DiPS
Dansk Infektionspædiatrisk Selskab

9th Danish Paediatric

Infectious Diseases Symposium

7-8 OCTOBER 2016

Comwell Klarskovgaard, Korsør

Pertussis

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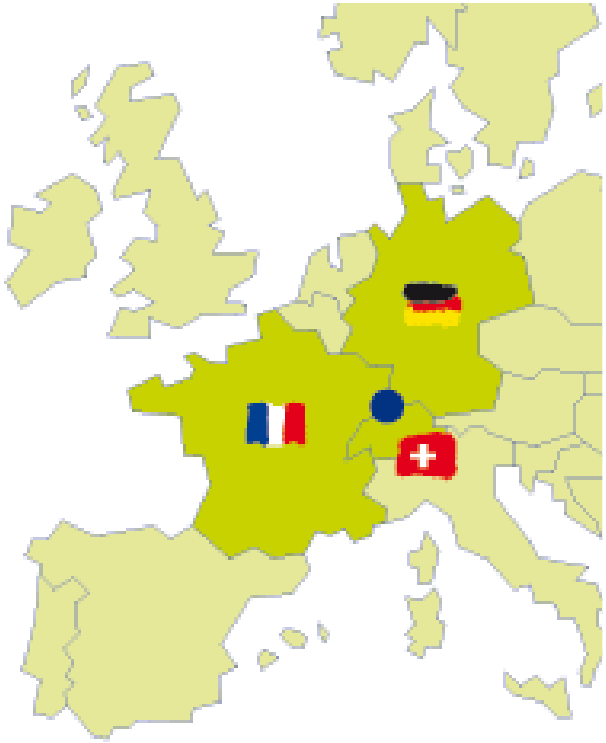
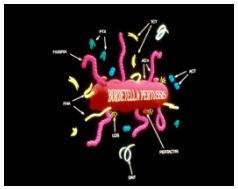


Pertussis - Facts



- Caused by *Bordetella pertussis* or *B. parapertussis*
- Transmission: droplets, human→human
- Incubation period: 7-10 (4-21) days
- Diagnosis is challenging
- Treatment is challenging
- Symptoms: highly variable,
  disease is most severe in infants

- Prevention by immunisation is challenging

Pathogenesis: Attachment to ciliated cells and aggregation of leukocytes in pulmonary arteries

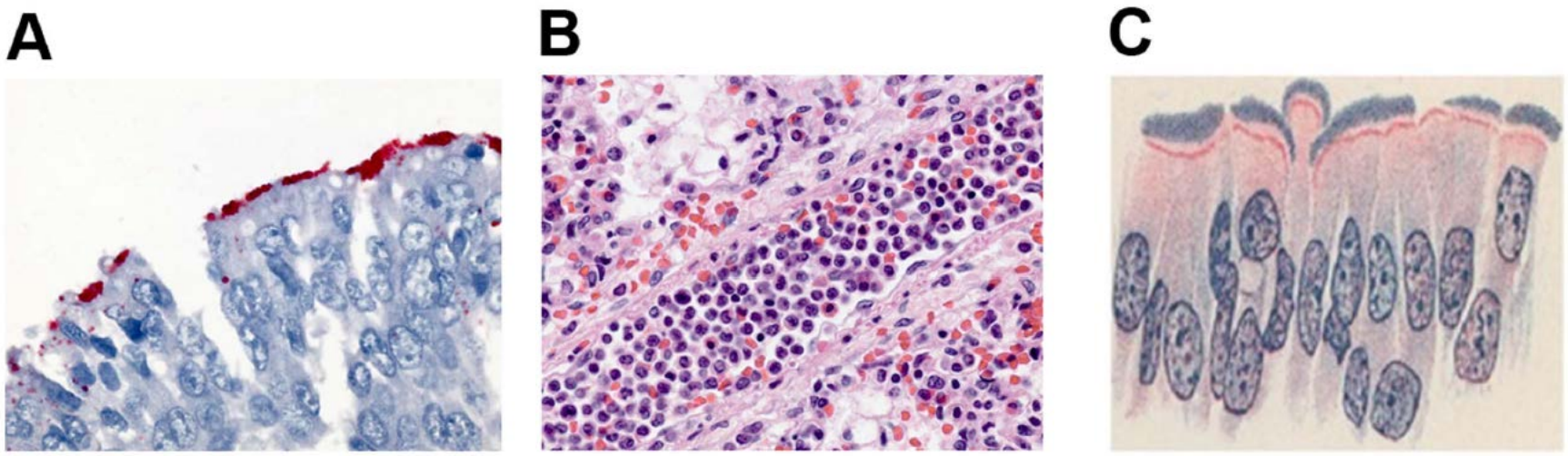
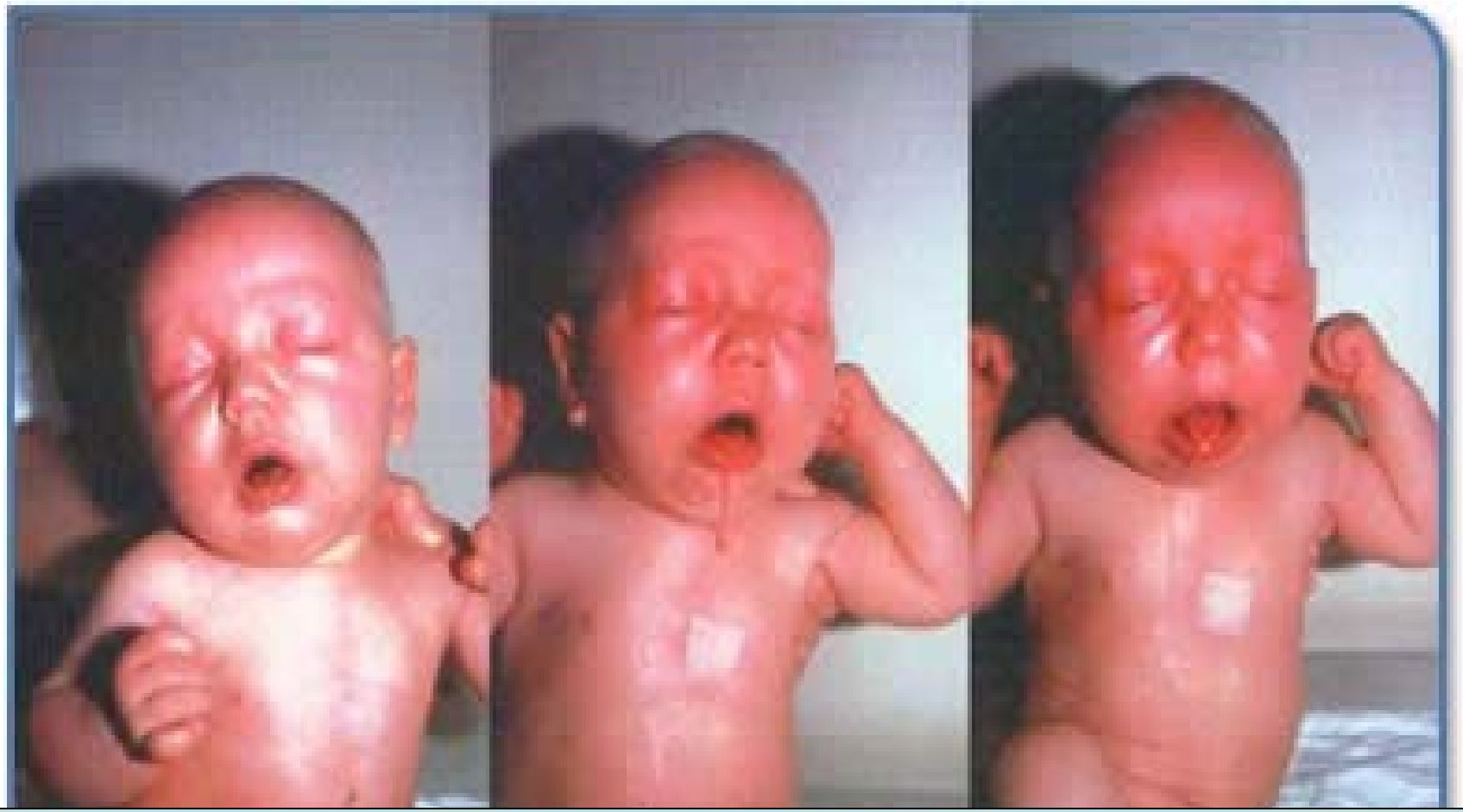


