The resurgence of pertussis

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Capital Health

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Disclosures

- **Research Funding**
  - Government
    - CIHR
    - Public Health Agency of Canada
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    - GlaxoSmithKline
    - Novartis
    - Sanofi Pasteur
    - Pfizer
    - Merck
    - PREVENT
    - Novavax
    - Janssen

- **Consultant/Advisory Board/Committee**
  - Government
    - NACI Influenza Working Group
    - CDC Pertussis Working Group
    - WHO SAGE Pertussis WG
    - NS, PEI, and NB Depts of Health
  - NGO
    - PATH
    - Gates Foundation
  - Industry
    - PREVENT
    - ImmunoVaccine
    - GlaxoSmithKline
    - Sanofi Pasteur
    - Novartis
    - Medicago
    - Folia

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Outline

- Has there been a resurgence of pertussis?
- What are the causes of the resurgence?
- What are mitigation strategies?
  - Short term
  - Mid term
- What are long term solutions?

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Pertussis surveillance

- Pertussis is a notifiable disease in most jurisdictions
  - Surveillance is passive
  - Underreporting estimated to be 10-1000 fold
    - National statistics tend to be misleading
    - More reliable data from smaller local or regional reports with better surveillance

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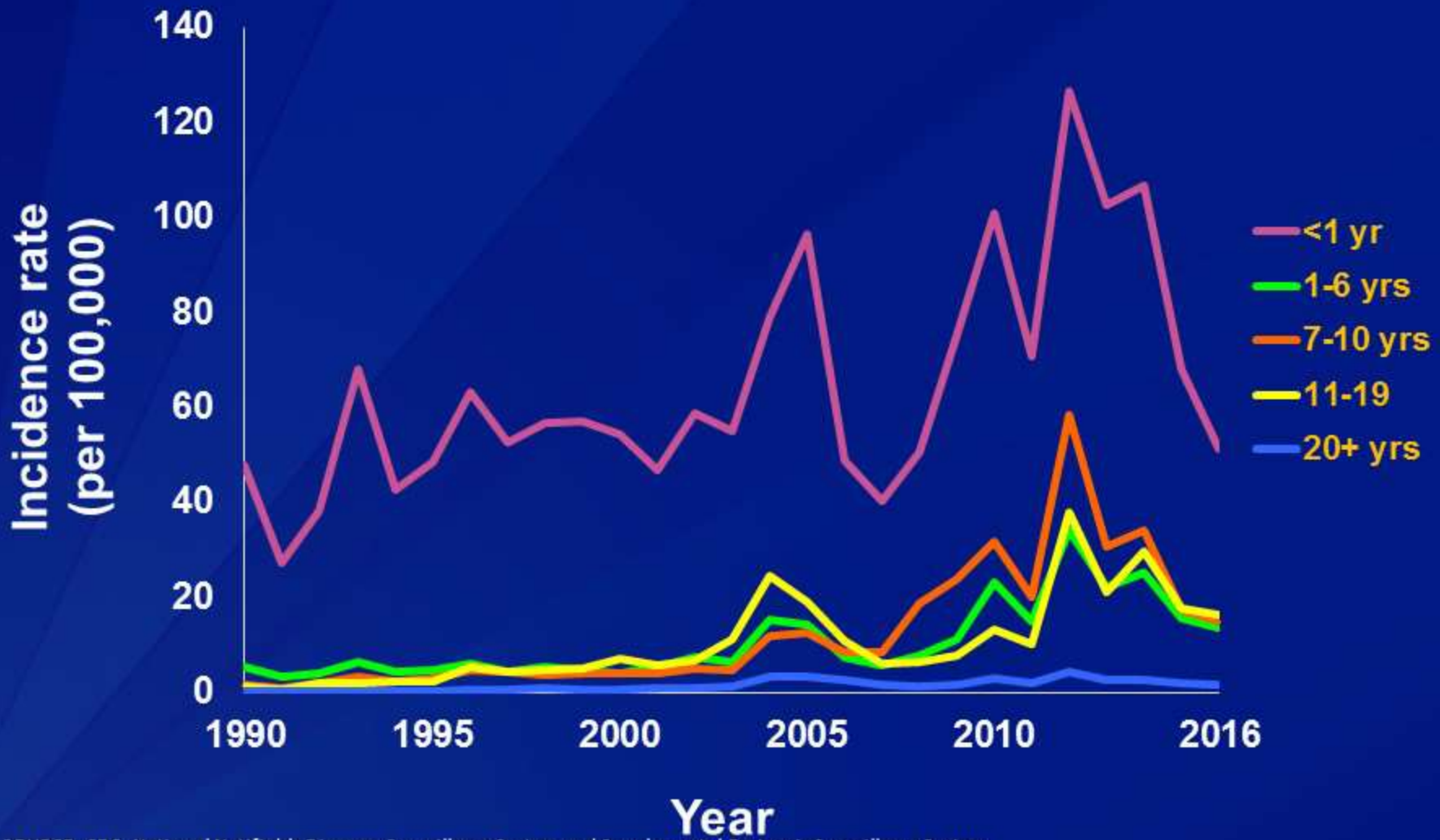
Reported NNDSS pertussis cases: 1922-2016

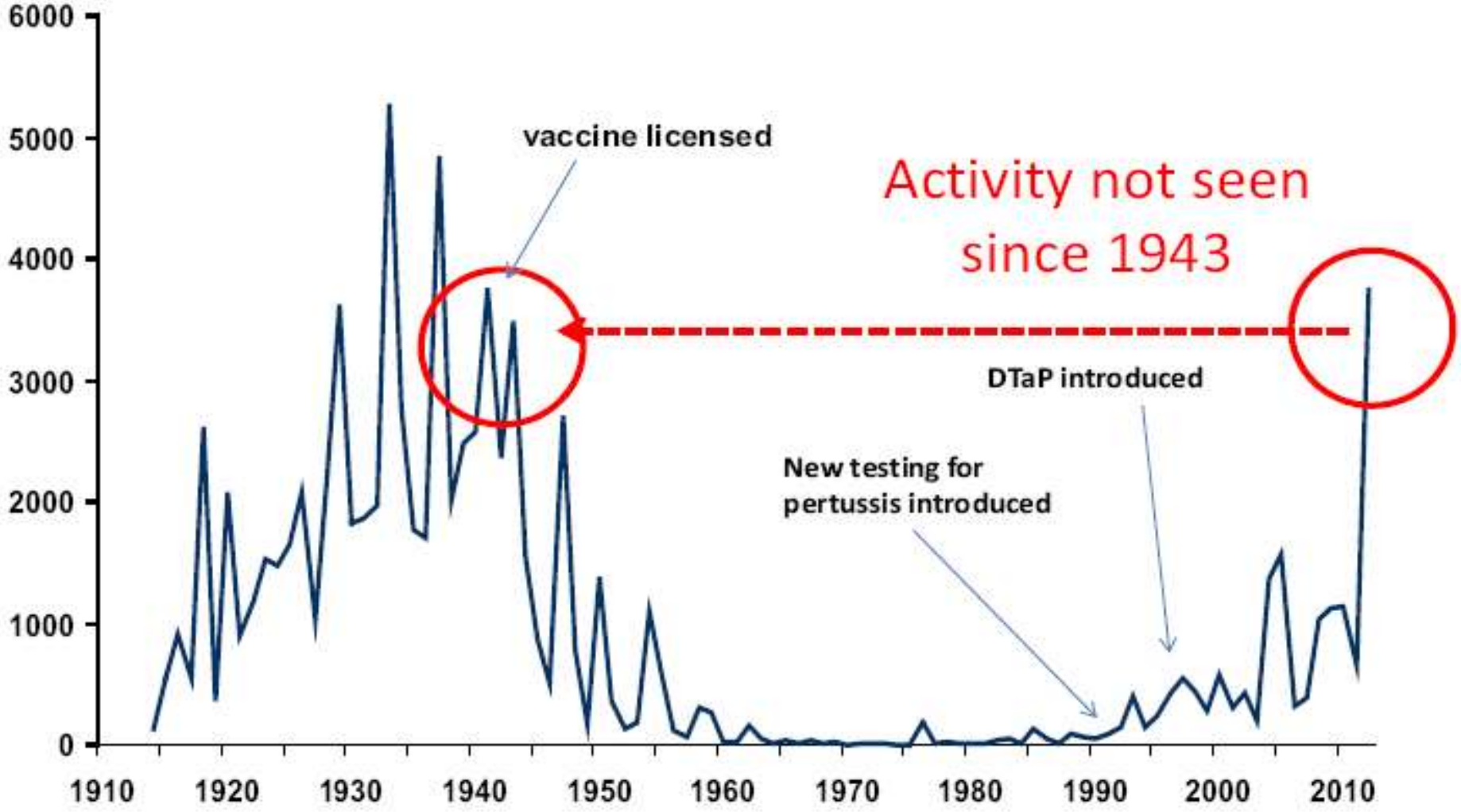
SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service

Reported pertussis incidence by age group: 1990-2016



SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System

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



MINNESOTA MDH DEPARTMENT OF HEALTH
Vaccine Preventable Disease Surveillance
651-201-5414 or 1-877-676-5414
www.health.state.mn.us/immunize

