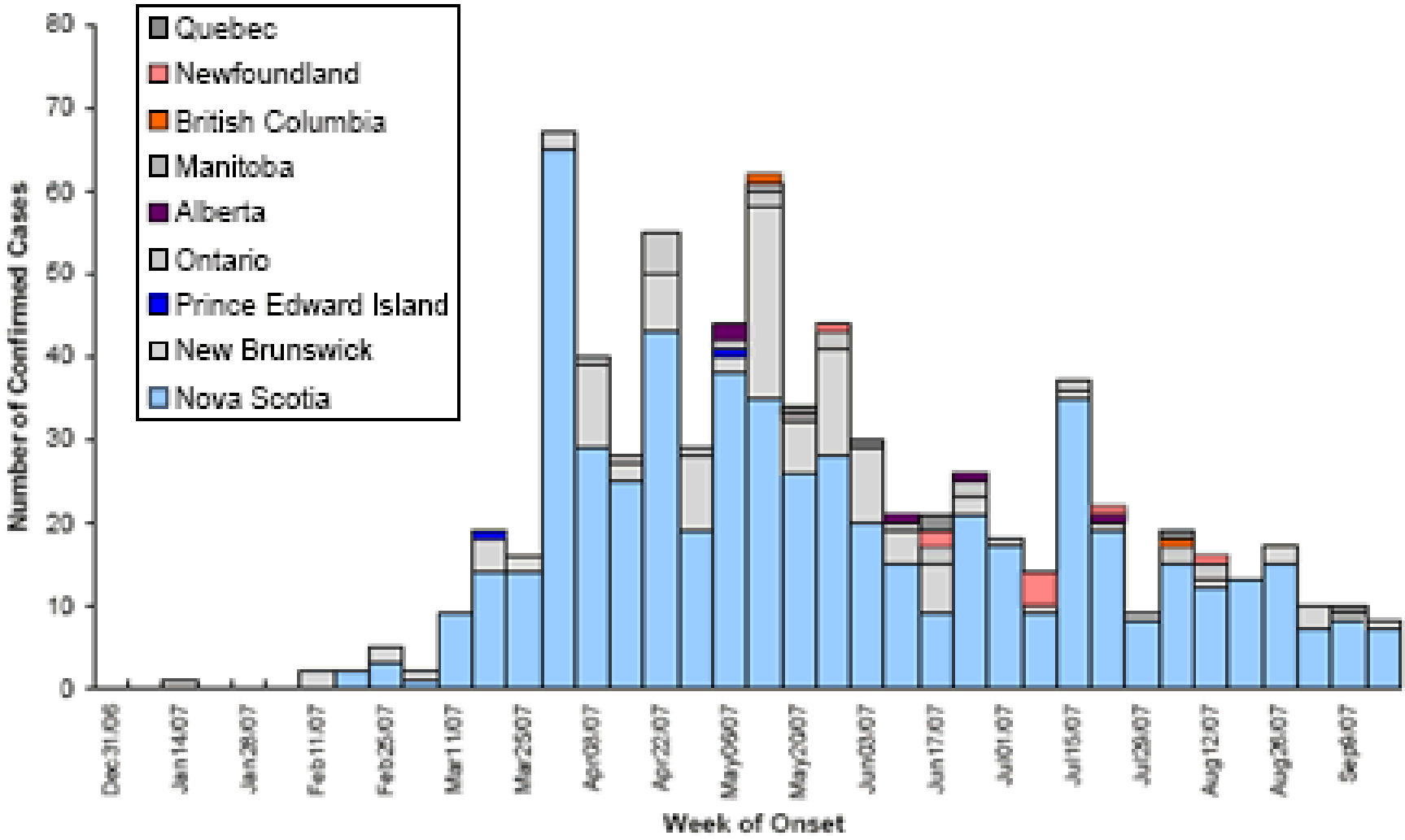
'Old Timey Diseases' in the Here and Now:
Current Status of Pertussis (Whooping Cough) in Toronto

David N. Fisman, MD MPH FRCP(C)
Scientist, Research Institute of the Hospital for Sick Children
Medical Epidemiologist, Ontario Public Health Laboratories

Fields Institute Center for Mathematical Medicine Seminar Series
Toronto, Ontario, Canada
January 25, 2008

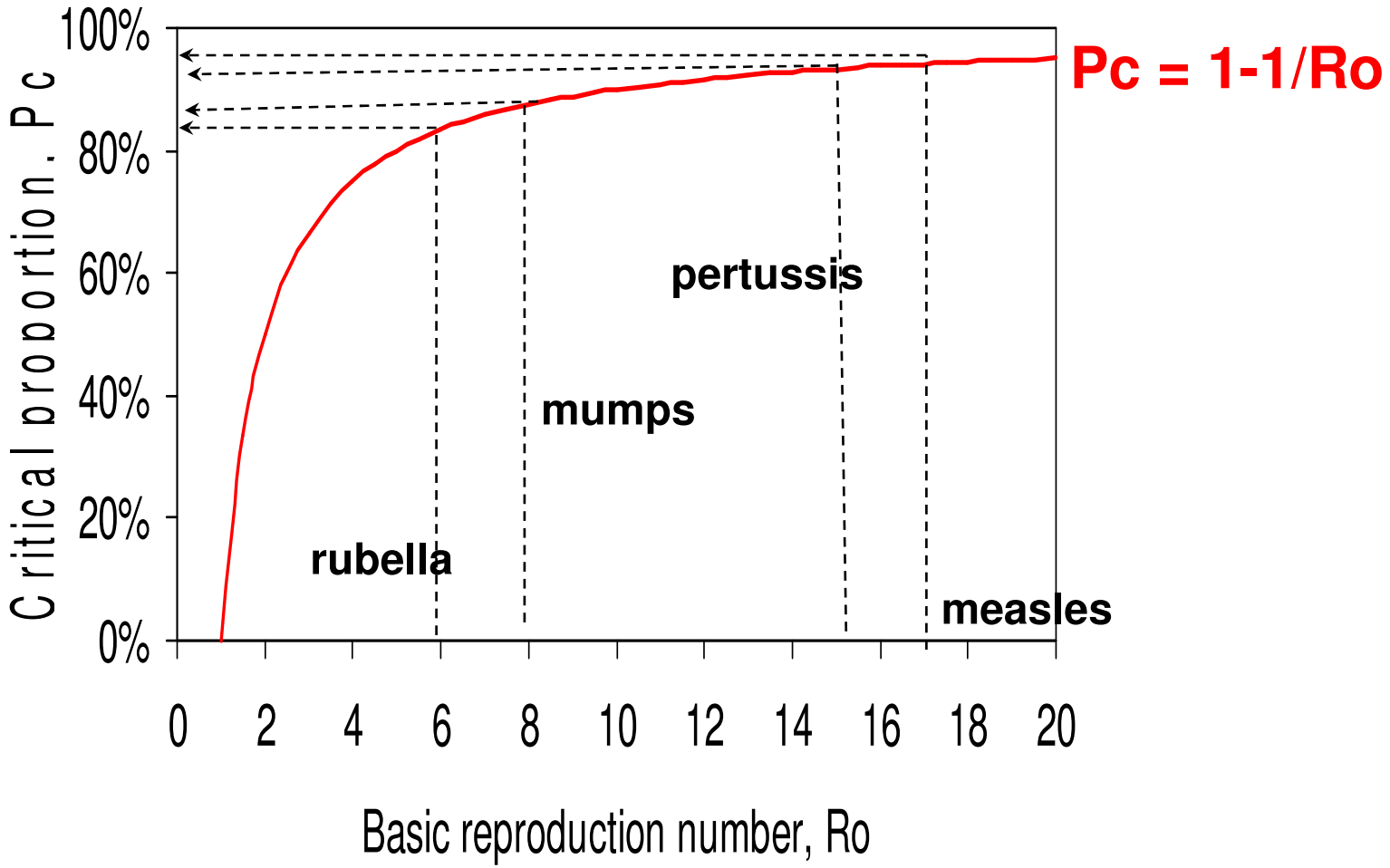
Scenario 1

- Mumps rare in Canada since introduction of vaccination in 1952 (< 400 cases/year). 2007: large mumps outbreak in N.S., with spread across Canada. Recent disease activity in southern Alberta, centered around U of Lethbridge. Similar outbreaks in recent years in the U.S., U.K., and Australia despite high levels of vaccination.
  - What are the epidemiological conditions for herd immunity?
  - How do these influence disease control strategies?



[Source: PHAC, Update on Mumps Outbreak in the Maritimes, National Summary, September 21, 2007. Available at: http://www.phac-aspc.gc.ca/mumps-oreillons/prof_e.html

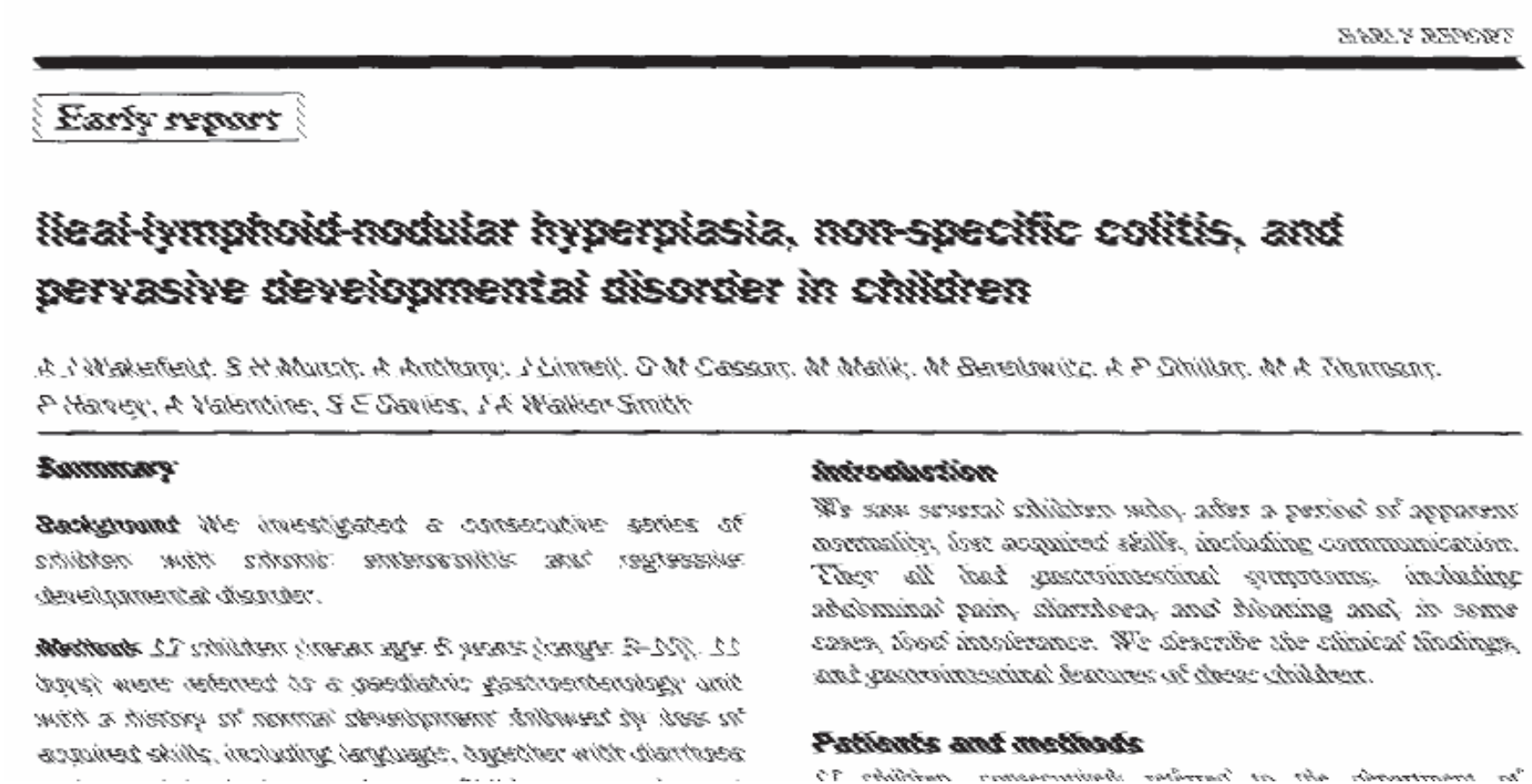
Coverage Required for Elimination



Vaccination and “Free Riders”

- Immune herd is classic economic “public good”: **non-excludable**, **non-rival**.
  - Public goods always subject to “free-ridership” problem (ergo taxation and government regulation).
- Vaccines: parental **risk calculus** weighs vaccine ADR against perceived risk of infection.
  - If other parents continue to comply, compliance with vaccination brings risk without apparent benefit.
  - “Nobody gets (measles/mumps/rubella/diphtheria/pertussis) anymore”.

