



**What's New
in Prevention of Pertussis**

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**2003-2004 Public Health Works
Speaker Series**

Objectives

- At the conclusion of this presentation, the participant will:
 - understand the changing epidemiology of pertussis in Canada and abroad;
 - recognize the clinical presentation and be familiar with options for prevention of pertussis;
 - be prepared to contribute to the optimal control of pertussis.

Outline

- Do adolescents and adults get pertussis?
 - How frequent is it?
 - What does it look like?
 - Where do they get it?
 - What do they do with it?
 - What can be done about it?



From seroepidemiology studies...

- frequent infections in UCLA health care workers; 30-40% with evidence of infection/yr. (*Deville, Clin Infect Dis 1995*)
- rate of 6.1% per year in Cleveland adolescents (*Cromer, AJDC 1993*)
- high antibody titers against pertussis antigens in both German and American young adults (*Cherry, Clin Infect Dis 1995*) and Italian adults (*Rota, Clin Infect Dis 1998*)

From institutional outbreaks...

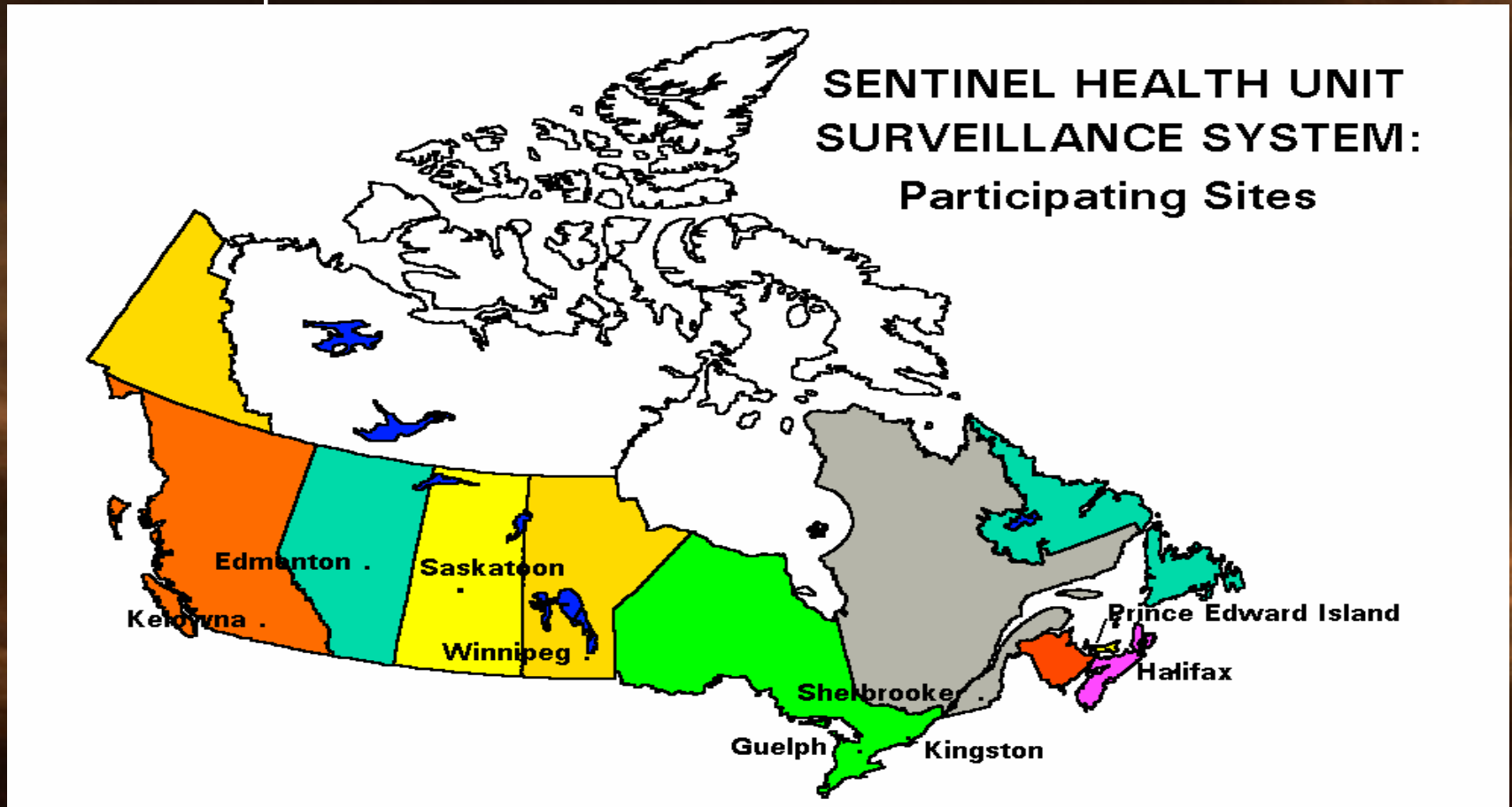
- Wisconsin Nursing Home: 36% of residents and 7.7% of staff
- Wisconsin home for developmentally disabled: 149 adolescents and adults (6-9% of affected wards)
- In Japan, rehabilitation hospital (ages 8-25 years): 82% with evidence of infection

From studies of adult cough illness...

- Australia: 25.7% of adults referred for persistent cough (*Robertson, Med J Aust 1987*)
- Chicago: 26% of adults presenting to an ambulatory clinic with unexplained cough (*Rosenthal, J Infect Dis 1995*)
- Nashville: 21% of adults presenting to an emergency department (*Wright, JAMA 1995*)
- LA: 26% of college students with cough (*Mink, CID 1992*)
- In US Marine Recruits: 6-17% of cough illness greater than 1 week (*Jansen, Clin Infect Dis 1997*)
- San Francisco: 12% of adults presenting to Kaiser Permanente with cough >2 weeks (*Nennig, JAMA 1996*)

From Cough Surveillance... SHUSS

A network* of 9 health units in 8 provinces, representing 10% of Canada's total population, mandated to conduct targeted research and surveillance to address public health issues.



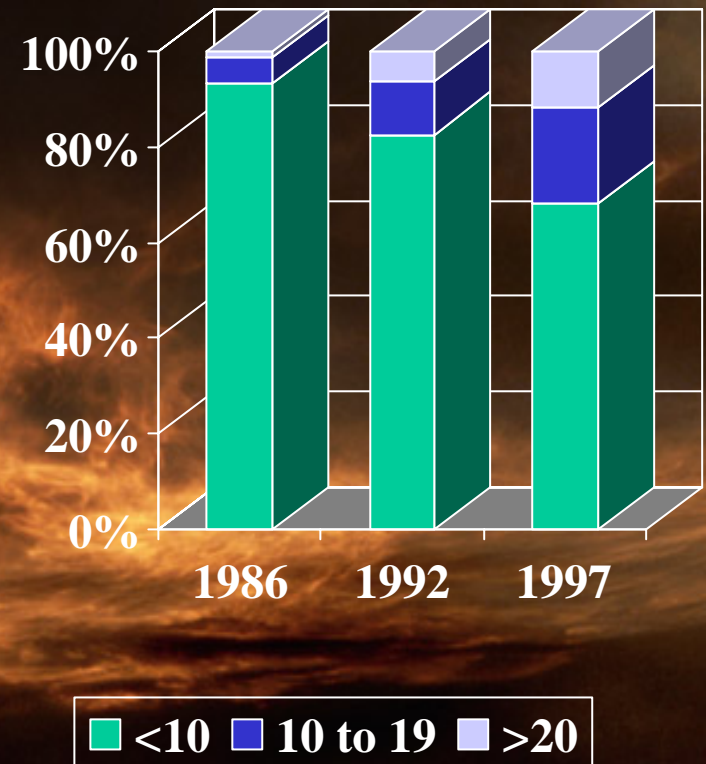
*Funded and coordinated by Laboratory Centre for Disease Control, Health Canada.

