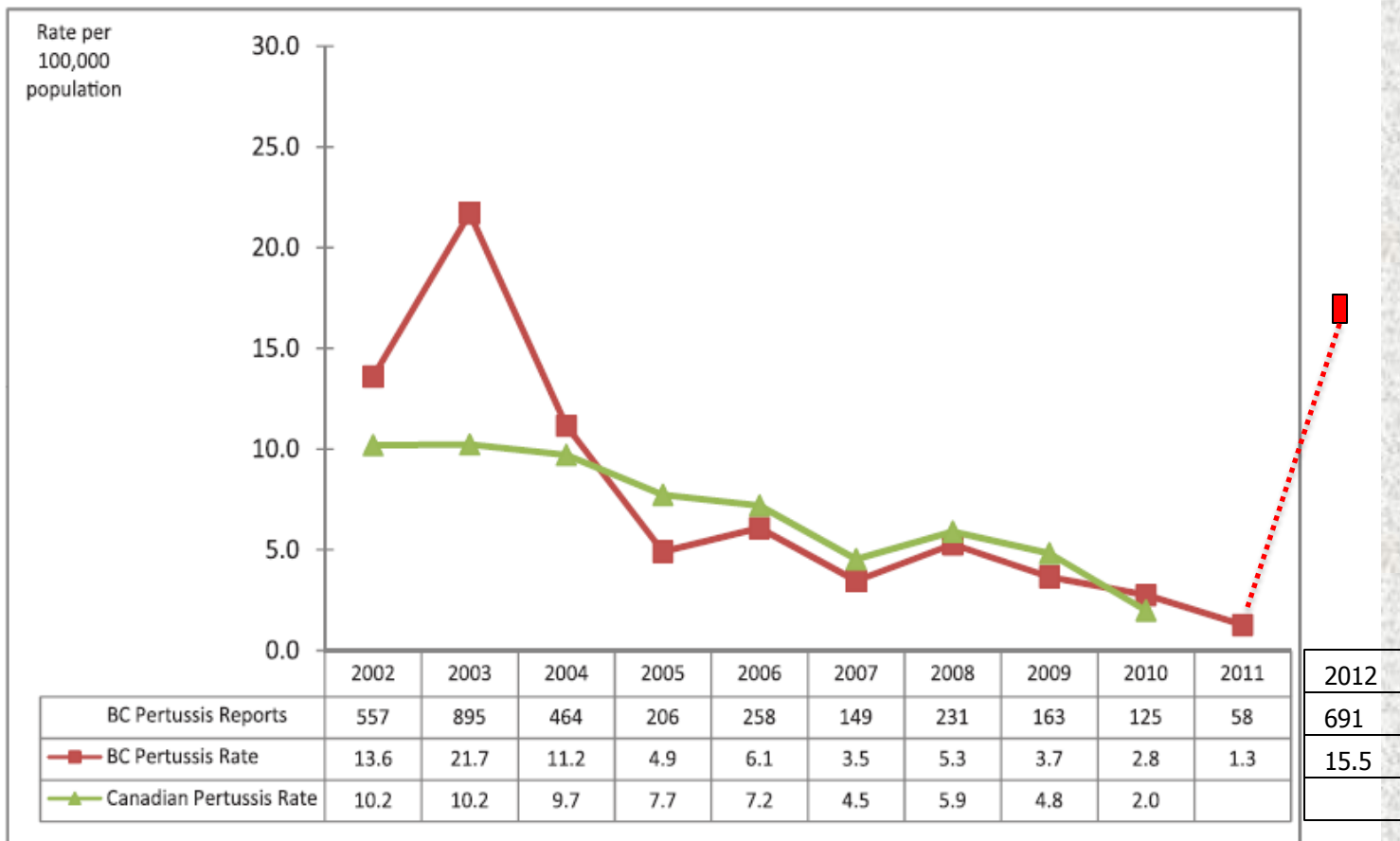
# Pertussis in Saskatchewan 2001-2009



# Pertussis in Saskatchewan

- 2008-April 2010
  - 35 lab confirmed cases in infants <1 year
    - 5% (2/35) had started immunization on time
    - 49% (17/35) were over 2 months of age and were unimmunized
    - 43% (15/35) were under 2 months of age (too young to be immunized)
  - 5 deaths
    - 4 younger than 1 month
    - 1 3 month old unimmunized