Thanks, Lancet J !



EARLY REPORT

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years (range 3–10), 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea

Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and bloating and, in some cases, food intolerance. We describe the clinical findings and gastrointestinal features of these children.

Patients and methods

12 children consecutively referred to the department of

[Source: Lancet 1998 Feb 28;351(9103):637-41]

Nash Equilibria: The Prisoner's Dilemma

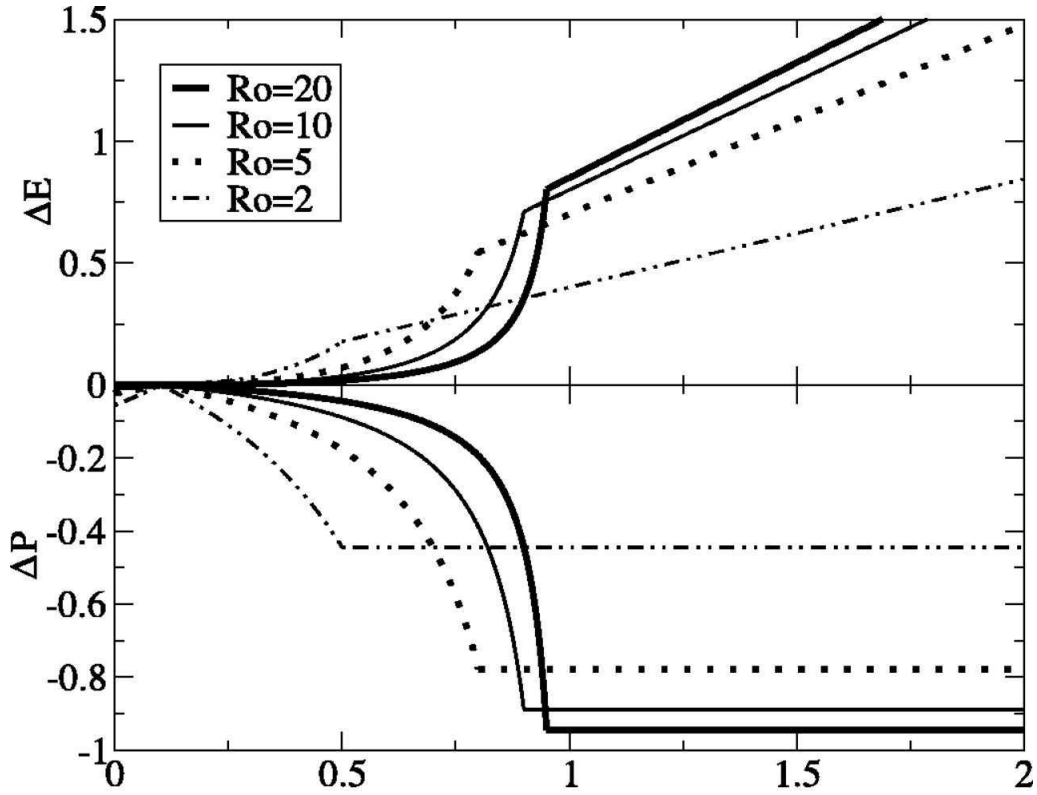
		Prisoner 2	
		Say nothing	Rat on friend
Prisoner 1	Say nothing	0.5,0.5	5,0
	Rat on friend	0,5	4,4

Nash Equilibria and Vaccination

(After Chris Bauch and David Earn, *PNAS 2004*)

		Parent 2	
		Vaccinate	Don't vaccinate
Parent 1	Vaccinate	Cost vaccination, Cost vaccination	Cost vaccination, Cost infection
	Don't vaccinate	Cost infection, Cost vaccination	Cost infection, Cost infection

SCARES PROJECTED TO BE MORE DESTABILIZING FOR HIGH R_0 DISEASES THAN LOW R_0 DISEASES



Risk of Vaccine/Risk of Disease

Bauch, Chris T. and Earn, David J. D. (2004) Proc. Natl. Acad. Sci. USA 101, 13391-13394

Other Recent Reappearances of "Old Timey V.P.D."

- **Rubella:** outbreak in Netherlands and southern Ontario, 2005.
  - > 592 cases, spread via religious network.
  - At least 22 pregnant women infected [Hahné et al, Euro Surveill 2005;10(5):E050519.1.]
- **Mumps:** as above.
- **Measles:** last major Canadian outbreak 1994.
  - Large outbreak (35 cases) in Indiana in 2005 following missionary travel to Romanian orphanage. [Parker et al., NEJM 2005; 355 (5): 447-55.]
- **Pertussis:** numerous recent reported outbreaks and case clusters in Texas, Massachusetts, New Hampshire, and Toronto.

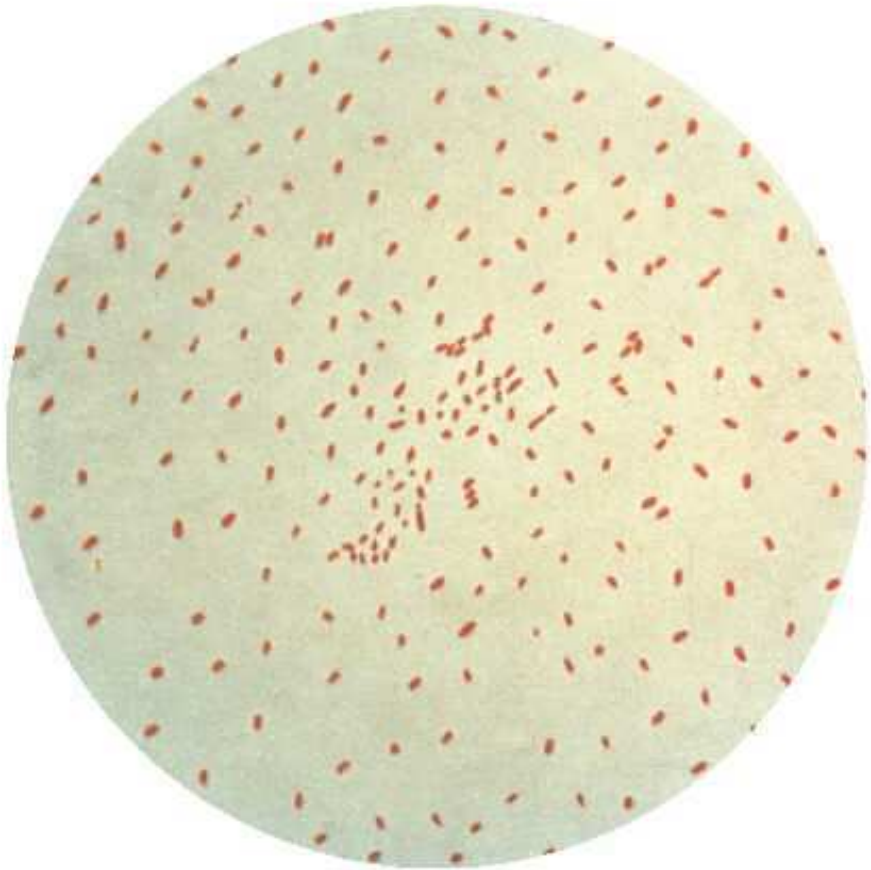
Pertussis: Clinical Background

www.brittanica.com

- Pertussis or whooping cough:
  - Highly transmissible respiratory infection, epidemics first described in 16th century (by Guillaume de Baillou, Dean of the Paris faculty of medicine).
  - Globally cause of ~ 40 million infections and 200,000-400,000 deaths each year.
  - Characterized by “paroxysmal, spasmotic cough that usually ends in a prolonged, high-pitched crowing inspiration or whoop” (IOM 1991).

Pertussis: Clinical (2)

- Causative bacterium identified, and serologic assay and vaccine introduced by Bordet and Gengou, Pasteur Institute, 1906.
- *Bordetella pertussis*: pleiomorphic aerobic GNR.

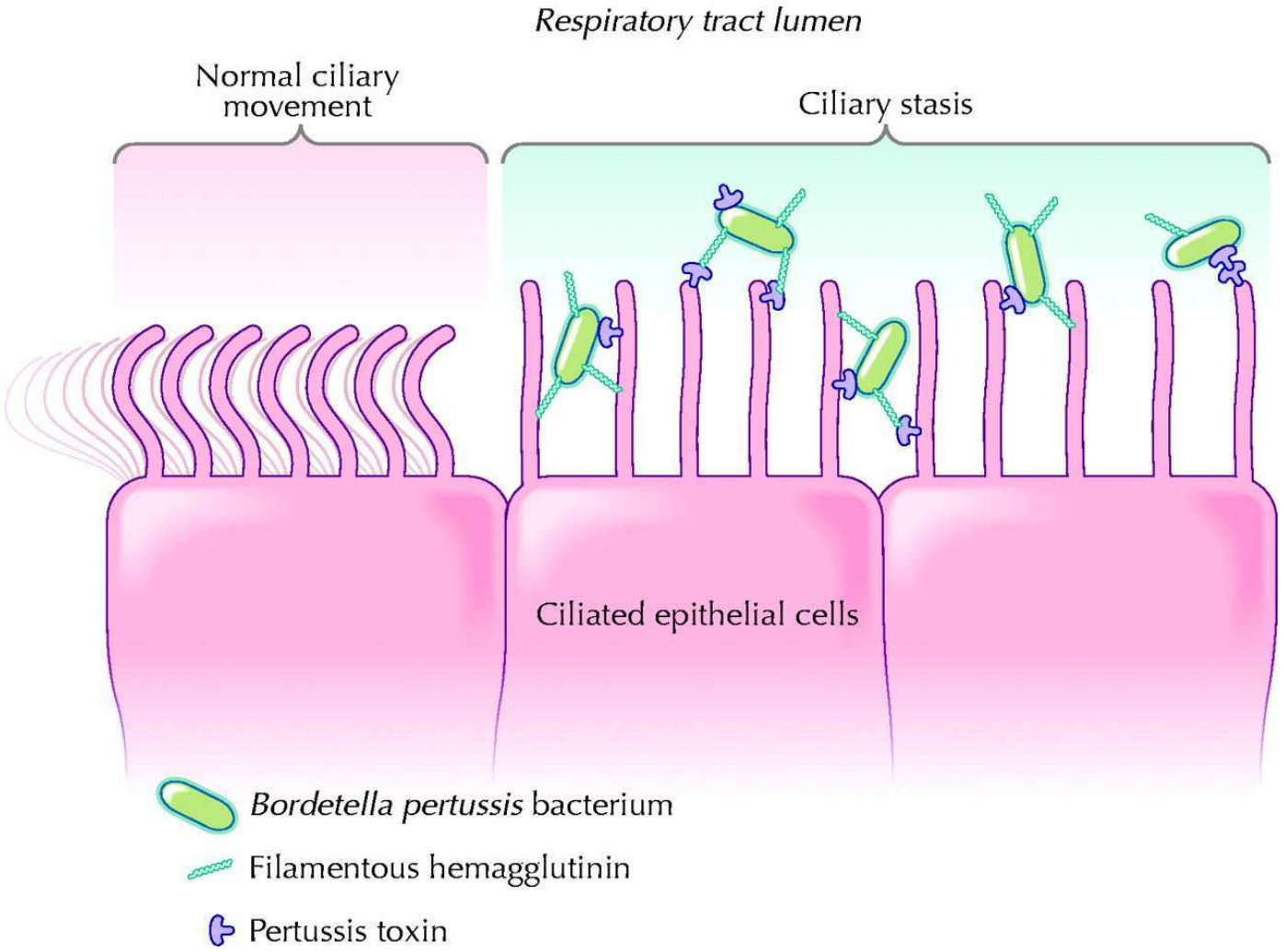


Source: www.vaccineinformation.org

Pathogenesis

- Pathogenesis of disease related to elaboration of **pertussis toxin** and other antigens (pertactin, filamentous hemaglutinin, tracheal cytotoxin, and others).
  - Antibody against toxins and other antigens confers immunity to disease.
- Bacterium adheres to cilia, elaborates toxins that paralyze cilia, disrupt immune response, and prevent clearance of respiratory secretions.

