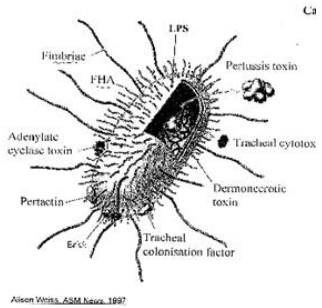
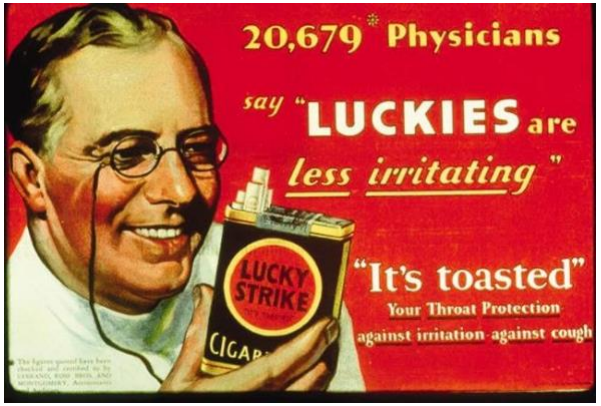
Pertussis

Gary Reubenson

10 September 2014



Conflicts of Interest



- Sanofi
  - Local Conference support
  - Study sponsor
- Pfizer
  - Local & International Conference Support
  - Speakers fee
- Abbvie
  - Speakers fee

Overview

- History
- Epidemiology
- Investigation
- Management
- South African Experience
- What now?
- Questions

History

First described in Paris, 1578

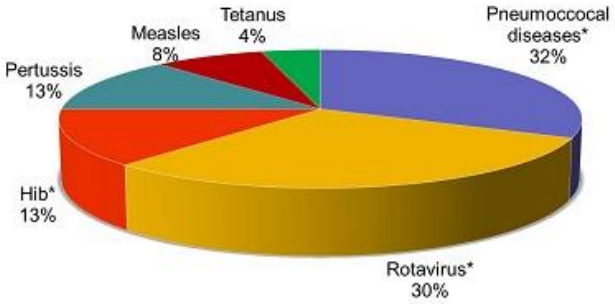
Guillaume de Baillou:

‘The lung is so irritated that, in its attempt by every effort to cast forth the cause of the trouble, it can neither admit breath nor easily give it forth again. The sick person seems to swell up, and, as if about to strangle, holds his breath clinging in the midst of his jaws…’

History

- First isolated in 1906 by Bordet & Gengou
  - Fastidious, fimbriated, Gram-negative bacilli
- 1920s: first whole-cell vaccines
- 1942: combined to form DTwP
- 1974: Added to EPI
- 1981: first acellular vaccine (aP)
- 2004: complete genome sequenced (±8m bp)

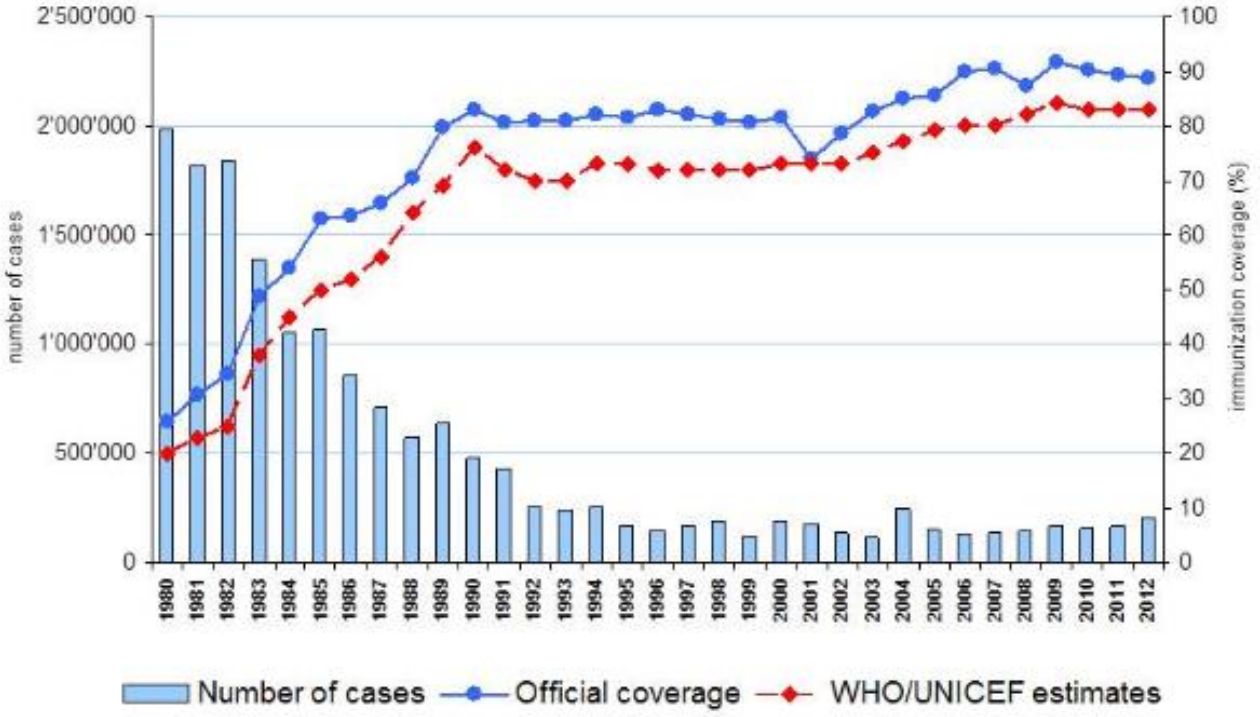
Epidemiology



Source: Black RE et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010 Jun 5;375(9730):1969-87. Epub 2010 May 11.
* WHO/IVB estimates

- Highly contagious (R_0 = 12-17)
- No lifelong immunity
- Droplet & Respiratory Spread
- Incubation 5-10d (up to 21d)
- Classic Pattern:
  - Catarrhal → Paroxysmal → Convalescent
- Exclusively human disease
- WHO Estimates (2008):
  - >16m cases, 95% in developing countries, 195 000 deaths (2012: 125 344) – vast majority <1y
  - 82% vaccine coverage, 687 000 deaths averted