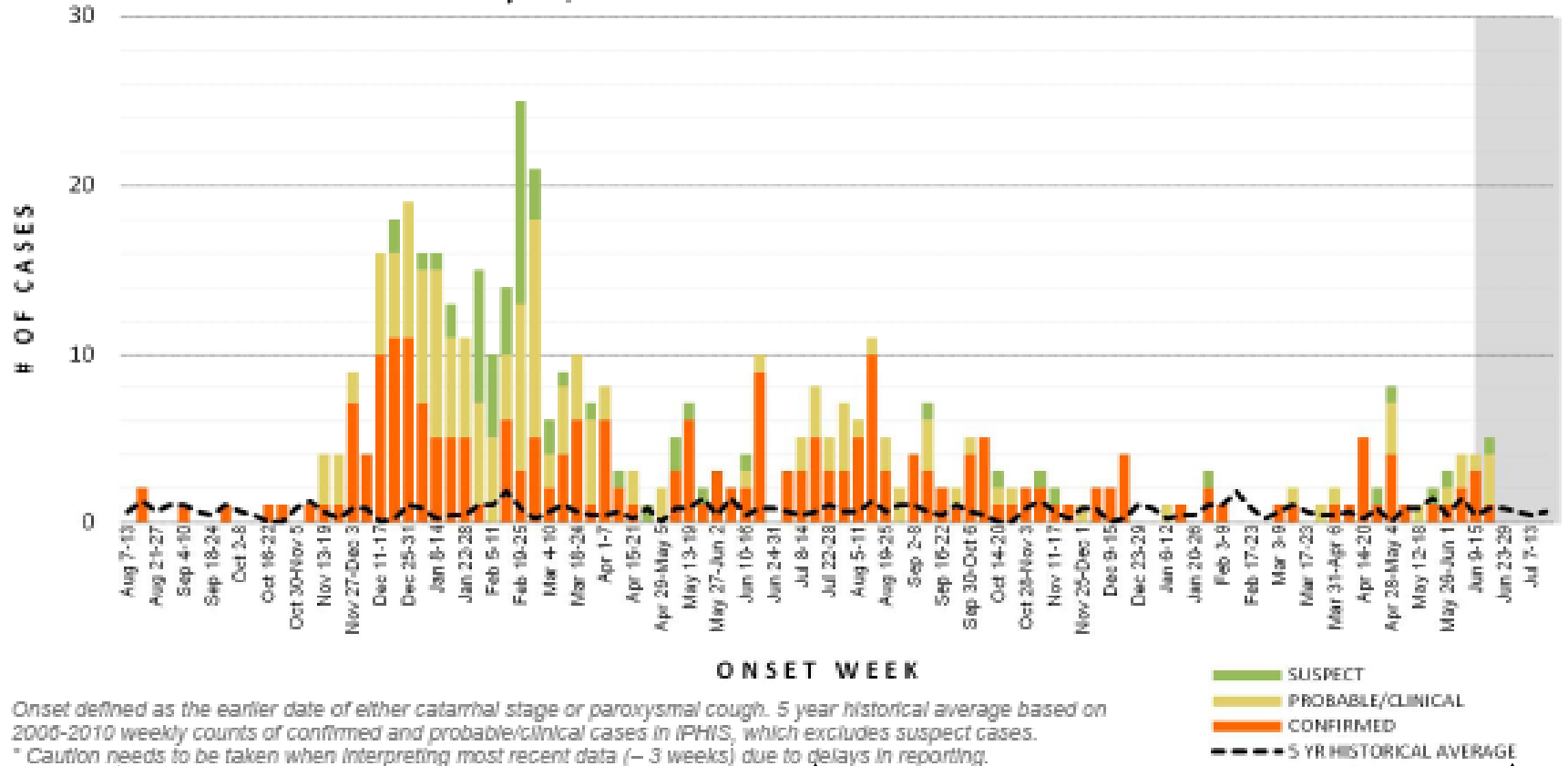
# BC Pertussis Rates by Year, 2002-2012



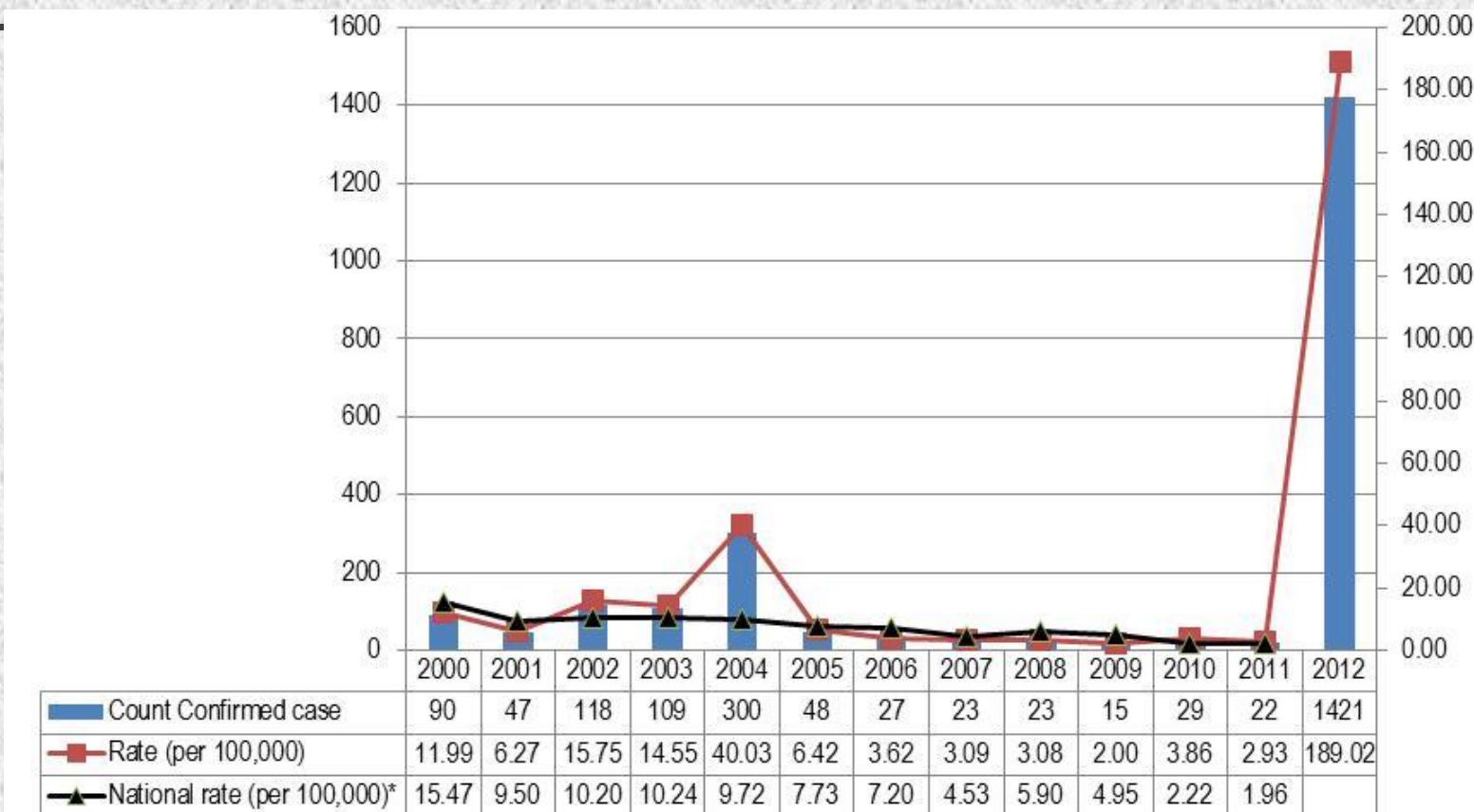


# Pertussis Cases in Fraser Health (Vancouver, BC), July 2011-July 2013

Pertussis Cases in Fraser Health as of July 9th, 2013

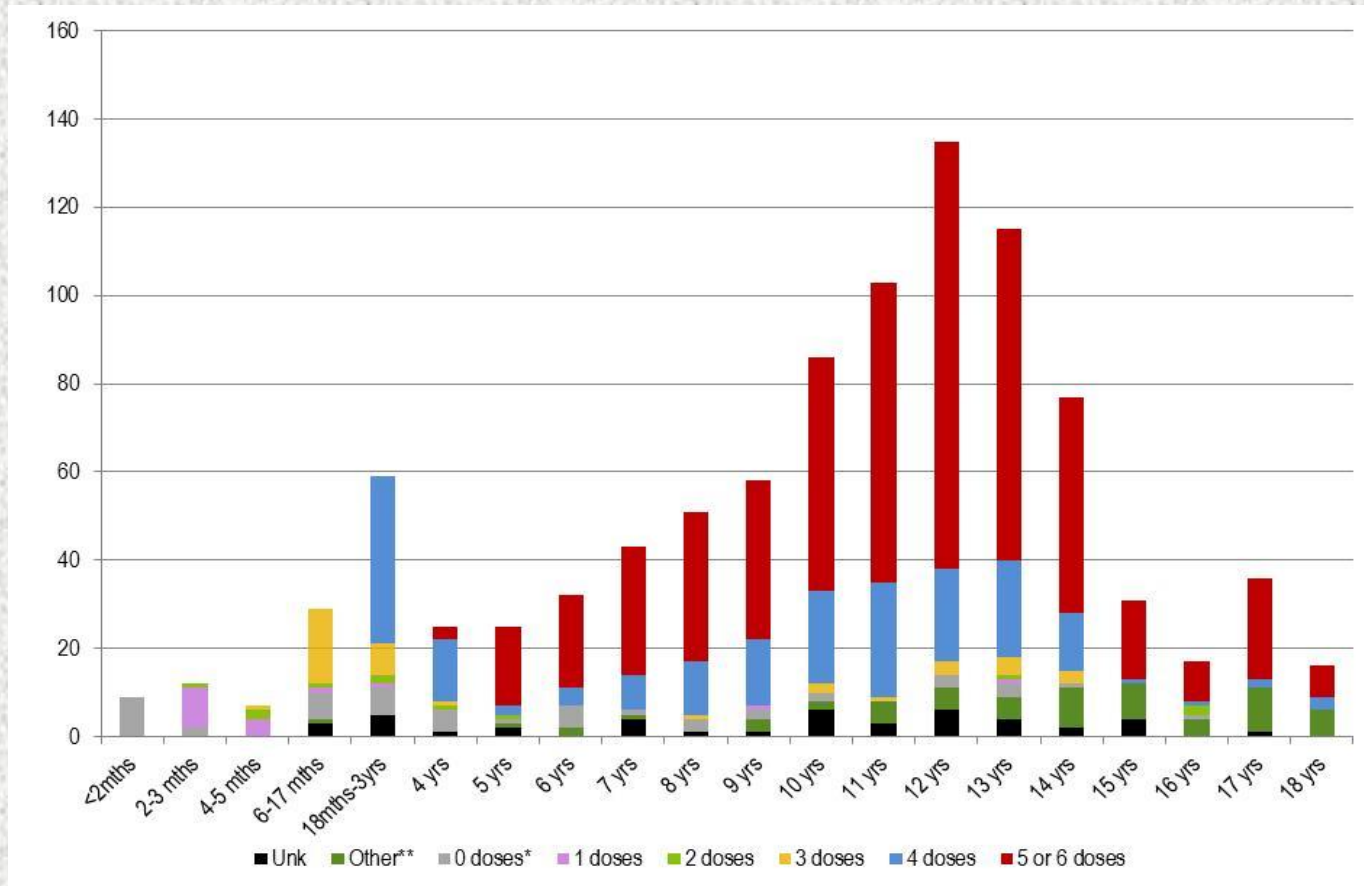


# NB pertussis case count, NB and national incidence rates (per 100,000), 2000-2012



Sources. National case data for 2000-2008 was obtained from the *Canadian Notifiable Diseases Surveillance System*, national data from 2009-2011 was obtained from P/T partners by CIRID (PHAC) and is preliminary. NB data source: CDC Branch, Office of the Chief Medical Officer of Health, New Brunswick