10/4/2012

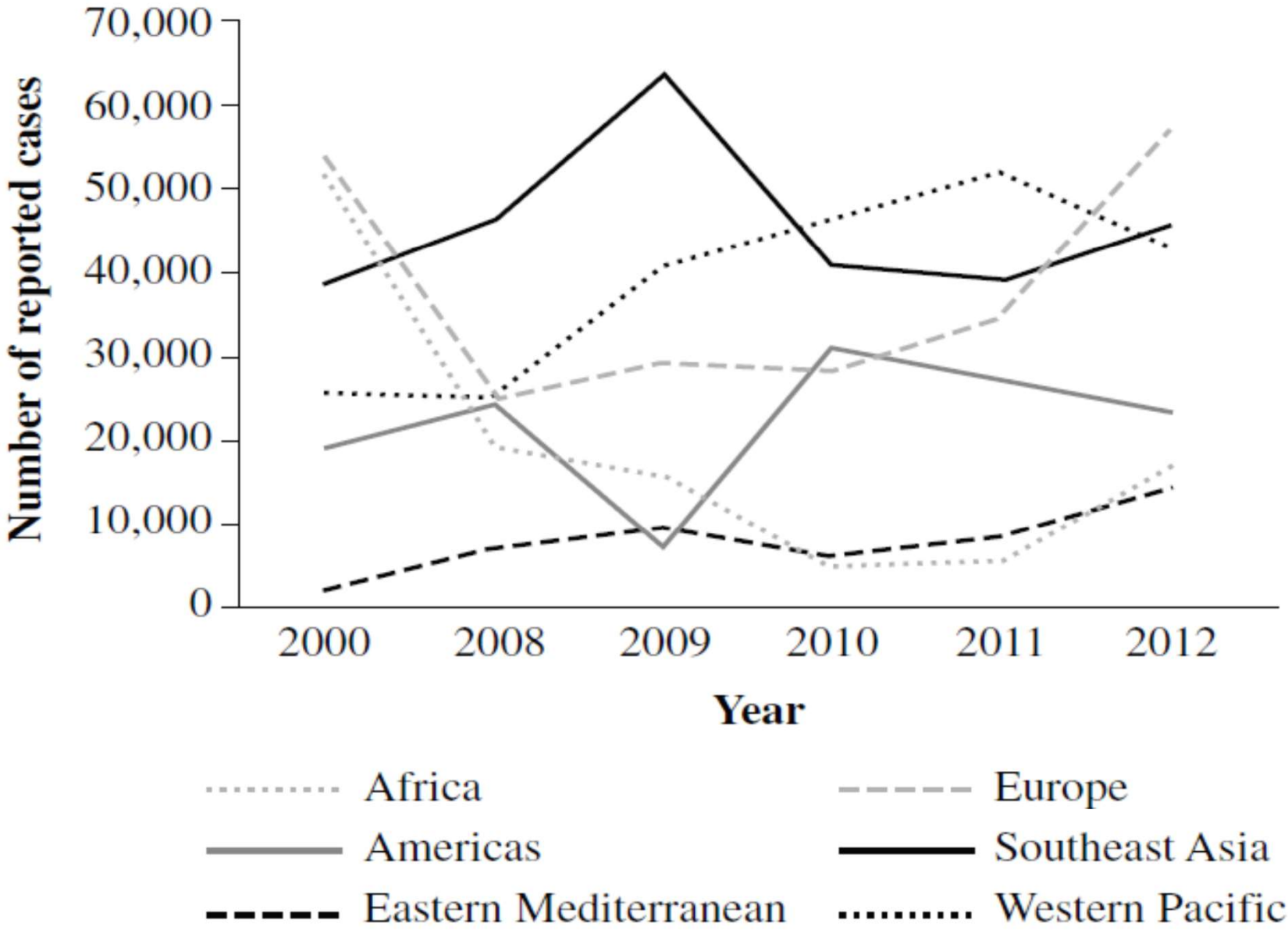
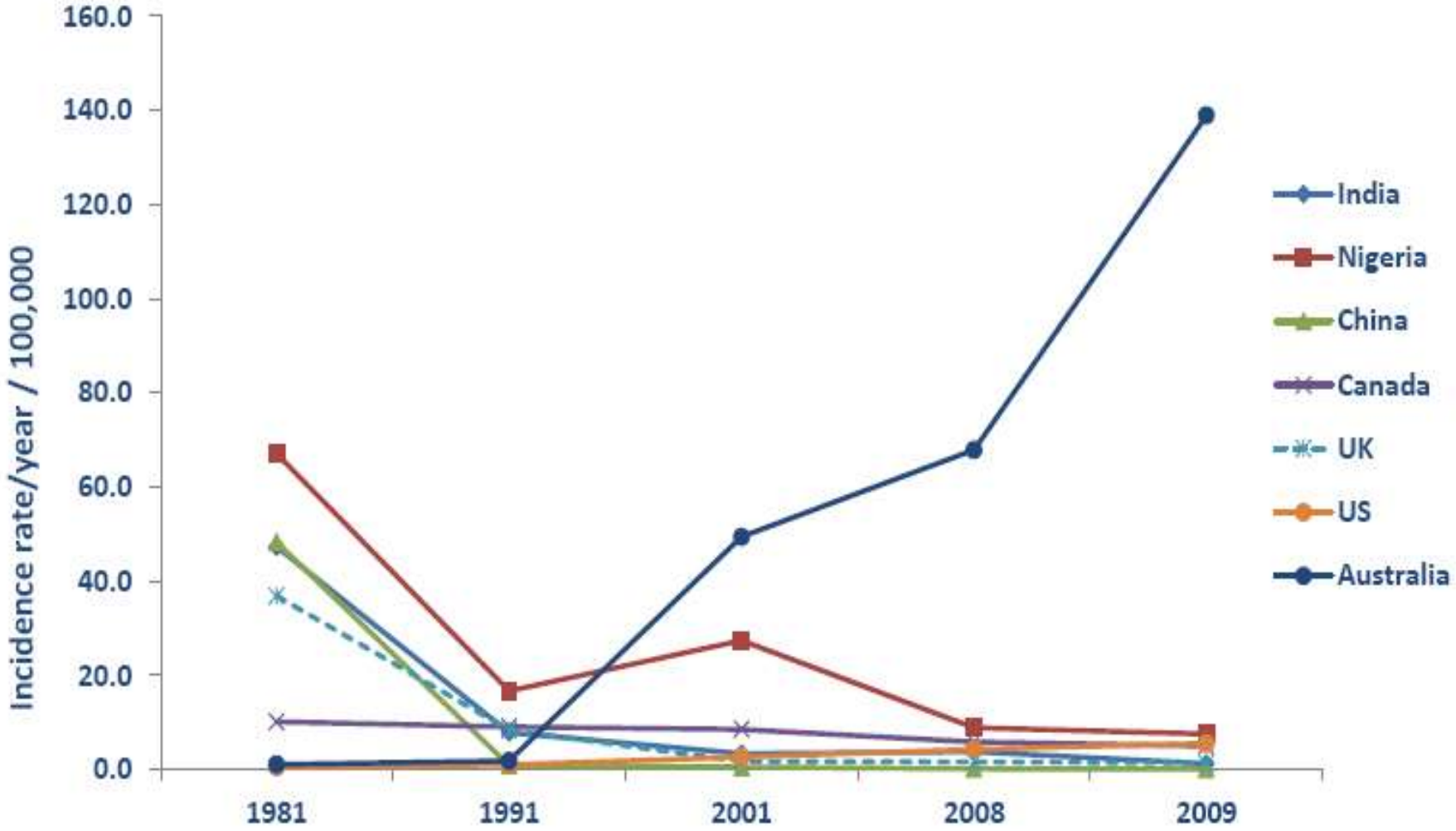


FIGURE 2. Number of reported pertussis cases across the 6 WHO regions in 2000 and 2008–2012.[23,25–29]

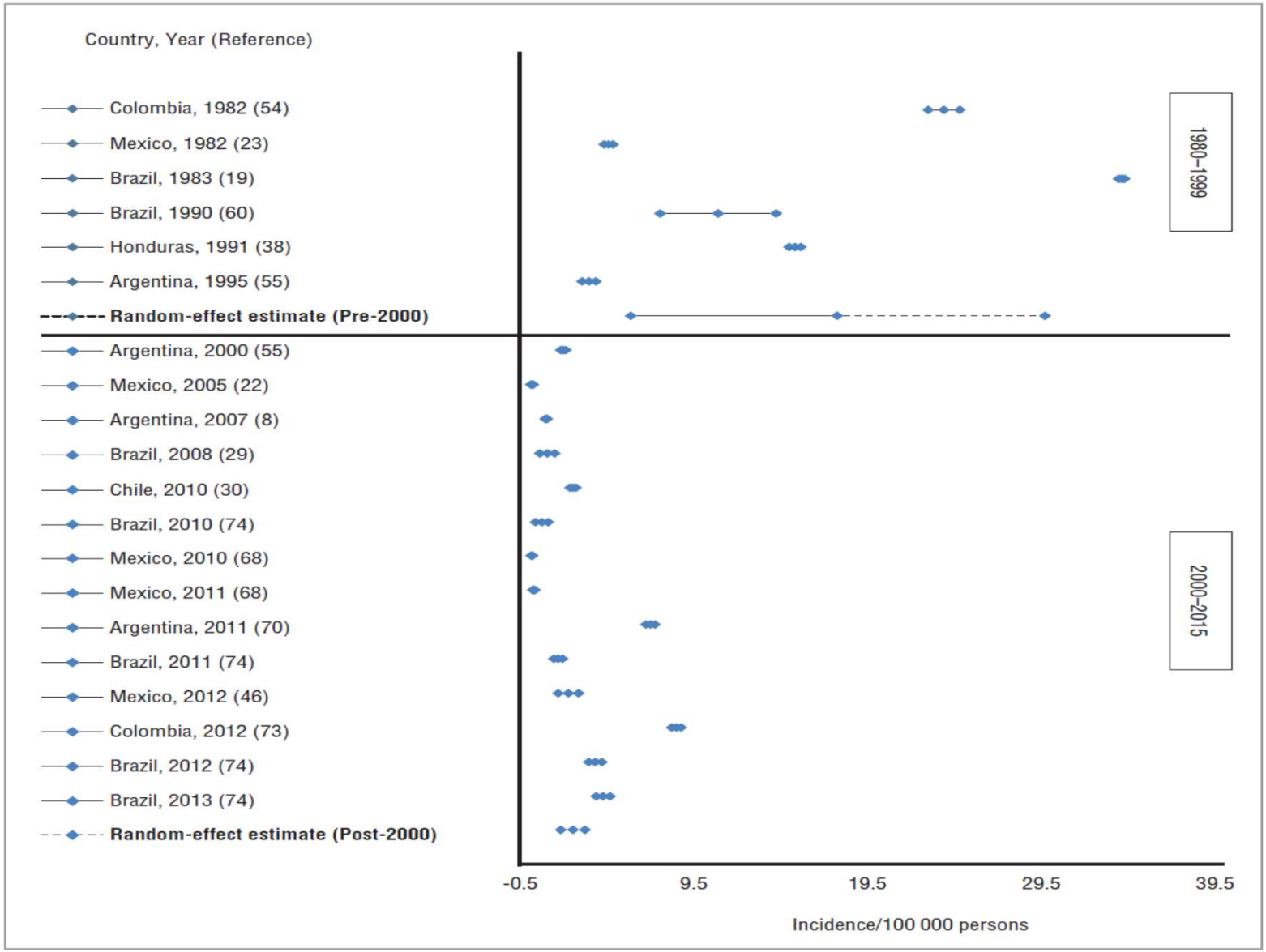
Tan T et al. *Pediatr Infect Dis J* 2015;34:e222–e232

Pertussis incidence rate by WHO region



Courtesy of Peter McIntyre

FIGURE 2. Random-effect estimate of pertussis incidence, 1980–2015



Source: Produced by authors from the results of the analysis.
Note: Random-effect estimate is a pooled estimate which allows for variations in the treatment effect from study to study. The effects in individual studies are assumed to be random realizations of the "true" effect. The data being analyzed in individual studies are then assumed to be drawn from populations with the randomly realized effects.

Folaranmi T, Pinell-McNamara V, Griffith M, Hao Y, Coronado F, Briere EC. Systematic review and meta-analysis of pertussis epidemiology in Latin America and the Caribbean: 1980–2015. Rev Panam Salud Publica. 2017;41:e102. doi: 10.26633/RPSP.2017.102.

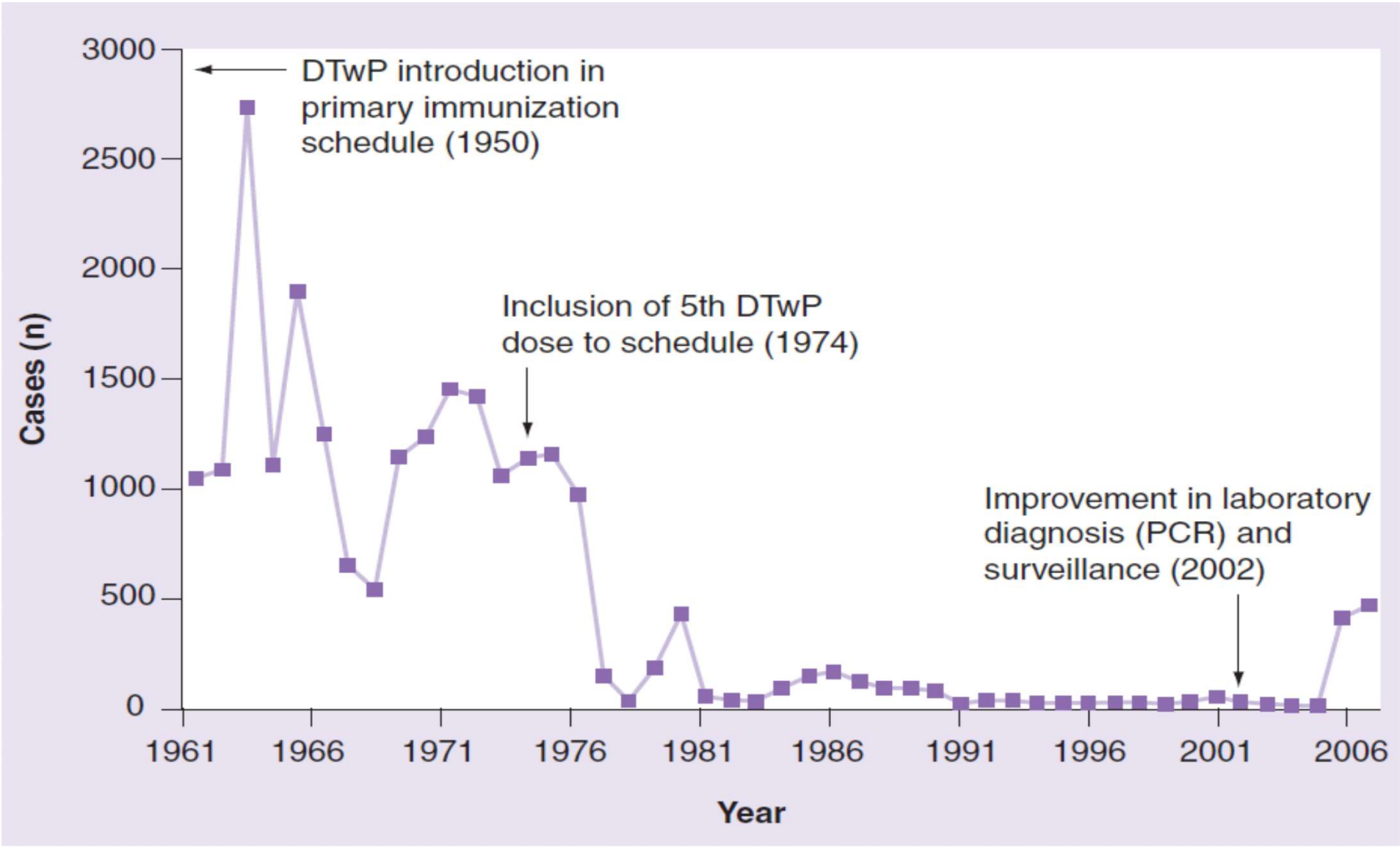


Figure 1. Reported pertussis cases in Costa Rica, 1961–2007.
DTwP: Diptheria, tetanus, whole-cell pertussis.
Data from Ana Morice, Viceminister of Health of Costa Rica. Obligatory Reports, Epidemiological Surveillance Division, Ministerio de Salud de Costa Rica.