Fig. 1: Synergy between pertussis toxin and filamentous hemagglutinin in binding to ciliated respiratory epithelial cells

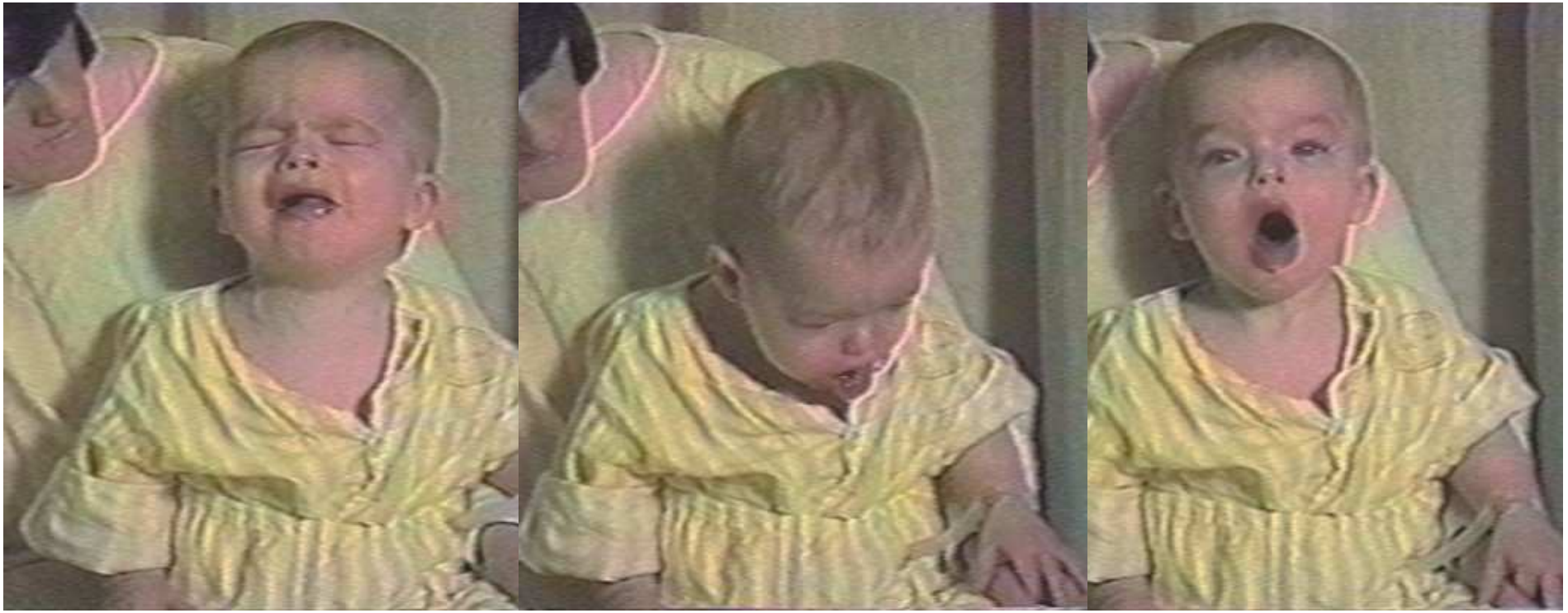


Tozzi, A. E. et al. CMAJ 2005;172:509-515

Pertussis: Clinical (3)

- Clinical features:
  - Incubation period 7-10 days (range 4 to 21).
  - **Catarrhal phase** (1-2 weeks)—runny nose, mild cough, fever, indistinguishable from common cold.
  - **Paroxysmal phase** (1-6 weeks)—paroxysms of multiple, rapid-fire coughs, which end with inspiratory "whoop". May be associated with cyanosis, vomiting or (infants) apnea.
    - Average ~ 15 paroxysms/24 hour period.
    - Children typically appear ill and exhausted.
  - **Convalescent phase** (2-3 weeks)—cough gradually diminishes in frequency and violence, but may return with subsequent URI.

Paroxysmal Phase: “Whoop”



Source: www.vaccineinformation.org

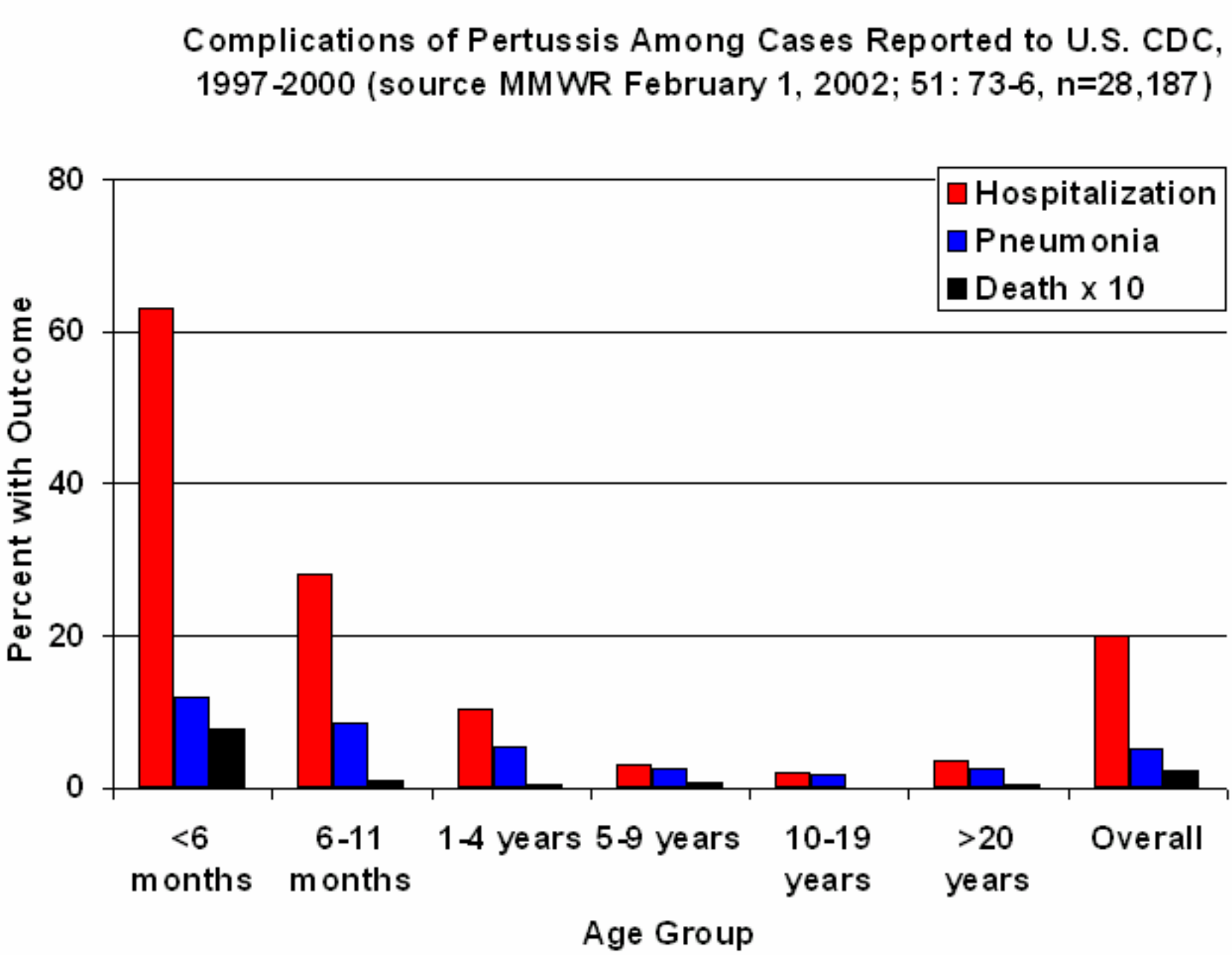
Pertussis Complications*

Condition	Percent reported
Pneumonia	5.2
Seizures	0.8
Encephalopathy	0.1
Hospitalization	20
Death	0.2

*Cases reported to CDC 1997-2000 (N=28,187)

Other complications: anorexia, dehydration, otitis media, hernia, pneumothorax, subconjunctival hemmorhage, epistaxis.

Source: U.S. National Immunization Program, www.cdc.gov/vaccines


Complications of Pertussis Among Cases Reported to U.S. CDC, 1997-2000 (source MMWR February 1, 2002; 51: 73-6, n=28,187)
Hospitalization
Pneumonia
Death x 10
Percent with Outcome
80
60
40
20
0
<6 months
6-11 months
1-4 years
5-9 years
10-19 years
>20 years
Overall
Age Group

Pertussis: Periodicity and Seasonality

- 2-5 year periodicity in disease activity.
- Autumn seasonality in Toronto.
- Persistent periodicity and seasonality despite vaccination.