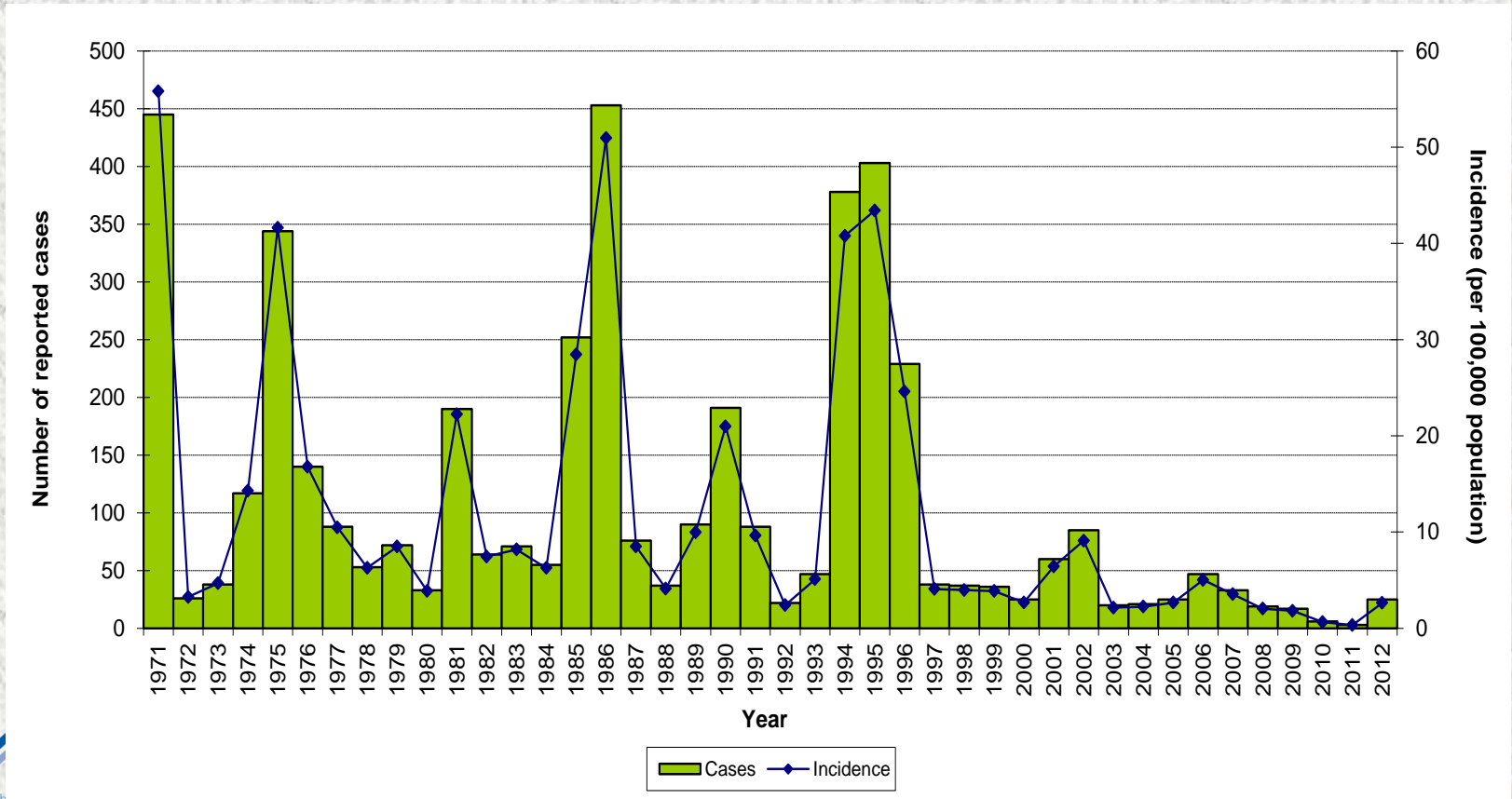
# Number of doses of pertussis containing vaccine according to NB schedule for NB cases 0-18 years



\*Source: CDC Branch, Office of the Chief Medical Officer of Health, New Brunswick

Not to be distributed electronically without permission of CDC Branch.

# Reported cases and incidence (per 100,000 population) of pertussis in Nova Scotia by year, 1971 to 2012





# Pertussis in Nova Scotia, 2012

- 25 cases reported  
(2.6/100,000)

	<u># cases</u>
■ <1 year	0
■ 1-4 years	5
■ 5-9 years	6
■ 10-14 years	3
■ 15-25 years	0
■ 25-39 years	3
■ 40-59 years	5
■ >60 years	3

- 3 clusters

- 7 members of a family attended event in NB where case attended
  - 4 of 6 cases not appropriately immunized
- 6 cases in religious community in health district close to NB unimmunized
- 3 cases unimmunized family in area not close to NB

# Current Pertussis Vaccines

## Whole Cell Pertussis Vaccine

- Increased rates of local and systemic adverse events
- More difficult to standardize production
- Best WCVs have high efficacy than ACV
- Less expensive
- Balanced immune response
- Short duration of protection

## Acellular Pertussis Vaccine

- Better tolerated because of lower rates of adverse events
- Easier to standardize production
- Lower efficacy than the best WCV
- More expensive
- Th2 biased immune response
- Short(er?) duration of protection

# Whole cell pertussis vaccine: effective, but maligned

- Where used widely, whole cell pertussis vaccines successfully reduced the incidence of pertussis by 90-95%
- Concerns about rare but severe adverse effects led to termination of vaccine programs in some countries
  - in Japan 2 deaths led to withdrawal of vaccine
  - this led to over 13,000 cases and 41 deaths from pertussis

# Acellular Pertussis Vaccines: new and improved

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- Intensive research effort in Japan and elsewhere to develop vaccine from purified antigens of *Bordetella pertussis*
- Increasing evidence that the whole cell pertussis vaccines did not cause the rare severe adverse events but were more likely unmasking conditions in abnormal children
- Acellular pertussis vaccines were associated with fewer of the common adverse events



# DTaP vaccines are all LESS REACTOGENIC compared to whole-cell vaccines

Reaction	DTaP3 Bio	DTaP3 SB	DTP PMC-US	DT Bio
Swelling	7	9	26	6
Tenderness	4.6	4.6	30	4.5
Irritability	30	30	50	30
Fever				
>38	4.3	7.2	41	3.4
>40	0.029	0.036	0.24	0.044
Cry >3 hrs	0.066	0.044	0.4	0
HHE	0.007	0	0.067	0.044
Cyanosis	0	0	0.015	0
Seizure	0	0.007	0.022	0



Dalhousie University  
IWK Health Centre  
Capital Health

# DTaP vaccines are all IMMUNOGENIC compared to whole-cell vaccines

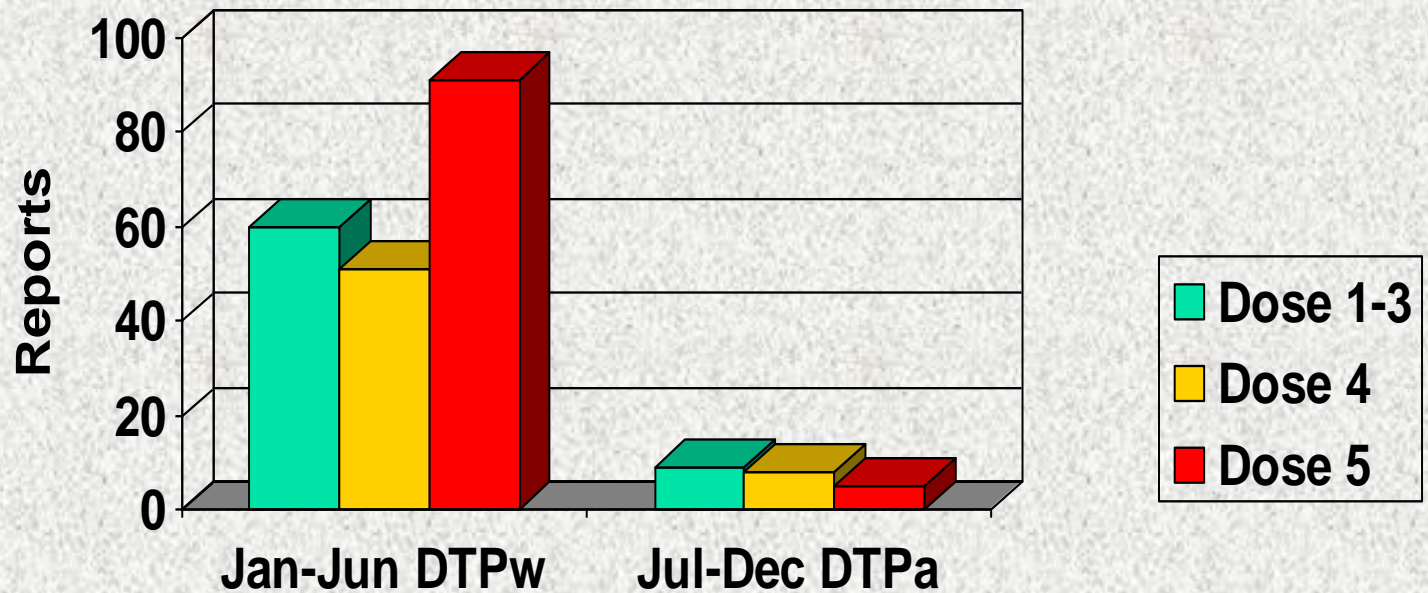
	DTaP5	DTaP2	DTP	DTaP3	DTaP3
Ag	PMC-Can	SB	PMC-US	Bio	SB
PT	49	60	1.9/1.2	94	51
FHA	34	111	8.7/5.2	53	147
PRN	116	0.6	13/9.9	137	274
FIM	351	0.8	15	--	--