Ulloa-Gutierrez, Expert Rev. Vaccines 7(10), 1569–1580 (2008)

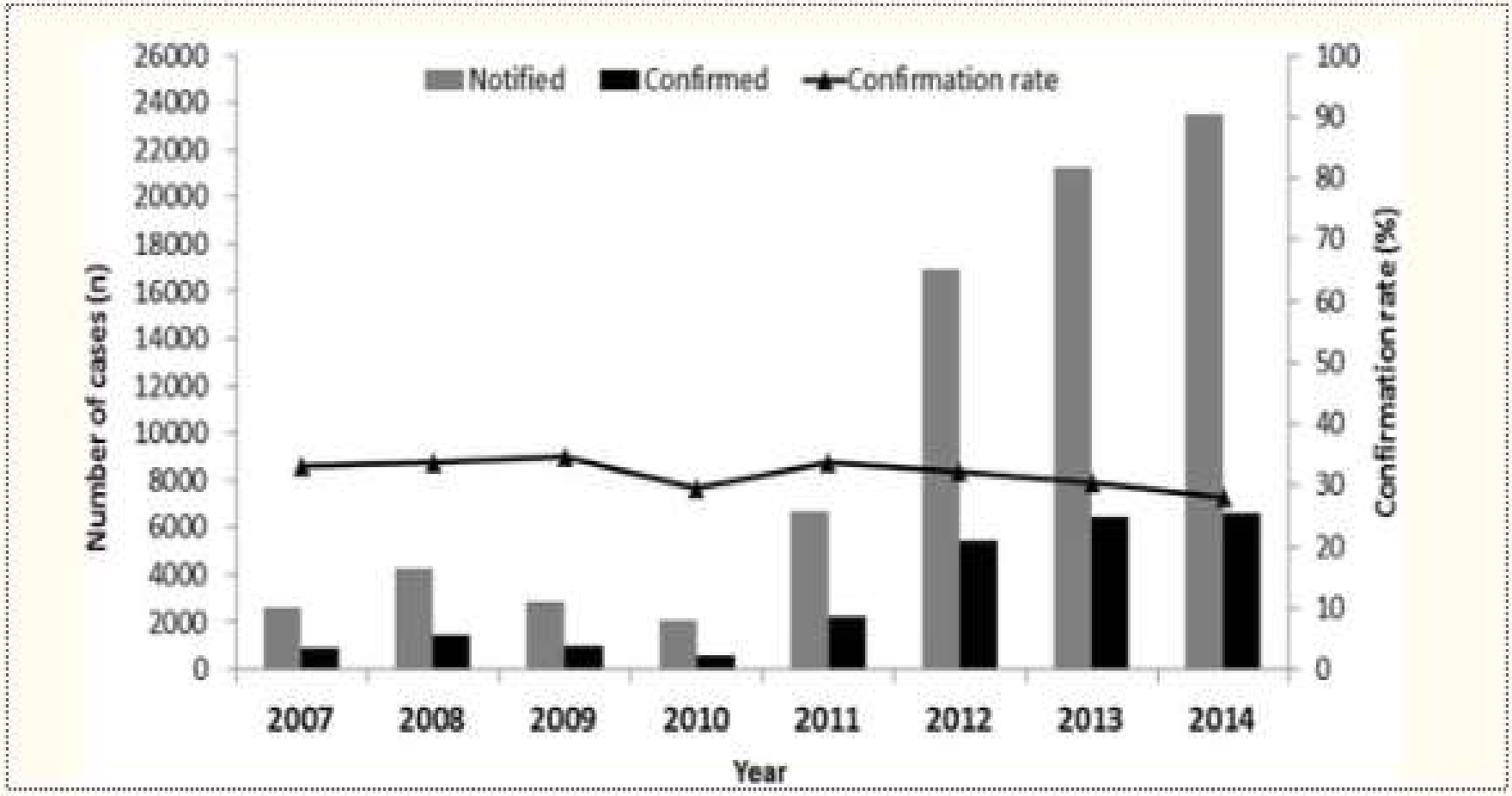
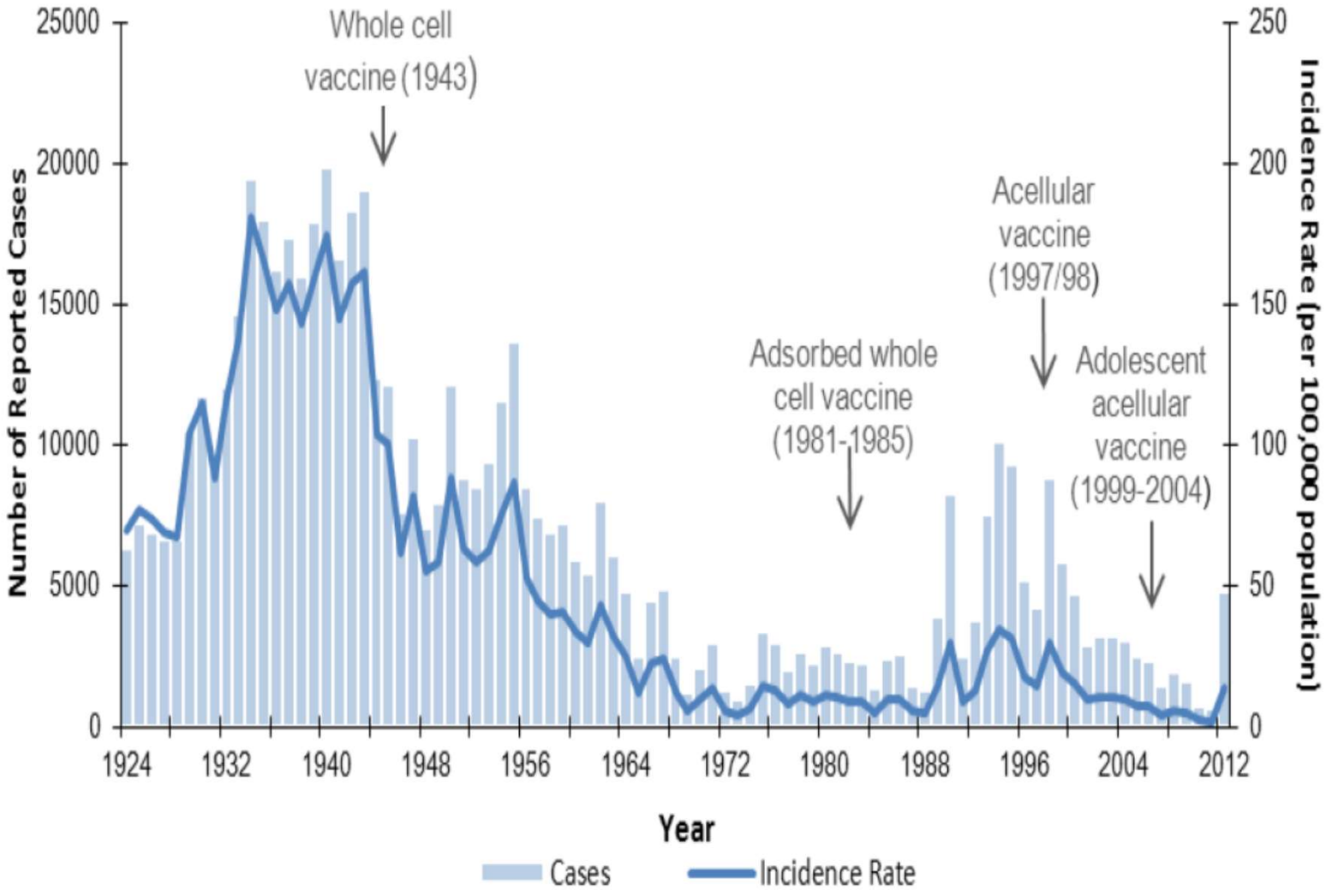


Fig. 1

Absolute numbers of reported and confirmed cases of pertussis and confirmation rates (confirmed cases/reported cases X 100) in Brazil, from 2007 to 2014 per year

Guimarães LM et al. BMC Infect Dis. 2015 Oct 23;15:442.

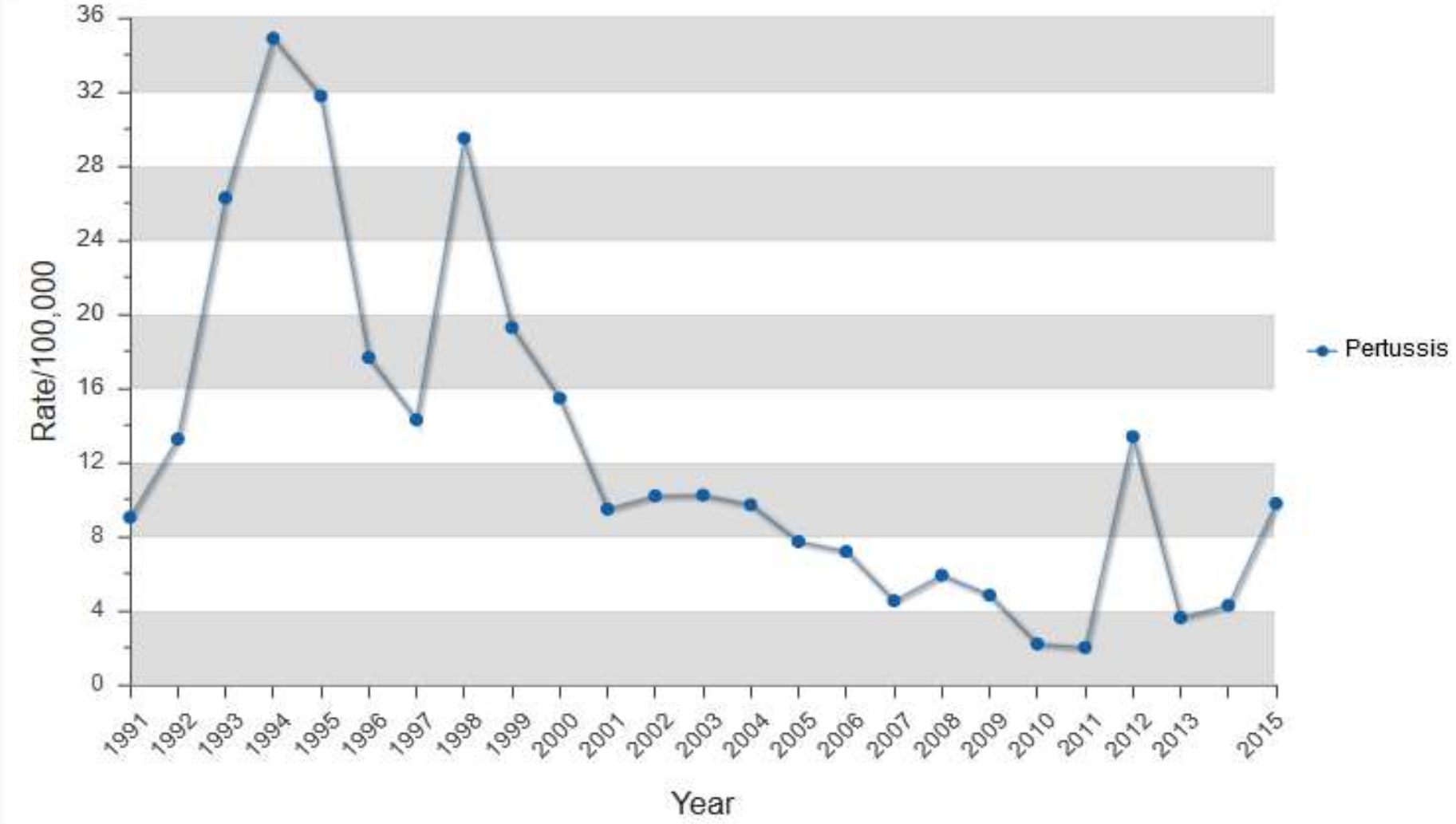
Figure 1. Reported cases and incidence rate (per 100,000 population) of Pertussis in Canada by year, 1924 to 2012*