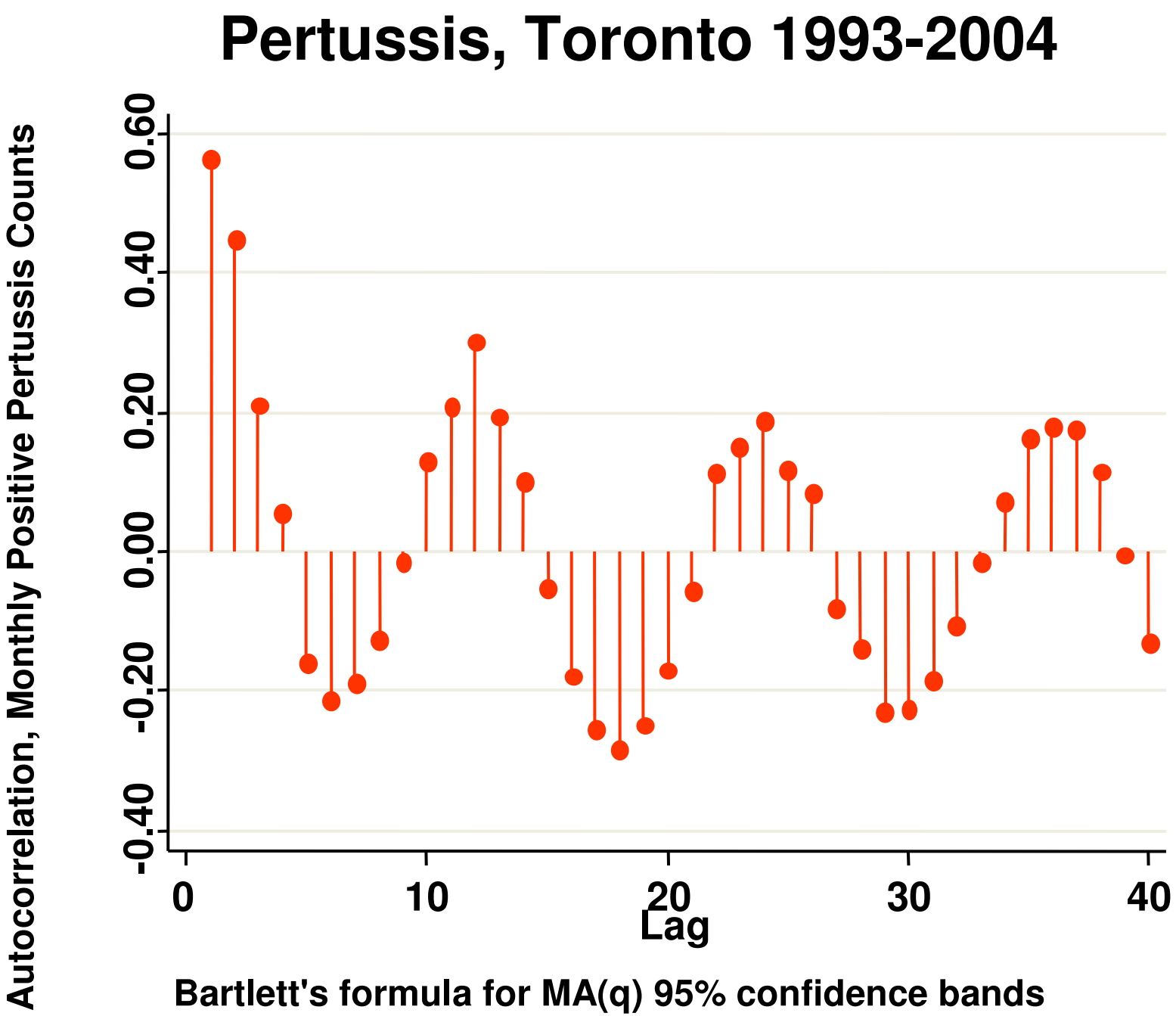
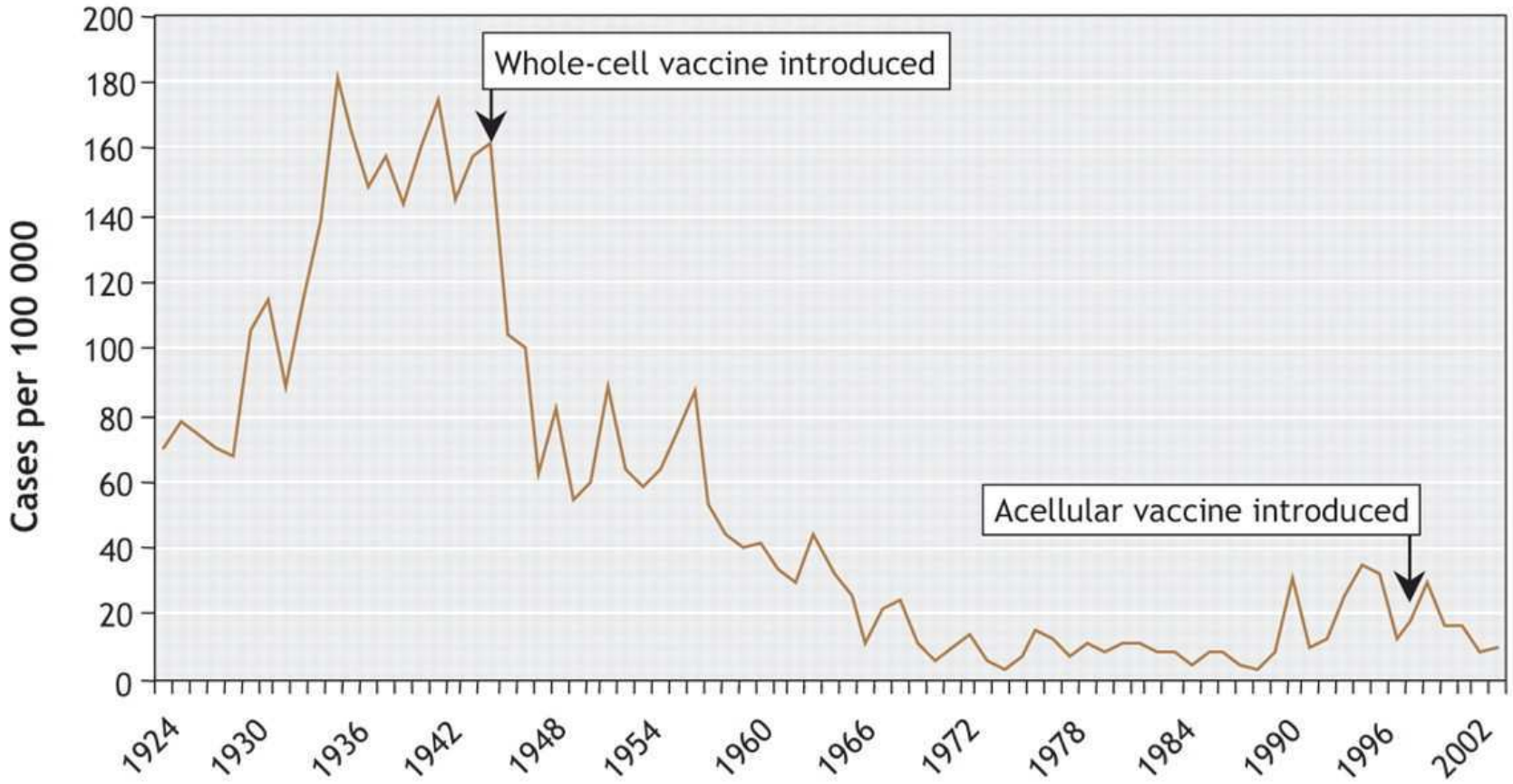

Pertussis, Toronto 1993-2004
Autocorrelation, Monthly Positive Pertussis Counts
-0.40
-0.20
0.00
0.20
0.40
0.60
0
10
20
30
40
Lag
Bartlett's formula for MA(q) 95% confidence bands

Fig. 1: Pertussis incidence rate, Canada, 1924-2002



Galanis, E. et al. CMAJ 2006;174:451-452

CMAJ·JAMC

“Marching Cohort” in Canada

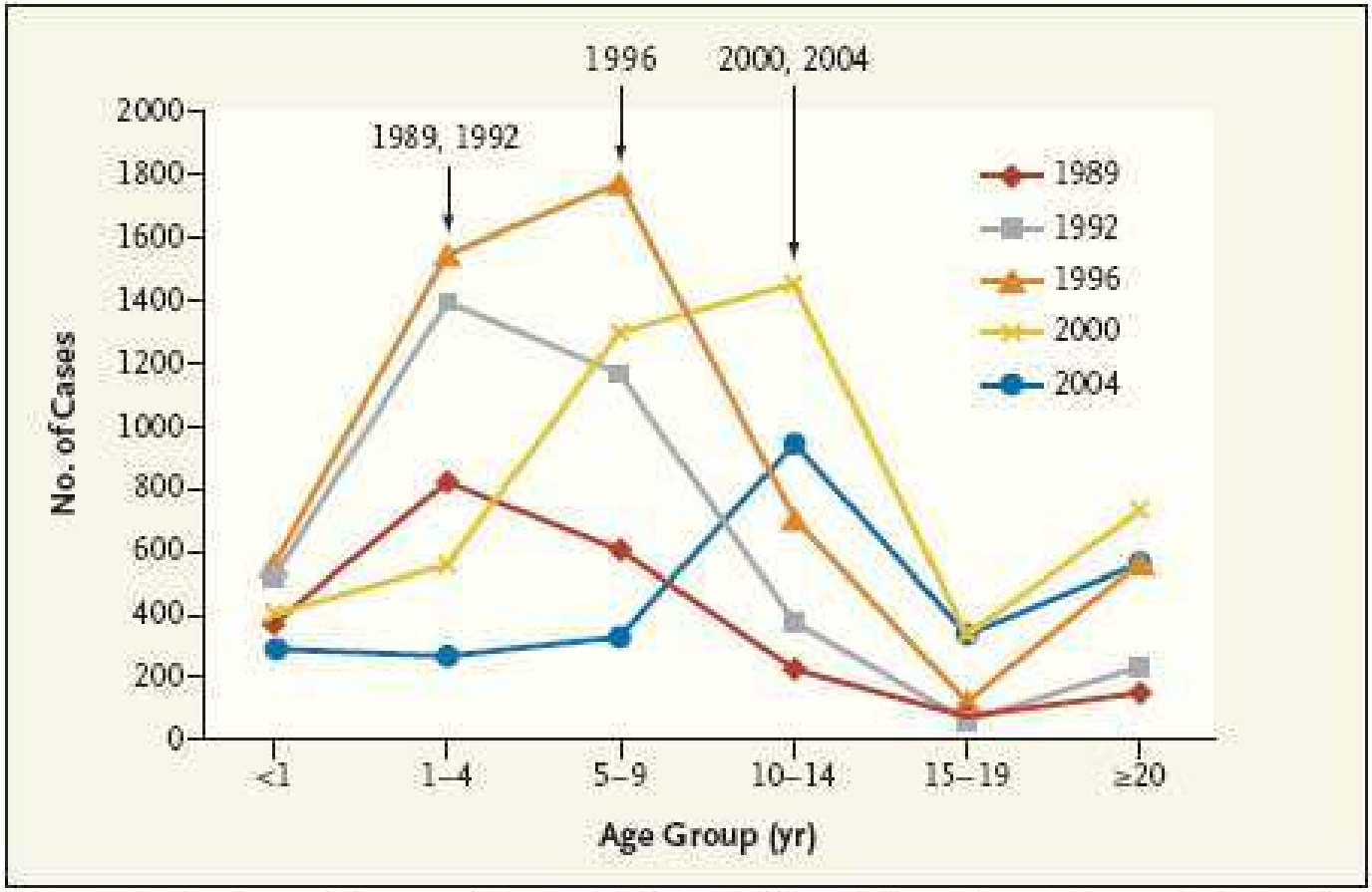
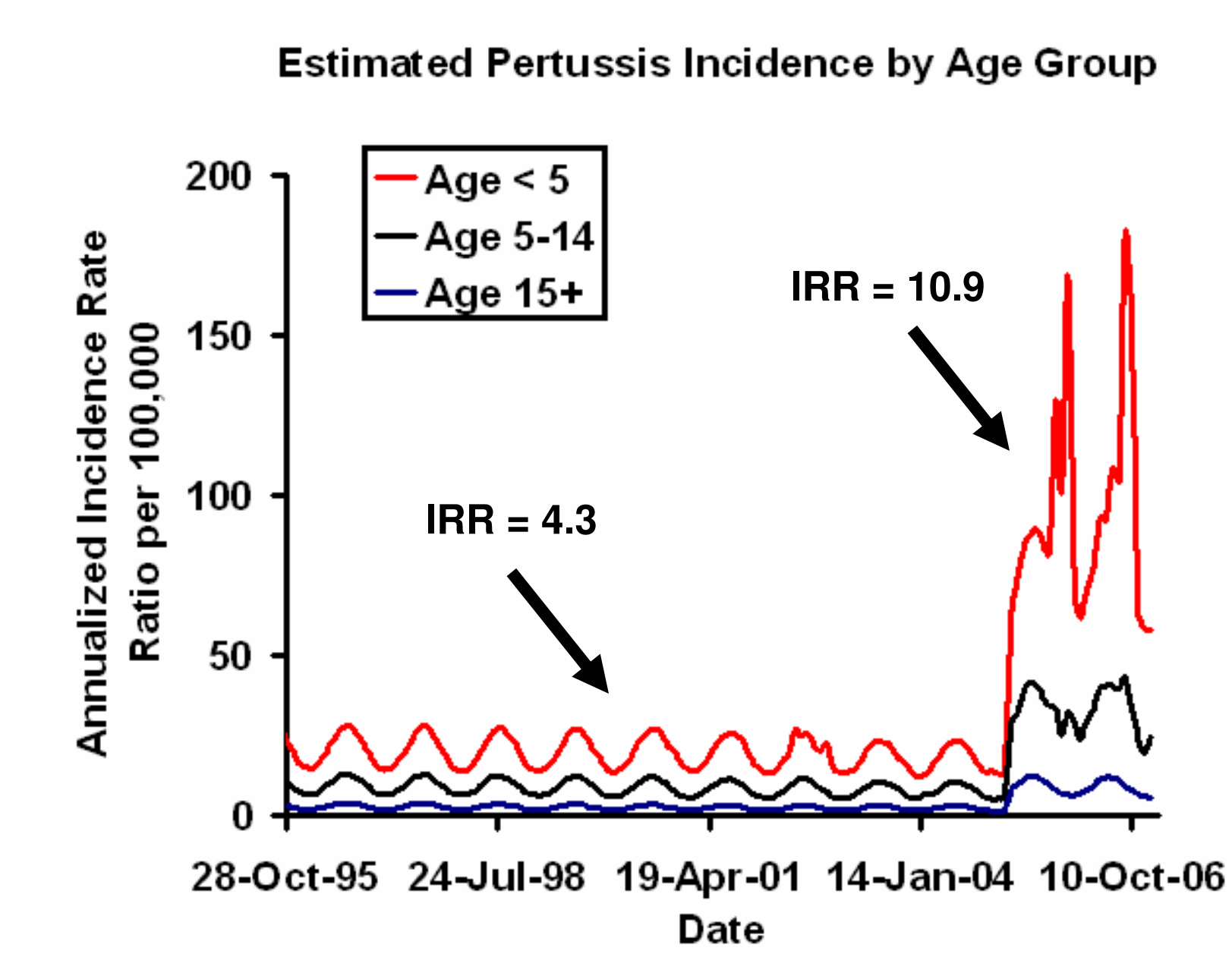