Figure 1. A: ***Bordetella pertussis*** **on Ciliated Cells of Bronchus.** Immunohistochemical localization of *B. pertussis* bacteria in the cilia of respiratory epithelium lining a bronchus of an infant who died from pertussis. Image courtesy of Christopher Paddock, M.D., Centers for Disease Control and Prevention. **B: Aggregates of Leukocytes in a Pulmonary Arteriole in Pertussis.** Pulmonary arteriole from an infant with fatal pertussis, showing intravascular aggregates of mixed leukocytes, comprising predominantly mature and band neutrophils, eosinophils, and monocytes. Image courtesy of Christopher Paddock, M.D., Centers for Disease Control and Prevention. **C: Drawing of** ***Bordetella pertussis*** **on Ciliated Cells in the Trachea. Published over 100 Years Ago.** Ciliated epithelium lining trachea of child dying in acute stage of whooping cough. Large numbers of minute bacilli present between the cilia. x1,000 [27].
doi:10.1371/journal.ppat.1003418.g001

Cherry JD: PLOS Pathogen 2013

Pertussis in infants



Cyanosis, apnoic spells, bradycardia, hyperleukocytosis → resp. failure, sudden death

H. Moll, Papenburg

Pertussis in Adults

"The physician, who considers pertussis in any patient with a nasty cough, will also get to know this disease in its less typical presentations."

Schwenkenbecher A; Med Klinik 48:1447-8 (1921)

Presentation of *B. pertussis* Infections by Age in **Unimmunized** Children

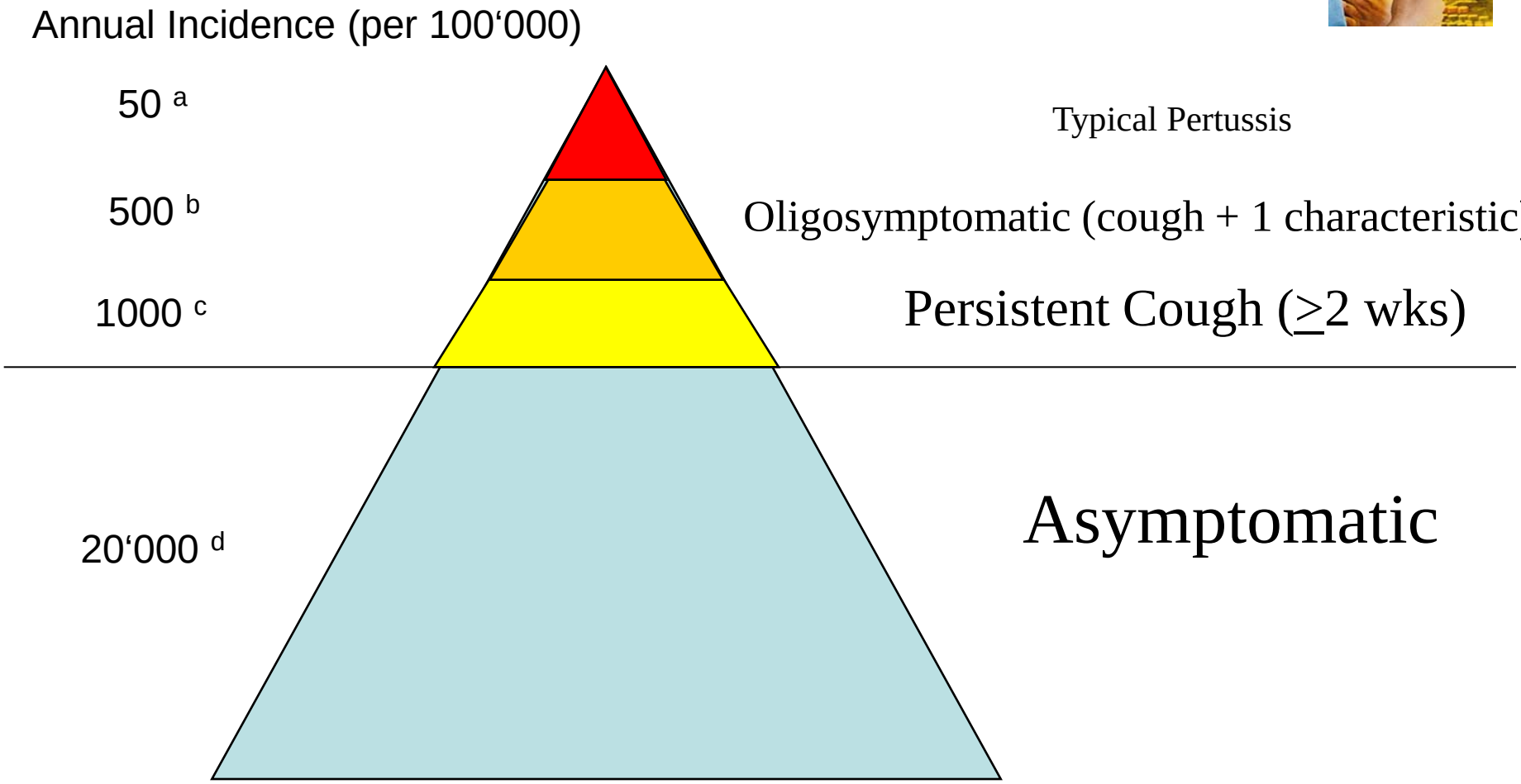
TABLE 1. Percent Occurrence of Selected Findings in Unvaccinated Patients With *Bordetella pertussis* Infections by Age Group as Reported in Initial and Follow-up Questionnaires

	Age										
	<6 Months	6–12 Months	1–2 Years	2–3 Years	3–4 Years	4–5 Years	5–6 Years	6–9 Years	>9 Years	Total*	
(N) Characteristics	(101) % pos	(84 % pos	(202) % pos	(280) % pos	(341) % pos	(383) % pos	(314) % pos	(338) % pos	(87) % pos	(2135) % pos	N With Data Avaliable
Initial											
Cough ≤2 wk	86.2	84.0	73.8	85.8	78.2	78.2	80.2	76.4	76.8	79.4	2045
Paroxysmal cough	89.2	81.8	77.7	79.5	80.8	84.3	82.4	87.6	78.8	82.4	1948
Vomiting	58.6	47.6	60.0	58.4	49.3	52.7	52.8	54.1	44.3	53.3	1390
Temperature ≥38°C	4.5	11.2	12.6	5.6	5.2	4.3	4.1	5.6	1.6	5.7	1526
Probable or definite pertussis†	69.6	65.4	61.8	54.8	51.7	50.1	46.9	49.5	43.5	52.8	1998
Follow-up											
Cough >4 wk	70.7	62.3	62.7	63.5	57.4	60.1	64.4	63.2	64.5	62.1	1546
Paroxysmal cough	92.6	92.7	92.3	90.2	89.3	88.9	92.0	90.3	84.8	90.2	1604
Whoop	69.1	91.7	80.6	82.8	83.7	78.8	74.5	77.4	66.1	78.9	1378
Probable or definite pertussis†	100	100	97.2	98.0	97.9	95.3	97.1	97.0	98.4	97.3	1574

* Includes 5 patients with unknown age.
† Physician's clinical diagnosis.

Heininger et al, Pediatrics 1997

Presentation of *B. pertussis* Infections in the **Vaccine Era**



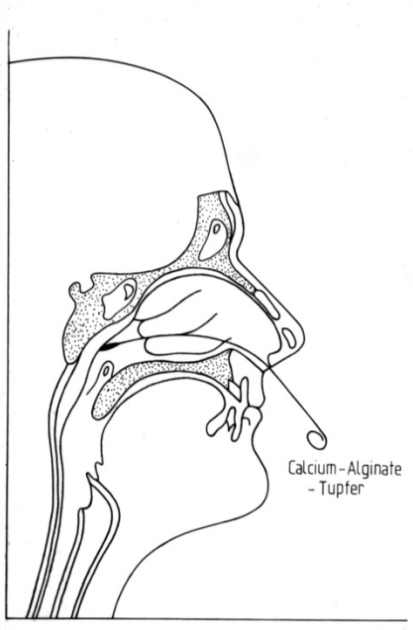
[a] Wymann et al, 2011 [b] Ward et al, 2005 [c] Rothstein & Edwards, 2005 [d] DeVille et al, 1995

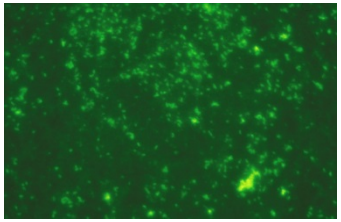
Good to know

Pertussis is *not* an exclusive childhood disease – it occurs at any age.