Pertussis global annual reported cases and DTP3 coverage, 1980-2012



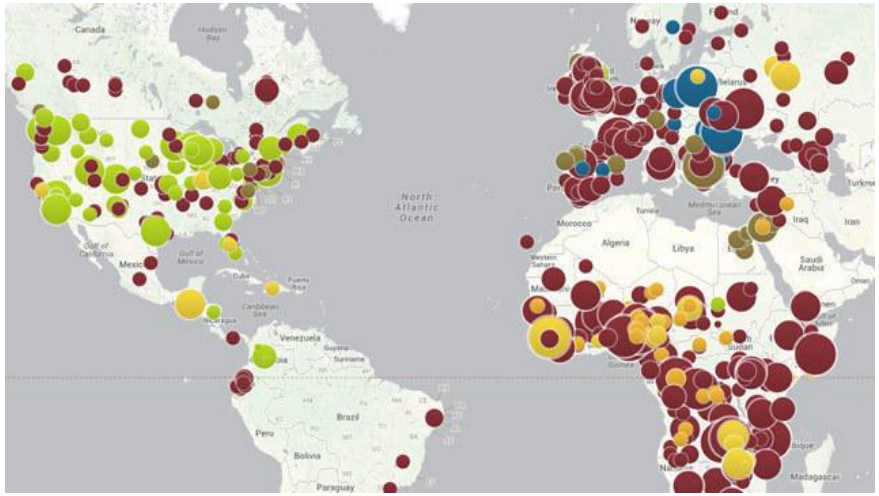
Source: WHO/IVB database, 2013
194 WHO Member States.
Data as of July 2013

Date of slide: 23 July 2013

WHO

http://www.who.int/immunization_monitoring/diseases/pertussis/en/index.html (July 2013)

Epidemiology



- Peaks every 3-5y
- Adults & adolescents main source of infection
- Increasing incidence in UK, France, USA, etc.
  - Waning immunity (aP *vs.* wP)
  - Limited subclinical boosting
  - Vaccine evasion
- Less severe in vaccinated individuals

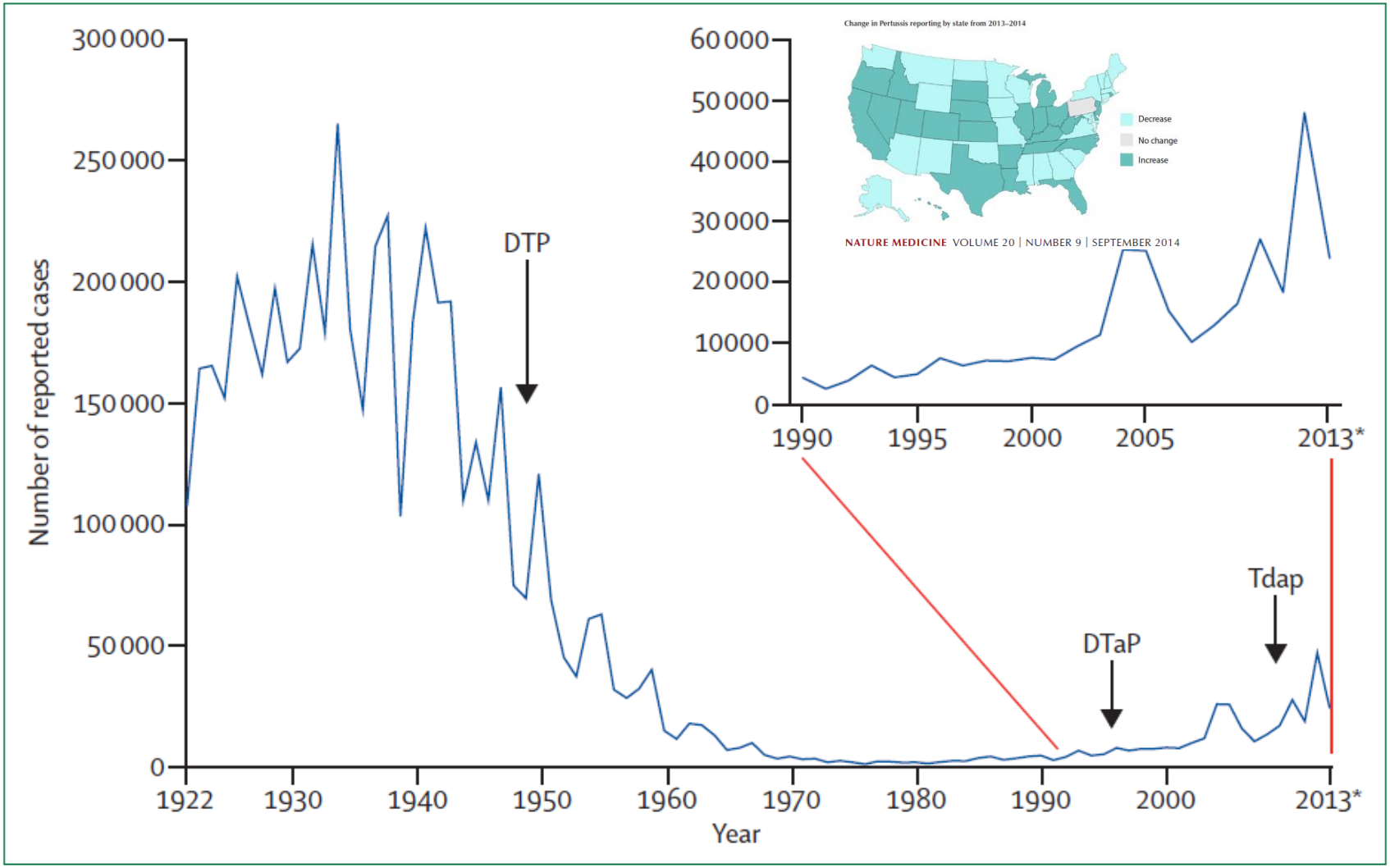


Figure 1: **US pertussis cases reported between 1922 and 2013***

DTP=diphtheria and tetanus toxoids and whole-cell pertussis vaccine. DtaP=diphtheria and tetanus toxoids and acellular pertussis vaccine, adsorbed. Tdap=tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed. *2013 data are provisional. Data source: Centers for Disease Control and Prevention, National Notifiable Diseases Surveillance System, Supplemental Pertussis Surveillance System 1922–49, passive reports to the Public Health Service (http://www.cdc.gov/nndss).