LABORATORY RESULTS: ADULTS AND ADOLESCENTS* (n=473)

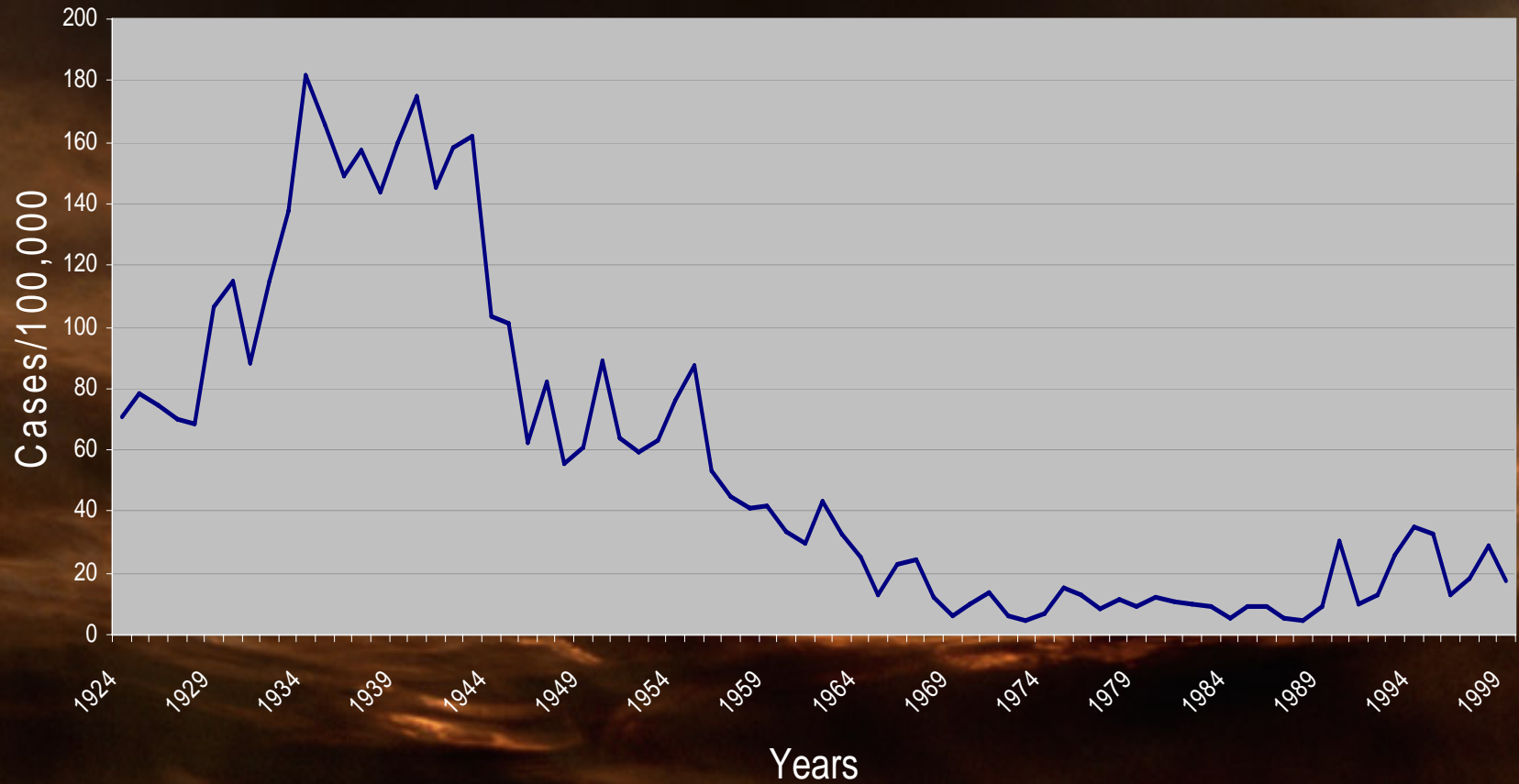
	Positives /n	Prevalence Rate (Conf. Limits)	Age range (Mean age)
A) Culture	2/471	0.4% (0.1, 1.7%)	12 yrs; 24 yrs. (18.4 yrs)
B) PCR	3/338	0.9% (0.2, 2.8%)	12 - 37 yrs. (24 yrs)
C) 4-fold increase	7/473	1.5% (0.6, 3.2)	12 – 70 yrs. (28.1 yrs)
D) > 99.99 percentile of GMTc	36/473	7.6% (5.5, 10.5)	14 - 69 yrs. (36.6 yrs.)
E) > 3 SD of GMTc	90/473	19% (15.6, 22.9)	12-87 yrs. (38.4 yrs.)
F) A + /or B + /or C + /or D	44/473	9.3% (6.9, 12.4)	12 – 70 yrs. (35.3 yrs.)
G) A + /or B + /or C+ /or E	94/473	19.9% (16.4, 23.8)	12 – 87 yrs. (37.8 yrs.)

From disease surveillance...

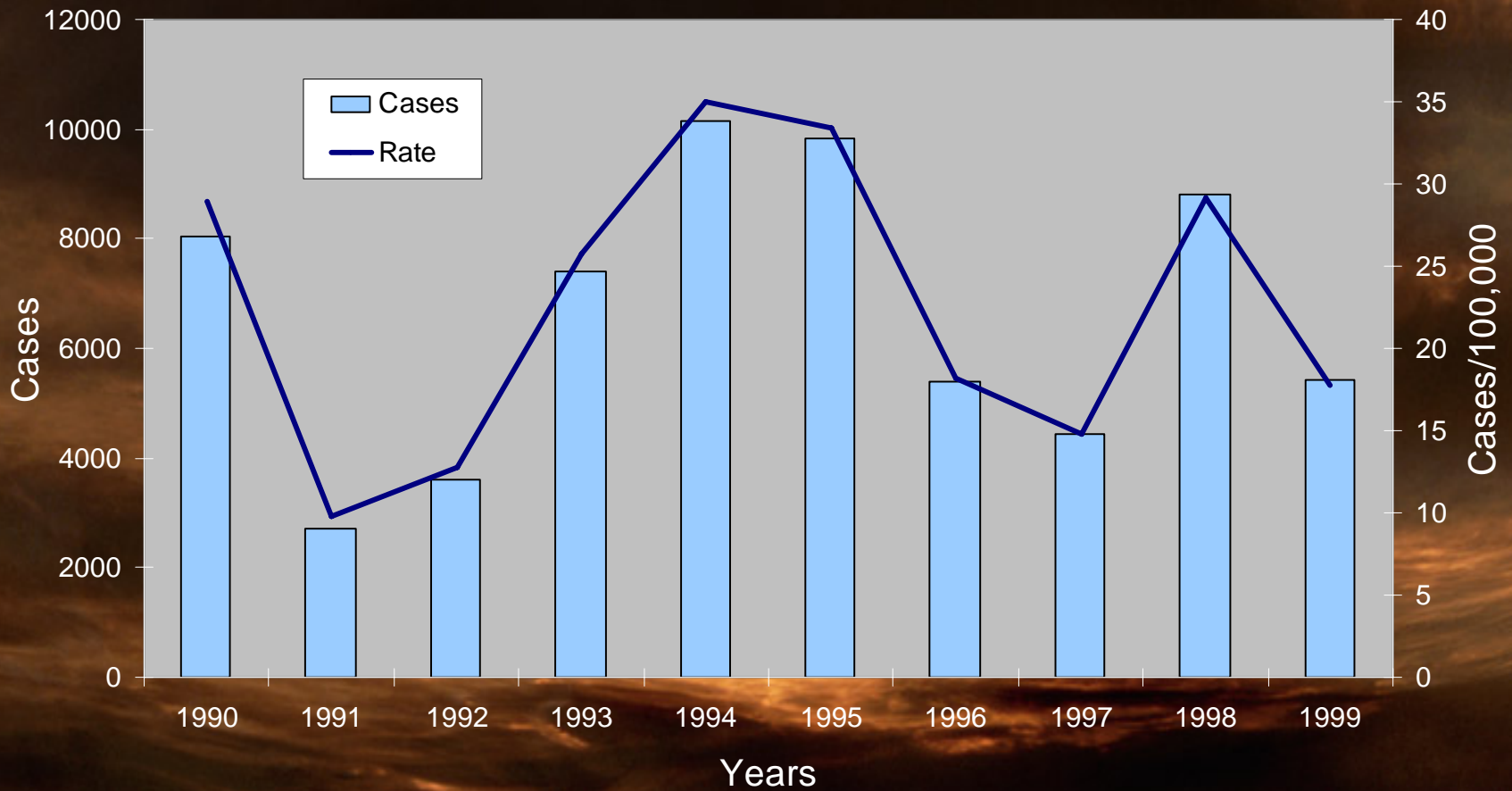
- Trends in the US and Canada have indicated that as pertussis is controlled in pre-school age, both the proportion and absolute numbers of cases are increasing in adolescents and adults