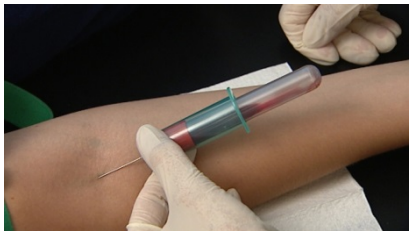
In immunized individuals, clinical presentation of pertussis is frequently *atypical*.

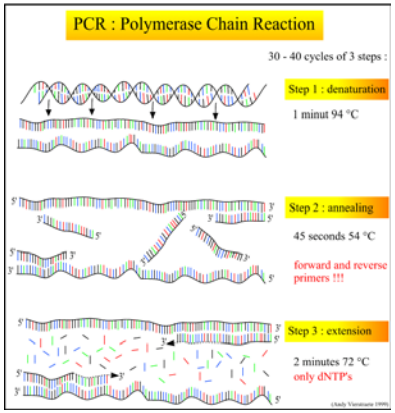
Diagnosis





Immunofluorescence of *B. pertussis* culture

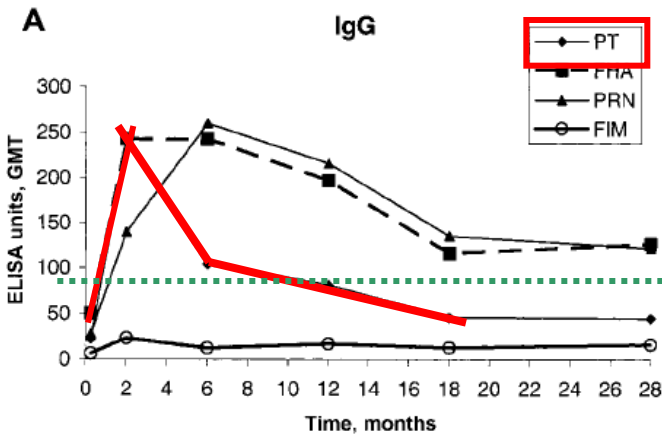


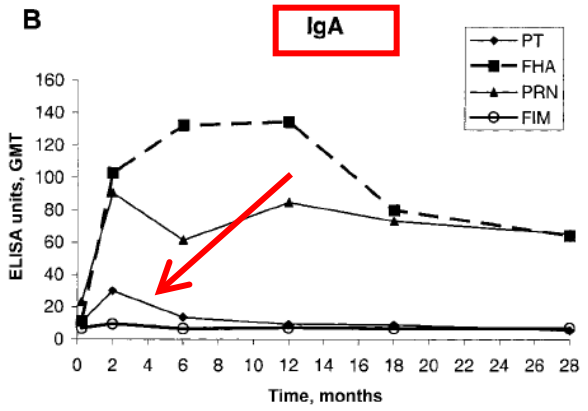


How to diagnose pertussis?

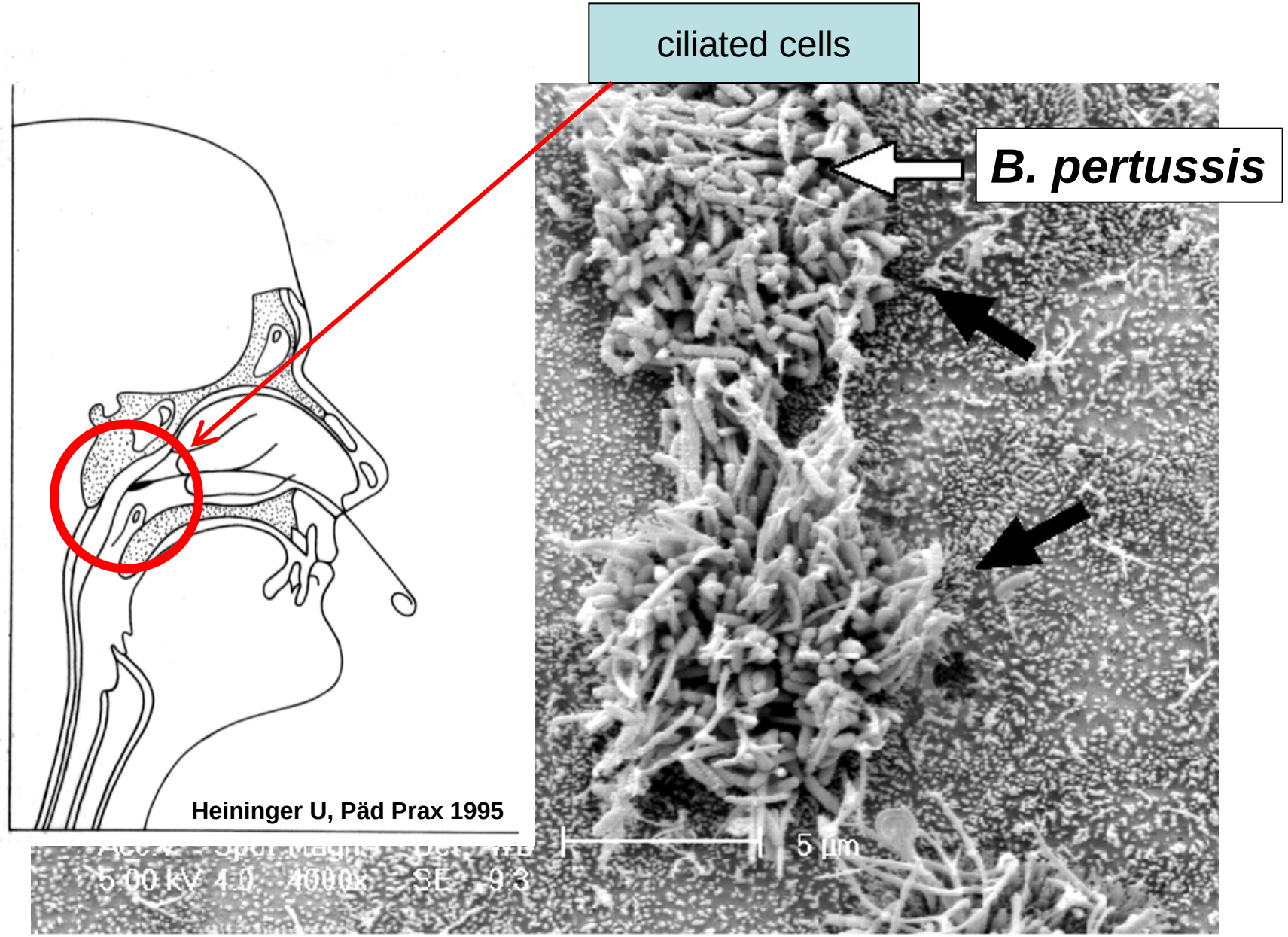
- Neonates/infants
  - PCR (and/or culture) from nasopharyngeal samples
- Children/adolescents and adults
  - <2 weeks of cough: PCR (and/or culture) from NPS
  - 2-3 weeks of cough: PCR and IgG-anti-PT
  - >3 weeks of cough: IgG-anti-PT

Guiso et al, Eur J Clin Microbiol Infect Dis 2011;30:307-12





Heininger et al, Clin Infect Dis 2004;38:591-4



Preston A CMAJ 2005;173:55-62

Good to know

Confirmation of *B. pertussis* infection requires microbiologic tests – PCR and/or anti-PT-IgG antibodies in serum.