Smith T, Rotondo J, Desai S and Deehan H, CCDR, 2014

Rate per 100,000 of reported cases over time in Canada

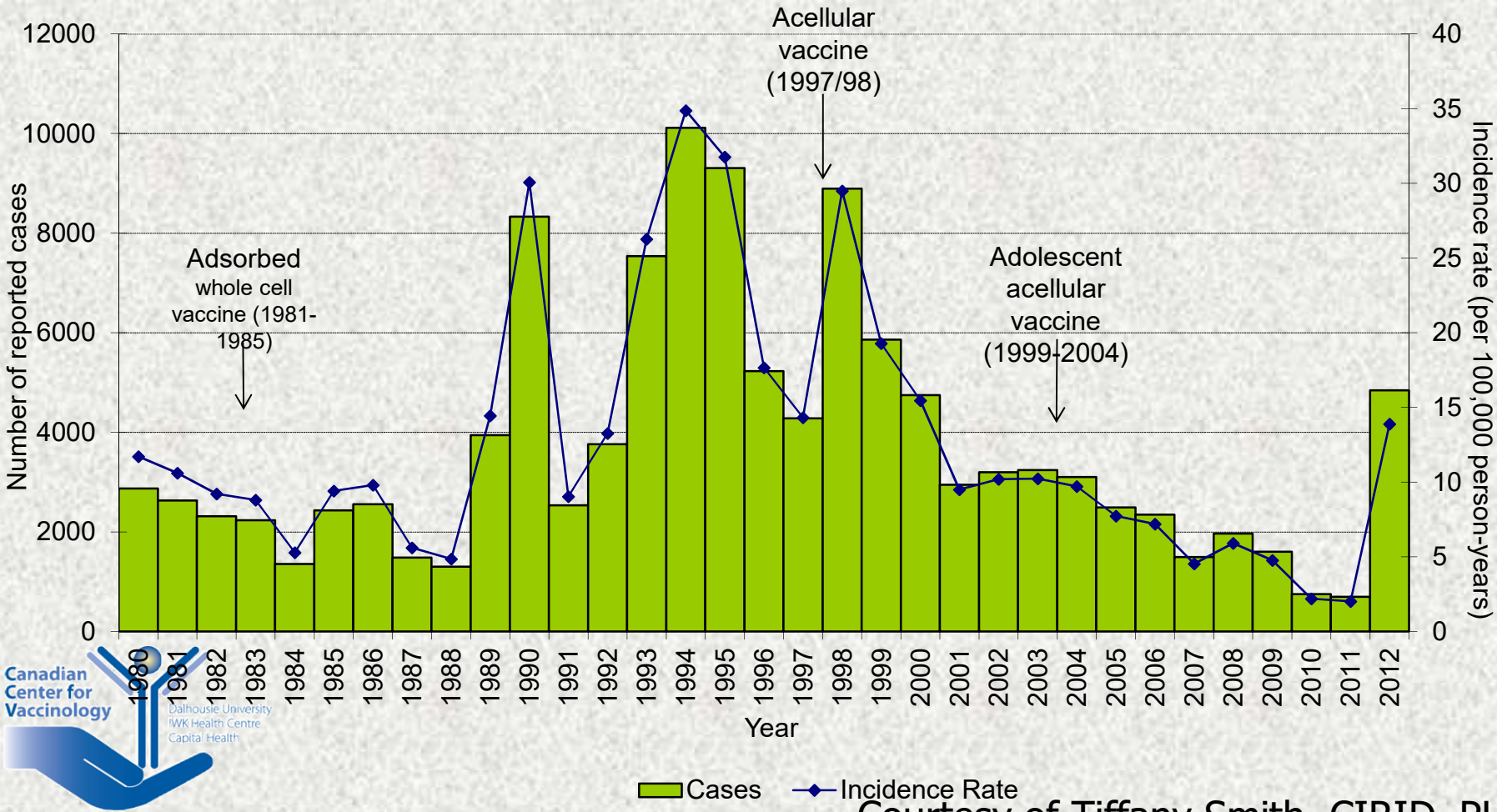
Both sexes (including unknown), all ages, 1991-2015



Rate per 100,000 of reported cases over time in Canada, both sexes (including unknown), all ages, 1991-2015

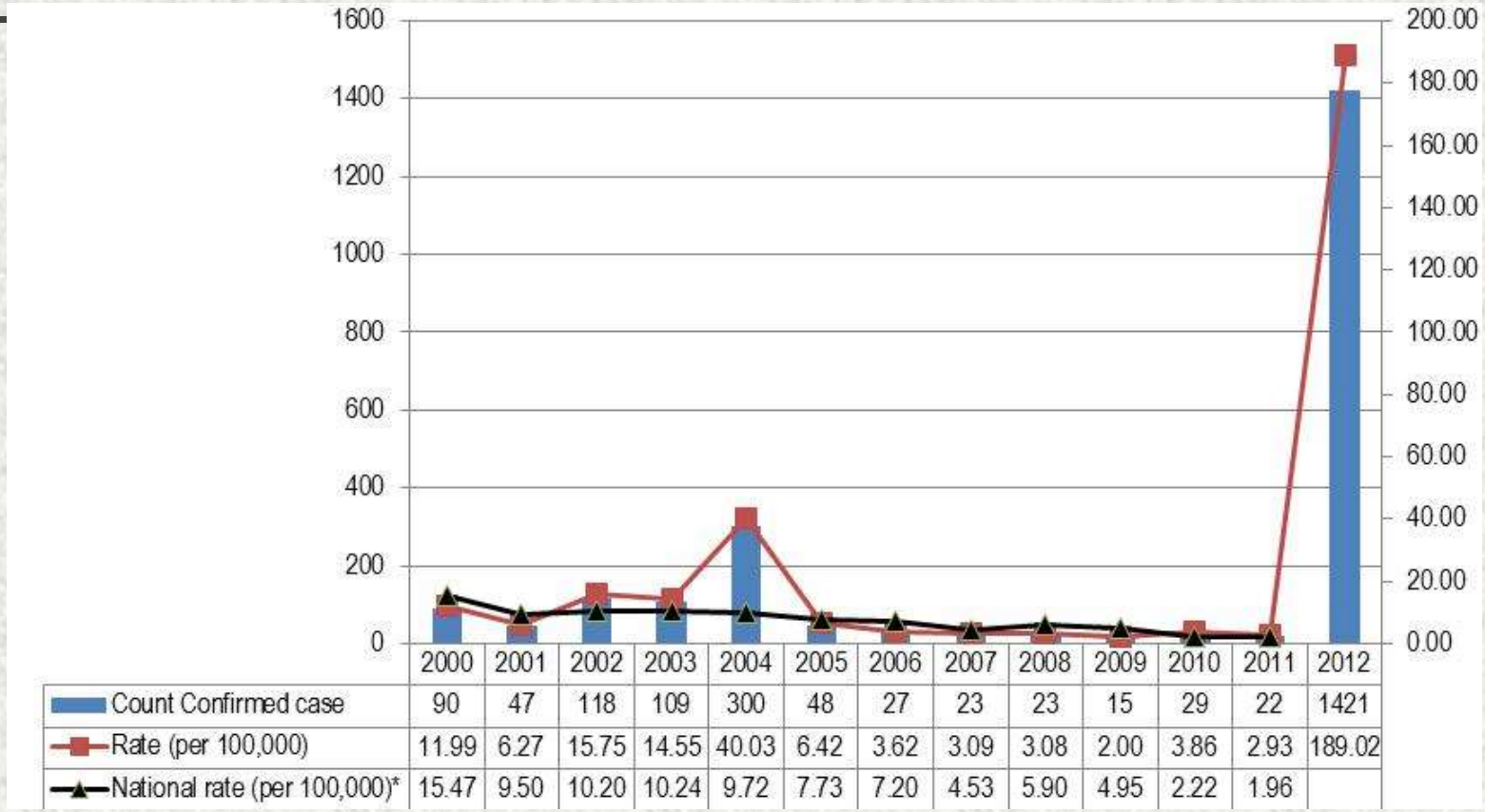
Public Health Agency of Canada

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



Courtesy of Tiffany Smith, CIRID, PHAC

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



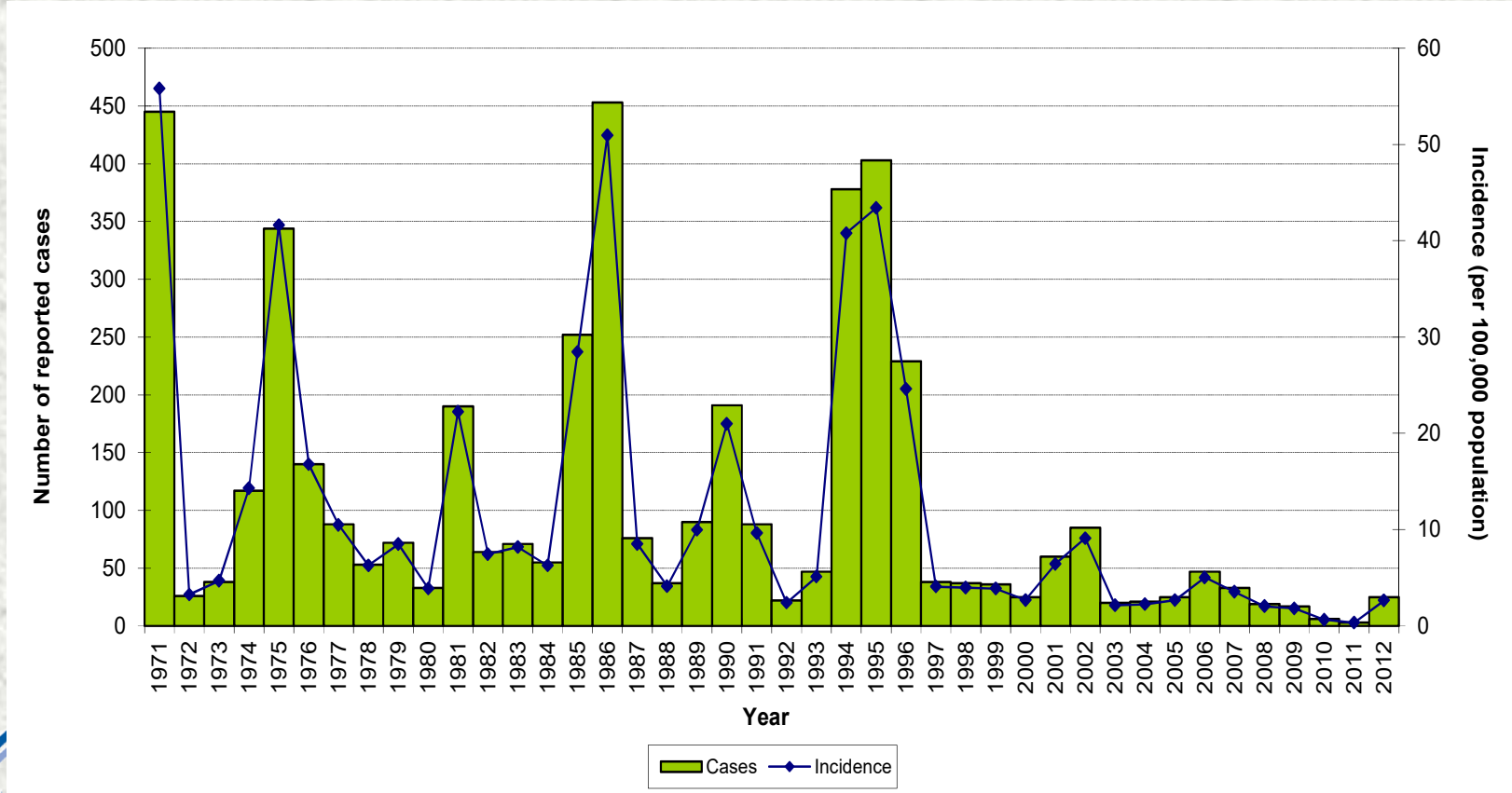
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Count Confirmed case	90	47	118	109	300	48	27	23	23	15	29	22	1421
Rate (per 100,000)	11.99	6.27	15.75	14.55	40.03	6.42	3.62	3.09	3.08	2.00	3.86	2.93	189.02
National rate (per 100,000)*	15.47	9.50	10.20	10.24	9.72	7.73	7.20	4.53	5.90	4.95	2.22	1.96	