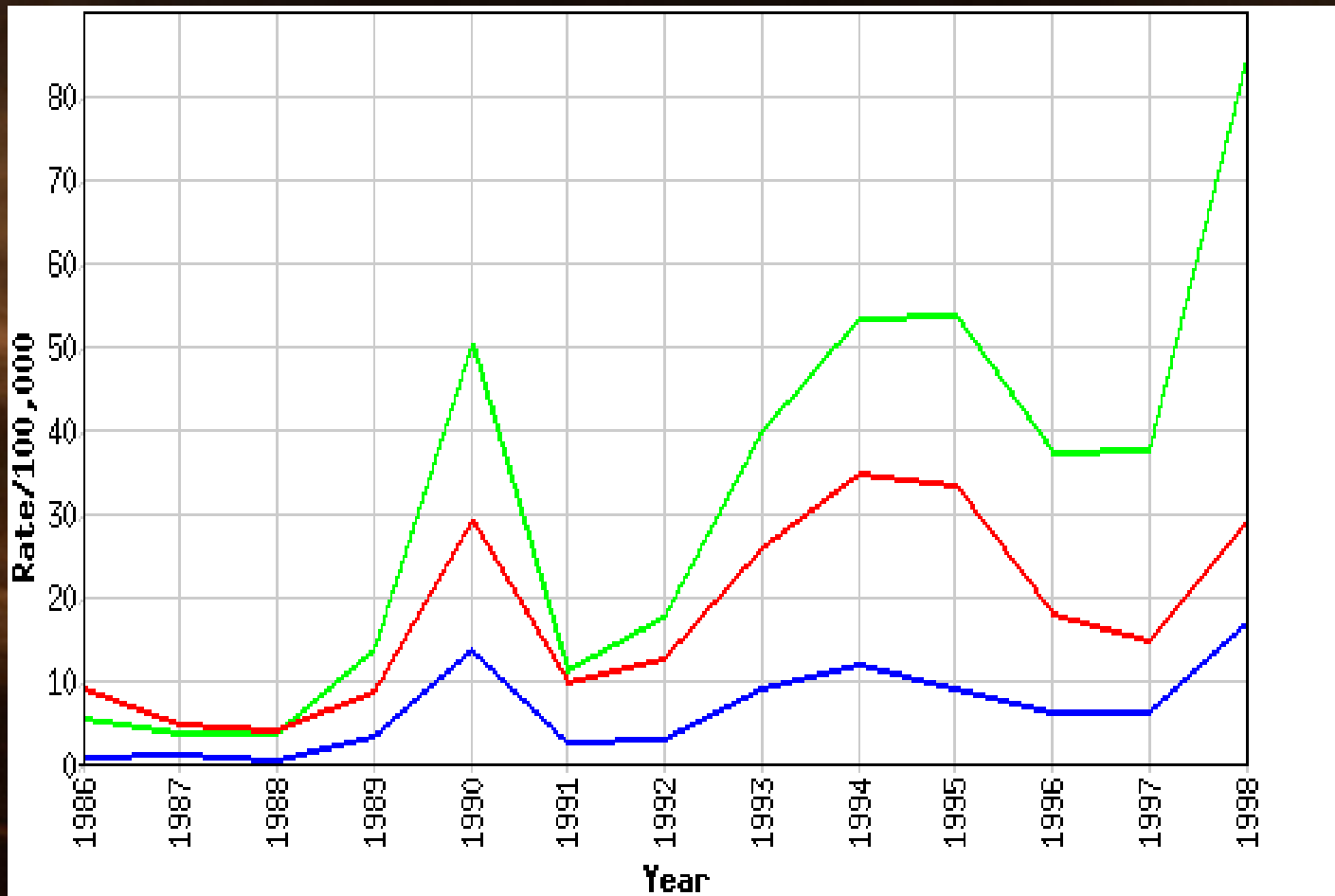
Pertussis Incidence Rates, Canada, 1924-1999.



Pertussis Cases and Incidence Rate, Canada, 1990-99.