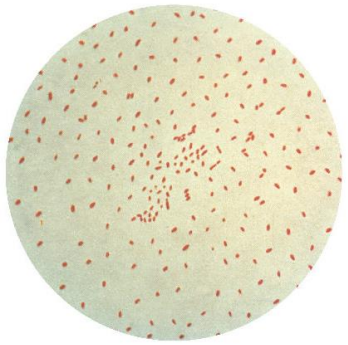
Lancet 2014; 384: 53–63

Healthcare Providers as Sources

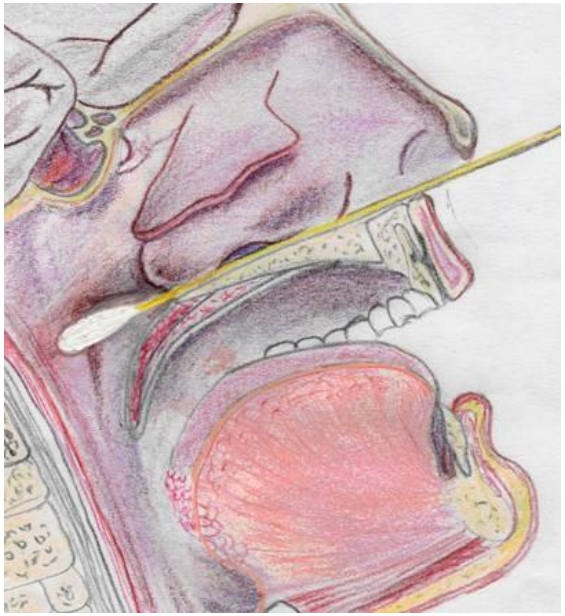
- Transmission to patients well described
- Initiated outbreaks
- ACIP:
  - Recommends Tdap as a one-time booster
    - Unknown duration of protection
  - Post exposure prophylaxis (regardless of vaccination status) – generally azithromycin

Vaccine 32 (2014) 4814–4822

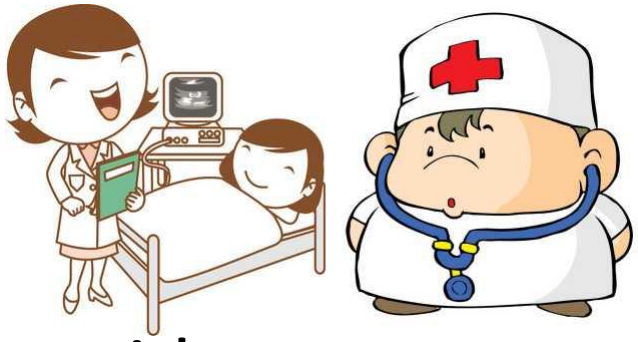
Investigation



- Culture (BG/RL)
  - Insensitive
  - Most useful early
- PCR: Dacron/Rayon swab of posterior NP
  - PtxA
  - IS481:
    - 50-238 copies per genome in *B pertussis*
    - 8-10 copies per genome in *B holmesii*
    - Occasionally in *B bronchiseptica*
  - IS1001: *B parapertussis*
  - hIS1001: *B holmesii*
- Serology
  - Low sensitivity and specificity
  - Very high levels may be of value with prolonged symptoms



Management



- Largely supportive, though no evidence to support opioids or antihistamines

- Antibiotics (usually macrolide)
  - Effective if used early (catarrhal or ?early paroxysmal stages)
  - Generally prescribed to reduce infectivity (21→5d)

- Appropriate Infection Prevention & Control

Prevention

- Chemoprophylaxis
  - Family & close contacts
  - Questionable efficacy
  - Not if >21d since onset of cough
- Vaccination
  - wP, aP & ap
  - 1/2/3/4/5 components
  - Many countries adding booster doses to children, adolescents and pregnant women

- Pentaxim®:
  - Pertussis toxoid + filamentous haemagglutinin
  - NOT: Pertactin or either fimbrial agglutinogens
  - 6, 10 & 14 weeks and 18 months
- June 2011, ACIP recommended routine immunisation of pregnant women
  - All women
  - Every pregnancy
- ‘Cocooning’ – expensive & logistically challenging

Maternal Vaccination

- Why?
  - Increases transplacental Ab
  - Mothers often inadvertently transmit to infants
  - Infants vulnerable pre-vaccination
- When?
  - Pre- vs. Postpartum
  - Optimally 30-32 weeks
- ?Reduces Ab response when infant immunized
  - Slightly, but likely insignificant

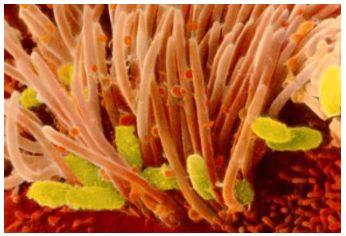
July 28, 2012 | World News | Placebo

Whooping Cough Cases On the Rise in Canada and the US

I was a big fan of the anti-vaccine movement.
Until I got really sick....

Exposure to antigens

1960		1980		2010	
Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins / polysaccharides
Diphtheria	1	Diphtheria	1	Diphtheria	1
Tetanus	1	Tetanus	1	Tetanus	1
Pertussis (wP)	3000	Pertussis (wP)	3000	Pertussis (aP)	2–5
Polio	15	Polio	15	Polio	15
				Hib	2
				Hepatitis B	1
				Pneumococcus	14
Smallpox	200				
		Measles	10	Measles	10
		Mumps	9	Mumps	9
		Rubella	5	Rubella	5
				Varicella	69
Total	3217	Total	3041	Total	128–131

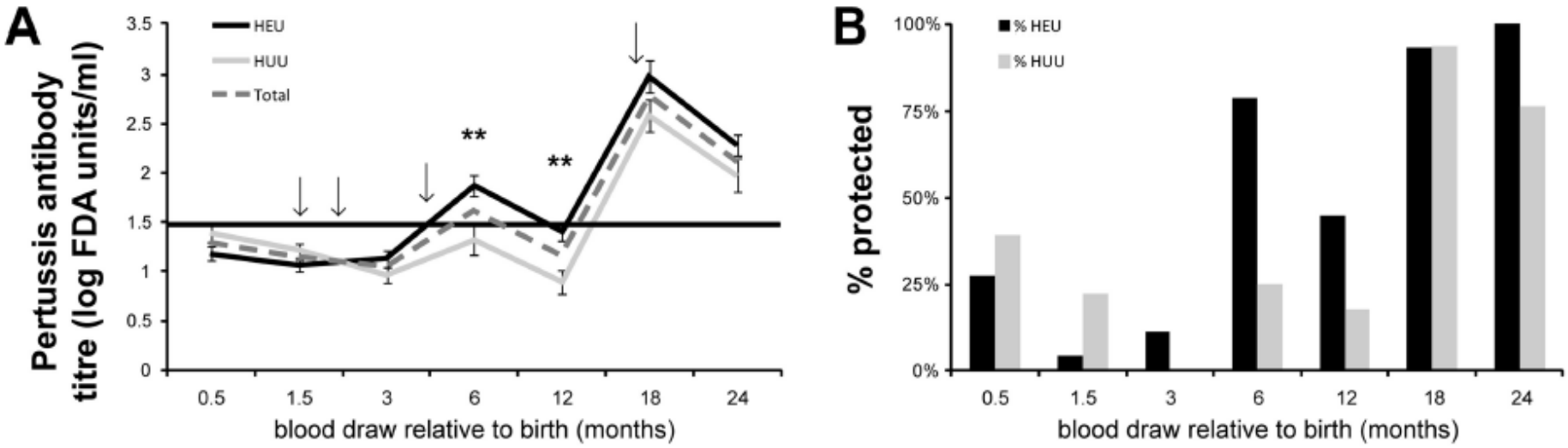


Adapted from Offit *et al*. *Pediatrics* 2002;109:124–9

Effect of HIV Exposure on Vaccination

Antibody Responses to Vaccination among South African HIV-Exposed and Unexposed Uninfected Infants during the First 2 Years of Life