Epidemiology

Pertussis surveillance systems in Europe

Table 1
Characteristics of surveillance systems of the sixteen participating countries

Country	Type of data provided	Type of surveillance	Population coverage	Recommended case definition	Laboratory methods available for case confirmation	Minimum requirement for case notification	Other surveillance systems in place
Austria	Aggregated	Clinical	General population	WHO	Serology	Laboratory confirmation	No
Denmark	Case-based	Clinical	Population <2 years	WHO	Culture, PCR	Laboratory confirmation	No
England, Wales, and Northern Ireland	Case-based	Laboratory-based	General population	None	Culture, serology, PCR 2002-	Laboratory confirmation	Yes
France	Case-based	Clinical-, hospital-based	Sentinel system, population coverage not determined	WHO modified: 3 weeks of cough or 1 week of typical cough + lab confirmation or epi link	Culture, serology, PCR	Clinical symptoms and physician examination	Yes
Germany	Case-based, aggregated in 2001	Clinical	General population, East Germany only	WHO clinical definition	Culture, serology	Clinical symptoms and physician examination	No
Greece	Case-based	Clinical	General population	WHO clinical definition	Serology	Clinical symptoms and physician examination	Yes
Iceland	Aggregated 1998–March 2001; case-based 2001	Clinical	General population	None	None	Clinical symptoms and physician examination	No
Ireland	Aggregated 1998–1999; case-based 2000	Clinical	General population	None	None	Clinical symptoms and physician examination	No
Italy	Case-based	Clinical	General population	None	None	Clinical symptoms and physician examination	Yes
Malta	Case-based	Clinical	General population	None	None	Clinical symptoms and physician examination	Yes
Norway	Case-based	Clinical	General population	WHO	Culture, serology, PCR	Laboratory confirmation or epidemiological link	No
Portugal	Case-based	Clinical	General population	WHO clinical definition	Culture, serology, PCR	Clinical symptoms and physician examination	No
Spain	Aggregated 1998–2000; case-based 2001	Clinical	General population	WHO clinical definition	None	Clinical symptoms and physician examination	No
Sweden	Case-based	Clinical	General population	WHO	Culture, serology, PCR	Clinical symptoms and physician examination	Yes
Switzerland	Case-based	Clinical, GP-based	Sentinel system	WHO clinical definition	PCR	Clinical symptoms and physician examination	No
The Netherlands	Case-based	Clinical	General population	WHO	Culture, serology, PCR	Laboratory confirmation or epidemiological link	No

A.E. Tozzi et al. / Vaccine 25 (2007) 291–297

Incidence of pertussis by country

TABLE 1. Mean Annual Number of Pertussis Cases per 100,000 Population by Country and Age Group, 1998–2002

Country	Total	<1 yr	1–4 yr	5–9 yr	10–14 yr	>14 yr
Switzerland	123.9	1039.9	673.9	583.9	342.8	40.17
Norway	57.1	172.5	39.3	150.9	208.9	36.3
The Netherlands	32.7	117.8	152.5	148.9	67.0	9.4
Sweden	22.3	71.2	102.9	182.0	38.3	1.8
Germany	10.1	32.7	13.5	22.2	39.3	7.4
Italy	6.1	104.1	36.8	54.0	19.3	0.2
Ireland	4.5	—	—	—	—	—
Malta	3.7	4.0	2.1	6.9	0.7	0.00
Iceland	3.4	155.0	8.2	4.4	2.8	0.1
Austria	1.8	—	—	—	—	—
Spain	0.7	23.0	3.5	4.3	2.1	0.1
Greece	0.5	8.8	0.9	0.3	0.3	0.01
England, Wales and Northern Ireland	0.5	30.9	1.5	1.0	0.4	0.05
Portugal	0.1	6.2	0.2	0.04	0.1	0.01
Denmark	—	253.1	—	—	—	—

Celentano et al, PIDJ 2005;24:761-6

Table 1. Pertussis vaccination schedules by country.

Country	Time period	Primary series	Reinforcing/Booster doses						Coverage[∞]
			Toddlers		Pre-school age		Adolescence		(min–max)
Bulgaria	From 1992 to 2007	wP♦ 2, 3, 4 months	wP♦	2 years					89.7–94.0%
	From 2008 to 2009	wP♦ 2, 3, 4 months	aP	>16 months	aP	6 years			93.2–93.7%
	Since 2010	aP 2, 3, 4 months	aP	>16 months	aP	6 years			94.3% (2013)
Czech Republic	Until 2006	wP□ 3, 4, 5 months	wP□	18–20 months	wP□	4–5 years			99.6–99.6%
	From 1 January 2007 to 14 February 2009	aP 3, 4, 5 months	aP	18 months	aP	5–6 years			92.8–99.3%
	Since 15 February 2009	aP 3, 4, 5 months	aP	18 months	aP	5–6 years	aP	10 years	92.1–98.0%
Estonia	From 2000 to 2007	wP□ 3, 4.5, 6 months	wP□	2 years					91.7–95.8%
	Since 2008	aP 3, 4.5, 6 months	aP	2 years	aP	6–7 years	aP	15–16 years	96.0–96.7%
Hungary	Before 2006	wP♦ 3, 4, 5 months	wP♦	3 years	wP♦	6 years			99.9–100%
	Since 2006	aP 2, 3, 4 months	aP	18 months	aP	6 years	aP	11 years	99.6–99.9%
Latvia	From 1958 to 2004	wP□ 2, 4, 6 months	wP□	12–15 months					89.7–94.7%
	From 2005 to 2009	aP 2, 4, 6 months	aP	12–15 months					92.3–98.1%
	Since 2010	aP 2, 4, 6 months	aP	12–15 months	aP	7 years			90.0–97.9%
Lithuania	From 1961 to 2003	wP□ 3, 4.5, 6 months	wP□	18 months					92.8–94.8%
	From 2004 to 2006	wP□ 2, 4, 6 months	wP□	18 months					93.9–94.0%
	Since 2007	aP 2, 4, 6 months	aP	18 months	aP	6–7 years[§]			92.8–97.4%
Poland	From 1960 to 2002	wP□ 2, 3, 5 months	wP□	16–18 months					94.7–94.8%
	Since 2003[#]	wP□ 2, 3, 5 months	wP□	16–18 months	aP	6 years[‡]			94.7–96.0%
Romania	From 1961 to September 2008	wP♦ 2, 4, 6 months	wP♦	12 months	wP♦	30–35 months			95.3–99.0%
	From 1 October 2008 to March 2009	aP 2, 4, 6 months	aP	13–15 months	aP	4 years			81.7–95.3%
	Since 1 April 2009	aP 2, 4, 6 months	aP	12 months	aP	4 years			81.7–93.8%
Serbia	Since 1960[†]	wP♦ 2, 3.5, 5 months	wP♦	1–2 years					93.1–97.6%
Slovakia	From 2000 to 2006	wP□ 3–4, 5–6, 11–12 months	wP□	3 years	wP□	6 years			98.5–99.4%
	From 2007 to 2008	aP 3–4, 5–6, 11–12 months	wP□	3 years	wP□	6 years			99.3–99.4%
	In 2009	aP 3–4, 5–6, 11–12 months			aP	6 years			99.2% (2009)
	Since 2010	aP 3–4, 5–6, 11–12 months			aP	6 years	aP	13 years	96.8–99.1%

Heininger et al
PLOS One 2016
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Table 2. Surveillance system, clinical and laboratory criteria used by country.

Country	Surveillance system	Clinical case definition	Microbiologic confirmation	Laboratory diagnosis		
				Culture	Serology	PCR
Bulgaria	Passive; Mandatory notification; Population-based surveillance; Aggregate reporting	WHO criteria	Yes[#]	Until 2008	≥ 1 change; Qualitative to quantitative tests (PHT & IF to ELISA); Serology assessment ended 2009	Since 2007[#]
Czech Republic	Passive; Mandatory notification; Population-based surveillance; Aggregate reporting	WHO criteria	Yes	Until 2000	≥ 1 change; Qualitative to quantitative test; kit change 2010	RT-PCR since 2009
Estonia	Passive; Mandatory notification; Population-based surveillance; Case-based reporting	WHO criteria	Yes	Rarely used	≥ 1 change; Qualitative to quantitative test	Since 2012, but rarely used
Hungary	Passive; Mandatory notification; Population-based surveillance; Case-based reporting	WHO/ECDC criteria	Yes	Until 2000	≥ 1 change; Qualitative to quantitative tests (hemagglutination to ELISA)	Since 2012
Latvia	Passive; Mandatory notification; Population-based surveillance; Case-based reporting	ECDC criteria	Yes	Rarely used	≥ 1 change; Qualitative to quantitative tests (PHT & WB to ELISA)	RT-PCR since 2012
Lithuania	Passive; Mandatory notification; Population-based surveillance; Case-based reporting	WHO/ECDC criteria	Yes	Until 2000	≥ 1 change; Qualitative to quantitative tests; Labsystem (2005–2010) & Euroimmun since 2010	Since 2010[‡]
Poland	Passive; Mandatory notification; Population-based surveillance; Case-based reporting	ECDC criteria	Yes	Rarely used	≥ 1 change; Qualitative to quantitative tests; introduced kits such as Novatec	Rarely used
Romania	Passive; Mandatory notification; Population-based surveillance; Case-based reporting	Reported cases diagnosed based on prolonged cough and a high level of WBC	Yes	Rarely used	≥ 1 change; No serology testing until 2008, then qualitative tests introduced	Sporadic since 2012
Serbia	Passive; Mandatory notification; Population-based surveillance (sentinel surveillance in one city [Novi Sad]); Case-based reporting	GPI clinical Case Definition used in 2012, in part, for sentinel surveillance in one city (Novi Sad)	Yes (since 2012)	Not used	≥ 1 change; Clinical case definition only until 2012, then quantitative tests introduced (Euroimmun)	Since 2012
Slovakia	Passive; Mandatory notification; Population-based surveillance; Case-based reporting	ECDC criteria	Yes	Until 2000	≥ 1 change; Qualitative to quantitative test	Since 2007