Reported Rate of Pertussis in Adolescents in Canada, 1986-1998

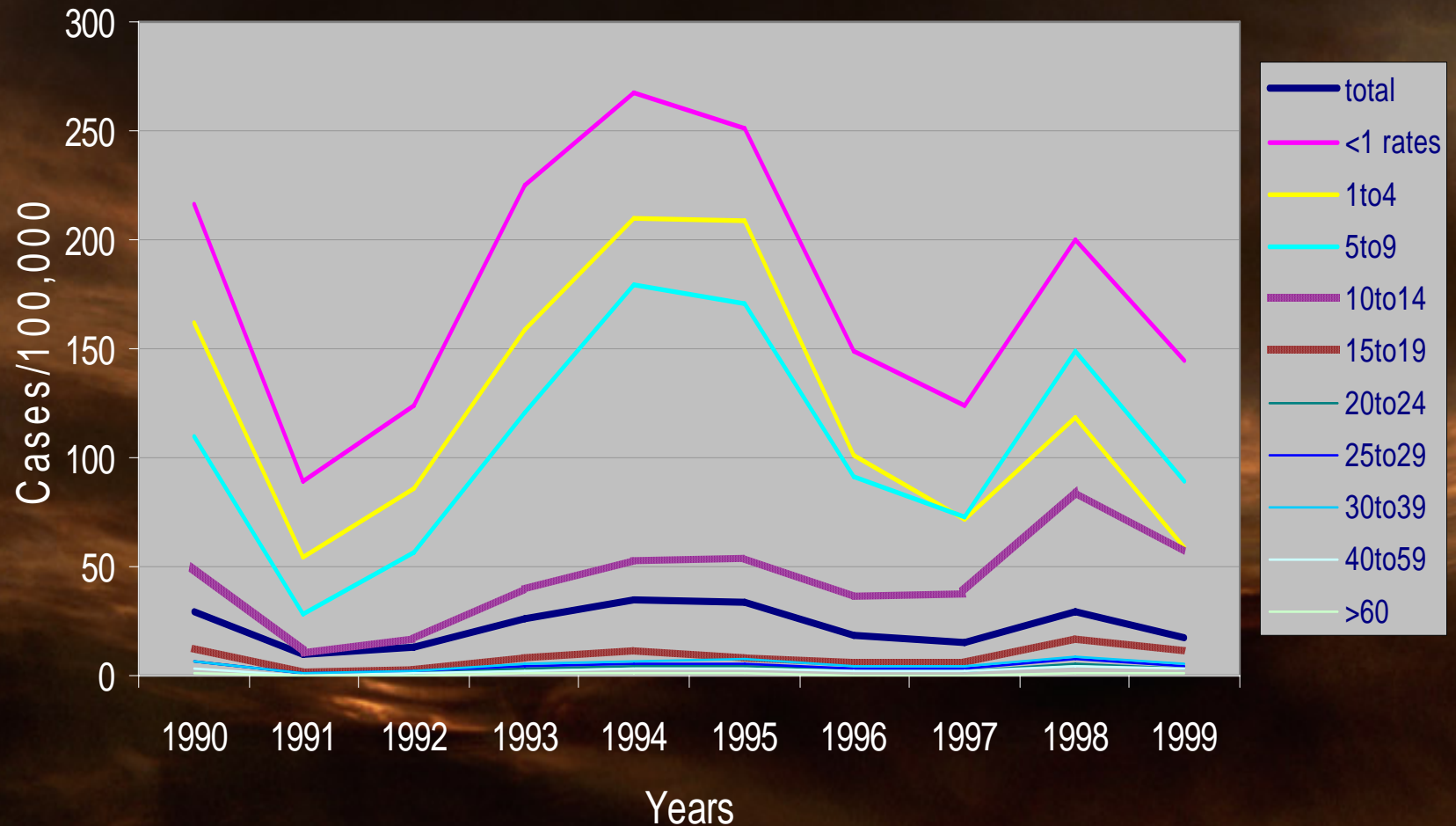


10-14 years

All Ages

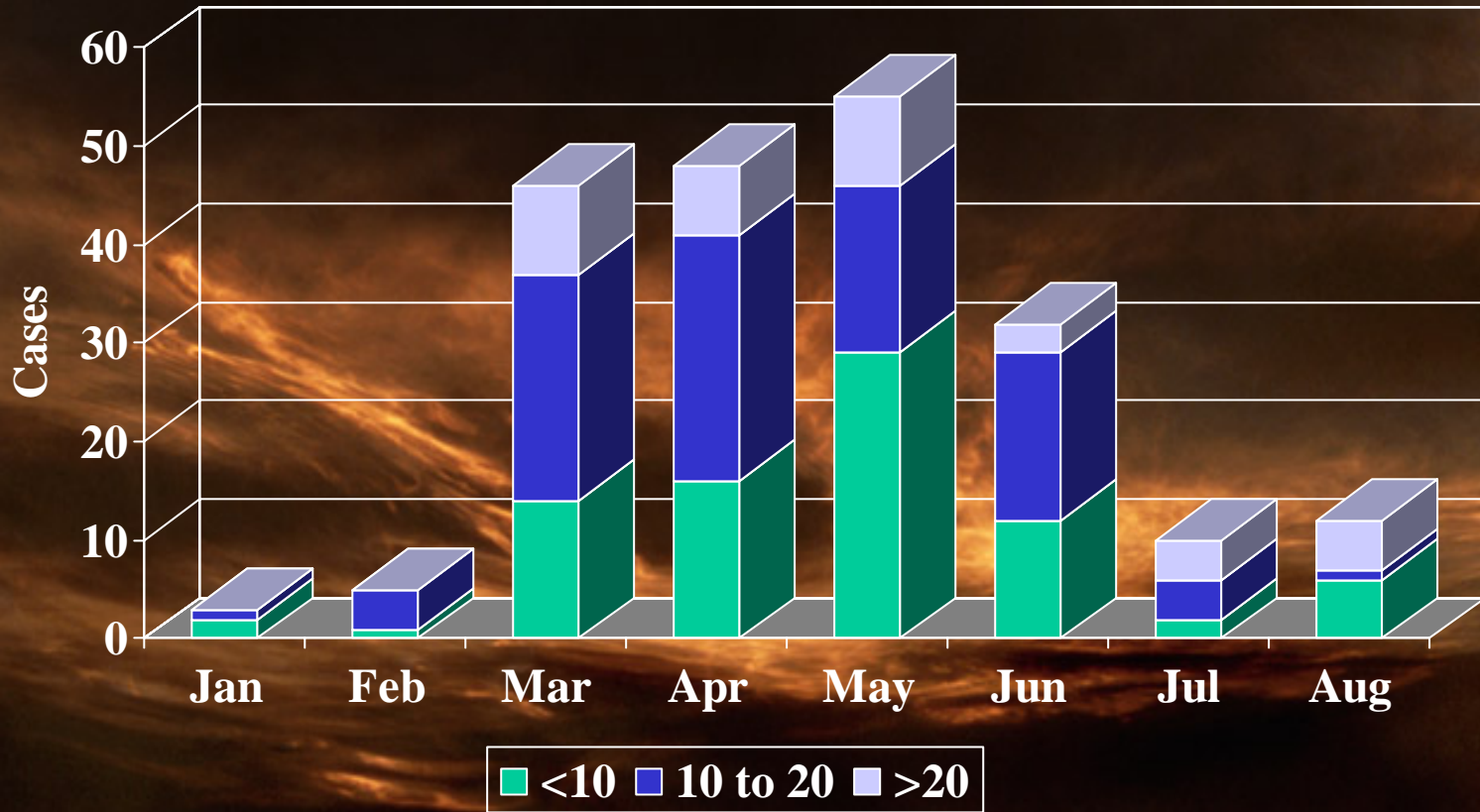
15-19 years

Age-Specific Pertussis Incidence Rates, Canada, 1990-99.



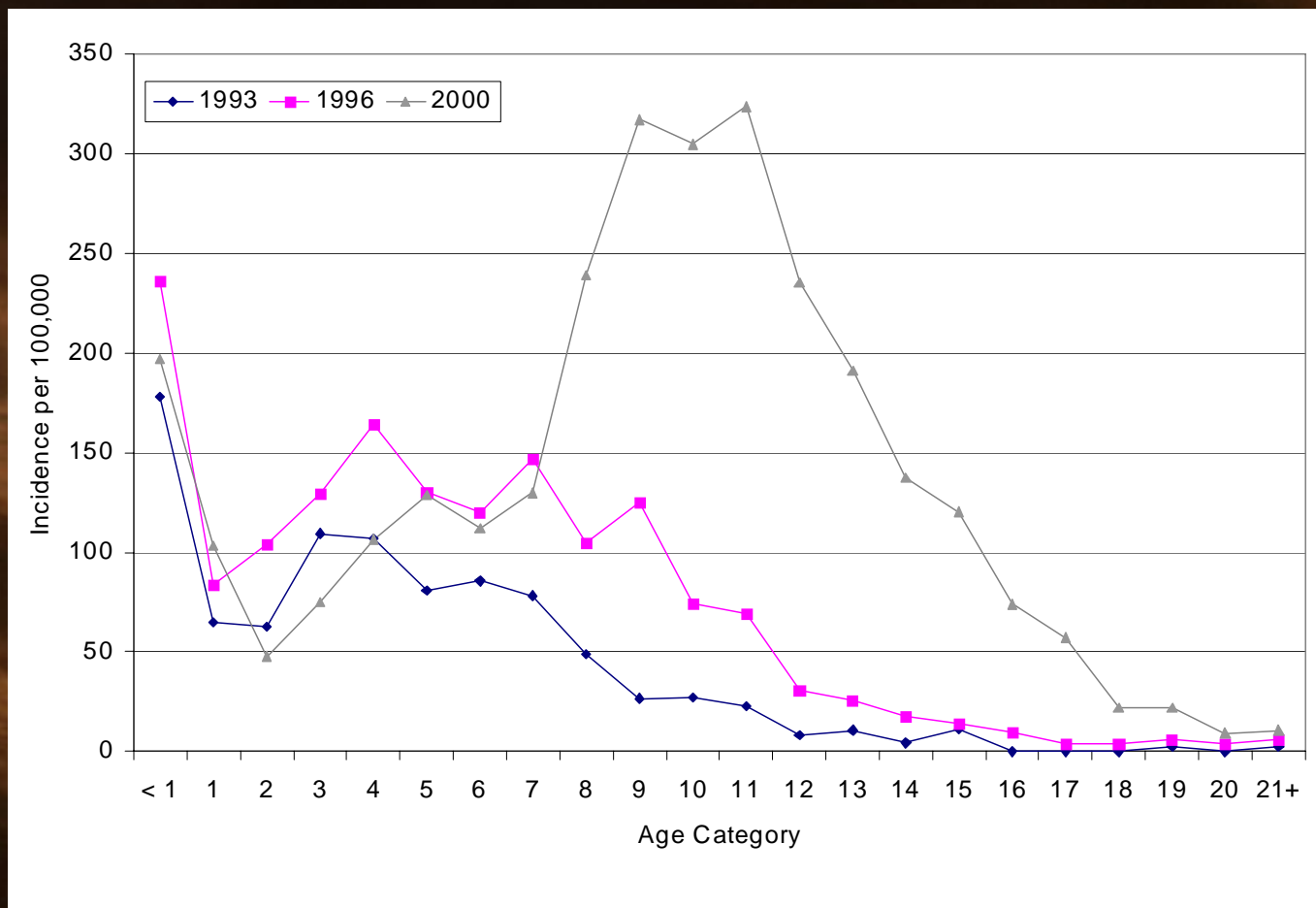
Capital Health District British Columbia, 2000