# DTaP vaccines are all efficacious

	Vaccine	Efficacy* (%)	95% CI
<b>Sweden</b>	DTaP PMC 5c	85	81-89
	DTaP SB 2c	59	51-66
	DTwP	48	37-58
	DT	--	--
<b>Italy</b>	DTaP 3c Biocine	84	76-90
	DTaP 3c SB	84	76-89
	DTwP	36	14-52
	DT	--	--

# Passive Reporting System Alberta, Canada

## Moderate Local Adverse Events After Pertussis Containing Vaccines

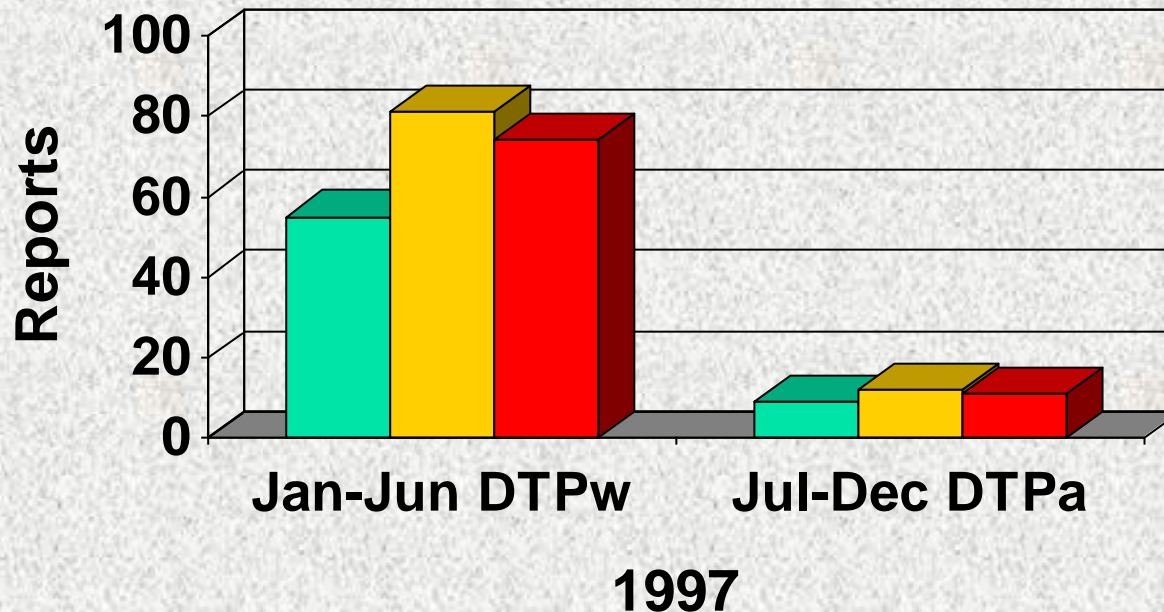


1997



# Passive Reporting System Alberta, Canada

## Severe Systemic Adverse Events After Pertussis Containing Vaccines



# Pertussis controlled in children but outbreaks amongst adolescents and adults: Tdap Products




## ■ Adacel™

Sanofi Pasteur

- PT 2.5  g
- FHA 5  g
- PRN 3  g
- FIM 5  g
- Dip 2 Lf
- Tet 5 Lf
- AlPO<sub>4</sub> 1.5 mg
- 2-phenoxyethanol

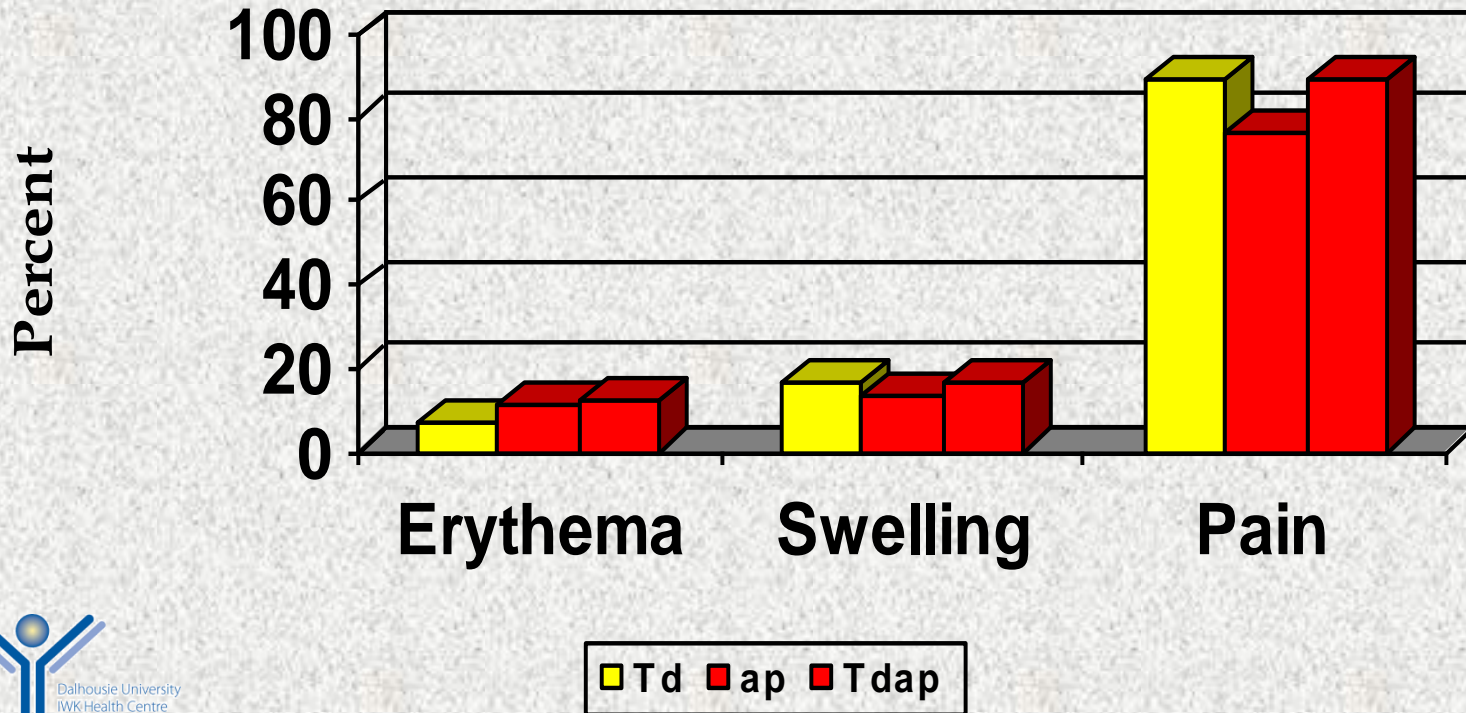
## ■ Boostrix™

GlaxoSmithKline

- PT 8  g
- FHA 8  g
- PRN 2.5  g
- Dip 2.5 Lf
- Tet 5 Lf
- AlOH 0.3 mg
- 2-phenoxyethanol