Brian A. Reikie,[a,e] Shalena Naidoo,[b] Candice E. Ruck,[a] Amy L. Slogrove,[a,d] Corena de Beer,[c] Heleen la Grange,[c] Rozanne C. M. Adams,[b] Kevin Ho,[a] Kinga Smolen,[a] David P. Speert,[a] Mark F. Cotton,[d] Wolfgang Preiser,[c] Monika Esser,[b] Tobias R. Kollmann[a]



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IDSA
Infectious Diseases Society of America

hivma
hiv medicine association

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The Journal of Infectious Diseases

Prevention and Control of Pertussis

A Supplement to *The Journal of Infectious Diseases*

The Journal of
Infectious Diseases

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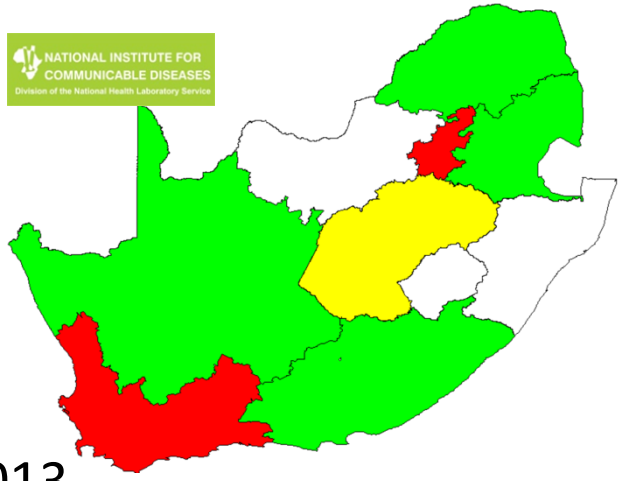
PREVENTION AND CONTROL OF PERTUSSIS

SA Experience



- Historical
- Bloemfontein
  - Clinician initiated, April 2008-March 2013
- Cape Town
  1. Retrospective Folder Review, May 2009-December 2012
  2. Prospective Case-control Sept 12-Sept 13
- Johannesburg
  - CHBAH (PERCH)
    - Case-control study, August 2011-13
  - RMMCH (NHLS)
    - Surveillance study from August 13
- National
  - Public & Private Sector LIS

WHOOPING COUGH IN SOUTH AFRICA *

ITS OCCURRENCE AND CONTROL

DAVID ORDMAN, B.A., M.B., CH.B., CAPE TOWN, D.P.H., RAND.
The South African Institute for Medical Research, Johannesburg.

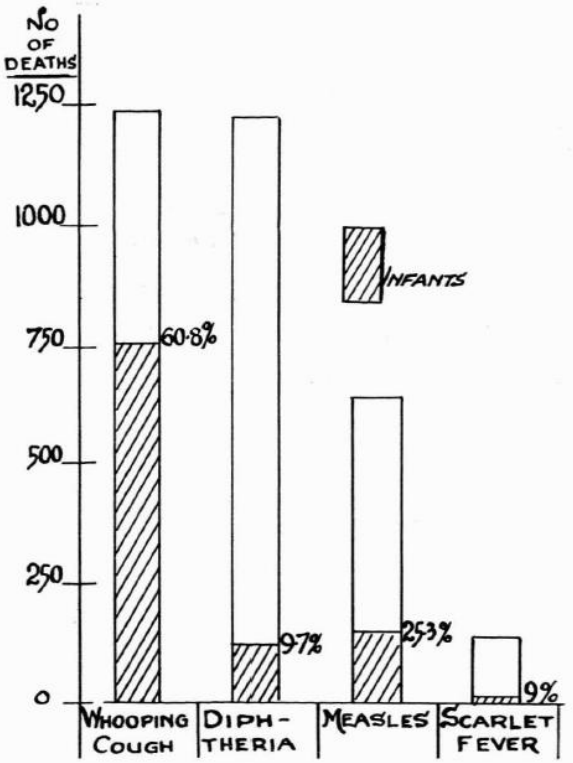


Fig. 4. An analysis of the deaths from whooping cough, diphtheria, measles and scarlet fever in Europeans in the Union of South Africa in the nine-year period 1936-1944. (The infant deaths are shown as hatched portions of the columns.)

1. Statistics of morbidity and mortality in whooping cough are considered to be unsatisfactory in that they underestimate the number of cases and deaths due to the disease.

4. It is considered that whooping cough is too lightly regarded by the public and even by medical men.

12. The question is considered of the immunization of the Native mother in the last months of pregnancy to provide passive antibodies for the new-born baby until it can be adequately protected by the use of a prophylactic vaccine.

Bloemfontein

Pertussis Apr 2008 – Mar 2013

Age	Total n=154 (%)
0-4 weeks	15 (9.7%)
5-16 weeks	63 (40.9%)
17wks – 6 months	22 (14.3%)
7 – 12 months	21 (13.6%)
>12 months	33 (21.4%)

154 cases:
148 *B pertussis*
2 *B parapertussis*
2 dual infection

With Thanks to Ute Hallbauer

Bloemfontein

- 87.4% admitted
- 21.8% to ICU
- 3 deaths (all <4m)
- Only 19 had a history of exposure to someone with a cough!

Age / Days of cough before admission	0-4 weeks n=12	5-16 weeks n=51	≥ 17 weeks n=55
Nil	2 (16.7%)	6 (11.7%)	5 (9.1%)
≤ 7 days	10 (83.3%)	38 (74.5%)	29 (52.7%)
8-14 days	0	3 (5.9%)	7 (12.7%)
≥ 15 days	0	4 (7.8%)	14 (25.5%)