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

Courtesy of Jastej Dhaliwal, NB Health

NOVA SCOTIA
Health and Wellness

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



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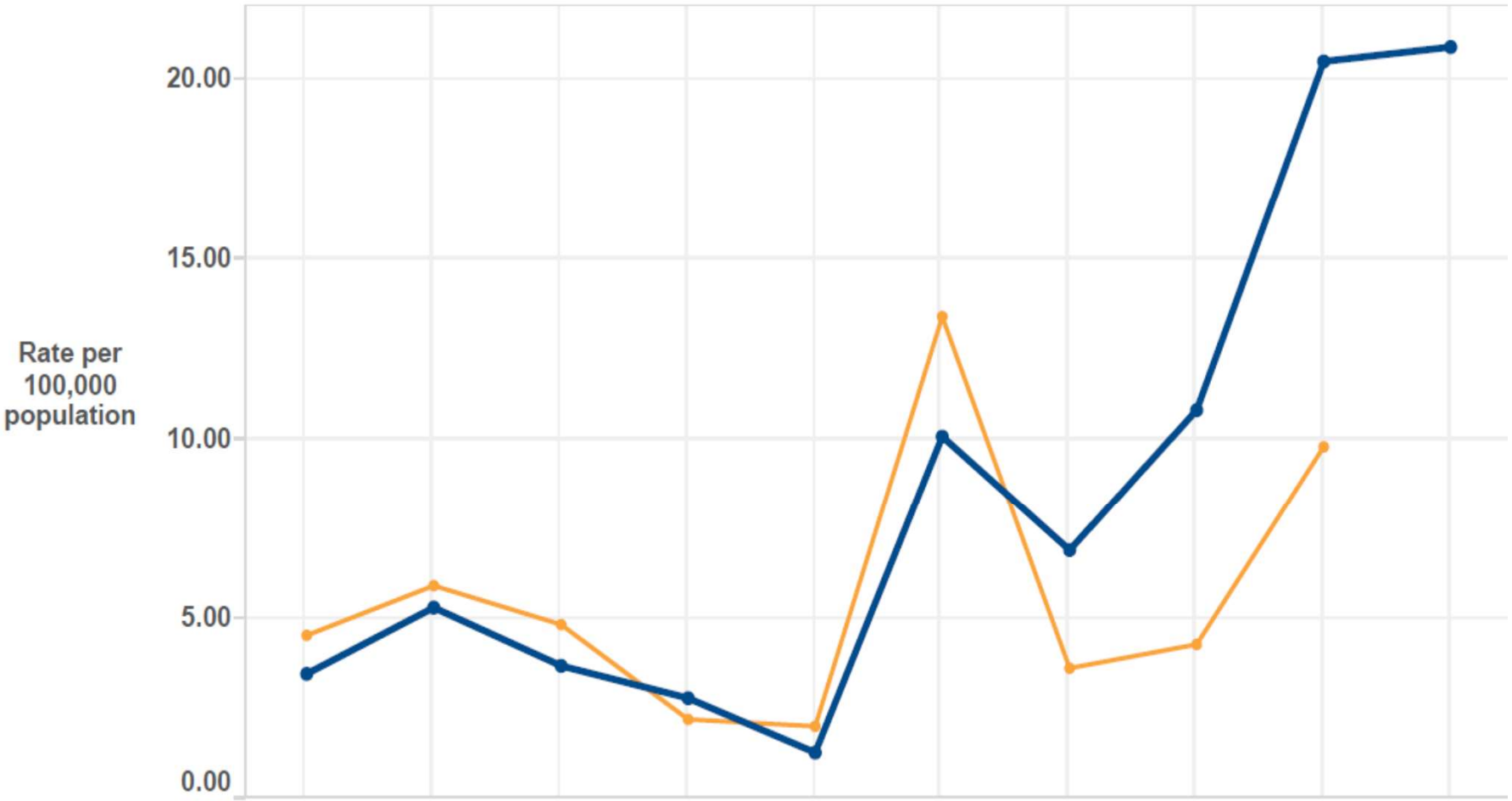
Courtesy of Beverly Billard, NS Health

28.1 Pertussis Rates by Year, 2007-2016



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Reports	149	231	163	125	58	458	317	502	962	993
BC Rate	3.47	5.31	3.70	2.80	1.29	10.07	6.91	10.81	20.50	20.90
Canada Rate	4.54	5.92	4.84	2.21	2.02	13.40	3.63	4.29	9.79	

Alberta

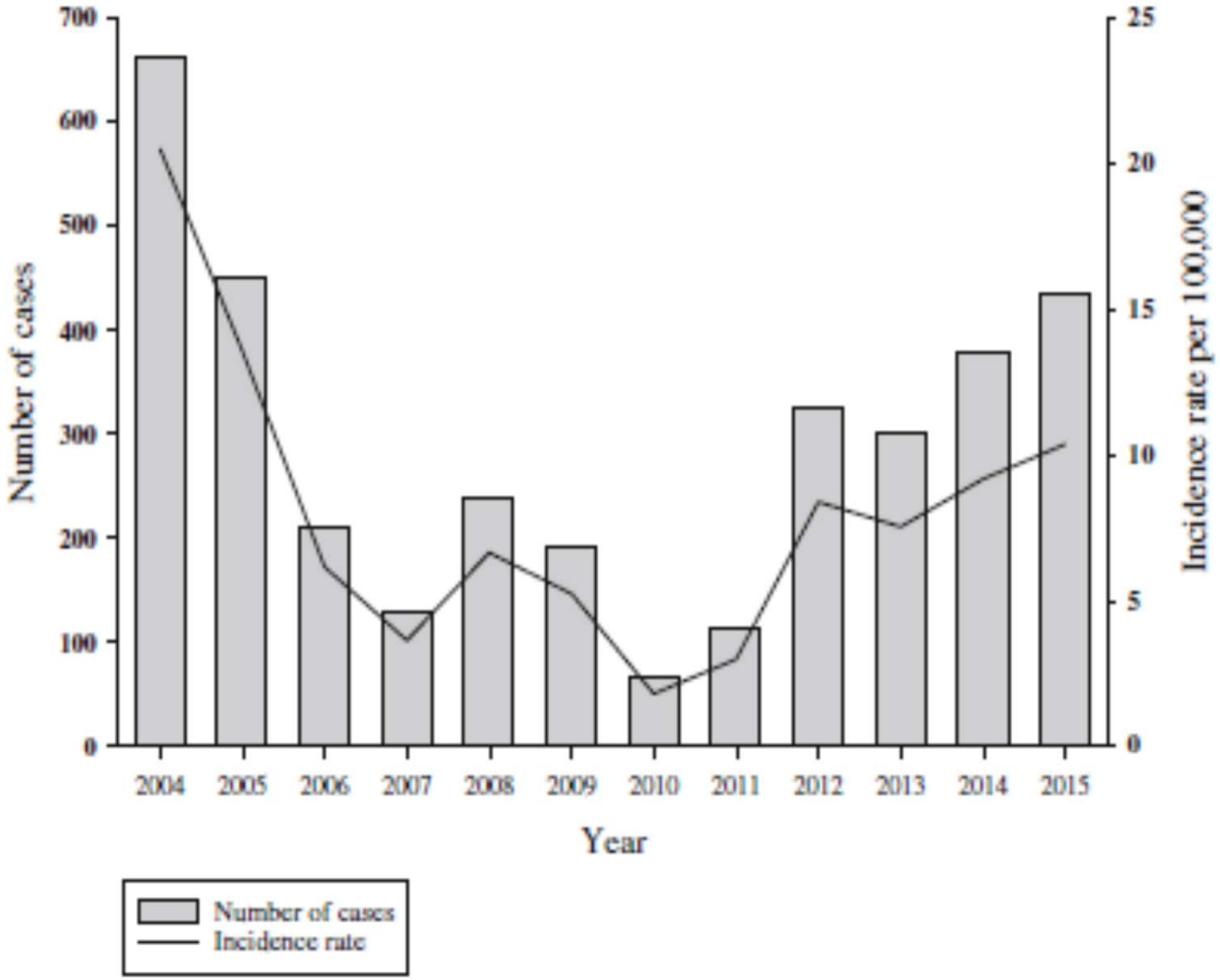


Fig. 1: Number of pertussis cases and incidence rate by year

Pertussis

Increase observed

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

No increase observed

- France
- Denmark
- Sweden
- Germany
- Finland

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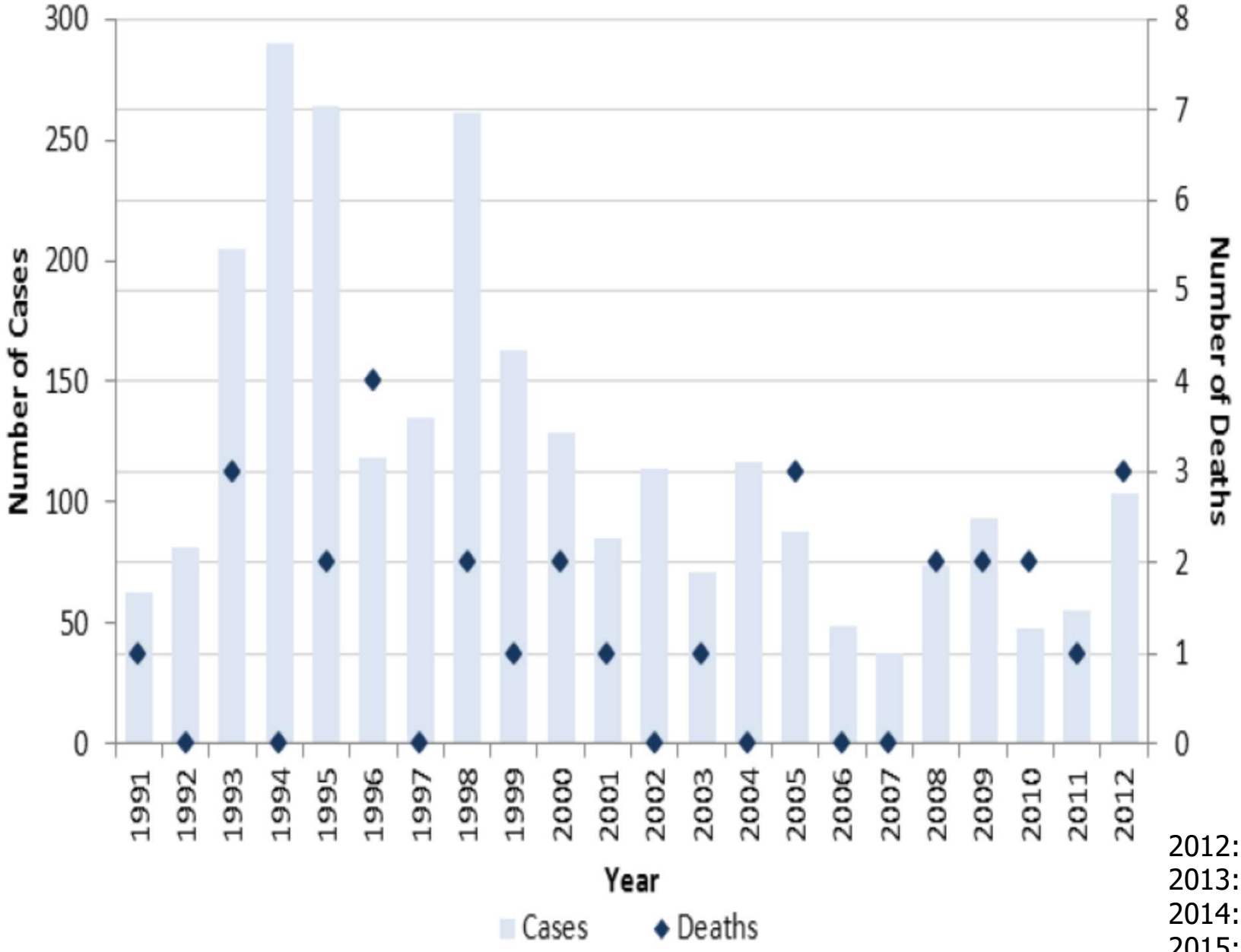
Figure 6. The number of pertussis cases and deaths, IMPACT, 1991 to 2012*



2012: 4
2013: 1
2014: 2
2015: 0

Smith T, Rotondo J, Desai S and Deehan H, CCDR, 2014

Outline

- Has there been a resurgence of pertussis?
  - Yes, but….
    - Local/regional….not all jurisdictions
      - Some just having typical cycling
- What are the causes of the resurgence?
- What are mitigation strategies?
  - Short term
  - Mid term
- What are long term solutions?

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Why is there a resurgence of pertussis?