# Tdap: Well-tolerated

## Local Adverse Events



# Tdap: Immunogenic

Comparison of antibody responses of Swedish infants and Canadian adolescents, 12-17 years of age, and adults, 18-54 years of age

Antigen	2, 4, 6 mo		Tdap	
	Sweden I	Sweden II	Adolescents	Adults
PT	49.4	51.6	181	139
FHA	39.1	57.0	333	333
PRN	116	134	362	269
FIM	351	352	1471	930



# Tdap: efficacious

## APERT Study

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- Randomized controlled trial
  - ap (GSK: PT/FHA/PRN) vs HAV
  - 15-65 years of age
- Monitored from cough of 5 days duration
  - Culture, PCR, acute/convalescent serology
- ap vaccine was effective in preventing culture/PCR positive pertussis in adolescents and adults
- Control arm (HAV) n=1390 provides prospective population-based data
  - 3.7-4.5 cases/1000 person years
  - ~800,000-1,000,000 cases annually in the US

# ACIP Recommendations

## Adolescents

- All adolescents should receive single dose of Tdap in place of Td (preferred age 12 yrs)
  - If already received Td, can still give Tdap
    - 5 year interval recommended
    - Less is acceptable

# ACIP Recommendations

## Adults

- All adults should receive single dose of Tdap in place of Td
- HCWs with direct patient contact should receive Tdap as soon as possible
  - Intervals since previous Td as short as 2 years are acceptable
  - HCWs without direct patient care should receive at their next 10 yr interval (encouraged to get it sooner)
- Institutions should provide Tdap for HCWs

# No effect on deaths in young infants: Intervention Strategies

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- Potential strategies being explored to improve protection of young infants include
  - Neonatal immunization
  - Pre-conceptual immunization of women
  - Targeted immunization of adults in close contact with newborns (cocoon strategy)
  - Maternal immunization



# Rationale for Maternal Immunization

- This absence of protection leaves open a window of susceptibility in the newborn
- Vaccinating women during pregnancy offers the possibility of protecting infants from birth until immunity is induced by active vaccination



# ACIP: October 24, 2012

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ACIP recommends that providers of prenatal care implement a Tdap immunization program for all pregnant women. Health-care personnel should administer a dose of Tdap during each pregnancy irrespective of the patient's prior history of receiving Tdap. If not administered during pregnancy, Tdap should be administered immediately postpartum.

# Recommendations: UK



Search

## Department of Health

Public health, adult social care, and the NHS

“9 infants have died as a result of whooping cough this year and there have been 302 cases of the disease in children under 3 months old.

[Home](#) > [Chief Professional Officers](#) > [Chief Medical Officer](#) > Pregnant women to be offered...

## Pregnant women to be offered whooping cough vaccination

28 September, 2012

Following a rise in the number of cases of [whooping cough](#) in young babies, the Chief Medical Officer, Professor Dame Sally Davies, has announced that pregnant women will be offered vaccinations to protect their newborn babies.

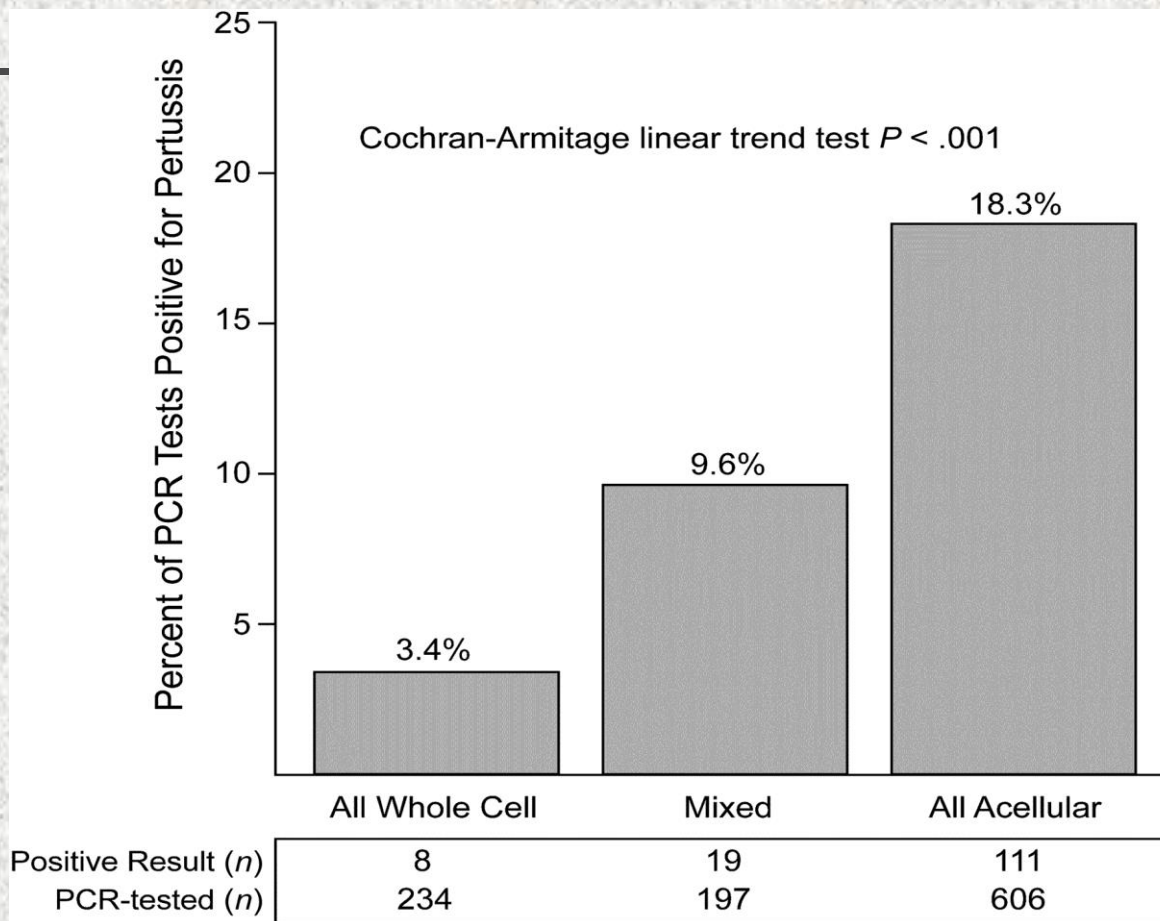


# Will immunizing more cohorts with more doses work?

- Recent outbreaks from US and Australia suggest better protection from wP compared to aP
  - Observed with even a single dose of wP in the series
  - duration of protection from aP may also be less than from wP
- Not observed in all countries; may be related to prior level of pertussis circulating and population levels of natural immunity
  - Hypothesized related to immune response stimulated
    - wP Th1/Th17 response
    - aP Th2 response