Heininger et al; PLOS One 2016
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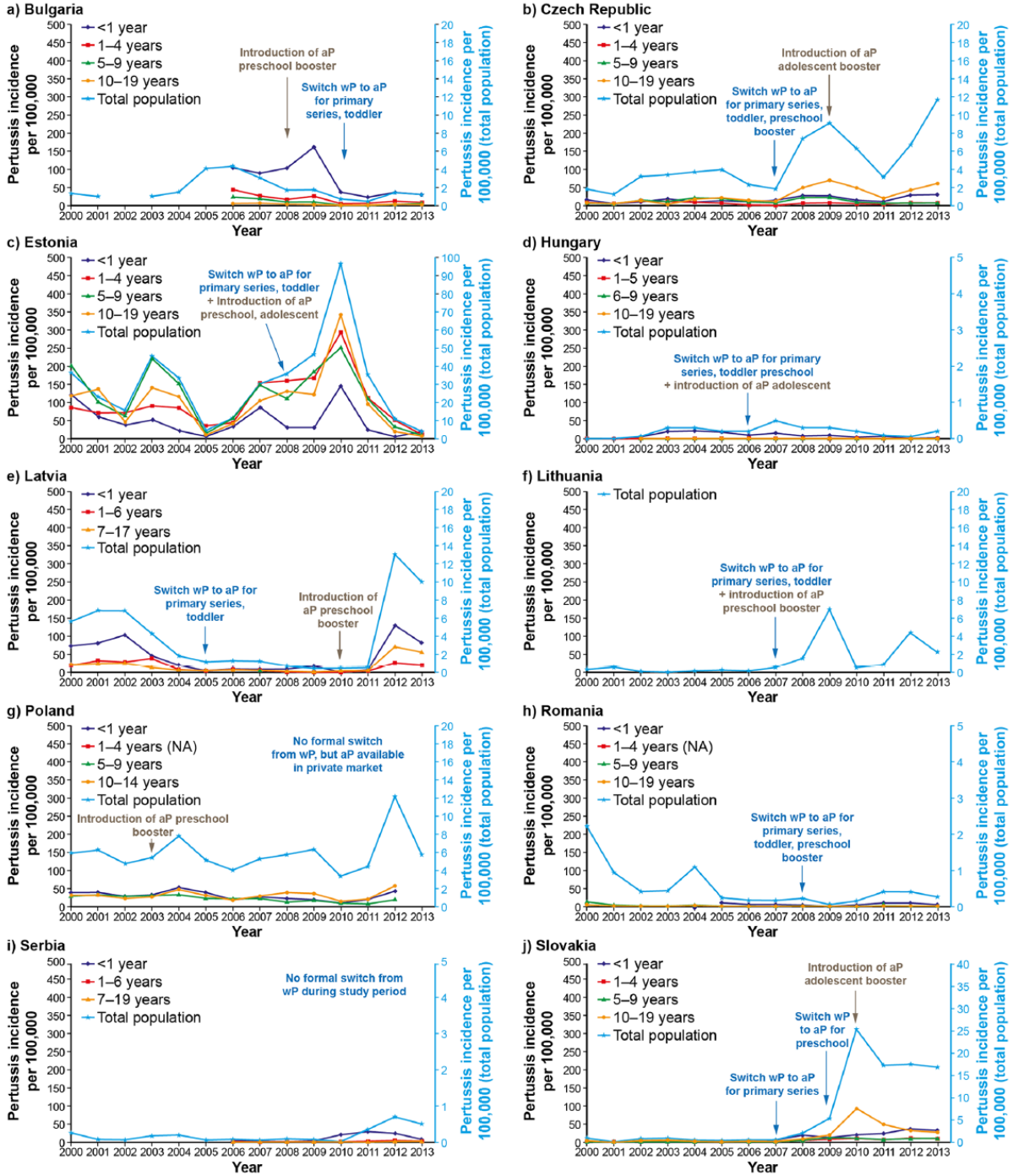

Heininger et al; PLOS One 2016
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True Burden of Pertussis is Underestimated

Even if there is a cough present,

- Lack of physician visit - *underconsulting*
- Lack of suspicion - *underrecognition*
- Lack of diagnostic tests - *underdiagnosis*
- Lack of reporting - *underreporting*

Best clinical estimates derive from sentinel studies

„John Constable and a remedy for whooping cough“
(Alan McBride *1931)

The ill child was passed 3 times under and over a donkey

Clin Infect Dis, May 2007

Treatment of Pertussis –Then and Now

„warme Bäder und reichliche Lüftung unter strengster Bettruhe“

"warm baths and ample ventilation under strict bed rest"

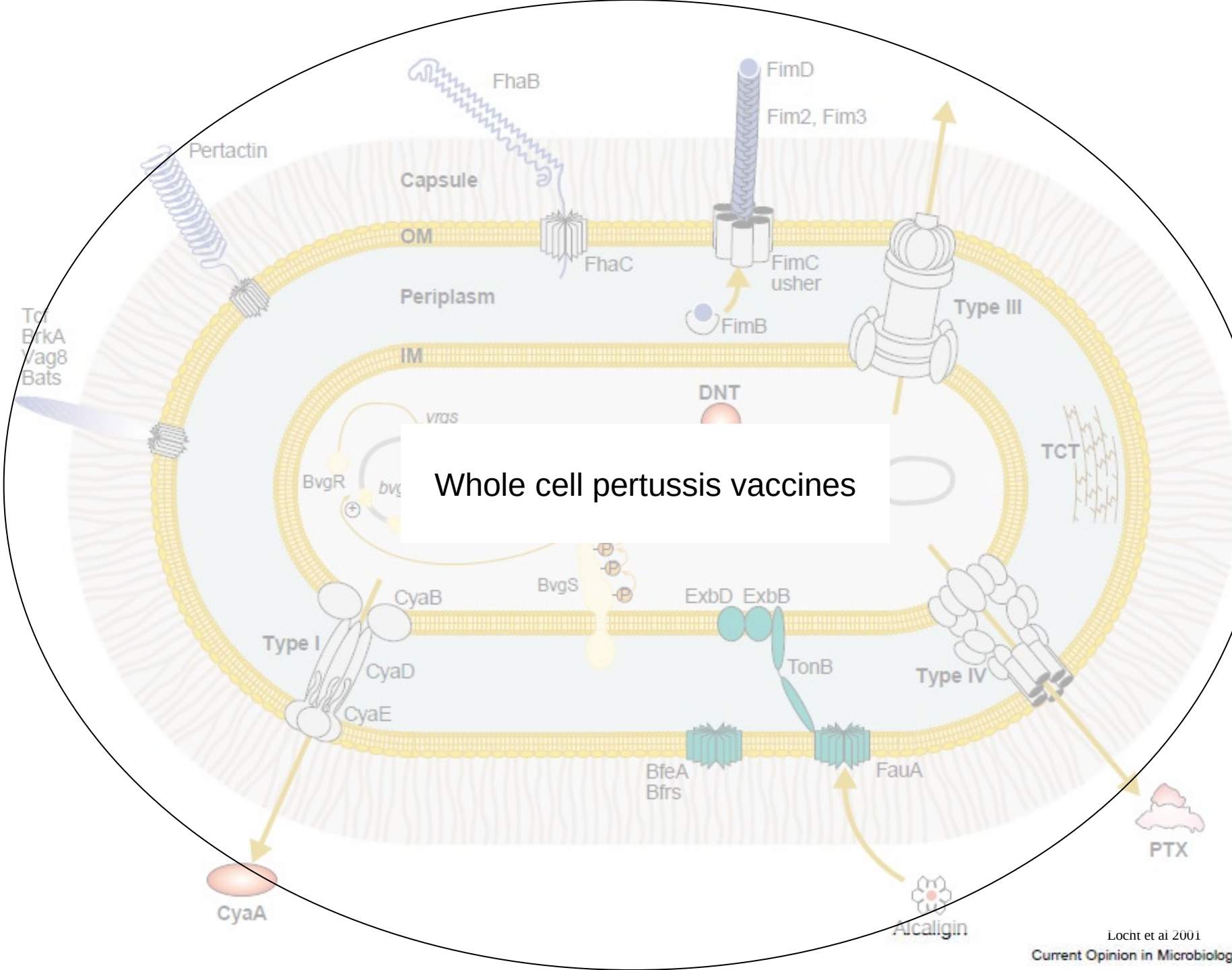
E. Wieland, Kinderspital Basel
SMW 1928; 25:638-640