With Thanks to Ute Hallbauer

Cape Town:
Retrospective Folder Review

May 2009-December 2012

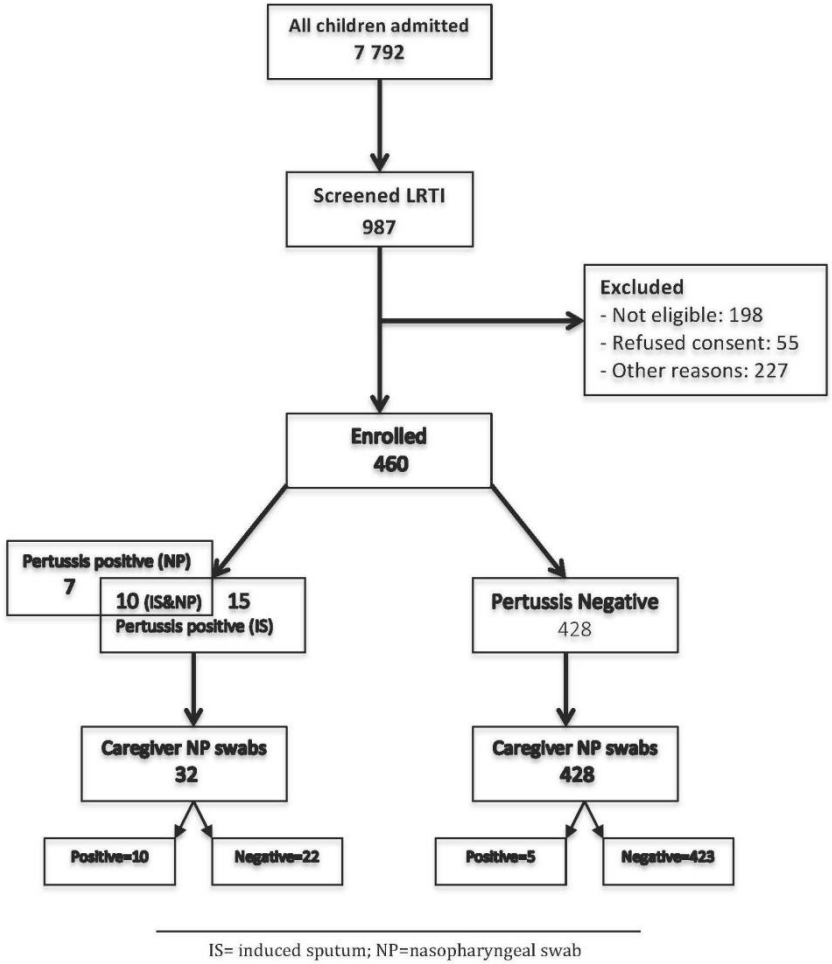
- 75/305 (25%) PCR-positive, only 14 (19%) notified
- Median age 1.8m
- Cough duration median 7d (IQR 3-14d)
- Sensitivity of WHO definition = 31%

With Thanks to Rudzani Muloiwa

Cape Town: Prospective

September 2012-
September 2013

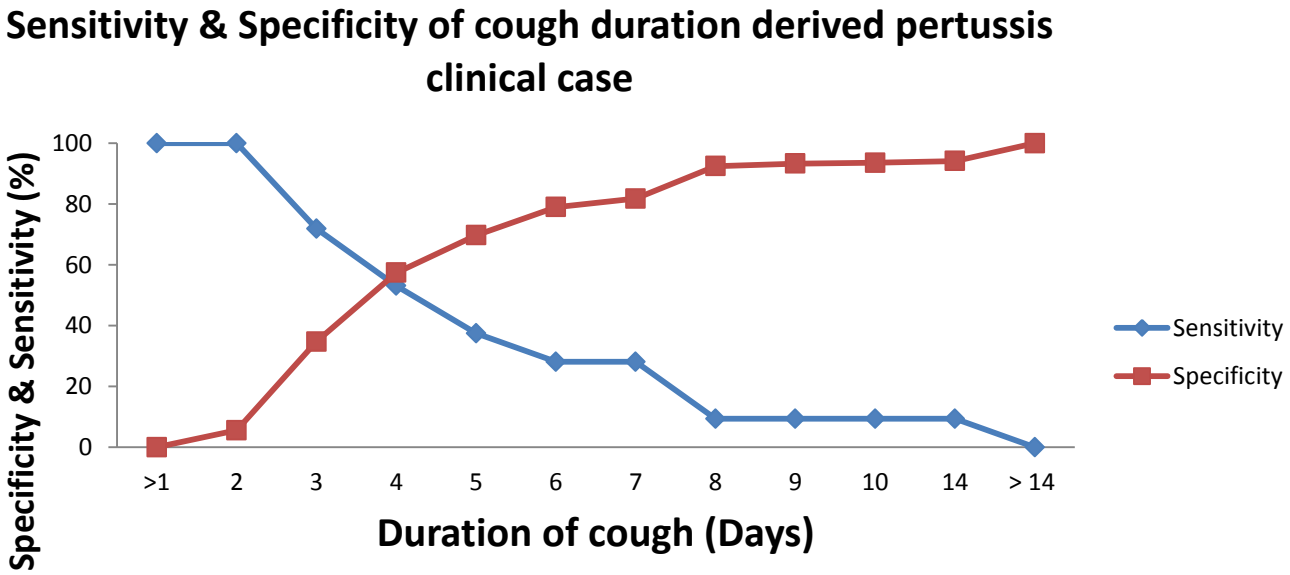
- Inclusion: <13y, <48h after adm, WHO defined pn
- Specimen types – induced sputum & NP swabs
- PCR assays – IS*481*, IS*1001* and hIS*1001*



With Thanks to Rudzani Muloiwa

Cape Town: Prospective

- Median age 8m (IQR 4-18)
- *Bordetella sp*: 41/460 (8.9%)
- *Bordetella pertussis*: 32/460 (7.0%); NP=17/460 (3.7%)
- No strong signal of seasonality
- Caregiver as source: RR = 13 (8-23)



With Thanks to Rudzani Muloiwa

PERCH (Soweto)

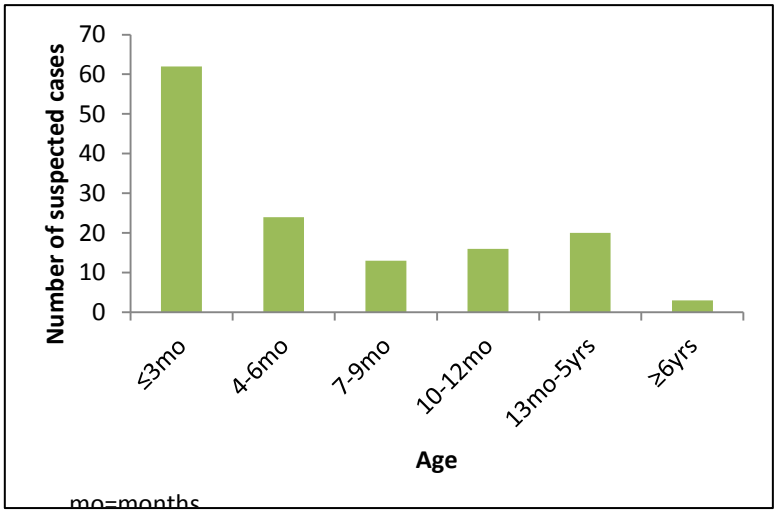
- 2.7% of admissions, 0.5% of controls (OR=6)
- Median cough duration 3d (range 2-15)
- 5 deaths (9.4% of deaths), OR = 4