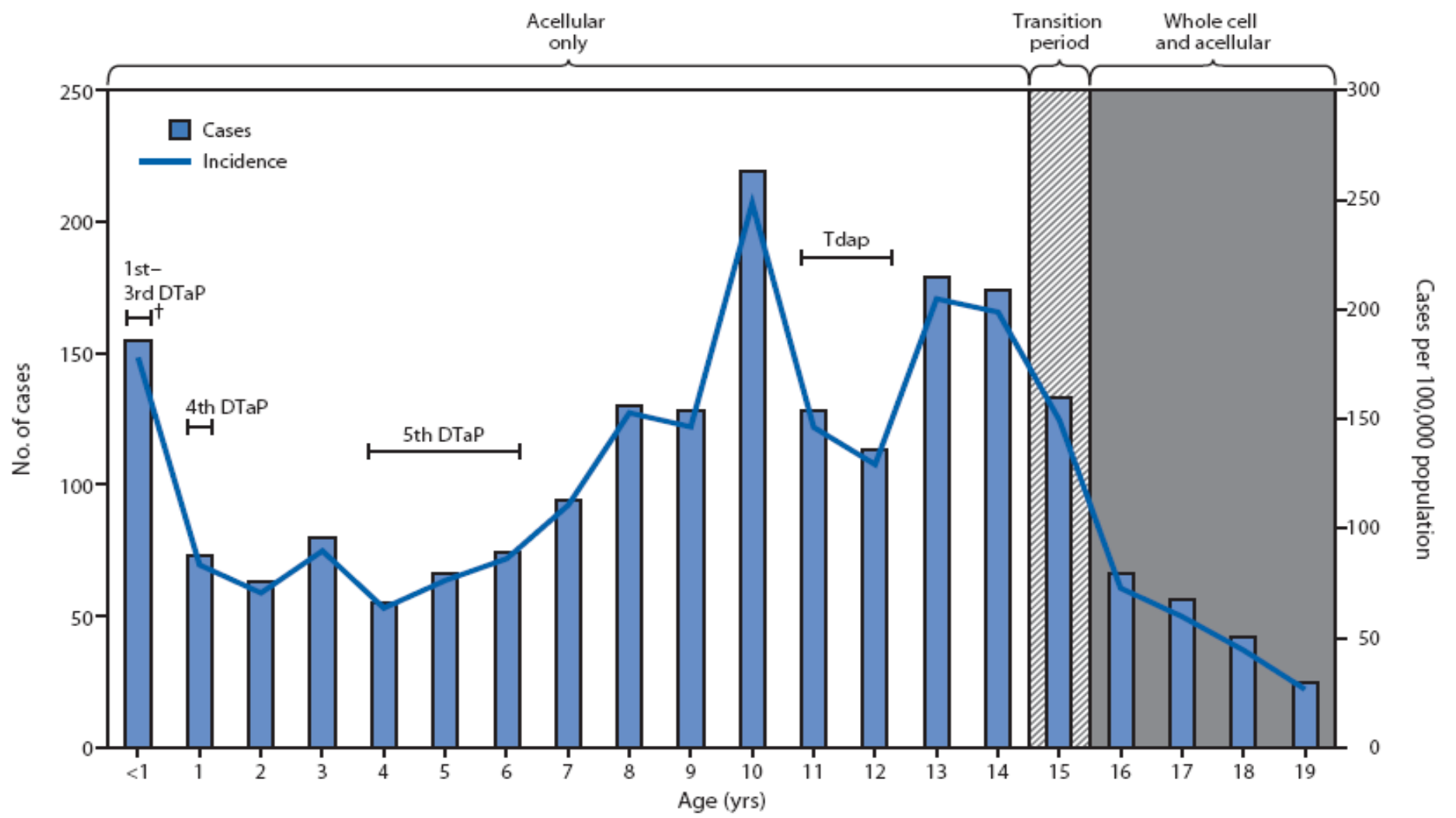


# Percentage of pertussis PCR tests with a positive result in the study population by pertussis vaccine type for the first 4 doses received between 1 and 24 months of age, January 2010 to December 2011.



**Klein N P et al. Pediatrics**  
**2013;131:e1716-e1722**

FIGURE 2. Number and incidence of confirmed and probable pertussis cases among persons aged ≤19 years, by patient age and vaccines received\* — Washington, January 1–June 16, 2012



**Abbreviations:** DTaP = diphtheria and tetanus toxoids and acellular pertussis; DTwP = diphtheria and tetanus toxoids and whole-cell pertussis; Tdap = tetanus and reduced diphtheria toxoids and acellular pertussis.

\* Acellular vaccines (DTaP) replaced whole-cell vaccines (DTwP) for the 4th and 5th doses in 1992 and all 5 doses of the childhood series in 1997. Tdap was recommended for adolescents aged 11–12 years in 2006. Thus, all children aged ≤14 years are likely to have received acellular vaccines for the complete childhood series. Adolescents aged 15 years were born during a transition year from whole-cell to acellular vaccines for the childhood series. Adolescents aged ≥16 years received whole-cell vaccines for the first 3 doses, and acellular vaccines for the 4th and 5th doses.

† Ages during which the Advisory Committee on Immunization Practices recommends that specified vaccine doses be administered.

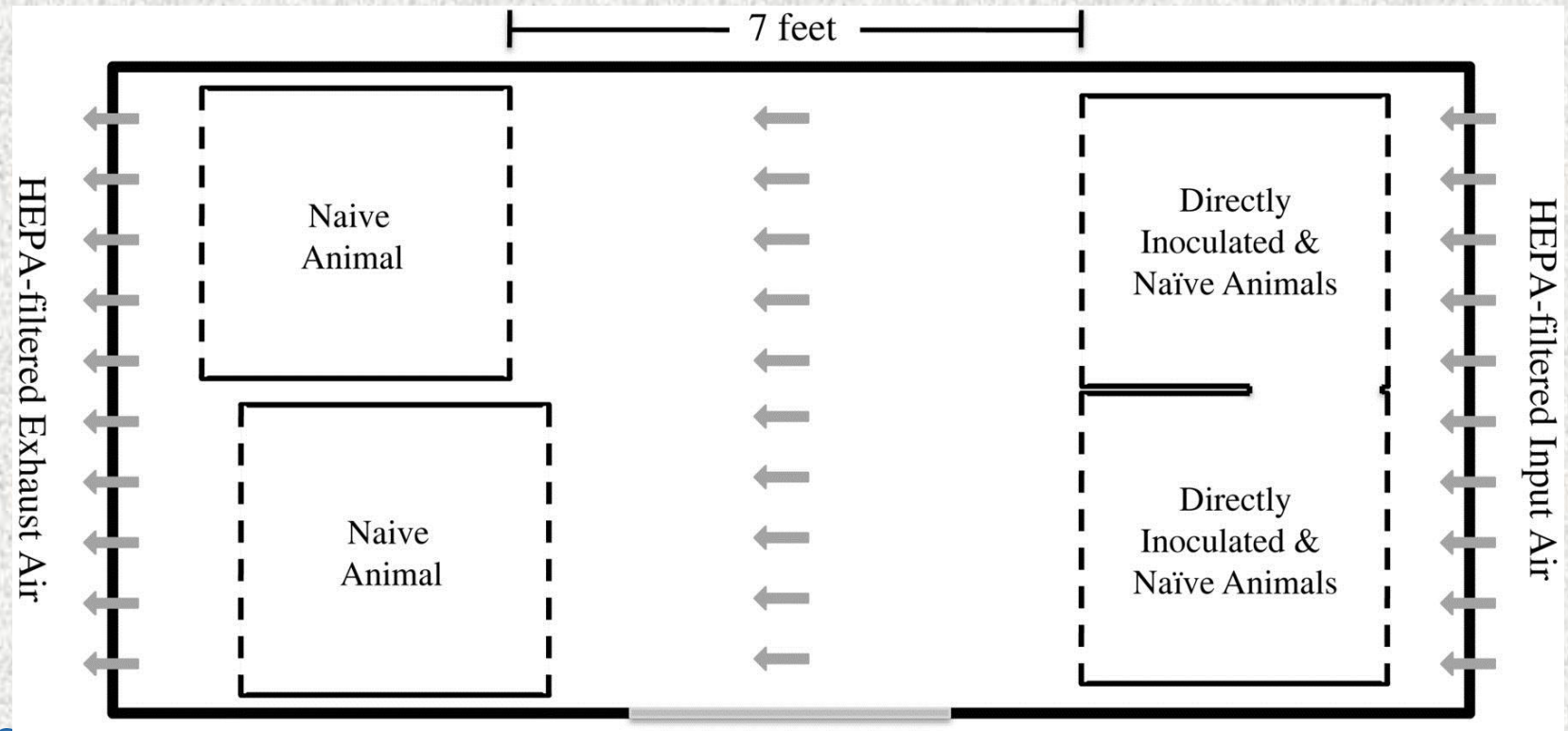
# Baboon Model of pertussis



- Mouse models have been useful but limited since the animals don't develop pertussis
- Baboons develop classical symptoms and paroxysmal cough
- Useful for studying transmission and infection, pathogenesis, and immune response