Azithromycin (5d) or Clarithro-/Erythromycin (7d)

- will terminate contagiousness of patient
- little effect on signs and symptoms

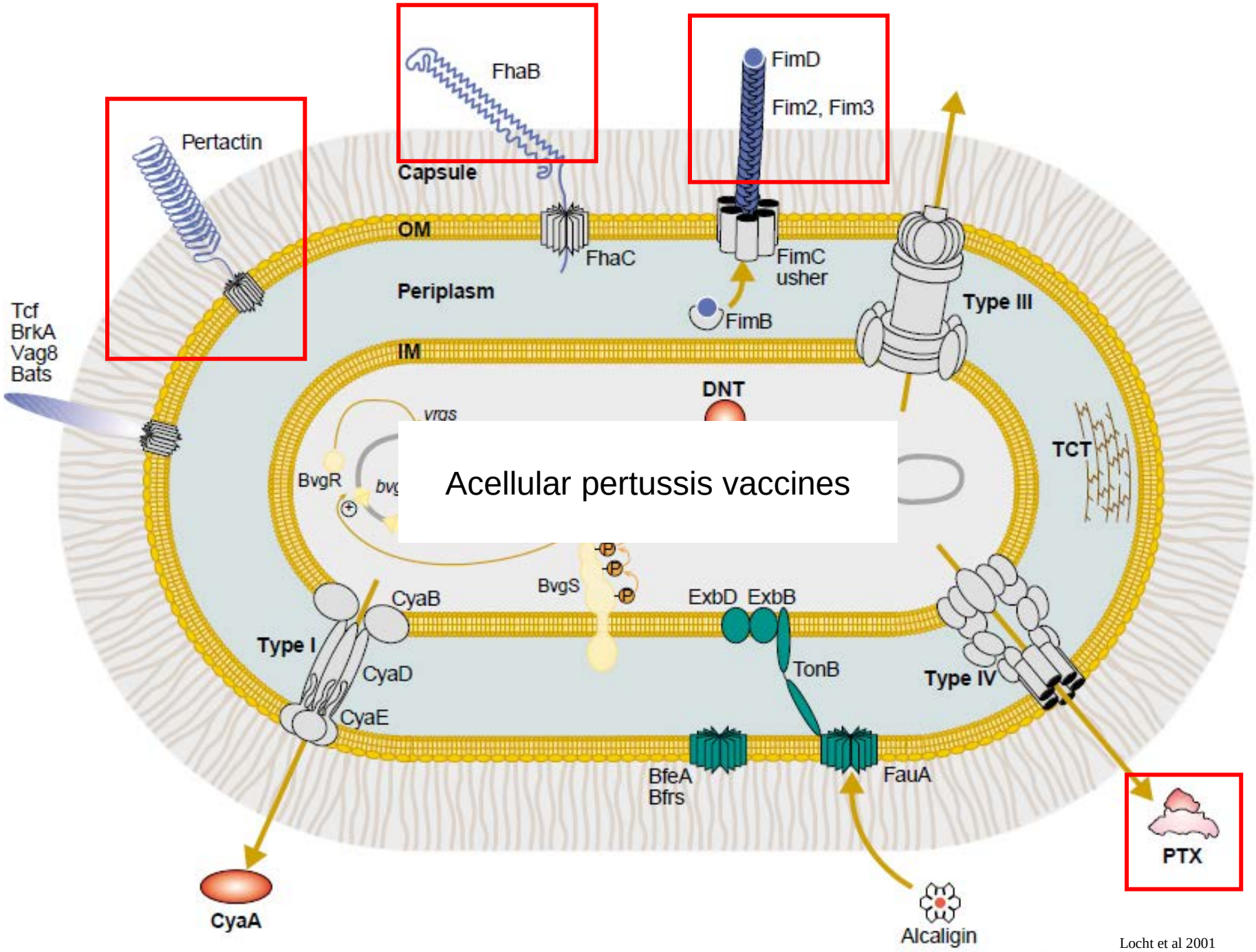
Unfortunately

Treatment of pertussis is frustrating.



Whole cell pertussis vaccines

Locht et al 2001
Current Opinion in Microbiology



Acellular pertussis vaccines

Locht et al 2001
Current Opinion in Microbiology

The sequential development of pertussis immunization recommendations…

Swiss Immunization Recommendations

Vaccine	Age in Months					Age in Years		
	0	2	4	6	15-24	4-7	11-15	every 10 yrs
Tetanus		☐	☐	☐	☐	☐	☐	☐
Diphtherie		☐	☐	☐	☐	☐	☐	☐
Pertussis		1	2	3				

1950ies - 1994

Efficacy of Acellular Pertussis Vaccines

TABLE 129–5 Vaccine Efficacy Data for 10 Acellular Pertussis Vaccines Evaluated in Eight Trials Carried Out in the 1990s and the Earlier 1980s Swedish Trials

Location/References	Design	Vaccine	Schedule	Efficacy	
				Typical Pertussis (%)	Mild and Typical Pertussis (%)
Sweden, Stockholm[1,29,369]	Double-blind prospective cohort	JNIH-6	2 doses (2-3 mo apart starting at 5-11 mo of age)	84*	42
		JNIH-7		90	−7
Sweden, Göteborg[†385]	Double-blind prospective cohort	Certiva	3 doses (3, 5, 12 mo)	71	54
Sweden, Stockholm[145]	Double-blind prospective cohort	SKB-2	3 doses (2, 4, 6 mo)	59	42
		Daptacel		85	78
Italy, Rome[138]	Double-blind prospective cohort	Acelluvax	3 doses (2, 4, 6 mo)	84	71
		INFANRIX		84	71
Germany, Erlangen[362]	Prospective cohort	Acel-Immune	4 doses (3, $4^1/_2$, 6, 15-18 mo)	83	72
Germany, Mainz[351]	Household contact	INFANRIX	3 doses (3, 4, 5 mo)	89	81
Germany, Munich[‡231]	Case control	Tripedia	4 doses (2, 4, 6, 15-25 mo)	80, 93	—
Senegal[§357]	Household contact	Triavax	3 doses	31, 74	—

**Efficacy against typical pertussis based on positive culture without serologic analysis.*

[†] Significant observer bias occurred in this trial.[56]

[‡] Laboratory diagnosis based on culture only; 80 percent efficacy was against cough illness of 21 or more days, and 93 percent efficacy was against the World Health Organization (WHO) case definition.

[§] Thirty-one percent efficacy based on 21 days or more of cough illness; 74 percent efficacy was against the WHO case definition.