Population 334,000



Dr. Danuta Skowronski
BC Center for Disease Control

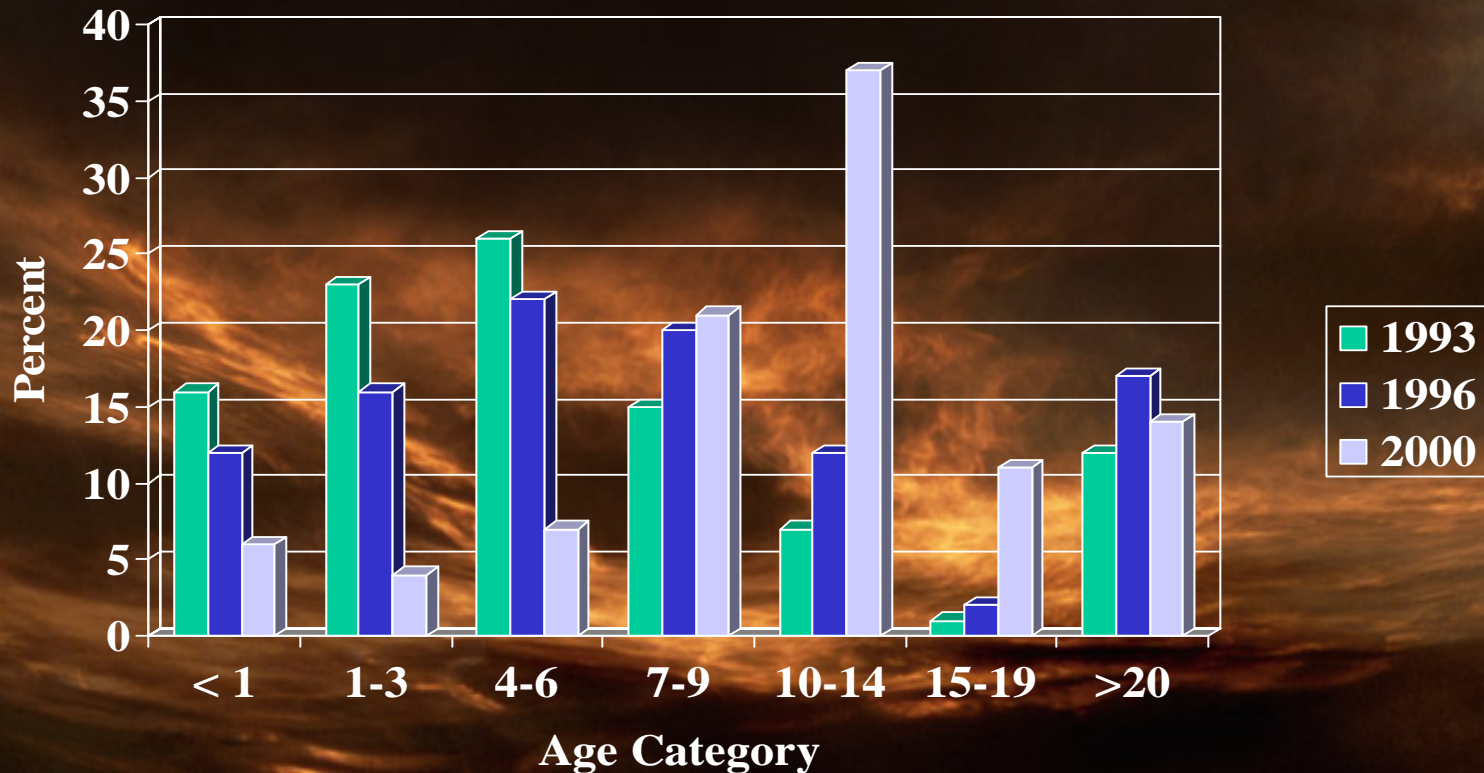
Three Peak Pertussis Years in BC



Dr. Danuta Skowronski

BC Center for Disease Control

Pertussis in BC: Age Profile



Dr. Danuta Skowronski

BC Center for Disease Control

How frequent is pertussis in adolescents and adults?

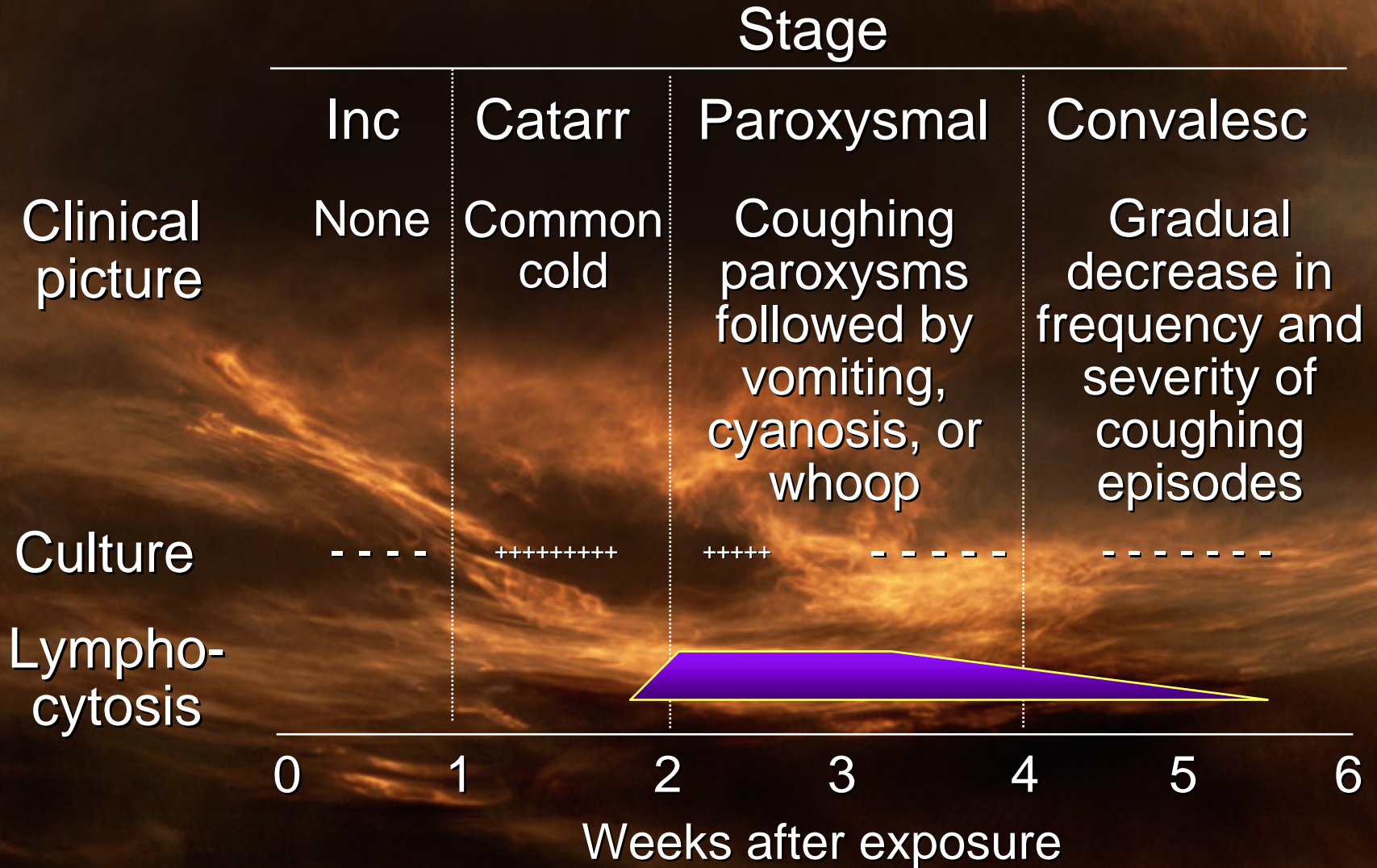
- We still don't know.
 - it occurs
 - it is under-recognized
 - it is under-reported
- Prospective population-based data
 - 3.7-4.5 cases/1000 person years
 - Ward et al, APERT study

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Clinical and Laboratory Course of Pertussis





Pertussis in Adolescents and Adults: The disease

- Wide spectrum of illness
 - mild respiratory infection, “bronchitis”
 - typical pertussis
 - severe disease (cough syncope, seizures)
- Distribution of cases by severity not known because of problems in diagnosis
 - Adolescents and adults less likely to have positive cultures
 - serological diagnosis not well standardized

Pertussis in Adults: Sweden

- 174 culture-positive adults
- symptoms
 - whooping 82%
 - vomiting 50%
 - mean duration 8 weeks (range 2-26)

Trollfors and Rabio BMJ 1981

Adult Pertussis: Germany

- Household contact study; members of household where child was immunized
- 15% of index cases were adults
- symptoms
 - cough 91%
 - paroxysmal cough >21 days 63%
 - sleep disturbance 52%
 - cough with vomiting 42%
 - whoops 8%

Complications of Pertussis

- 79 adults: 18 (23%) with complications
 - otitis media 4
 - transient urinary incontinence 3
 - pneumonia 2
 - pneumonia/hospitalization 1
 - painful cervical adenopathy 2
 - aspiration 1
 - inguinal hernia, hearing loss
 - rib fracture, severe weight loss 1 each

Adult Pertussis: Germany again

- Household contacts of another vaccine trial
- 64 adults with laboratory evidence of pertussis (most serological)
- symptoms:
 - paroxysms 70%
 - vomiting 17%
 - duration 4 weeks

Pertussis in Adults: Canada (SHUSS)

- 77 adults with laboratory confirmed pertussis
- symptoms:
 - violent cough 96%
 - whoop 34%
 - vomiting 49%
 - cough duration 44.5 days

Morbidity of Pertussis in Adolescents and Adults in Quebec

Percent Reporting Complication

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

What does pertussis look like in adolescents and adults?