Figure 2. Number of Cases of Pertussis Reported in Different Age Groups in Canada in 1989, 1992, 1996, 2000, and 2004.

Source: Halperin SA, N Eng J Med 2007; 356: 110-3.

Pertussis in Toronto, 2005-2007

- Reported rates of disease in Toronto 6-fold increase since 2004.
  - Cases highly vaccine compliant (94%) [V. Waters et al., CACMID, Halifax 2007].
  - No apparent change in circulating pertussis strains [I. Martin, National Microbiology Laboratory].
  - No increase in severe respiratory illness attributable to pertussis noted in GTA during apparent increase.
  - No apparent change in pertussis hospitalizations in Ontario [J. Kwong, ICES].


Estimated Pertussis Incidence by Age Group
Age < 5
Age 5-14
Age 15+
IRR = 10.9
IRR = 4.3
Annualized Incidence Rate
Ratio per 100,000
200
150
100
50
0
28-Oct-95
24-Jul-98
19-Apr-01
14-Jan-04
10-Oct-06
Date

Pertussis Hospitalizations in Ontario

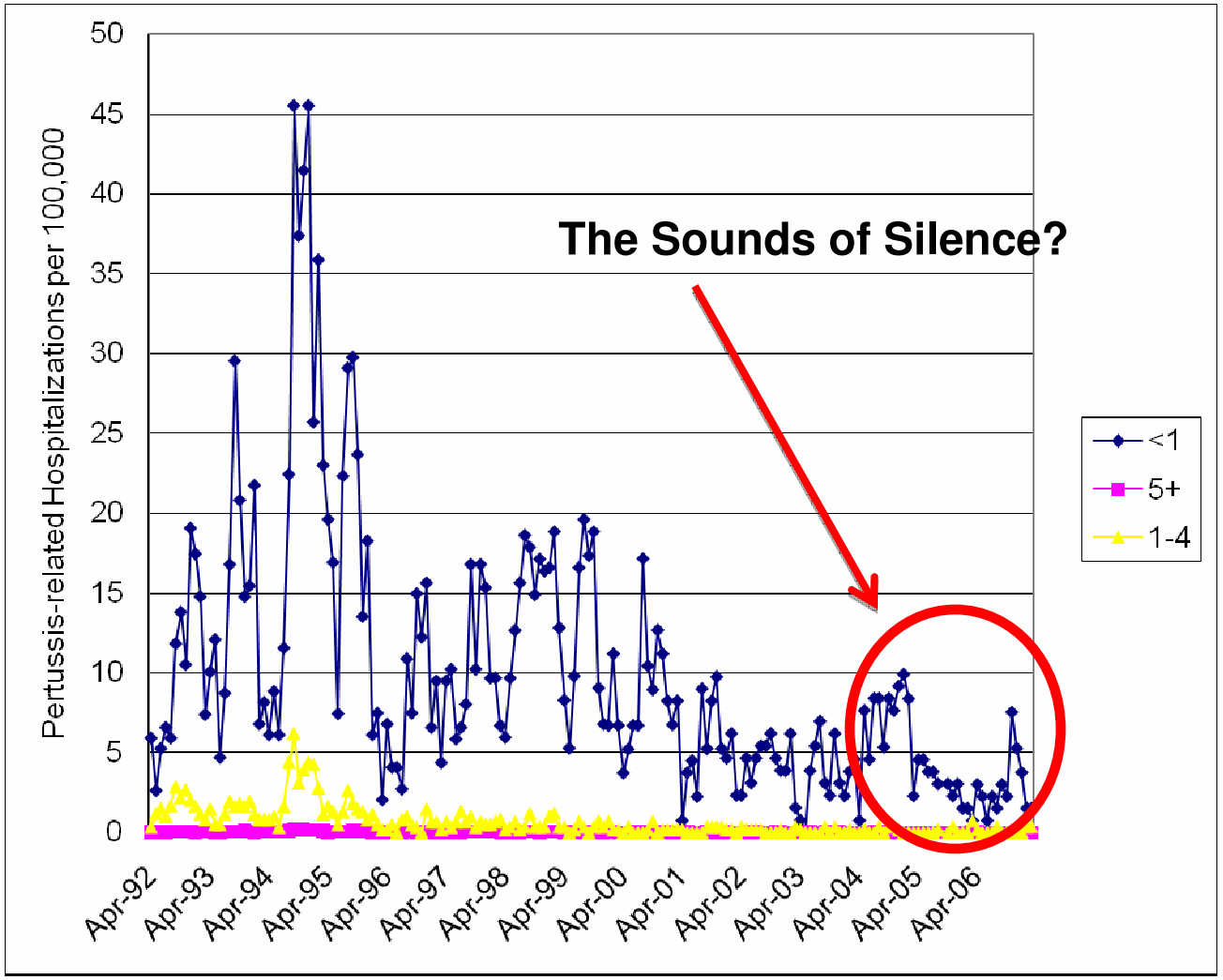


Figure courtesy of Dr. Jeff Kwong, ICES.

MMWR, August 24, 2007

CDC Home | Search | Health Topics A-Z

MMWR Weekly

August 24, 2007 / 56(33);837-842

Outbreaks of Respiratory Illness Mistakenly Attributed to Pertussis --- New Hampshire, Massachusetts, and Tennessee, 2004--2006

Pertussis, or whooping cough, is a highly infectious, nationally notifiable* respiratory disease associated with prolonged cough illness and paroxysms of coughing, inspiratory "whoop," or posttussive vomiting. Reported pertussis cases have tripled in the United States since 2001, with 25,616 probable or confirmed cases reported in 2005 (Figure 1). This increase has been attributed to increased circulation of *Bordetella pertussis*, waning vaccine-induced immunity among adults and adolescents, heightened awareness of pertussis among health-care providers, increased public health reporting, and increased use of polymerase chain reaction (PCR) testing for diagnosis (*1*). To minimize the spread of pertussis, control measures must be implemented early in the course of illness when the risk for transmission is highest. However, diagnosis of pertussis is complicated by nonspecific signs and symptoms, particularly in the early catarrhal stage of disease. In addition, the lack of rapid, sensitive, and specific laboratory tests makes early and accurate identification of pertussis challenging. This report describes two hospital outbreaks and one community outbreak of respiratory illness during 2004--2006 in New Hampshire, Massachusetts, and Tennessee that were attributed initially to pertussis. However, subsequent investigations revealed negative or equivocal laboratory results and epidemiologic and clinical features atypical of pertussis, suggesting that pertussis was not the cause of these outbreaks. The findings in this report underscore the need for thorough epidemiologic and laboratory investigation of suspected pertussis outbreaks when considering extensive control measures.

New Hampshire. In March 2006, a laboratory worker from a 396-bed hospital visited the occupational medicine clinic with a 3-week history of paroxysmal cough and posttussive vomiting. The laboratory worker tested positive with the hospital's single-target PCR assay for pertussis (IS*481*).† The worker subsequently was treated with azithromycin and furloughed for 5 days. Postexposure prophylaxis (PEP) with azithromycin was administered to all close contacts. Case investigation from mid-March to early April identified 15 additional health-care personnel (HCP) in the same laboratory with respiratory illness and either a positive

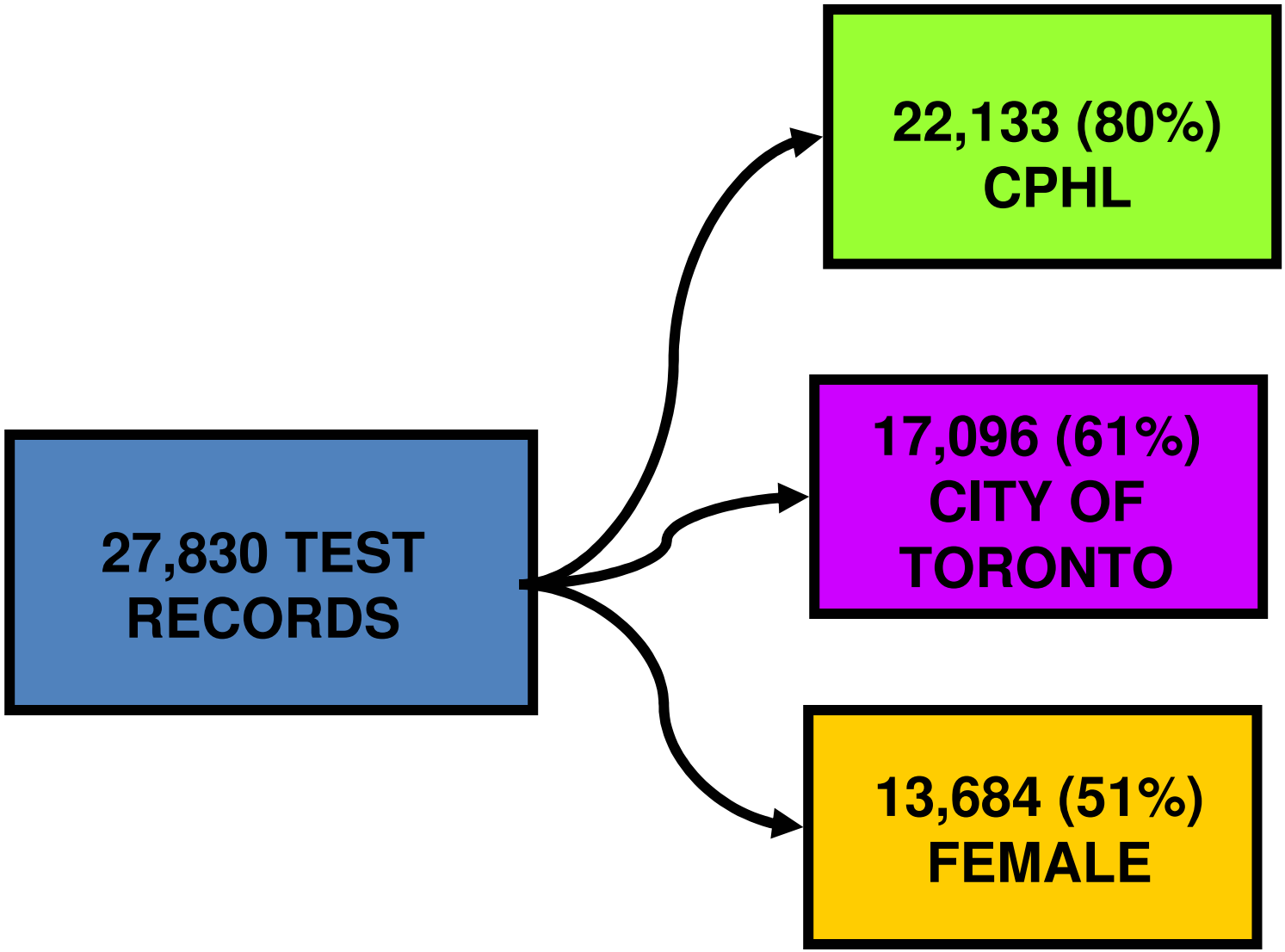
Pertussis in GTA: What Gives?