Cherry JD/Heininger U: Textbook of Pediatric Infectious Diseases, ed 7, 2013

Swiss Immunization Recommendations

Vaccine	Age in Months					Age in Years		
	0	2	4	6	15-24	4-7	11-15	every 10 yrs
Tetanus		☐	☐	☐	☐	☐	☐	☐
Diphtherie		☐	☐	☐	☐	☐	☐	☐
Pertussis		1	2	3	4	5	*	

* if <5 doses

1995 – 2011

Swiss Immunization Recommendations

Vaccine	Age in Months					Age in Years			
	0	2	4	6	15-24	4-7	11-15	25-29	+
Tetanus		☐	☐	☐	☐	☐	☐	☐	☐
Diphtherie		☐	☐	☐	☐	☐	☐	☐	☐
Pertussis		1	2	3	4	5	*	x	

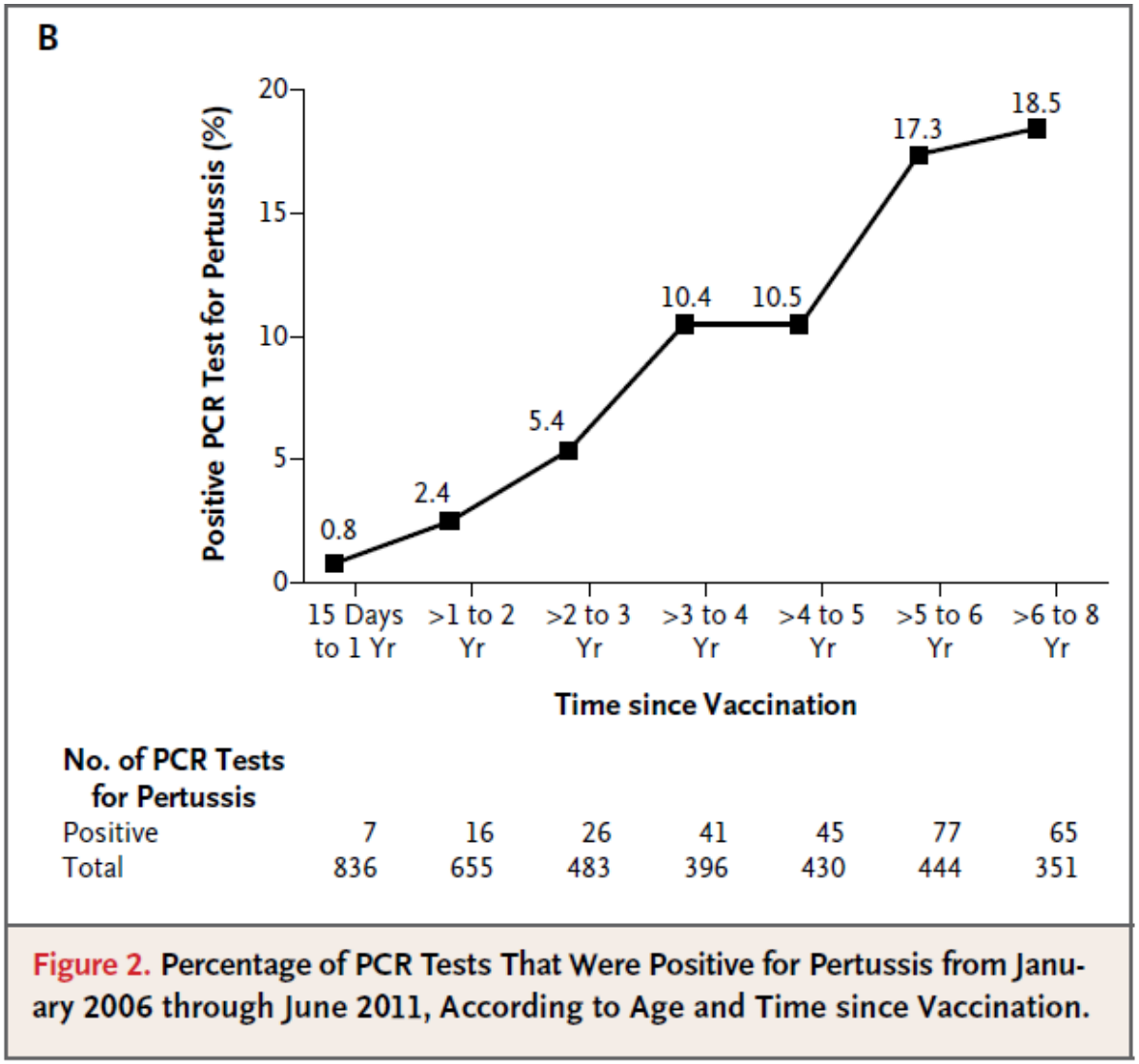
* if <5 doses

x= 1,2,3,4,5 or 6

2012

and „Cocoon Strategy“: Tdap for <u>all individuals</u>
regardless of age in close contact to infants < 6 months

The problem of waning immunity…



No. of PCR Tests for Pertussis							
Positive	7	16	26	41	45	77	65
Total	836	655	483	396	430	444	351

Figure 2. Percentage of PCR Tests That Were Positive for Pertussis from January 2006 through June 2011, According to Age and Time since Vaccination.

N Engl J Med 2012;367:1012-9.

Swiss Immunization Recommendations

Vaccine	Age in Months					Age in Years			
	0	2	4	6	15-24	4-7	11-15	25-29	+
Tetanus		☐	☐	☐	☐	☐	☐	☐	☐
Diphtherie		☐	☐	☐	☐	☐	☐	☐	☐
Pertussis		1	2	3	4	5	6	x	

2013

and Tdap for all pregnant women in 2nd or 3rd trimester!

Concept of Pertussis Immunization in Pregnancy

- *Direct* protection of the pregnant woman
- *Indirect* protection of the newborn by transplacental IgG antibody transfer

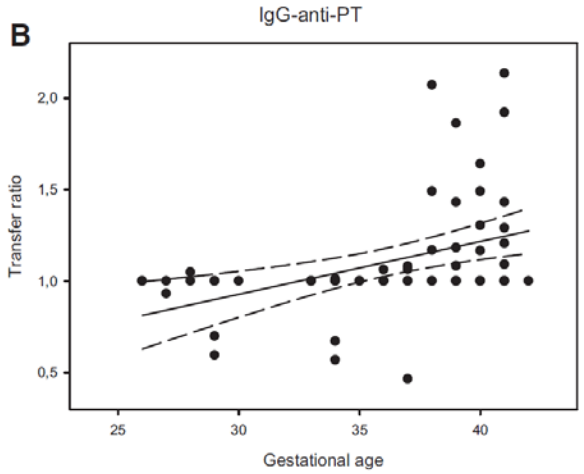


FIGURE 1. Transmission rates of IgG-anti–PT and IgG-anti–FHA in relation to gestational age.