# Biocontainment unit for airborne transmission studies.



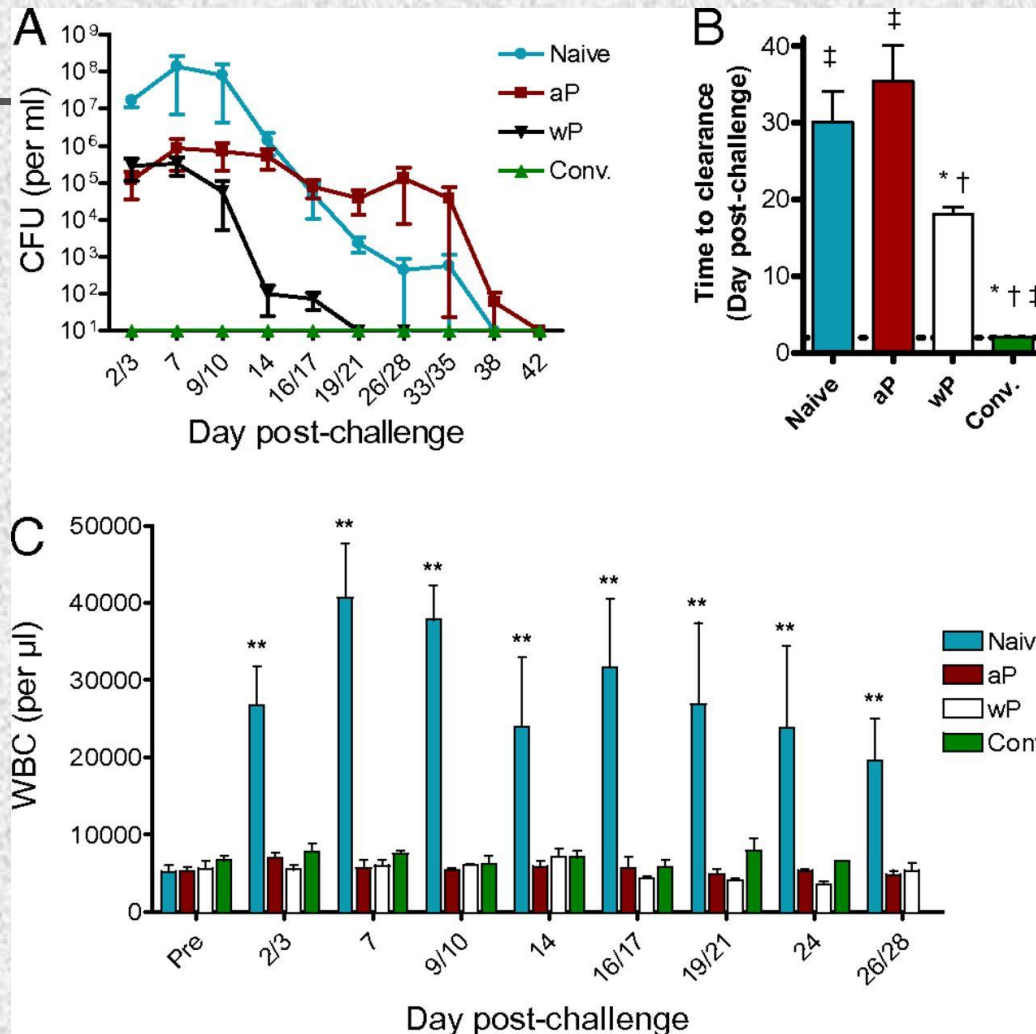


# aP vs. wP vaccine in baboon model

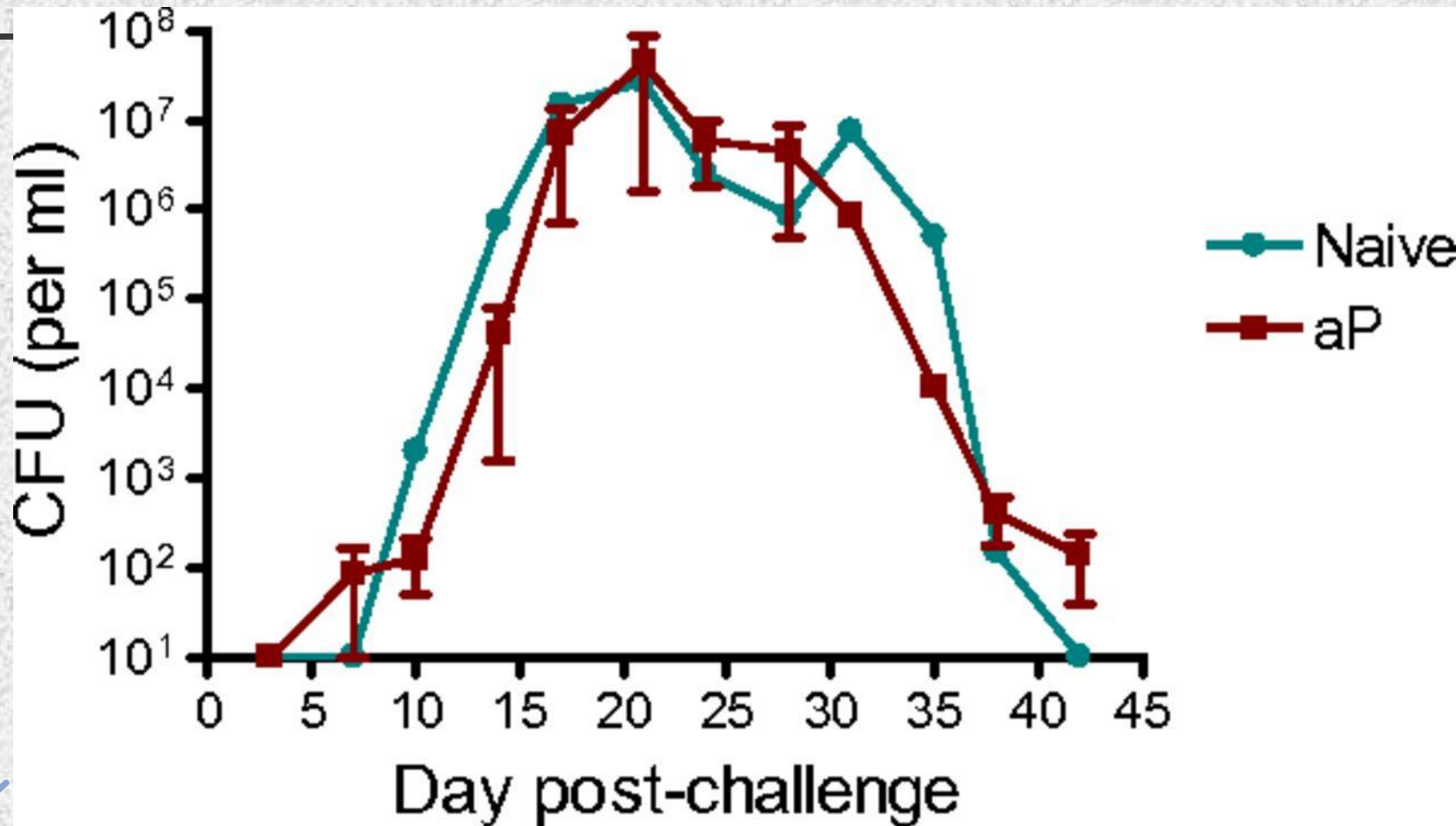
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- Disease
  - wP prevents
  - aP prevents
- Colonization
  - wP prevents
  - aP does not prevent
- Transmission
  - wP prevents
  - aP does not prevent