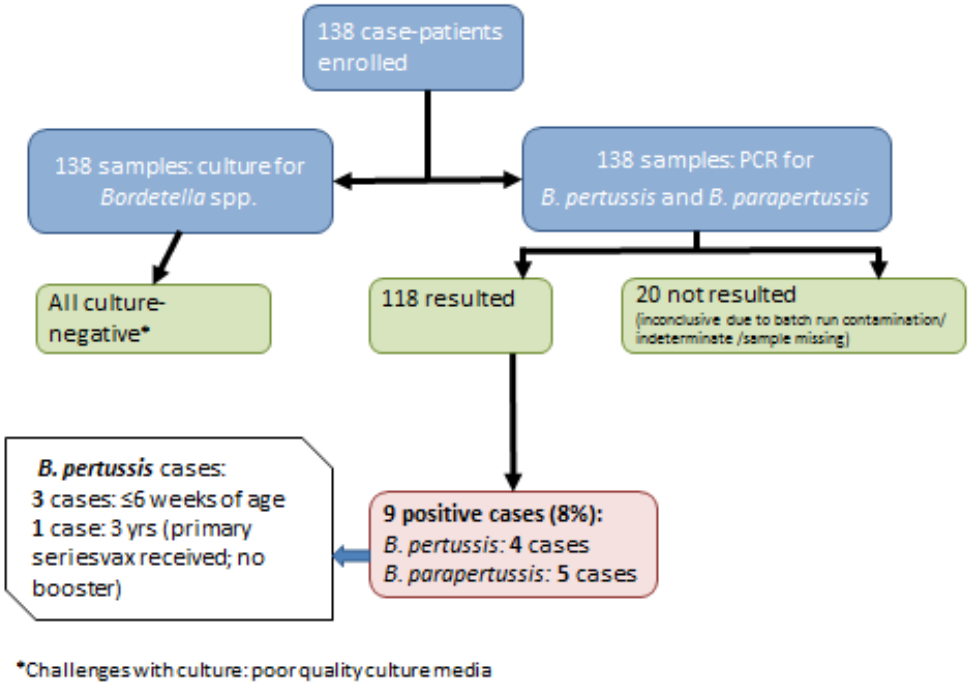
	a	b	c	d
	HIV-negative Case (n=803)	HIV-positive Case (n=116)	Community Control (n=829)	HIV-infected Control (n=135)
Pertussis Pos	23 (2.9%)	2 (1.7%)	4 (0.5%)	0 (0%)
Pertussis Neg	780	114	825	135
Statistical Comparisons				
a,b	OR 1.68 (95% CI, 0.41-14.9), P=0.759			
b,d		P=0.213		
c,d			P=1.000	
a,c	OR 6.01 (95% CI, 2.06-24.28), P<0.001			

With Thanks to David Moore

RMMCH: Prospective

- Enrolled if hospitalised since 15 August 2013 AND:
  - ≤ 10y and Cough ≥ 7d or Cough with any of paroxysms, whoop, apnoea, cyanosis, hypoxia or gagging; OR
  - ≤ 1y with apnoea

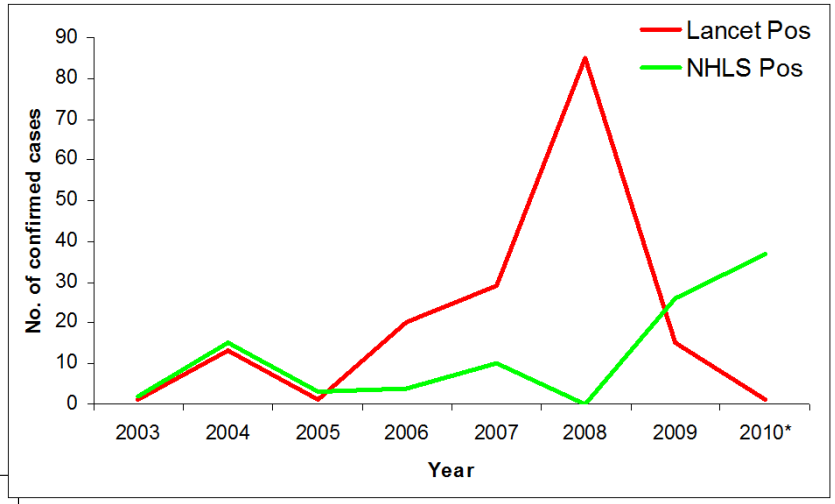


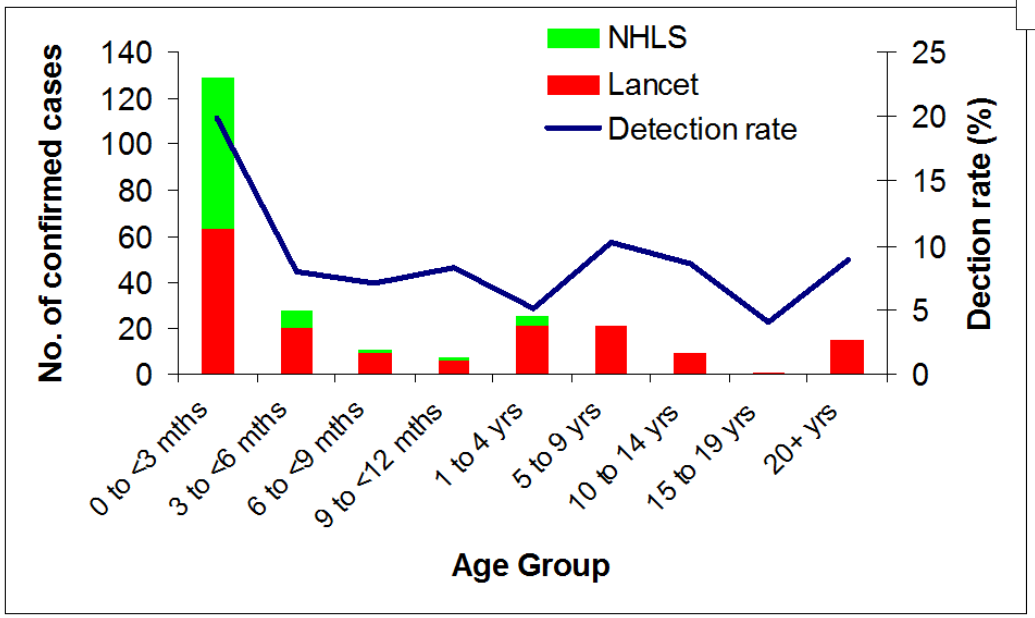


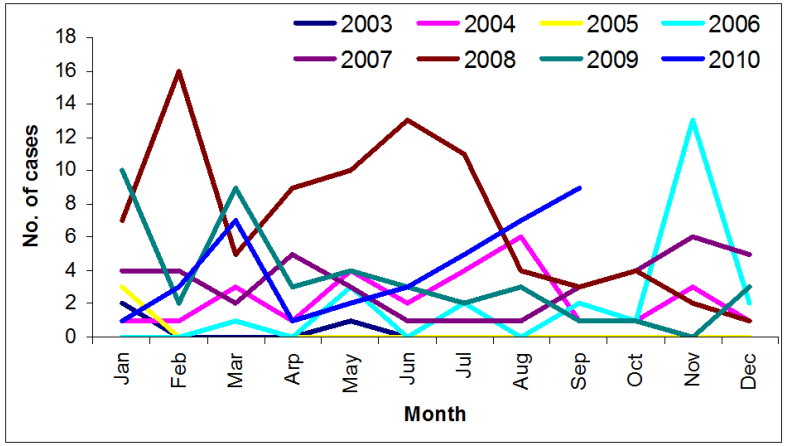
With Thanks to Juno Thomas

Public & Private Sectors (2003-10)