Heininger et al; Pediatr Infect Dis J 2009;28:443-5

The pertussis situation in England

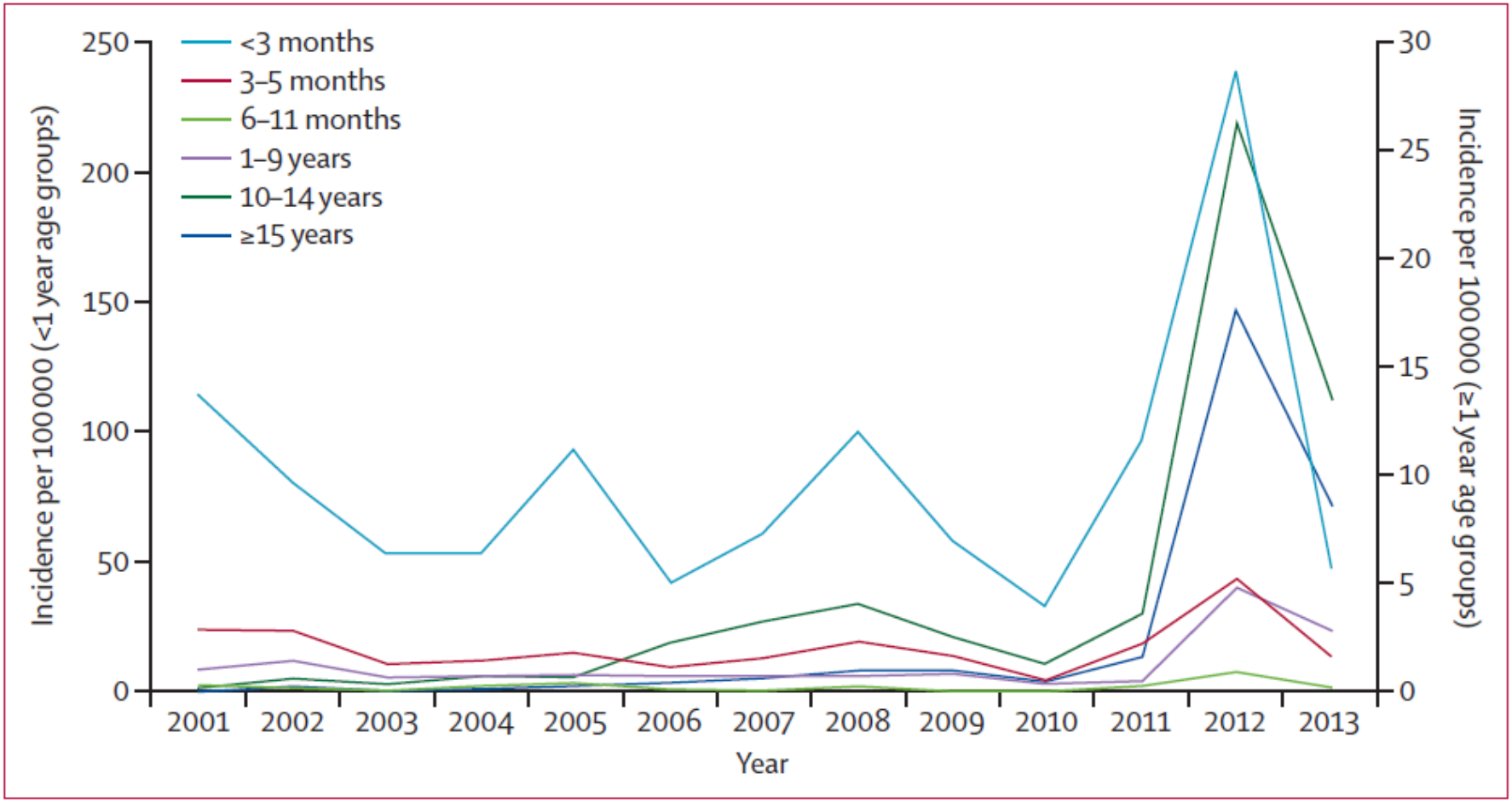


Figure 2: **Annual incidence of laboratory-confirmed cases of pertussis by age group**
Figure shows incidence from 2001 to 2013 in England only.

Amirthalingam et al; BMJ 2014

Effectiveness of maternal pertussis vaccination in England: an observational study

Gayatri Amirthalingam, Nick Andrews, Helen Campbell, Sonia Ribeiro, Edna Kara, Katherine Donegan, Norman K Fry, Elizabeth Miller, Mary Ramsay

BMJ

July 16, 2014
http://dx.doi.org/10.1016/S0140-6736(14)60686-3

October 2012: Start of Programme

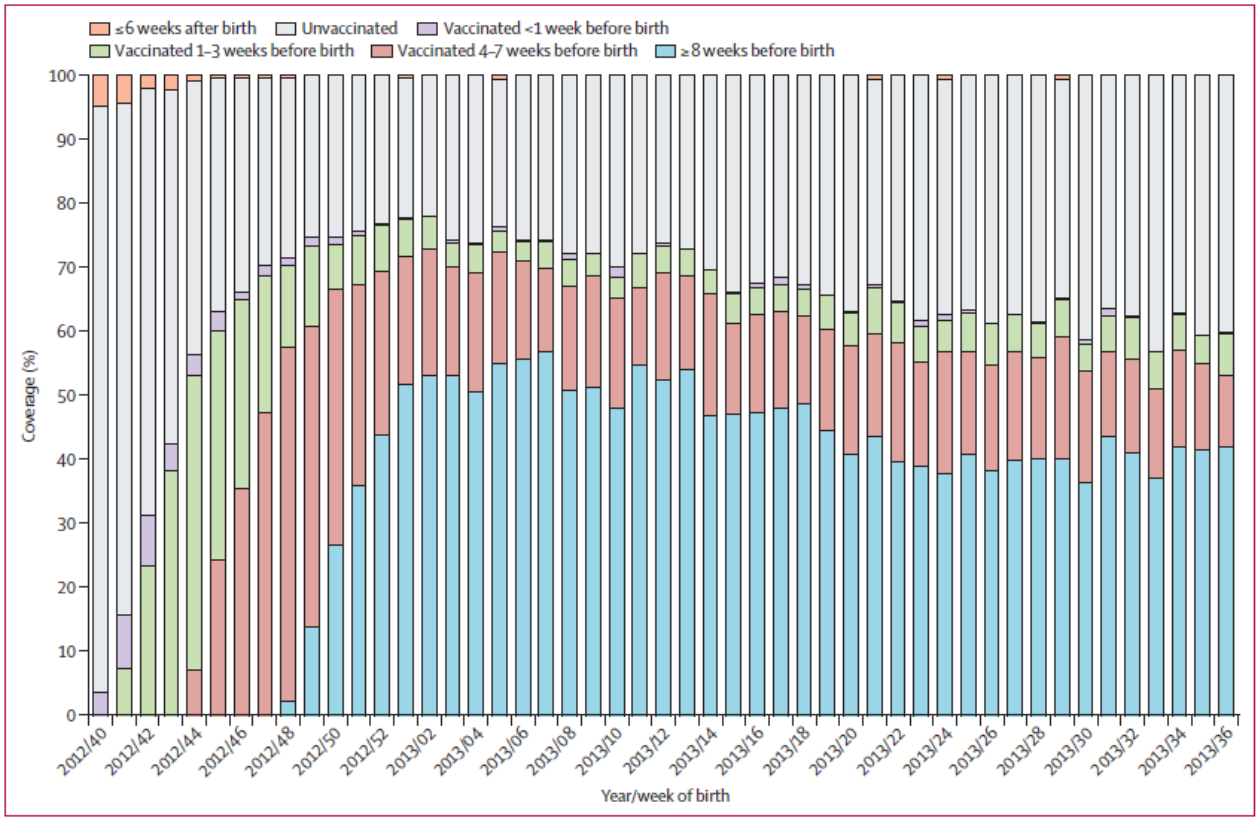


Figure 1: **Estimated maternal vaccine coverage by week of birth**
Figure shows coverage from week 40, 2012, to week 36, 2013. Figure based on data provided by the Clinical Practice Research Datalink.

Effect of maternal pertussis immunization in England

Table 1: Laboratory-confirmed cases by age group

	2012	2013	% change 2013 *vs* 2012 (95% CI)
<1 month	43 (0·7%)	10 (0·3%)	−77% (−90 to −53)
1 month	161 (2·7%)	37 (1·0%)	−77% (−84 to −67)
2 months	124 (2·1%)	25 (0·7%)	−80% (−87 to −69)
3–5 months	62 (1·0%)	22 (0·6%)	−65% (−79 to −41)
6–11 months	22 (0·4%)	7 (0·2%)	−68% (−89 to −23)
1–4 years	58 (1·0%)	41 (1·1%)	−29% (−54 to 7)
5–19 years	1128 (19·1%)	669 (17·6%)	−41% (−46 to −35)
≥20 years	4311 (73·0%)	2984 (78·6%)	−31% (−34 to −27)
Total number of cases	5909	3795	−36% (−38 to −33)
Reported deaths*	10 (CFR 3·0%)	2 (CFR 2·8%)	..

modified from Amirthalingam et al; BMJ 2014

Effect of maternal pertussis immunization in England

Table 2: Hospital admissions by age group

	2012	2013	% change 2013 vs 2012 (95% CI)
<1 month	73 (11·3%)	18 (6·5%)	−75% (−86 to −58)
1 month	209 (32·3%)	68 (24·7%)	−67% (−76 to −57)
2 months	158 (24·4%)	54 (19·6%)	−66% (−75 to −53)
3–5 months	108 (16·7%)	54 (19·6%)	−50% (−65 to −30)
6–11 months	30 (4·6%)	11 (4·0%)	−63% (−83 to −25)
1–4 years	29 (4·5%)	21 (7·6%)	−28% (−61 to 31)
5–19 years	23 (3·5%)	12 (4·4%)	−48% (−76 to 9)
20+ years	18 (2·8%)	37 (13·5%)	106% (14 to 284)
Total	648	275	−58% (−63 to −37)

modified from Amirthalingam et al; BMJ 2014

Pertussis in infants is less severe if mother was immunized during pregnancy

Table 3. Results of multivariate logistic regression models predicting hospitalization [Model 1] and ICU admission [Model 2] among infants <63 days of age with pertussis

	Model 1: Risk of hospitalization		Model 2: Risk of ICU admission	
Parameter	OR	(95% CI)	OR	(95% CI)
Tdap during pregnancy	0.42	(0.20-0.85)	0.49	(0.19-1.23)
Age in weeks (infant)	0.81	(0.72-0.91)	0.80	(0.72-0.90)
DTaP ≥14 days prior to onset	0.32	(0.06-1.77)	*	
Gestational age (weeks)	0.88	(0.78-0.99)	0.97	(0.91-1.00)

*DTaP vaccination dropped from the model to allow for convergence

Winter et al; ClinInfect Dis 2016;Sept 13, online

Conclusion

Prevention of pertussis by immunization is a moving target

(and probably a lifelong «family affair»)

We are paediatricians!