- The under-diagnosis of pertussis limits our understanding of the true clinical range of the disease
 - the disease ranges from asymptomatic to severe
 - the distribution of cases by severity remains unclear

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Transmission of Pertussis

- Adolescents get pertussis from community and household contacts
- Adults get pertussis from their school age children
- The disease ranges from asymptomatic to severe
- Adult and adolescent parents give pertussis to their young infants
- The young infants are at high risk of morbidity and even mortality



Clinical features of infant pertussis

108 infants <6 months of age with pertussis

- Rhinorrhea 43%
- Cough 100%
- Paroxysms 94%
- Whoop 44%
- Apnea 39%
- Cyanosis 69%

Complications of Pertussis

- Pulmonary

- Pneumonia 9.4%
- Atelectasis 3.0%

- Hernia

- Inguinal 0.4%
- Umbilical 0.4%

- Neurological

- Seizures 1.9%
- Encephalopathy 0.3%

- Weight Loss

1.3%

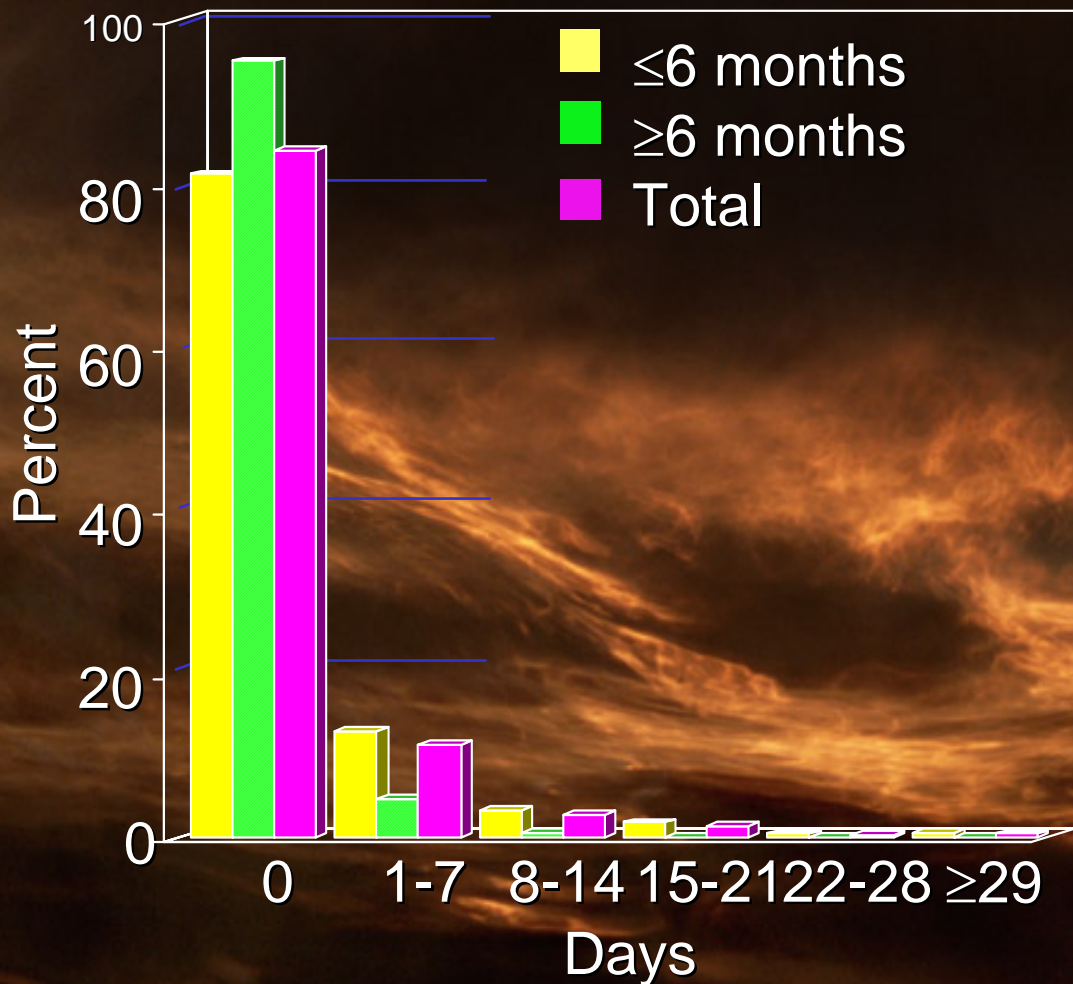
- Death

0.8%

*IMPACT data, 1991-1997. 1013 hospitalized cases <2 years old
Halperin et al. Clin Infect Dis 1999*

Pertussis Hospitalizations 1991-1997

Duration of Intensive Care



Intensive care was required by 18.9% of children <6 mo and 5.16% >=6 mo ($P<.0001$)

Mean 9.4 days
 9.8 days in children <6 mo
 4.6 days in children >=6 mo

Ventilator support required by 47 children (5.1%); ventilation >7 days was reported by 1.4%

From whom do infants get pertussis?

- Wisconsin Outbreak (1987)
 - Transmission of infection from adult relatives or babysitters was demonstrated in 6 of 8 primary cases in infants (< 6 mo of age)

Biellik et al. JID 1988

- Chicago outbreak (1993)
 - infants of adolescent mothers had increased risk of pertussis
 - odds ratio 6.4; 95% CI 1.3-41.4

Izurieta et al. Clin Infect Dis 1996

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 - ➔ What can be done about it?
 - ➔ Treatment/Chemoprophylaxis
 - ➔ Prevention



Treatment of Pertussis

Current Guidelines: United States

- Erythromycin: 40-50 mg/kg/day (maximum 2 gm) for 14 days
 - Preference for erythromycin estolate
 - Can consider newer macrolides (AAP)
 - Cotrimoxazole if erythromycin not tolerated (efficacy not established)
 - Should begin within 3 weeks of onset of symptoms (CDC)

American Academy of Pediatrics, 2000 Redbook
Centers for Disease Control, Guidelines for the Control of
Pertussis Outbreaks, 1999

Past Guidelines: Canada

- Erythromycin: 40-50 mg/kg/day (maximum 1 gm) for 10 days
 - Preference for erythromycin estolate
 - Cotrimoxazole if erythromycin not tolerated (efficacy not established)
 - Should begin within 3 weeks of onset of symptoms

National Advisory Committee on Immunization
Advisory Committee on Epidemiology
Canadian Paediatric Society
CCDR 1994;20(22):193-199

Current Guidelines: Canada

- Erythromycin: 40-50 mg/kg/day (maximum 1 gm) for 7 days
 - Preference for erythromycin estolate
 - Azithromycin or clarithromycin acceptable
 - Cotrimoxazole if erythromycin not tolerated (efficacy not established)
 - Should begin within 3 weeks of onset of symptoms

National Consensus Conference on Pertussis
May 2002

Antibiotic Therapy of Pertussis

- Antibiotics eradicate *Bordetella pertussis* from the nasopharynx
- No effect of antibiotics on clinical symptoms or course unless given in the catarrhal or early paroxysmal phase
- Treatment is therefore more for control of spread of infection than to benefit index case
- *In vitro* susceptibilities do not predict *in vivo* efficacy