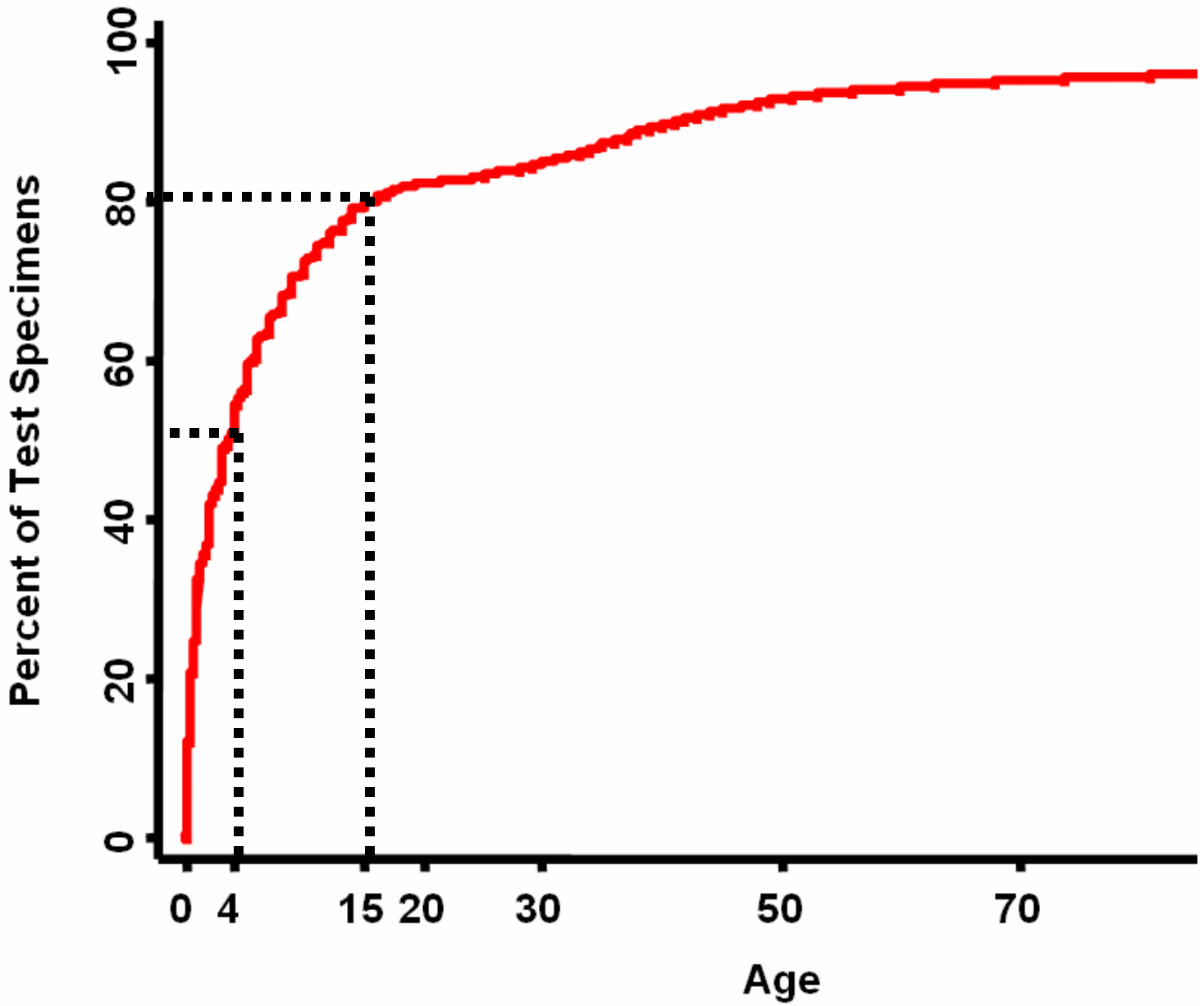
- Investigation: all pertussis testing in GTA performed at only **2 laboratories** (CPHL and SickKids).
- Pertussis testing records obtained from CPHL (1/1993-1/2007) and SickKids (10/1999-1/2007).
  - CPHL: parallel culture and PCR on all submitted sputum specimens.
    - PCR introduced 1/1999.
    - RT-PCR with probe in 5/2005 (increased sensitivity).
  - SickKids: qualitative IS481 PCR on all specimens.

Objectives

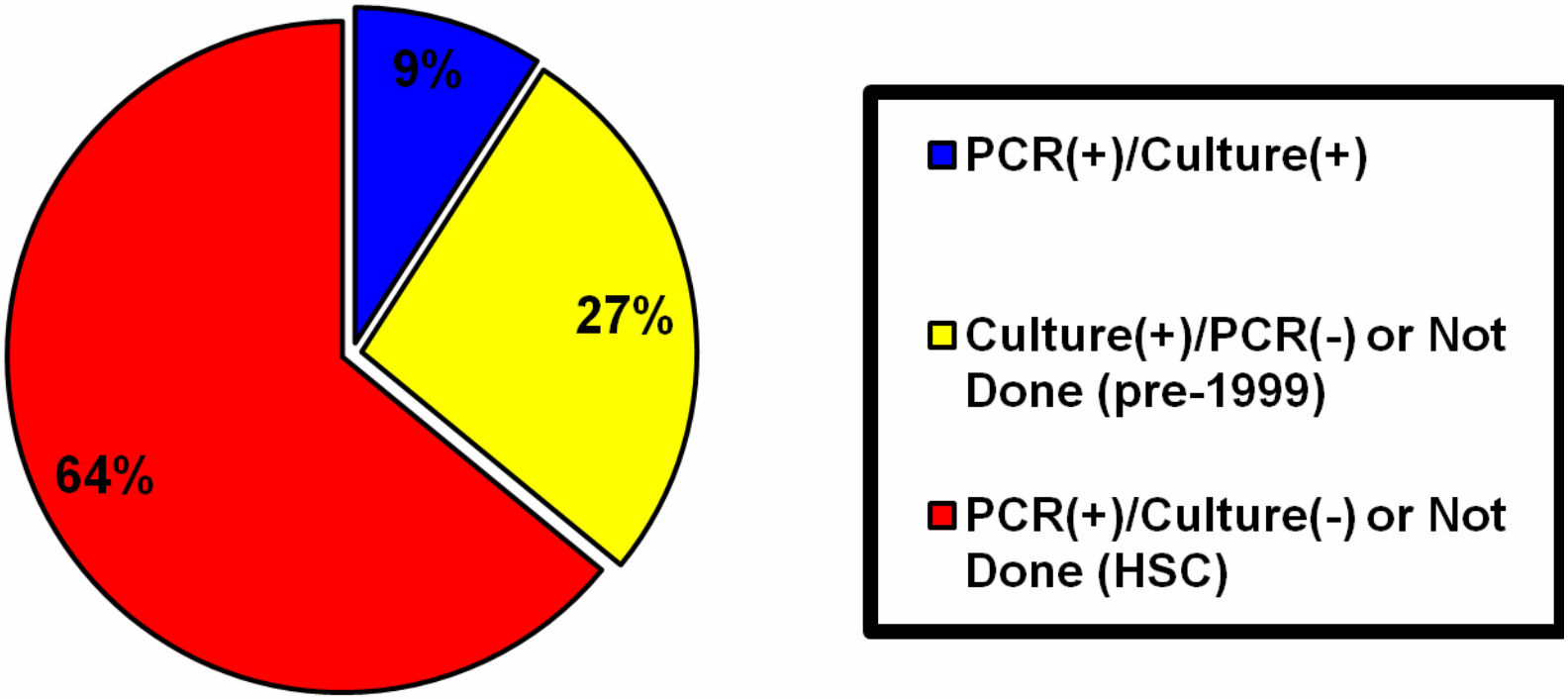
1. To evaluate trends in pertussis occurrence in the Greater Toronto Area using all available data on respiratory specimen testing.
    1. Control for changing testing patterns.
    2. Evaluate impact of changing diagnostic technologies.