Lab	No. of cases				Detection Rate
	Suspected & tested	PCR +	Culture +	Total confirmed	
NHLS	734	82	15	97	13%
Lancet	1615	165	-	165	10%
Ampath	985	155	-	155	16%
Total	**3334**	**402**	**15**	**417**	**13%**







With Thanks to Juno Thomas

LABORATORY-CONFIRMED PERTUSSIS IN THE PUBLIC HEALTH SECTOR, 2008-2011

Brett Archer[1] Warren Lowman[2,3], Ranmini Kularatne[3,4], Gary Reubenson[5], Juno Thomas[1]
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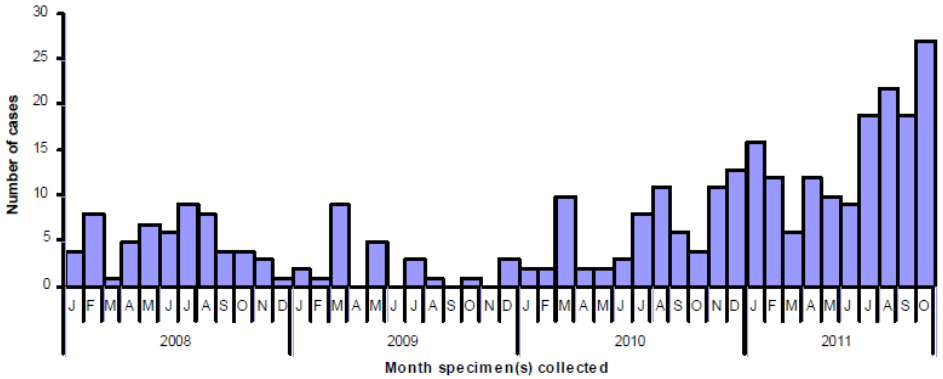
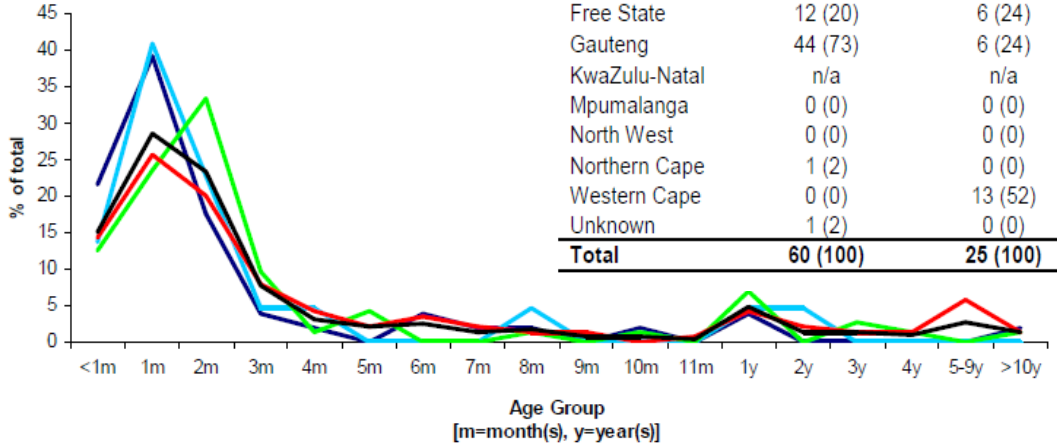


Province	n (%) 2008	2009	2010	2011*	Total 2008-2011*
Eastern Cape	2 (3)	0 (0)	0 (0)	0 (0)	**2 (<1)**
Free State	12 (20)	6 (24)	19 (26)	69 (45)	**106 (34)**
Gauteng	44 (73)	6 (24)	14 (19)	58 (38)	**122 (39)**
KwaZulu-Natal	n/a	n/a	n/a	2 (1)	**2 (<1)**
Mpumalanga	0 (0)	0 (0)	0 (0)	1 (<1)	**1 (<1)**
North West	0 (0)	0 (0)	0 (0)	1 (<1)	**1 (<1)**
Northern Cape	1 (2)	0 (0)	2 (3)	4 (3)	**7 (2)**
Western Cape	0 (0)	13 (52)	39 (53)	17 (11)	**69 (22)**
Unknown	1 (2)	0 (0)	0 (0)	0 (0)	**1 (<1)**
Total	**60 (100)**	**25 (100)**	**74 (100)**	**152 (100)**	**311 (100)**