- Change in the pathogen
- Expected epidemiology; predicted cycles
- Greater awareness and reporting
- Improved surveillance
- Improved diagnostics
- Failure to vaccinate
- Vaccine failure

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Bordetella pertussis

- Pertactin deficient strains
  - In 2010 California outbreak, 14% of isolates were PRN-
  - In 2012 Washington outbreak, 76% of isolates were PRN-

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Pertactin deficient strains in Australia

Figure 2

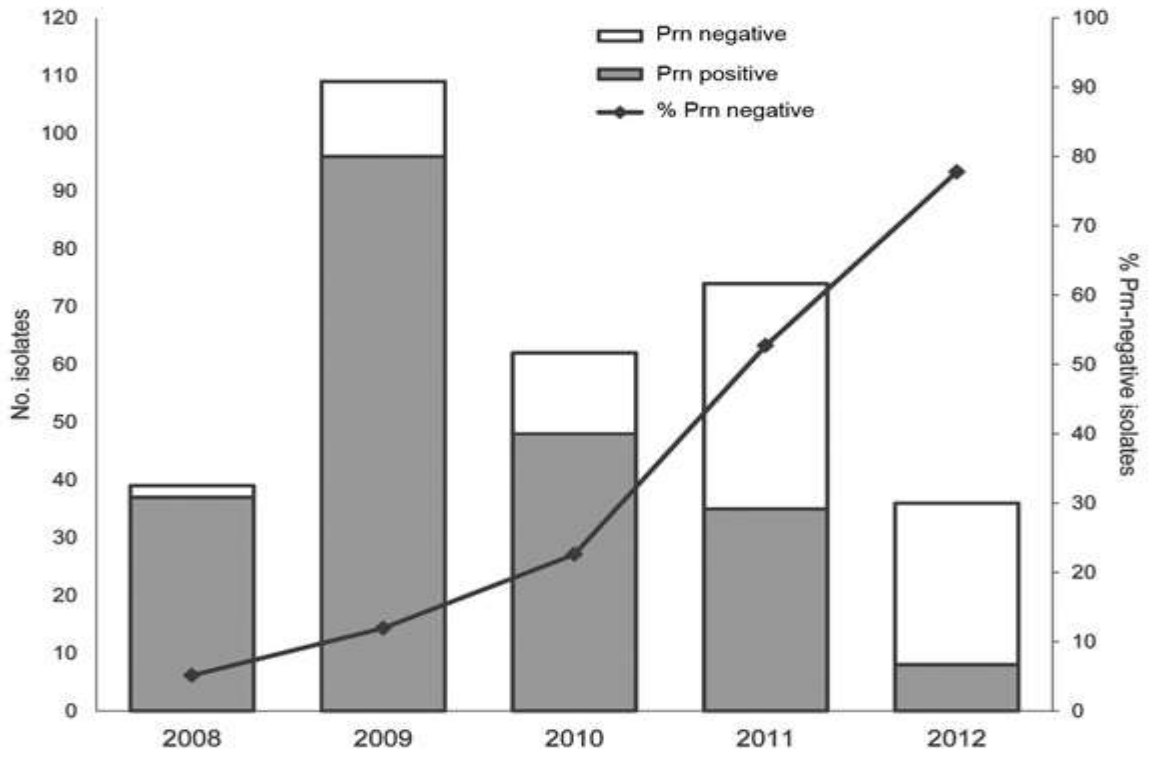

Figure 2. Number and percentage of pertactin (Prn)–negative *Bordetella pertussis* isolates in Australia, 2008–2012. During

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Lam C et al. Emerging Infect Dis, Volume 20, Number 4—April 2014

Pertactin deficient strains

- In Vermont 2011-2013, >90% strains PRN-
  - VE estimates same as with PRN+ strains
    - DTaP in children
    - Tdap in adolescents/adults

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Breakwell L et al, Pediatrics 2016;137(5):e20153973

Pertussis toxin mutations

- ptxP3 mutation
  - Associated with increased PT production
  - Increase in various locations
    - Netherlands increase from 0% of strains in 1989 to 100% of strains in 2004
      - Increased virulence noted
    - Clonal outbreak in Toronto

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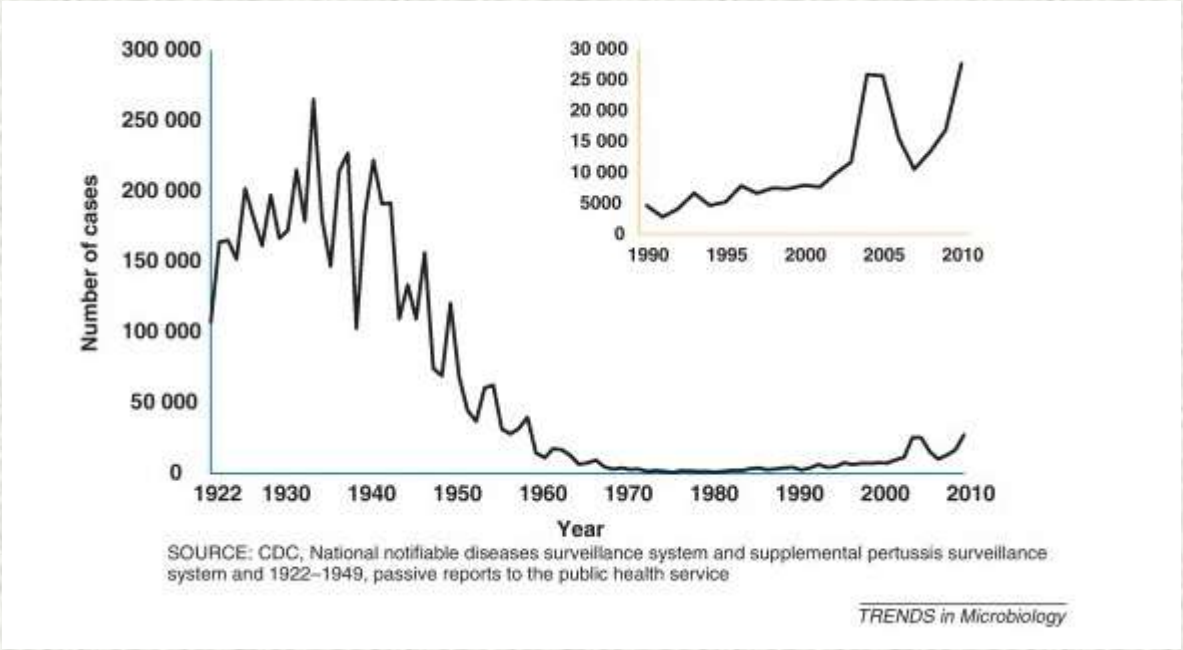
Pertussis as a cyclical disease

- Need to review multiple cycles
  - Are cyclical peaks higher



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Awareness, reporting, surveillance

- Awareness
  - Surveys show awareness of pertussis amongst adolescents and adults is low
  - Awareness increases during cyclical outbreaks
  - Better where there is better surveillance
- Reporting
  - Physicians poor at reporting
  - Laboratories better
  - No evidence for improved reporting (other than related to increased laboratory confirmation)
- Surveillance
  - Most systems passive
  - Sentinel active systems
  - Some efforts to improve surveillance
    - Latin America Pertussis Project
      - CDC, PAHO, Sabin Vaccine Institute, Ministries of Health in select Latin American countries

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Better diagnostics

- PCR increased sensitivity compared to culture
- Serology improved sensitivity amongst adolescents and adults
- Accounts for "blip" in a given jurisdiction (e.g., a reset of the baseline); however offset by underreporting
  - Not widely used globally so cannot account for changes where not implemented

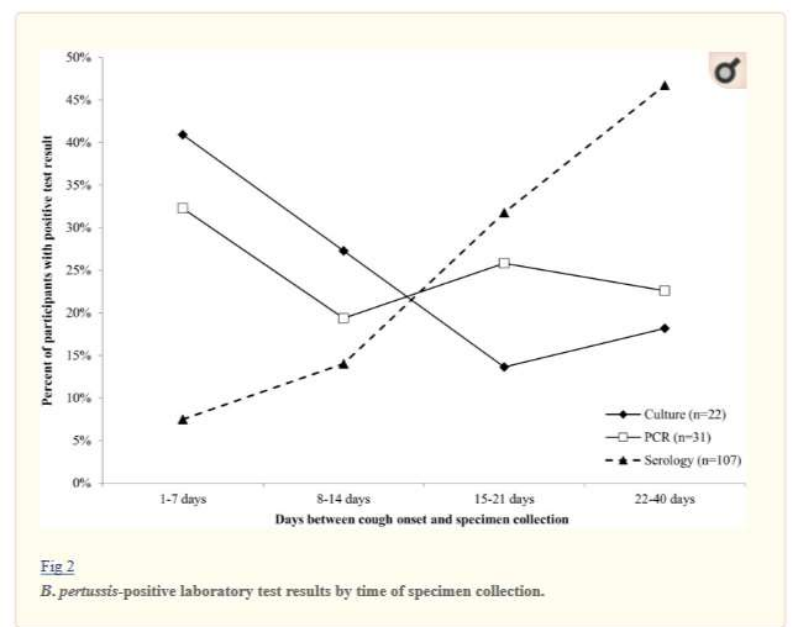

Fig 2

B. pertussis-positive laboratory test results by time of specimen collection.

Adria DL et al., PLoS One. 2018; 13(4): e0195979.

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Failure to vaccinate

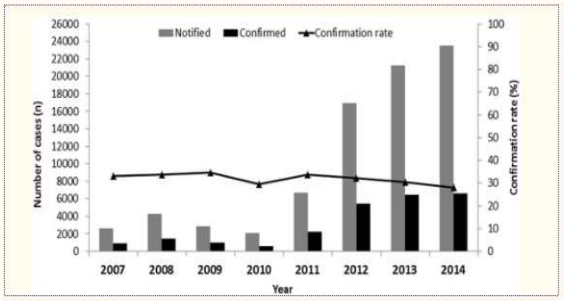

Fig. 1

Absolute numbers of reported and confirmed cases of pertussis and confirmation rates (confirmed cases/reported cases X 100) in Brazil, from 2007 to 2014 per year

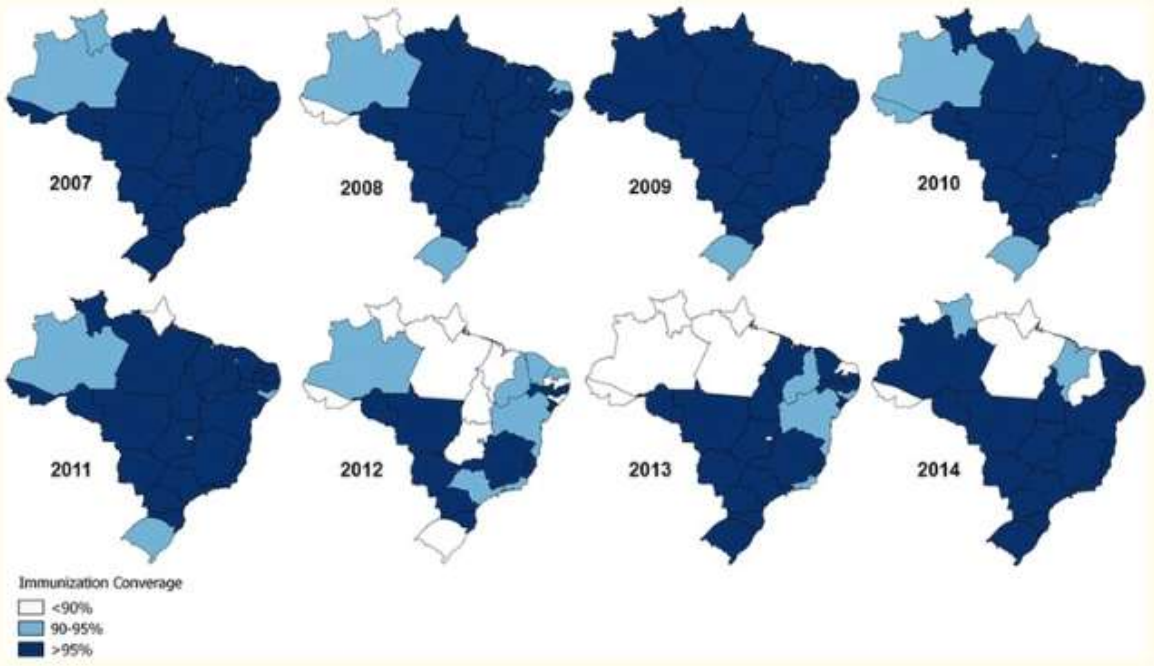

Fig. 8

Pertussis vaccine coverage in different Brazilian states by year, from 2007 to 2014. Immunization coverage rates are calculated as the number of children with complete basic scheme in the target age for a particular type of vaccine/number of children in the target age X 100 in different Brazilian states. The maps were made with the QGIS program using study data

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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