Results

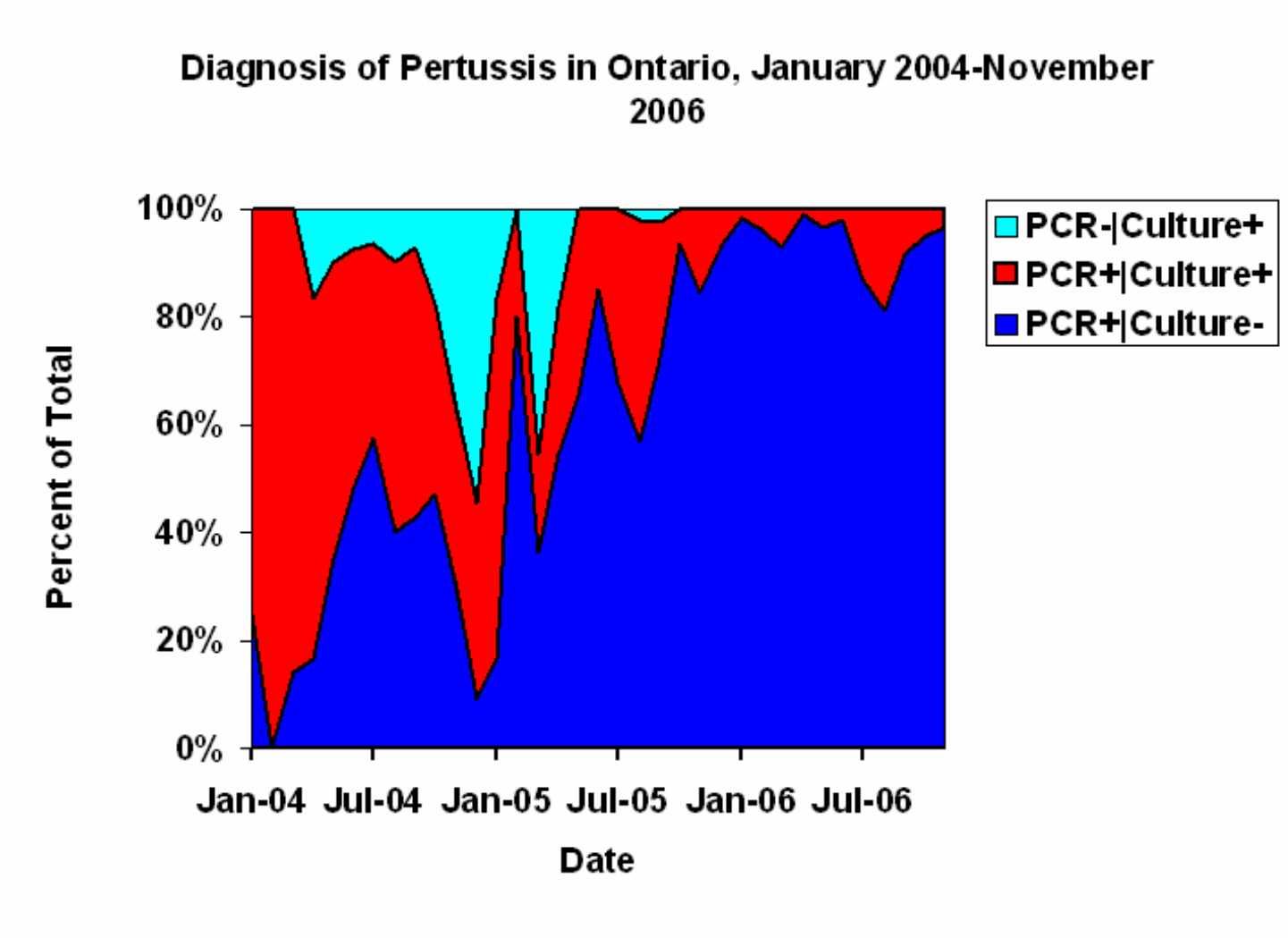

27,830 TEST RECORDS
22,133 (80%) CPHL
17,096 (61%) CITY OF TORONTO
13,684 (51%) FEMALE

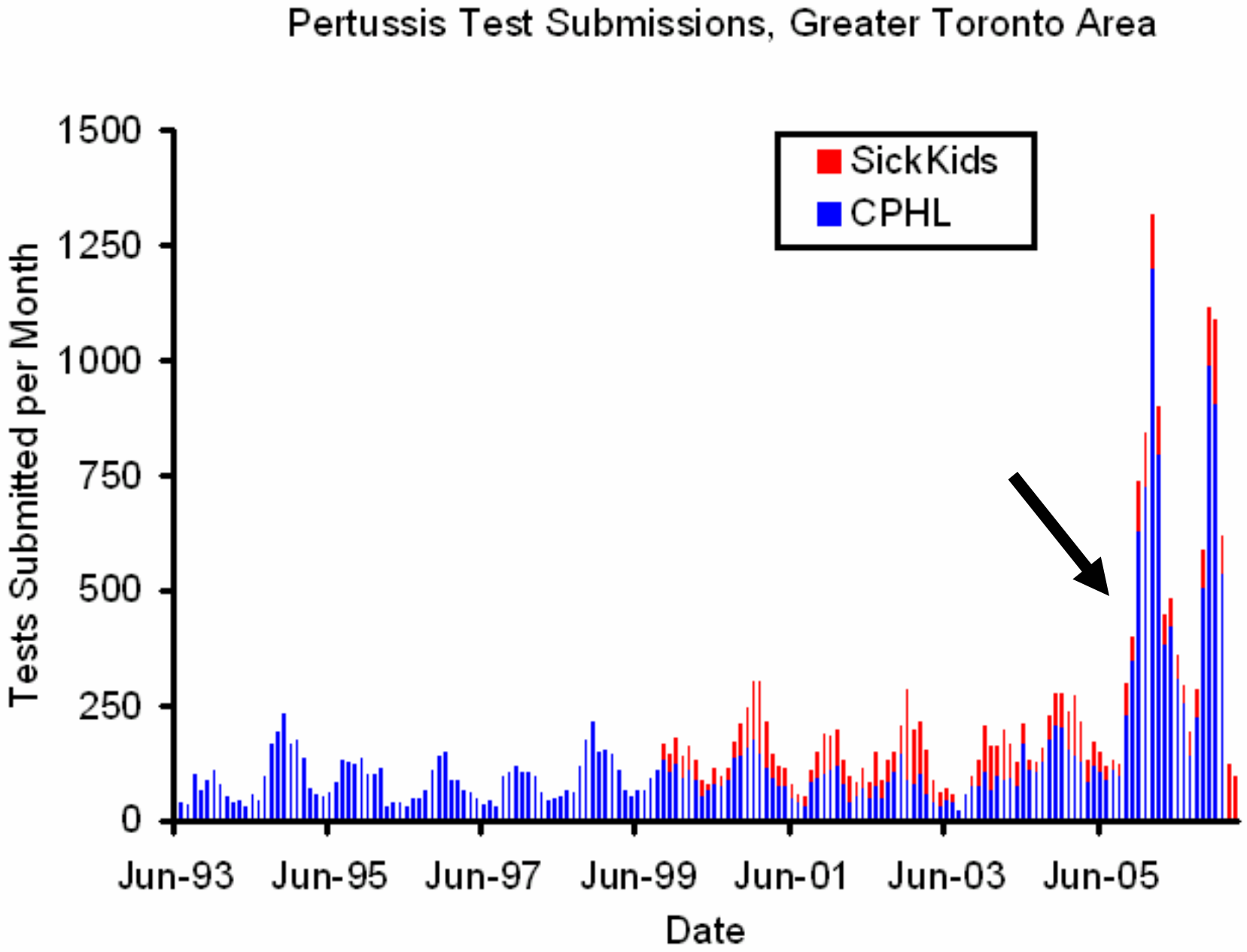

Percent of Test Specimens
0
20
40
60
80
100
0
4
15
20
30
50
70
Age

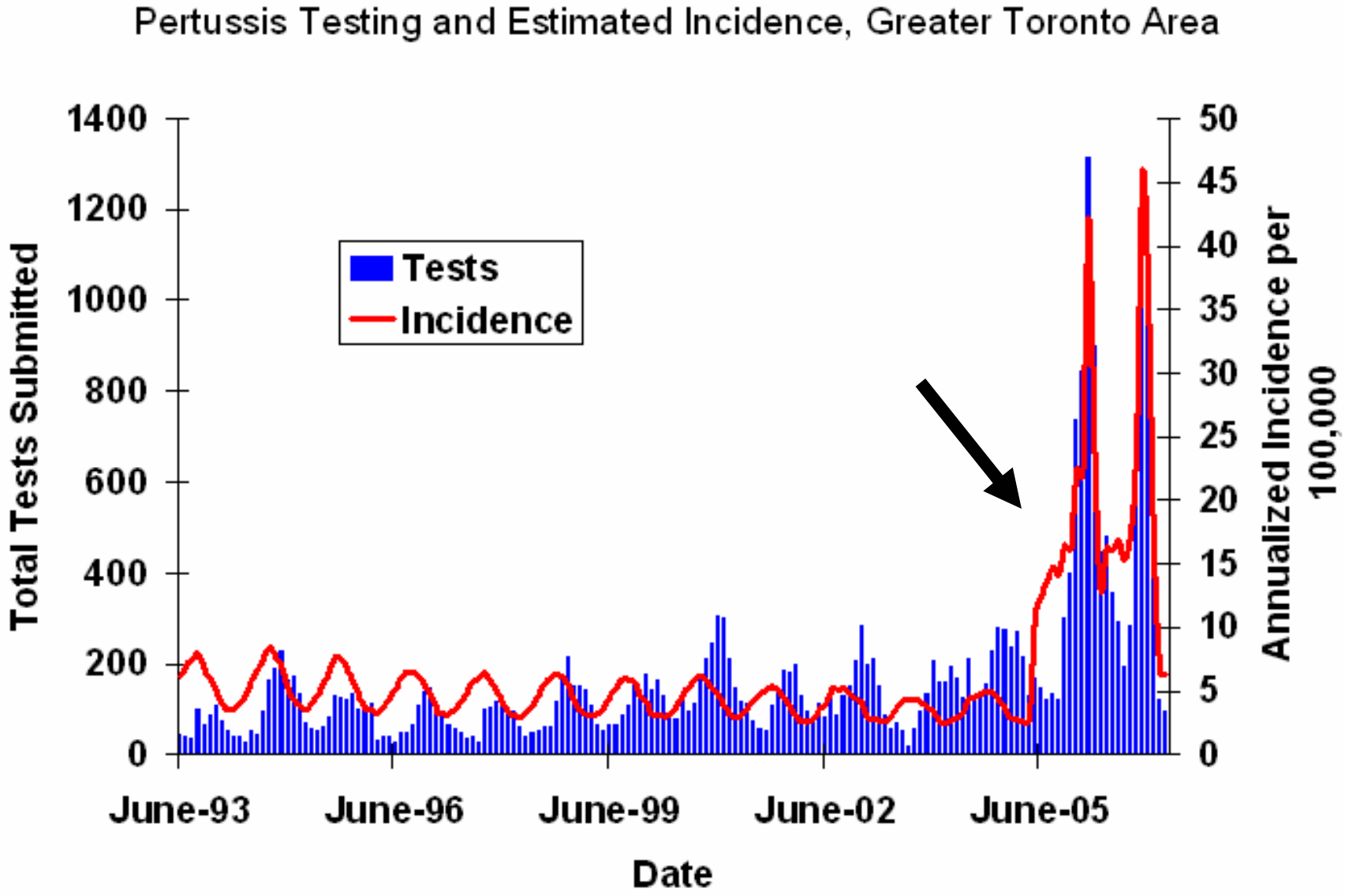
2,554 (9.2%) Positive Tests



Changing Source of "Test Positivity", 2004 to 2006



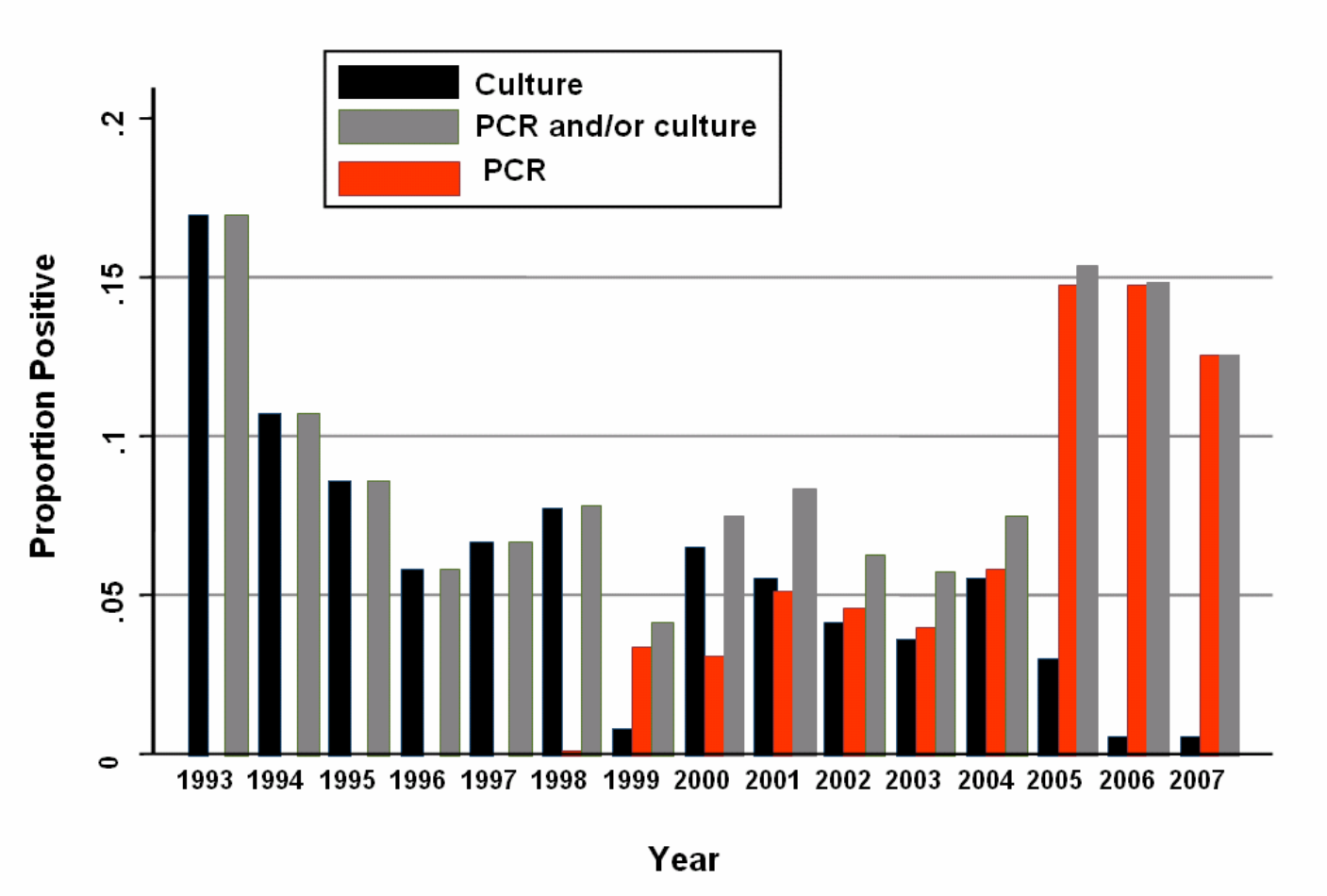

Pertussis Test Submissions, Greater Toronto Area
SickKids
CPHL
Tests Submitted per Month
1500
1250
1000
750
500
250
0
Jun-93
Jun-95
Jun-97
Jun-99
Jun-01
Jun-03
Jun-05
Date