Treatment Duration: Review

- 1960s-1970s
 - Pertussis treated for 5-14 days; eradication in 2-5 days
- Series of editorials/reviews ('80, '83, '85, '86)
 - Assertion: relapse only if therapy <14 days
 - Based on review of earlier study with single failure
- Subsequent reviews identified failures with 14 days of therapy but continued to recommend 14 days

Duration of Erythromycin

- Randomized controlled trial
- Single center
- Non-blinded
- 7 versus 14 days of therapy
- Bacteriological outcomes
 - End of therapy
 - One week post therapy

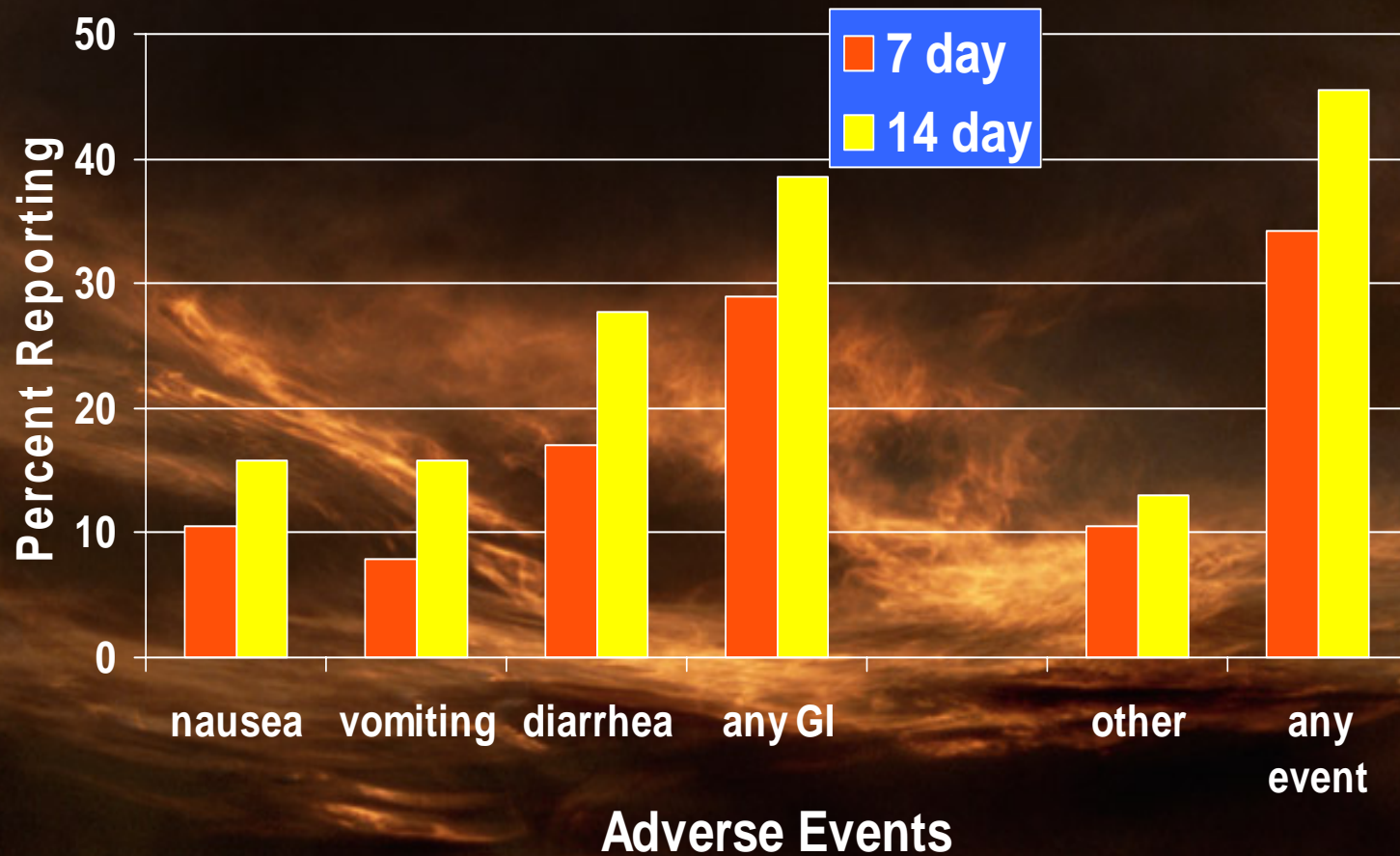
Halperin, Bortolussi, Langley et al. J Pediatrics 1997

Efficacy of Erythromycin Estolate

Comparison of 7 and 14 Days Therapy

<u>Treatment Group</u>	<u>Sample</u>	<u>No (%)</u>	<u>Rate Difference</u> <u>% (95% CI)</u>	<u>Significance</u>
Persistence				
7 day	69	1 (1.45)	0.2 (-7.7-10.4)	0.98
14 day	84	1 (1.19)		
Relapse				
7 day	72	1 (1.39)	1.39 (-5.8-10.8)	0.77
14 day	83	0 (0)		
Overall Failure				
7 day	74	2 (2.70)	1.64 (-6.0-11.7)	0.74
14 day	94	1 (1.06)		

Antibiotic-Associated Adverse Events



Duration of Therapy

Summary and Conclusions

- 7 days of erythromycin estolate is as effective as 14 days for the treatment of pertussis
- antibiotic-associated adverse events were less common with a 7 day course of therapy
- no improvement in compliance was demonstrated under study conditions; however, shorter therapy may provide an advantage under field conditions

Macrolides

Comparison of Attributes

Attribute	Erythro	Clarithro	Azithro
tissue penetration	++	++	+++
intracellular conc	+	++	+++
gi side effects	+++	+	+
cross resistance	+	+	+

Clarithromycin

- 153 subjects; 1 mo – 16 years
- Randomized, single blinded, two centre
 - erythromycin estolate (40 mg/kg/day divided TID) for 14 days
 - Clarithromycin (15 mg/kg/day divided BID) for 7 days
- 153 subjects enrolled
 - 62 subjects culture positive at baseline
 - 35 clarithromycin
 - 27 erythromycin
 - 4 subjects eliminated from the per protocol analysis because of other treatment or lack of follow up cultures

Baseline

Characteristics	Clarithro N=76	Erythro N=77
Male (%)	55	48
Age (mo)	44.7	38.5
History of asthma (%)	25	14*
Vaccinated (%)	89	90
Hospitalization (%)	21	23

* P<0.05

Signs at enrollment

Signs	Clarithro N=76	Erythro N=77
Paroxysmal cough (%)	93	92
Cough with vomiting (%)	64	55
Whoop (%)	54	47
Cyanosis (%)	21	21
Apnea (%)	4	9

Drug related adverse events

Adverse event	Clarithro N=76	Erythro N=77
All adverse events, n (%)	34 (45)	48 (62)*
GI adverse events	24 (32)	34 (44)
Otitis media	0	6 (8)*
Compliance (% doses)	98.5	88.6**

* P<0.05 ** p<0.001

Efficacy

Response	Clarithro N=76	Erythro N=77
At enrollment culture +	35 (46)	27 (35)
End of treatment		
culture done	31	23
culture positive	31	1
Eradication rate		
per protocol	31/31 (100;88.8-100)	22/23 (96;78.1-99.9)
intent to treat	31/35 (89;73.3-96.8)	24/27 (8970.8-97.6)

Conclusions

- 7 days of clarithromycin and 14 days of erythromycin were equally effective for the treatment of pertussis in children
- Clarithromycin was better tolerated than erythromycin
- Compliance better with clarithromycin than with erythromycin

Azithromycin

- ★ 6 mo – 16 years
- ★ Randomized, multicentered
 - erythromycin estolate (40 mg/kg/day divided TID) for 10 days
 - Azithromycin (10 mg/kg/day once daily for one day, then 5 mg/kg/day for four days)
- ★ 477 subjects enrolled
 - 114 subjects culture positive at baseline
 - ★ 58 azithromycin
 - ★ 56 erythromycin
 - ★ 3 subjects eliminated from the per protocol analysis because of pharmacy error (placebo 2) or withdrawal by parent and no follow up data

Baseline

Characteristics	Culture Positive N=111		Culture Negative N=358	
	Azithro n=56	Erythro n=55	Azithro n=179	Erythro n=179
Male (%)	50	33	44	51
Age in mo (range)	6.4 (0.5-16.4)	7.0 (0.5-14.8)	5.7 (0.6-15.9)	5.9 (0.5-15.5)
Vaccines (mean)	4.1	4.5	4.2	4.3