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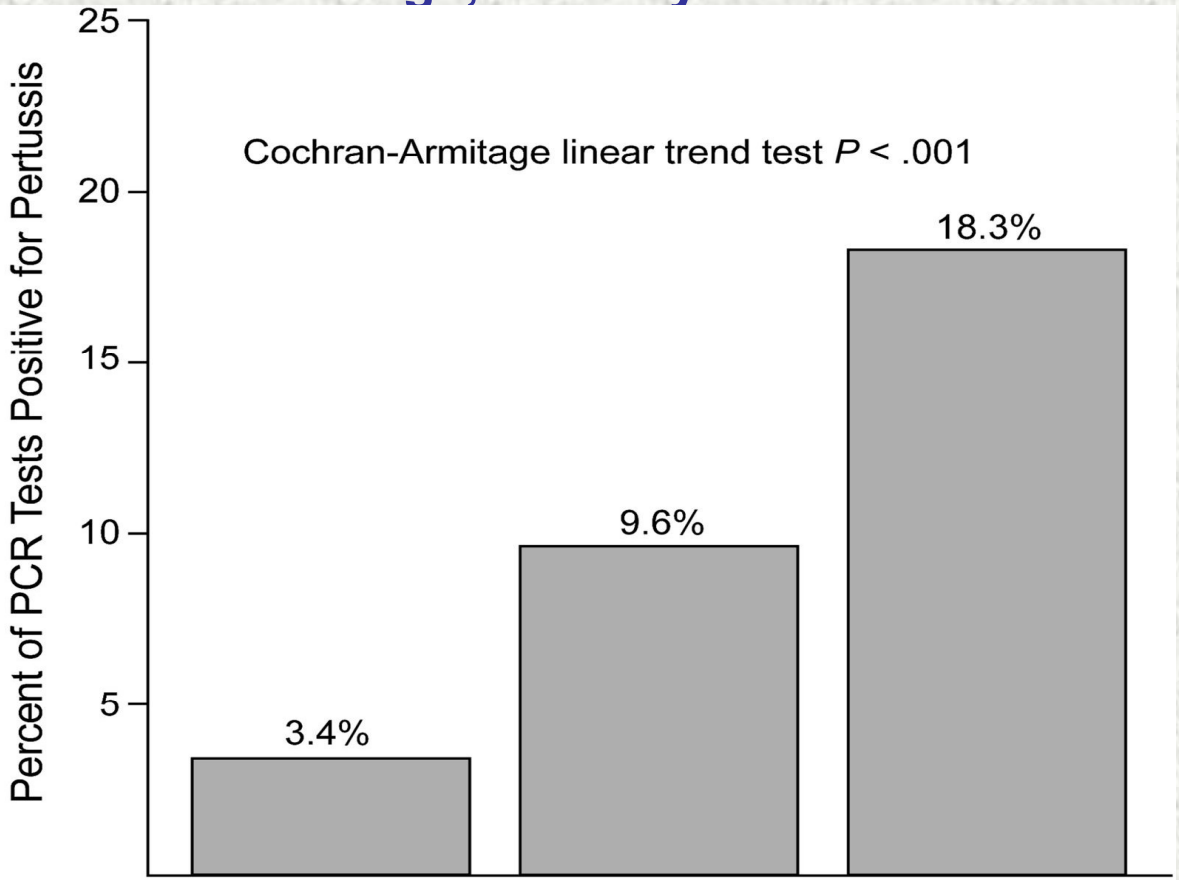
Percentage of pertussis PCR tests with a positive result in the study population by pertussis vaccine type for the first 4 doses received between 1 and 24 months of age, January 2010 to December 2011.



	All Whole Cell	Mixed	All Acellular
Positive Result (*n*)	8	19	111
PCR-tested (*n*)	234	197	606

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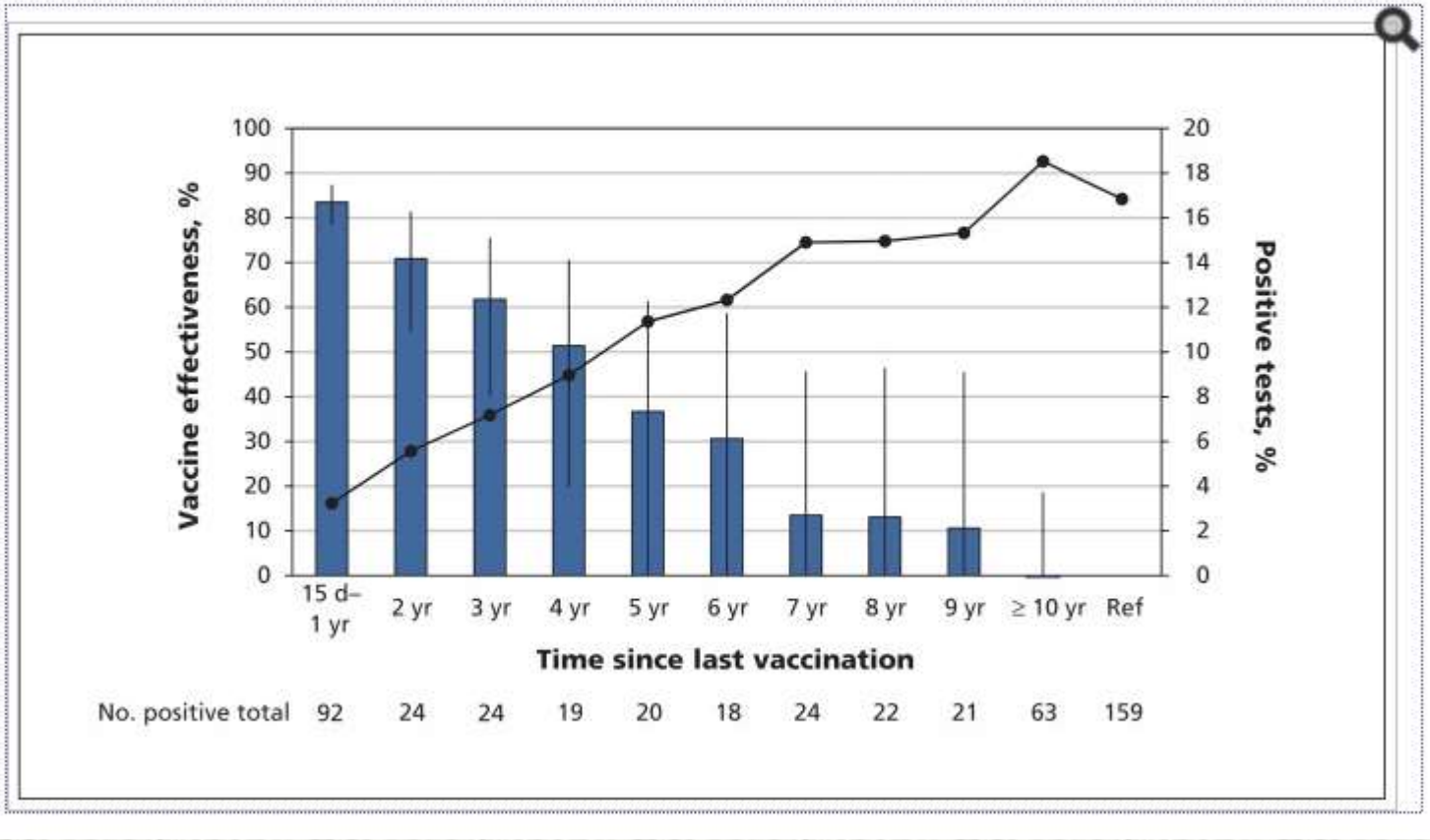
Klein N P et al. Pediatrics 2013;131:e1716-e1722

PEDIATRICS

Pertussis vaccine effectiveness

Figure 1:



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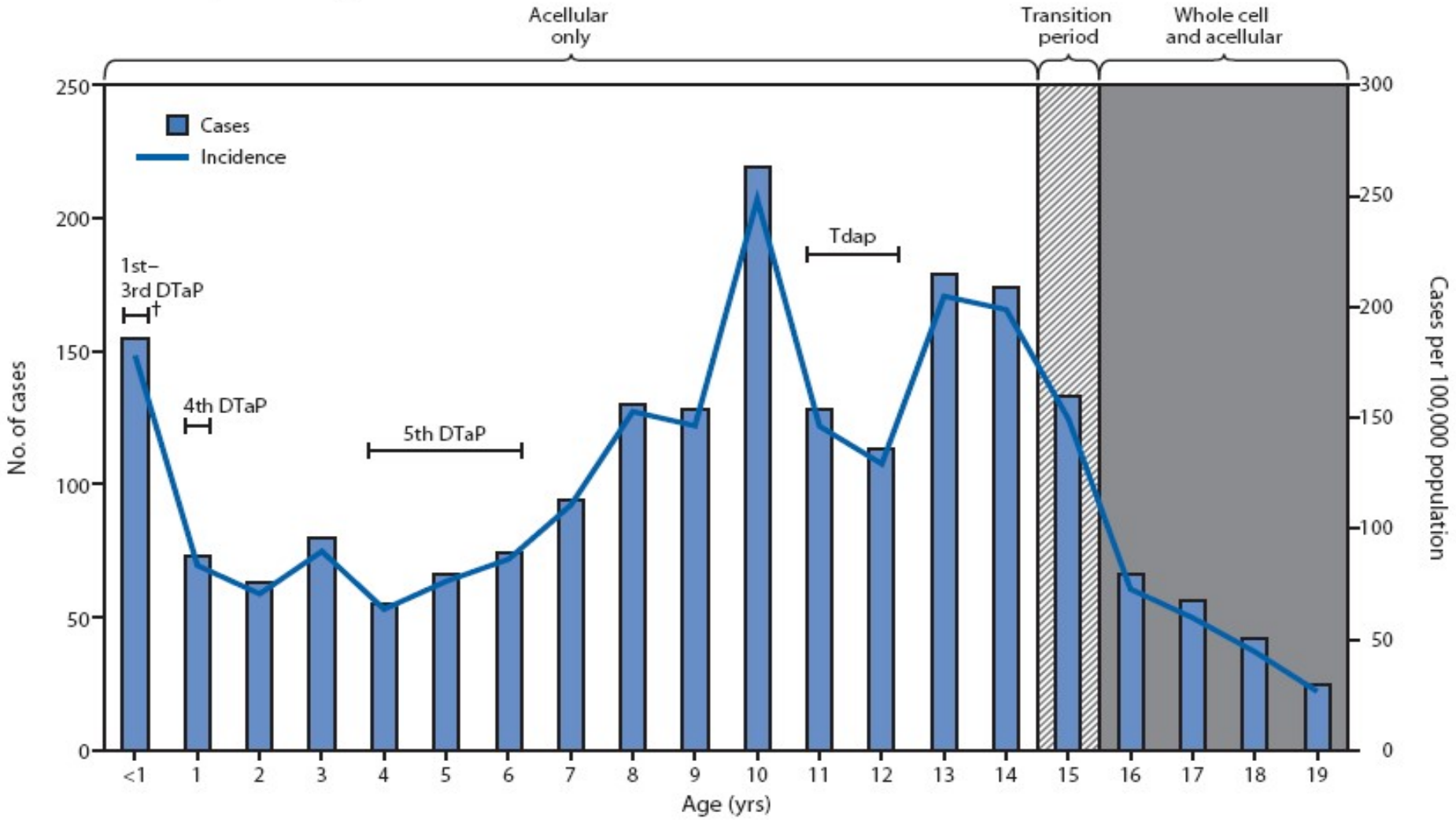
Schwartz KL et al. CMAJ, 2016

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.

Centers for Disease Control and Prevention. [Article title]. MMWR 2012;61

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

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aP vs. wP vaccine in baboon model

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

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Outline

- Has there been a resurgence of pertussis?
  - Yes, but….
    - Local/regional….not all jurisdictions
      - Some just having typical cycling
- What are the causes of the resurgence?
  - multifactorial
- What are mitigation strategies?
  - Short term
  - Mid term
- What are long term solutions?

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Mitigation strategies

- Short term
  - Optimize current vaccine use
  - On time immunization
  - Missed opportunities
  - Decreased exemptions
- Mid term
  - Maternal immunization
    - Protect the most vulnerable
      - Prevent death

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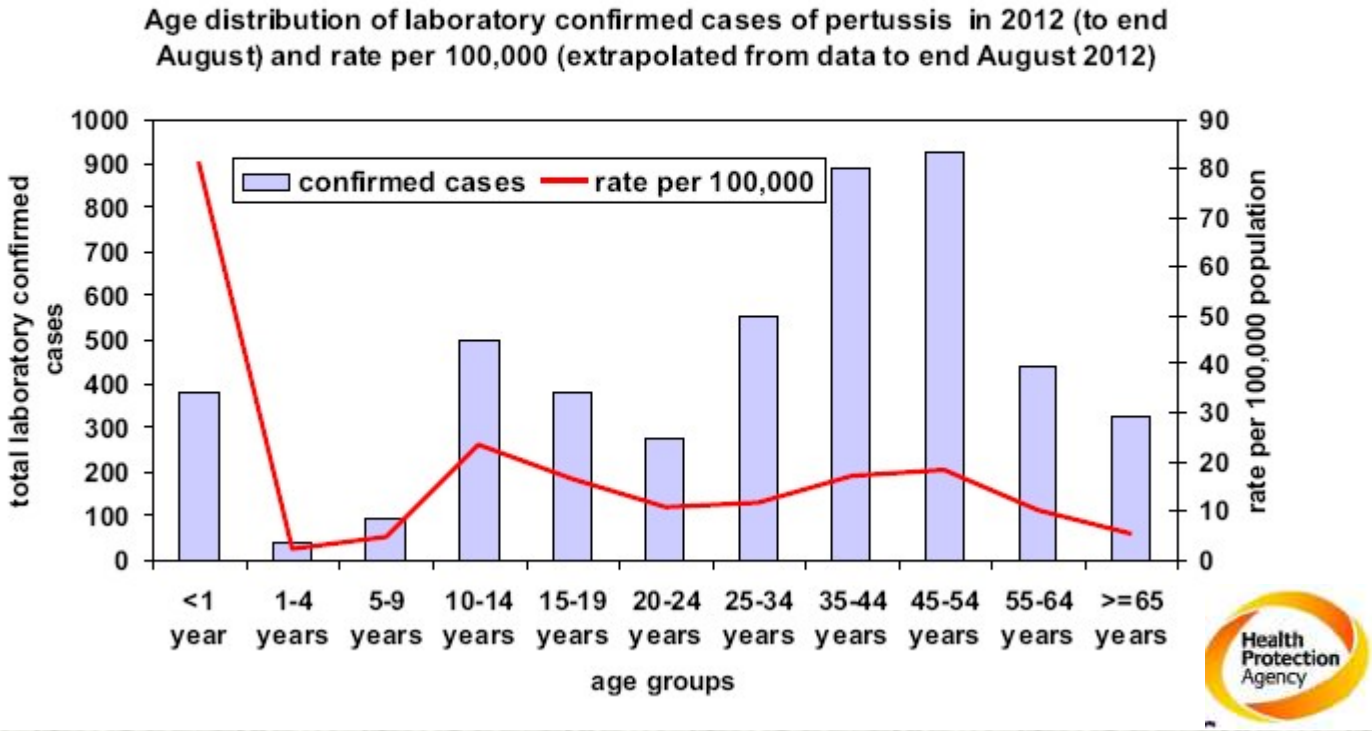
Pertussis in England and Wales