Pertussis Testing and Estimated Incidence, Greater Toronto Area
Total Tests Submitted
1400
1200
1000
800
600
400
200
0
Tests
Incidence
50
45
40
35
30
25
20
15
10
5
0
Annualized Incidence per 100,000
June-93
June-96
June-99
June-02
June-05
Date

Poisson Model

	Exclude Testing	Include Testing
PARAMETER	**IRR (95% CI)**	**IRR (95% CI)**
Sin(Month)	0.88 (0.83 to 0.94)	0.73 (0.68 to 0.77)
Cos(Month)	1.21 (1.15 to 1.28)	0.87 (0.81 to 0.93)
Year	0.96 (0.95 to 0.98)	0.95 (0.93 to 0.97)
Date > 4/2005	5.84 (5.09 to 6.69)	3.18 (2.72 to 3.72)
Test Volume (per 100 specimens)	—	1.16 (1.15 to 1.18)
Pseudo-R^2	0.50	0.61

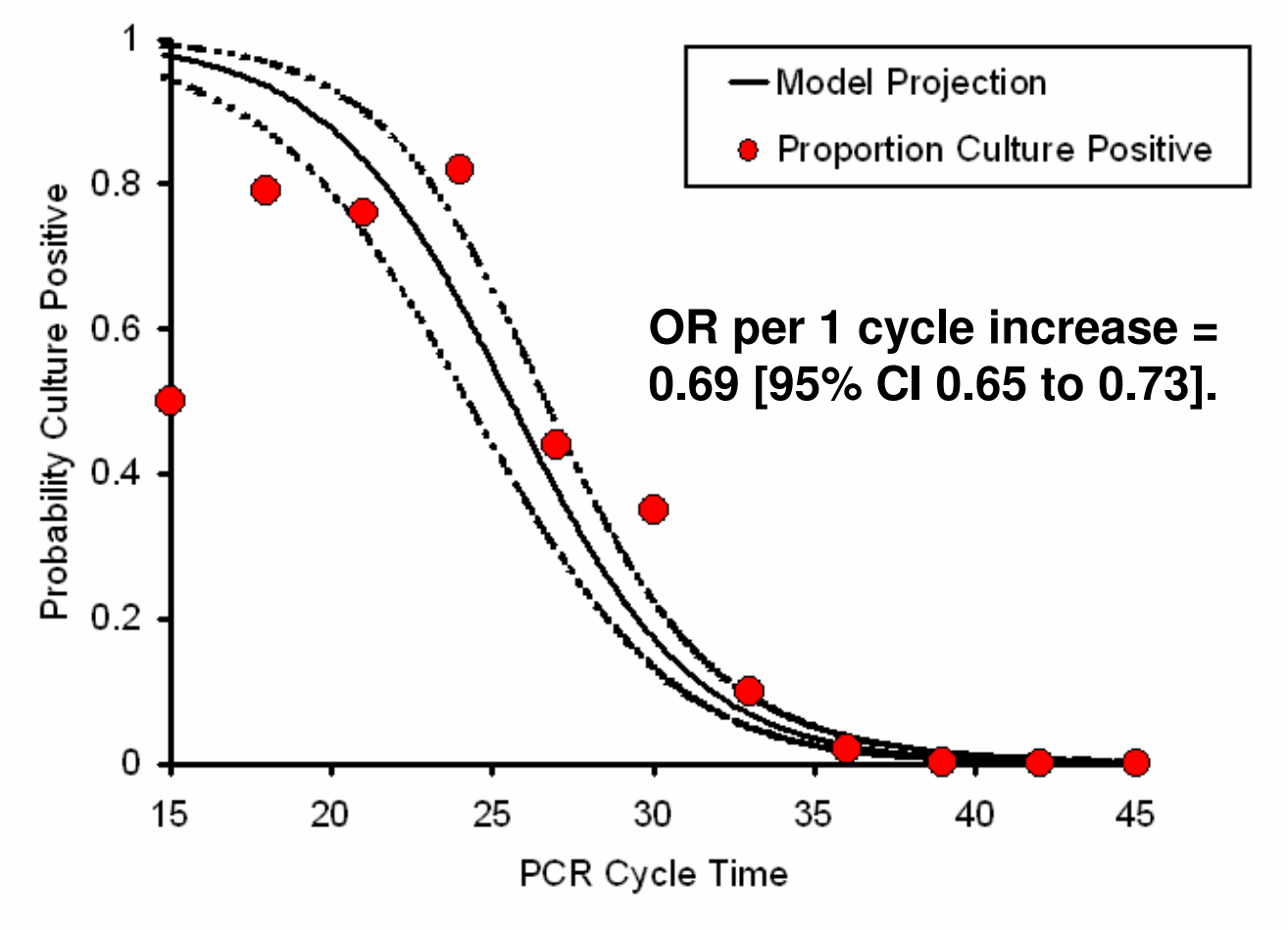
Per-Submission Test Positivity



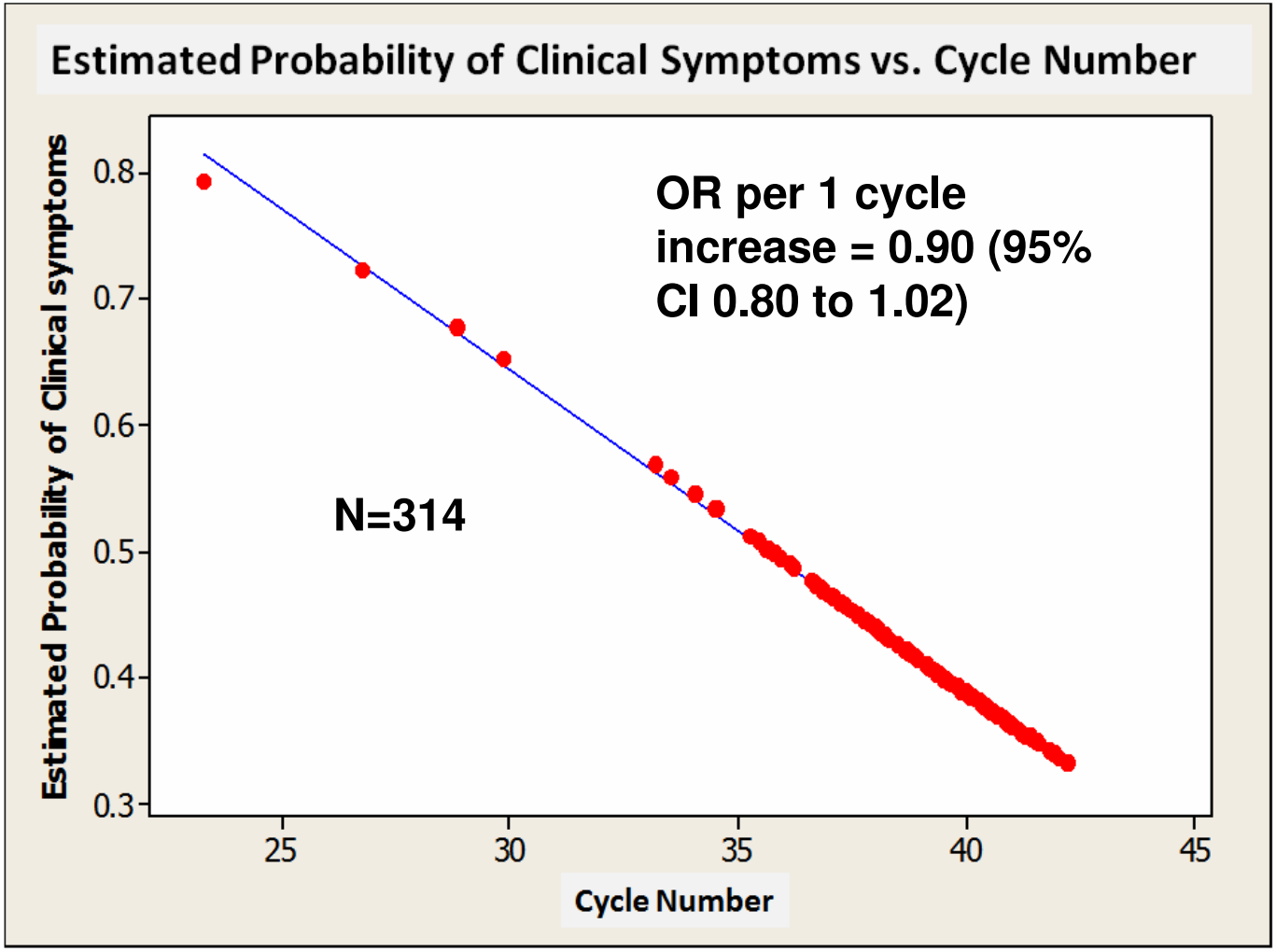
Autoregressive Models

- Number of monthly test positives highly predictive of subsequent month's test submissions *(P*=0.009).
  - Number of test submissions poorly predictive of subsequent month's positives (*P*=0.19).
- Strong evidence for causality by Granger's test (*P*<0.001).

Relationship Between Culture and Quantitative PCR Positivity (RT-PCR)



Relationship Between Quantitative PCR-Positivity and WHO-Defined Clinical Pertussis



Conclusions

1. Increase in pertussis incidence in Toronto, 2005-2007, likely represents combination of factors:
    1. Changing testing technologies.
    2. Healthcare provider response to increased test positivity.
    3. Persisting periodicity of disease occurrence

Conclusions (2)

2. Challenges of the “NAAT revolution”:
    1. Absent gold standards.
    2. Redefining spectrum of disease (vs. infection):
        1. Disease reflects high burden of infection or inability of immune response to control infection/toxin load?
    3. Extends beyond pertussis: latent class modeling as an emerging tool (stolen from social sciences).

Conclusions (3)

3. In contrast to surges in measles, mumps, and rubella associated with declining vaccine uptake, increased pertussis incidence may represent a PH “success” (?!):
    1. Vaccine protection prevents disease or high-level carriage among infected individuals.
        1. Improved test sensitivity...identifying the “missing” infected individuals imputed in other models and seroprevalence studies?

Conclusions (4)

- Not all positive: major challenges to PH with respect to resources, anxiety, and population antimicrobial exposure (prophylaxis).

Conclusions (5)

- The PH laboratory as an epidemiological resource:
  - Parallel tests permit nuanced evaluation of disease trends and assessment of impact of technological change.
  - Test *denominators*: critical but seldom available.
  - Other complexity not presented here: phenotypic information (e.g., antibiotic resistance), genotypic information.