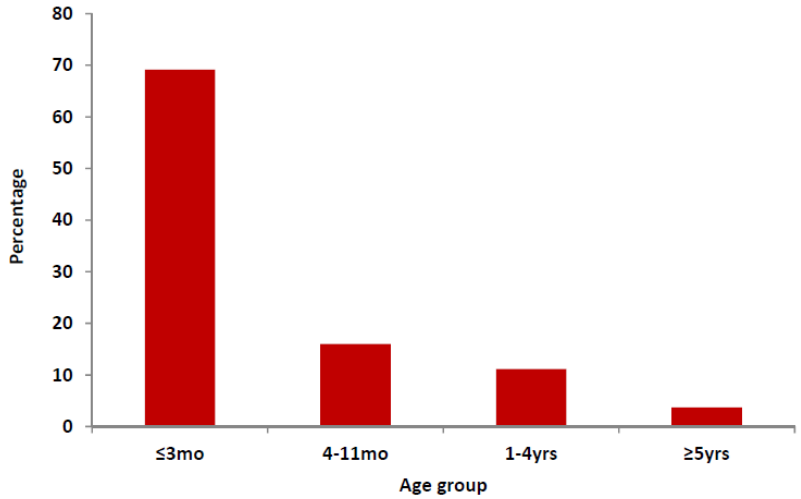


NHLS CDW-mined data: 2011-July 2014

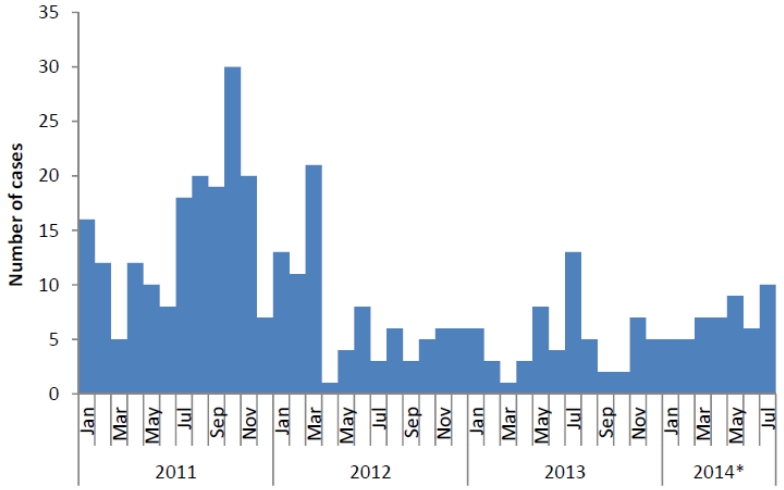
B. pertussis culture & PCR (IS481):

	Province									
Year	EC	FS	GP	KZN	LP	MP	NC	NW	WC	Total
2011	1	86	59	2		1	4	1	23	177
2012	1	18	36			6			26	87
2013		13	17			4	4		21	59
2014*	3	8	9	6			2		21	49*
Total	**5**	**125**	**121**	**8**	**0**	**11**	**10**	**1**	**91**	**372**

*Until July 2014



mo=months; yrs=years



* until July 2014

With Thanks to Juno Thomas

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division in the National Health Laboratory Service

Monthly Pertussis Surveillance Report: 01 January to 31 July 2014

Report prepared by: Outbreak Response Unit, Division of Public Health Surveillance and Response, NICD-NHLS

In collaboration with: National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW), Centre for Respiratory Diseases and Meningitis NICD-NHLS, Lancet, Ampath and Pathcare Laboratories

Table 1: Number of laboratory-confirmed *B. pertussis* cases by laboratory and month of specimen collection, South Africa, 2013 and 2014

	NHLS			CRDM (NICD-NHLS)			Private labs		
Month	**2013**	**2014**		**2013**	**2014**		**2013**	**2014**	
Jan	6	5		2	0		#	#	
Feb	3	5		0	0		3	2*	
Mar	1	7		0	1		6	2*	
Apr	3	7		3	4		12	1*	
May	8	9		5	3		6	#	
Jun	4	6		7	4		#	#	
Jul	13	5		4	5		#	#	
Aug	5			3			#		
Sep	2			2			#		
Oct	2			1			#		
Nov	7			1			#		
Dec	5			2			#		
Total	**59**	**44**		**30**	**17**		**27**	**5**	

Data not available at the time of generating this report

* Data incomplete

With Thanks to Juno Thomas

ENHANCED SURVEILLANCE FOR ADDITIONAL RESPIRATORY PATHOGENS, 2012-2013

Maimuna Carrim[1], Halima Dawood[5], John Frean[2], Melony Fortuin-de Smidt[2], Desiree du Plessis[2], Mignon du Plessis[1], Fahima Moosa[1], Jocelyn Moyes[1], Fathima Naby[5], Nazir Ismail[3], Bhavani Poonsamy[2], Sibongile Walaza[1], Nicole Wolter[1], Ebrahim Variava[4], Anne von Gottberg[1]

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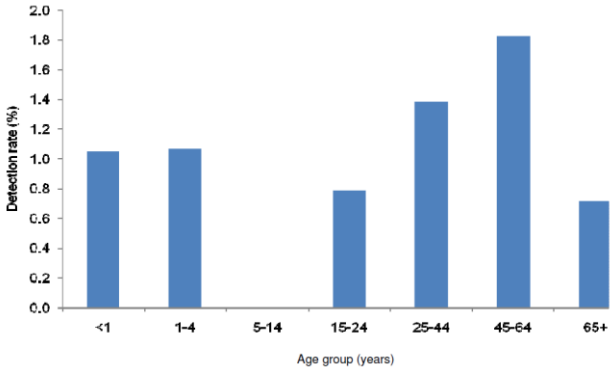
[2]Centre for Opportunistic, Tropical and Hospital Infections, NICD
[3]Centre for Tuberculosis, NICD
[4]Department of Medicine, Klerksdorp-Tshepong Hospital
[5]Pietermaritzburg Metropolitan Hospital and University of KwaZulu-Natal

Bacterial pathogens

Bordetella pertussis

Among the 3664 patients with severe respiratory infection and influenza-like illness who were tested for bacterial pathogens, 42 (1%) were positive for *B. pertussis* of which 31 (74%) presented with SRI and 11 (26%) with ILI. The majority of cases occurred in the winter and spring months (figure 2), and cases occurred at all study sites (figure 3). The highest detection rates of *B. pertussis* were in the 25-44 (17/1230, 1.4%) and 45-64 (10/549, 1.8%) year age groups (figure 4). Cases of *B. pertussis* were detected either in nasopharyngeal specimens (30/42, 71%), or induced sputa (8/42, 19%) or in both specimen types (4/42, 10%).



COMMUNICABLE DISEASES SURVEILLANCE BULLETIN

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Reported to WHO

- 2000: 8
- 2001: 24
- 2002: 5
- 2003: 8
- 2009: 4
- 2011: 181
- 2013: 116

World Health Organization

- Almost 900 cases detected 2008-2013!

What now?

- Improved assessment of disease burden:
  - Appropriate investigation of suspected cases
  - Ongoing surveillance & case-control studies
  - Vaccine effectiveness
  - Mortality burden
  - Collation of data
- ?Vaccine Evasion
- Change vaccination strategy
  - Maternal vaccination
  - Tdap instead of Td
  - Adolescents

The Pertussis Problem

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Table 1. Possible Vaccination Strategies to Control the Resurgence of Pertussis

Strategy	Remarks
Return to the use of wcP	Probably unacceptable
Develop less-reactogenic wcP	Not yet done
Maternal vaccination to provide transplacental antibody to protect newborn	Now generally recommended
Vaccination of newborn contacts (cocoon strategy)	Difficult to obtain complete coverage
More frequent boosters with acP	Costly and difficult to put in place
Change antigens in acP to those from currently circulating strains	Uncertain effect
Increase quantities of current antigens	Would require large trials
Inactivate PT by genetic mutation or milder chemical	Probably advisable to increase immunogenicity
Add new virulence factors	Would require large trials
Use stronger adjuvants	May require large trials
Administer live attenuated *Bordetella pertussis* intranasally	Early development Probably best as a boost strategy

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