Current epidemiology of pertussis in England and Wales



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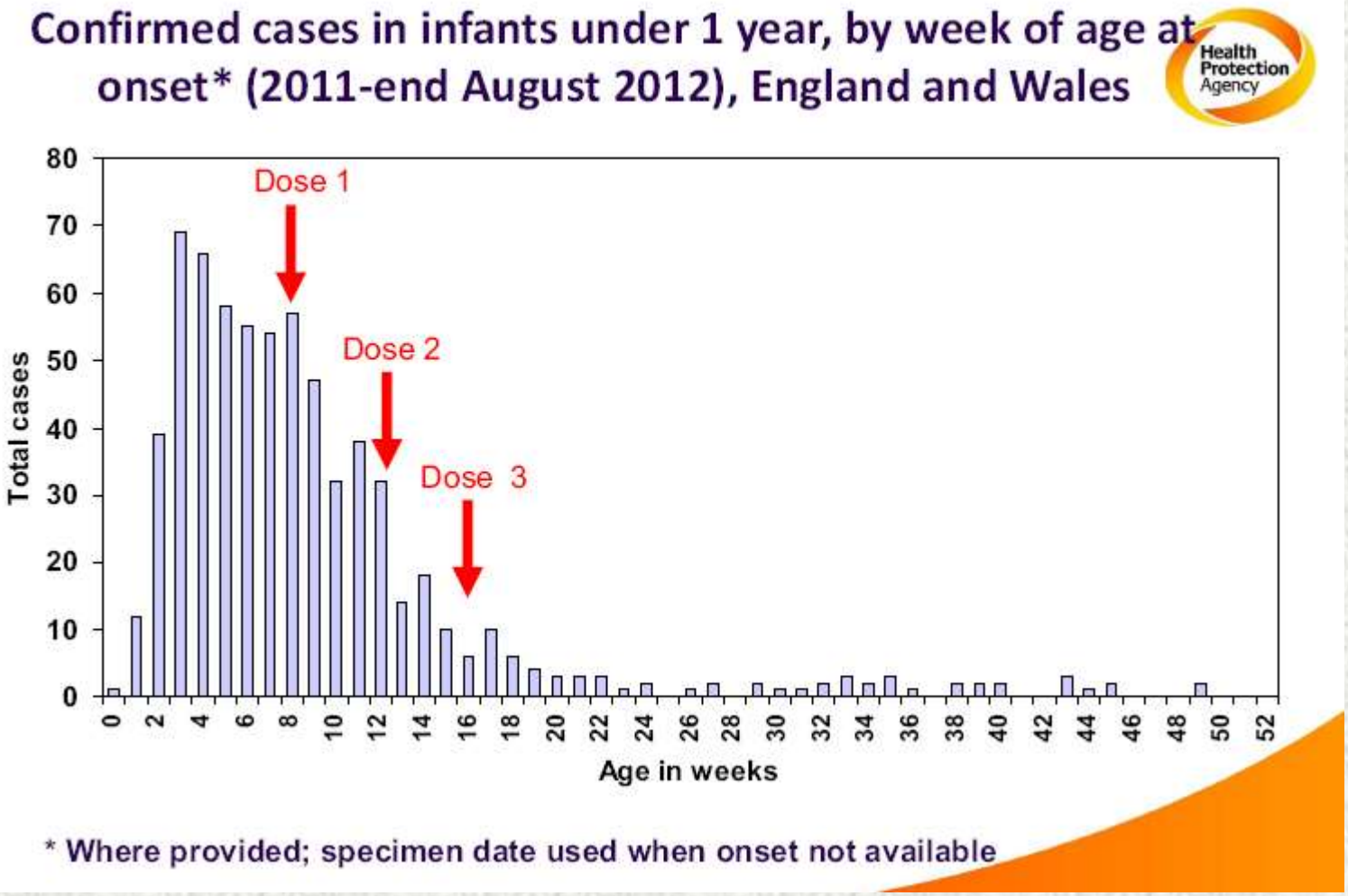
Pertussis in Infants, England and Wales



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Vaccine Coverage

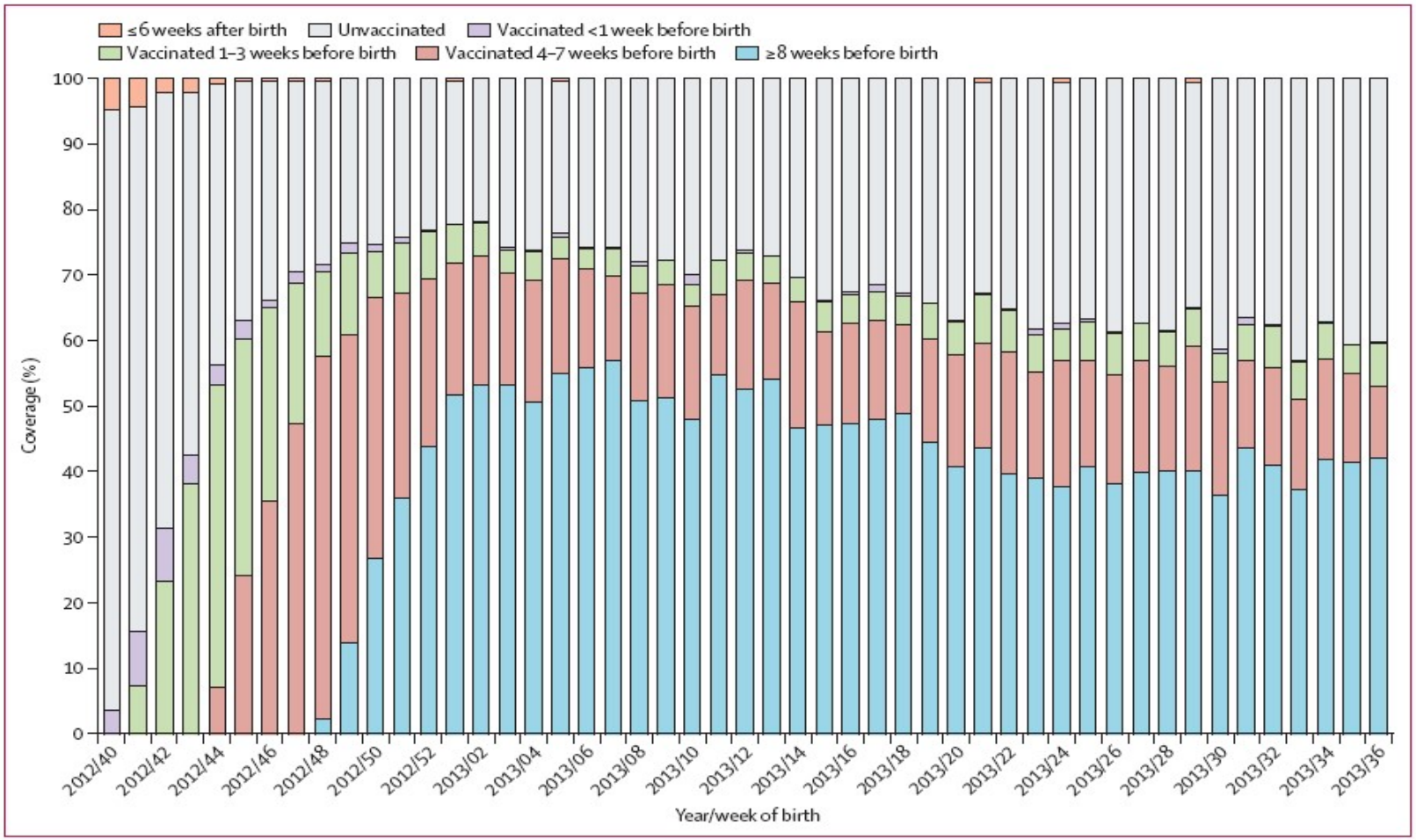

Figure 1: **Estimated maternal vaccine coverage by week of birth**
Figure shows coverage from week 40, 2012, to week 36, 2013. Figure based on data provided by the Clinical Practice Research Datalink.

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Amirthalingham, Lancet 2014

Vaccine Effectiveness

	Percentage of cases vaccinated	Average matched coverage*†	Vaccine effectiveness‡
Infants <3 months of age			
Vaccination at least 7 days before birth	15% (12/82)§	62%	91% (84 to 95)
Vaccination at least 7 days before birth with coverage reduced by a relative 20%	15% (12/82)§	49%	84% (71 to 93)
Infants <3 months of age by timing of maternal immunisation			
Vaccination at least 28 days before birth	14% (10/69)¶	63%	91% (83 to 95)
Vaccination 7–27 days before birth	3% (2/72)‖	19%	91% (70 to 96)
Vaccination 0–6 days before or 1–13 days after birth	3% (2/68)**	5%	38% (−95 to 80)
Infants <2 months of age			
Vaccination at least 7 days before birth	15% (11/71)	61%	90% (82 to 95)
Vaccination at least 7 days before birth with coverage reduced by a relative 20%	15% (11/71)	49%	82% (67 to 90)

Data are % (n/N), %, or % (95% CI). *Average matched coverage is the average of the matched population coverage estimates for all cases included in the analysis. †For cases in which the mother matched to zero coverage, that case was dropped from the analysis because it did not contribute information. ‡Vaccine effectiveness calculated on the basis of matched coverage on each individual, not with average matched coverage. §90 cases minus one case vaccinated within a week of birth and seven cases matched to zero coverage. ¶90 cases minus three cases vaccinated at other times before birth and 18 cases matched to zero coverage. ‖90 cases minus 11 cases vaccinated at other times before birth and seven cases matched to zero coverage. **90 cases minus 12 cases vaccinated at other times before birth and ten cases matched to zero coverage.

Table 4: **Effectiveness of maternal pertussis vaccine by infant age at onset and timing of vaccination**

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Amirthalingham, Lancet 2014

Vaccine Effectiveness

Table 2. Results of Vaccine Effectiveness Analysis

Cases		Controls			
Total No.	History of Maternal Pertussis Vaccination, No. (%)	Total No.	History of Maternal Pertussis Vaccination, No. (%)	Unadjusted VE, % (95% CI)	Adjusted VE[a], % (95% CI)
58	10 (17)	55	39 (71)	91 (77–97)	93 (81–97)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

[a] Adjusted for sex, geographical area, and birth period.

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Dabrera Clin Infect Dis 2015

Outline

- Has there been a resurgence of pertussis?
  - Yes, but….
    - Local/regional….not all jurisdictions
      - Some just having typical cycling
- What are the causes of the resurgence?
  - multifactorial
- What are mitigation strategies?
  - Short term
    - Optimize current vaccination
  - Mid term
    - Maternal immunization
- What are long term solutions?

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Options for new pertussis vaccines

- Whole cell vaccine
  - Return to old vaccine
  - Develop new vaccine
- Change antigens
  - Increase, decrease, eliminate, modify
- New adjuvants
- Change delivery system
  - Live attenuated
  - Other vectors
  - Vessicles, microparticles

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Challenges to developing a new pertussis vaccine

- 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

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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

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

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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[1,2], Anne-Sophie Debrie[1,2], Dominique Raze[1,2], Julie Bertout[1,2], Carine Rouanet[1,2], Amena Ben Younes[3], Colette Creusy[4], Jacquelyn Engle[5], William E. Goldman[5], Camille Locht[1,2*]

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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.

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.

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

Summary and conclusions

- Control of pertussis is not optimal
- Increased cases are the result of multiple factors
- Effective strategies to diminish the moribidity and mortality from pertussis are available
- Development of new, more effective vaccines that provide durable protection are needed

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Comments and Questions?

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