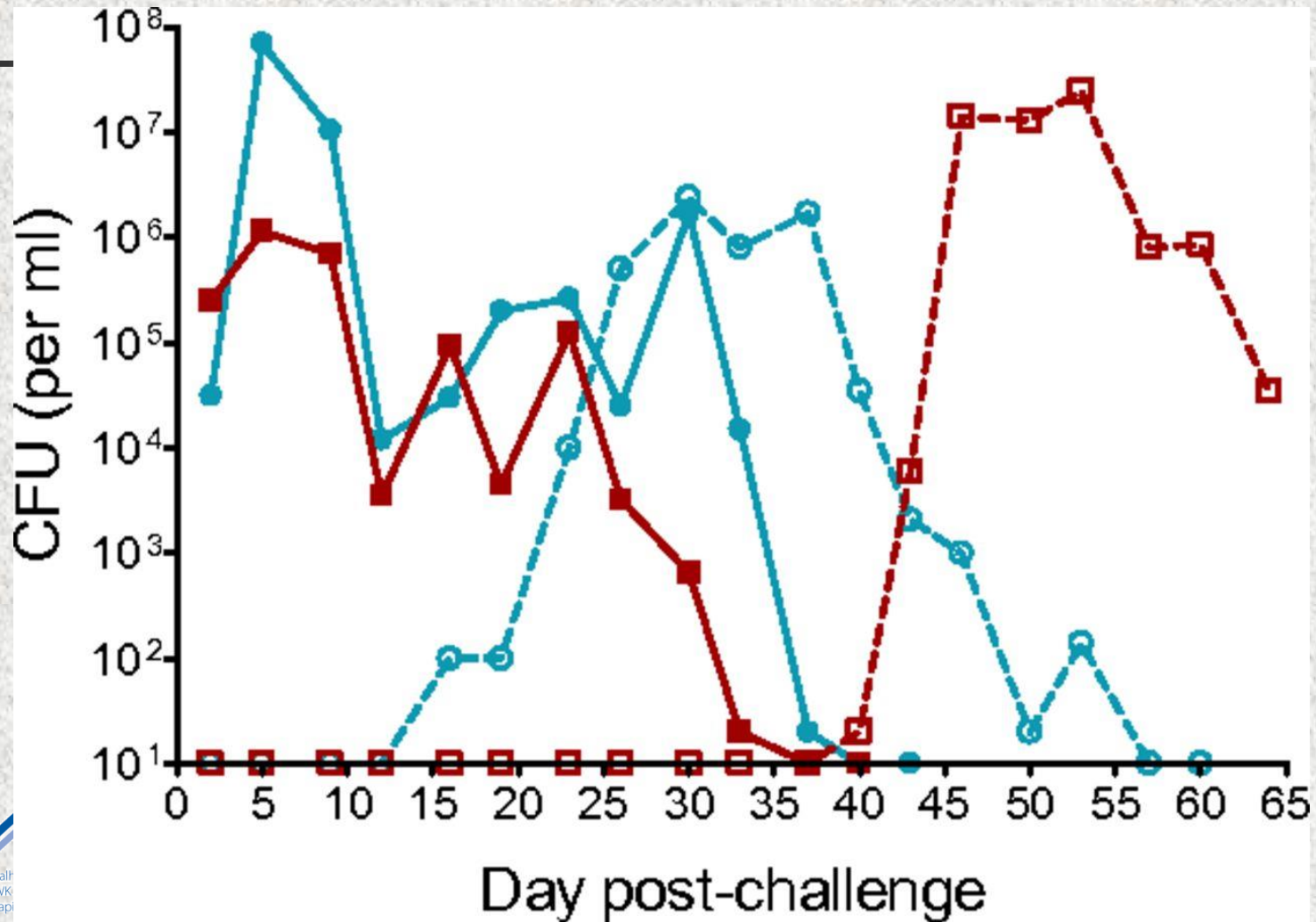
# The effect of vaccination or convalescence on colonization and leukocytosis.



# aP does not protect against colonization following natural transmission.



# Infected aP vaccinees can transmit pertussis to naïve contacts.



Warfel J M et al. PNAS

2014;111:787-792



# What have we learned from the baboon model to date?

- Characteristics of the immune response
  - strong induction of interleukin-6 (IL-6), IL-23, and transient expression of IL-1 $\beta$ .
    - implicated in the differentiation of IL-17-producing T cells (Th17 cells) and stimulation of innate  $\gamma\delta$ T cells
  - significant increases in nasopharyngeal IL-17 and cytokines and chemokines downstream of IL-17 immune responses.
  - IL-17- and IFN- $\gamma$ -secreting cells in convalescent but not naive animals. These cells are long-lived, having persisted at 2 years post-infection.
    - CD4+CD95+ T cells, consistent with the induction of Th17 and Th1 memory responses to *B. pertussis*.

# Novel Pertussis Vaccines

OPEN ACCESS Freely available online

PLoS PATHOGENS

## Live Attenuated *B. pertussis* as a Single-Dose Nasal Vaccine against Whooping Cough

Nathalie Mielcarek<sup>1,2</sup>, Anne-Sophie Debrie<sup>1,2</sup>, Dominique Raze<sup>1,2</sup>, Julie Bertout<sup>1,2</sup>, Carine Rouanet<sup>1,2</sup>, Amena Ben Younes<sup>3</sup>, Colette Creusy<sup>4</sup>, Jacquelyn Engle<sup>5</sup>, William E. Goldman<sup>5</sup>, Camille Locht<sup>1,2\*</sup>

1 INSERM U629, Lille, France, 2 Institut Pasteur de Lille, Lille, France, 3 IFR142, Lille, France, 4 Service d'Anatomie et de Cytologie Pathologique, Groupe Hospitalier de l'Institut Catholique de Lille, Faculté Libre de Médecine, Lille, France, 5 Washington University, St. Louis, Missouri, United States of America

**Pertussis is still among the principal causes of death worldwide, and its incidence is increasing even in countries with high vaccine coverage. Although all age groups are susceptible, it is most severe in infants too young to be protected by currently available vaccines. To induce strong protective immunity in neonates, we have developed BPZE1, a live attenuated *Bordetella pertussis* strain to be given as a single-dose nasal vaccine in early life. BPZE1 was developed by the genetic inactivation or removal of three major toxins. In mice, BPZE1 was highly attenuated, yet able to colonize the respiratory tract and to induce strong protective immunity after a single nasal administration. Protection against *B. pertussis* was comparable to that induced by two injections of acellular vaccine (aPV) in adult mice, but was significantly better than two administrations of aPV in infant mice. Moreover, BPZE1 protected against *Bordetella parapertussis* infection, whereas aPV did not. BPZE1 is thus an attractive vaccine candidate to protect against whooping cough by nasal, needle-free administration early in life, possibly at birth.**

# Novel Pertussis Vaccines

- Triple adjuvant
  - CpG
  - Polyphosphazene
  - Host defense peptides

Vaccine 29 (2011) 1595–1604



Contents lists available at ScienceDirect

Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)



Antibody responses in adult and neonatal BALB/c mice to immunization with novel *Bordetella pertussis* vaccine formulations

Aleksandra Gracia<sup>a</sup>, Monika Polewicz<sup>a</sup>, Scott A. Halperin<sup>c</sup>, Robert E.W. Hancock<sup>d</sup>, Andrew A. Potter<sup>a</sup>, Lorne A. Babiuk<sup>b</sup>, Volker Gerdtz<sup>a,\*</sup>

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<sup>b</sup> University of Alberta, Edmonton, Alberta, Canada

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<sup>d</sup> Department of Microbiology and Immunology, University of British Columbia, Vancouver, British Columbia, Canada

# Challenges to developing a new pertussis vaccine

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- Costly
- Better understanding of the disease, transmission, and immunity needed
- Regulatory pathway is complex
  - Most advances over last 20 years have been with bridging to efficacy studies from the 1990s
  - New field efficacy studies will be difficult
  - Vaccines that produce protection through different immune mechanisms won't be able to be bridged
    - Lack of reagents in any case



# Is there a role for a human pertussis challenge model?

- Human Challenge Experiment
  - The deliberate infection of human volunteers with a pathogenic strain of a virus, parasite, bacteria or fungus.
  - Used to study the pathogenesis, transmission and disease course of a particular infectious agent and to test the efficacy of candidate prophylactic or therapeutic agents.

Kalil et. al. Future Microbiol 2012  
Miller and Grady, Clin Infect Dis 2001  
Rosenbaum and Sepkowitz Clin Infect Dis 2002  
Acad Med Science 2005

# Principles of pathogen selection

- The pathogen is well-characterized
- The disease is self-limiting in healthy individuals, and/or
- A rescue therapy is available to bring the participant back to good health
- The pathogen is approved by FDA CBER/Health Canada BGTD for use in humans

# *Bordetella pertussis:* Uses of a human challenge model

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- Incubation period
- Early clinical manifestations
- Pathogenesis
- Nature of the immune response (innate and adaptive)
- Transmission
- Protective antigens
- Strain contribution to pathogenesis
- Diagnostic tests
- Chemoprophylaxis and therapy
- Regulatory pathway for novel vaccines



# CCfV Challenge Unit





# Summary and Conclusions

- Pertussis causes significant morbidity and mortality globally, despite widespread vaccination
- Outbreaks are being described in many but not all countries; in Canada, outbreaks are occurring regionally
- Multiple factors including duration of protection of acellular pertussis vaccines, timing of boosters, and suboptimal vaccine coverage amongst certain groups contribute to local outbreaks
- Novel strategies may be required to control pertussis while developing new and better pertussis vaccines.

# Acknowledgements

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- BC Center for Disease Control
- NS Department of Health and Wellness
  - Beverly Billard
- Saskatchewan Department of Health

# Comments and Questions?