Symptoms at enrollment

Symptoms	Culture Positive N=111		Culture Negative N=358	
	Azithro n=56	Erythro n=55	Azithro n=179	Erythro n=179
Paroxysmal cough (%)	66	73	85	83
Cough with vomiting (%)	34	35	27	34
Whoop (%)	64	60	69	68
Apnea/cyanosis (%)	50	48	30	30

Drug related adverse events

Adverse Event	Culture Positive N=111		Culture Negative N=358	
	Azithro n=56	Erythro n=55	Azithro n=179	Erythro n=179
Any	16 (29)	36 (66) ⁺	51 (29)	88 (49) ⁺
Any GI	11 (20)	27 (49) [*]	33 (18)	71 (40) ⁺
Nausea	2 (4)	8 (15) [^]	7 (4)	12 (7)
Vomiting	4 (7)	6 (11)	9 (5)	29 (16) ⁺
Diarrhea	4 (7)	7 (13)	14 (8)	23 (13)
Abdominal pain	5 (9)	21 (38) ⁺	13 (7)	36 (20) ⁺

[^]p<0.05 ^{*} p<0.01 ⁺p<0.001

Efficacy

Response	Azithro n=235	Erythro n=234
At enrollment culture +	56 (24%)	55 (24%)
End of treatment culture done	53	53
culture positive	0	0
Eradication rate	53/53 (100%)	53/53 (100%)
Post treatment culture done	51	53
culture positive	0	0
Recurrence rate	0 (0%)	0 (0%)

Conclusions

- ★ 5 days of azithromycin and 10 days of erythromycin were equally effective for the treatment of pertussis in children
- ★ Azithromycin was better tolerated than erythromycin
- ★ Compliance better with azithromycin than with erythromycin

Cost Comparison

Drug	10 kg child	Adult
Erythromycin 7 days	\$16.69	\$13.96
Erythromycin 10 days	\$19.15	\$15.86
Clarithromycin 7 days	\$40.19	\$54.72
Azithromycin 5 days	\$30.16	\$45.19

Cost to patient, Lawton's Drugs, May 2002

Pertussis Prevention: Chemoprophylaxis

- US Recommendations
 - Recommended for household and daycare contacts by AAP Redbook (all ages, regardless of immunization status)

Chemoprophylaxis

- Canadian Guidelines
 - Household contacts (including attendees at family day care centres) where there is a vulnerable person (infant <1 year of age or a pregnant woman in the 3rd trimester)
 - Out of household contacts, vulnerable individuals who have had face to face exposure and/or have shared confined air for >1 hour

Chemoprophylaxis: Efficacy data

- Anecdotal reports of successes (1955, 1969, 1975, 1977) and failures (1980, 1983)
- Two small, poorly controlled studies (Grob, 1981; Spencely, 1981) showed no benefit
- Epidemiologic evidence of benefit in institutional or community outbreaks; ie, lower rate of secondary infections in individuals treated than those not treated or treatment delayed

Effectiveness of Chemoprophylaxis

- Retrospective cohort study
- 246 families in Quebec
- Attack rate
 - 25% without prophylaxis
 - 17% with prophylaxis
- When prophylaxis started before onset of a secondary case, the secondary attack rate was 4% with prophylaxis compared with 35% if started after a secondary case

Erythromycin Estolate

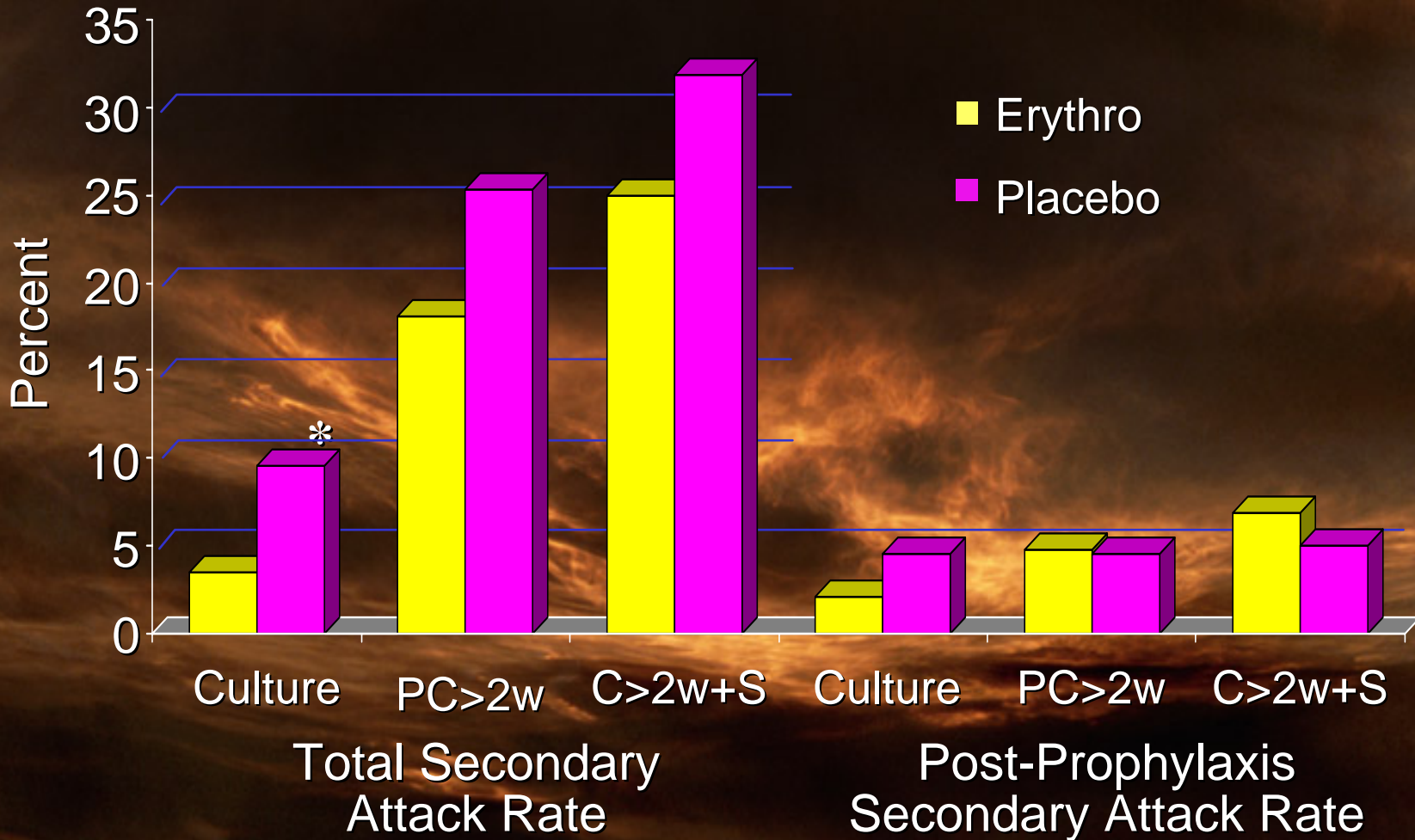
Chemoprophylaxis of Household Contacts of Pertussis

- Randomized, placebo controlled clinical trial
- Household contacts of children with culture-positive pertussis
- 10 days of erythromycin estolate therapy
 - 40 mg/kg/day, maximum 1 gram

Efficacy of Erythromycin Chemoprophylaxis

- All households secondary cases
 - Erythromycin households: 4 (6.6%)
 - Placebo households: 15 (20.3%)
 - Efficacy 67.5% ($P=.026$)
- Trend toward increased efficacy with smaller household size
- No effect of duration of therapy of index case

Efficacy of Erythromycin Chemoprophylaxis







Erythromycin Chemoprophylaxis

- Effective in prevention of culture-positive pertussis
- Does not appear to have effect on development of symptoms or antibody response
- Clinical effect may require earlier implementation

Adult Formulation Acellular Pertussis Vaccines

- Tdap Vaccines
 - Boostrix (GlaxoSmithKline)
 - 1/3 PT/FHA/PRN
 - Adult Td
 - Adacel (Aventis Pasteur)
 - 1/4 PT, same FHA/PRN/FIM
 - Adult Td

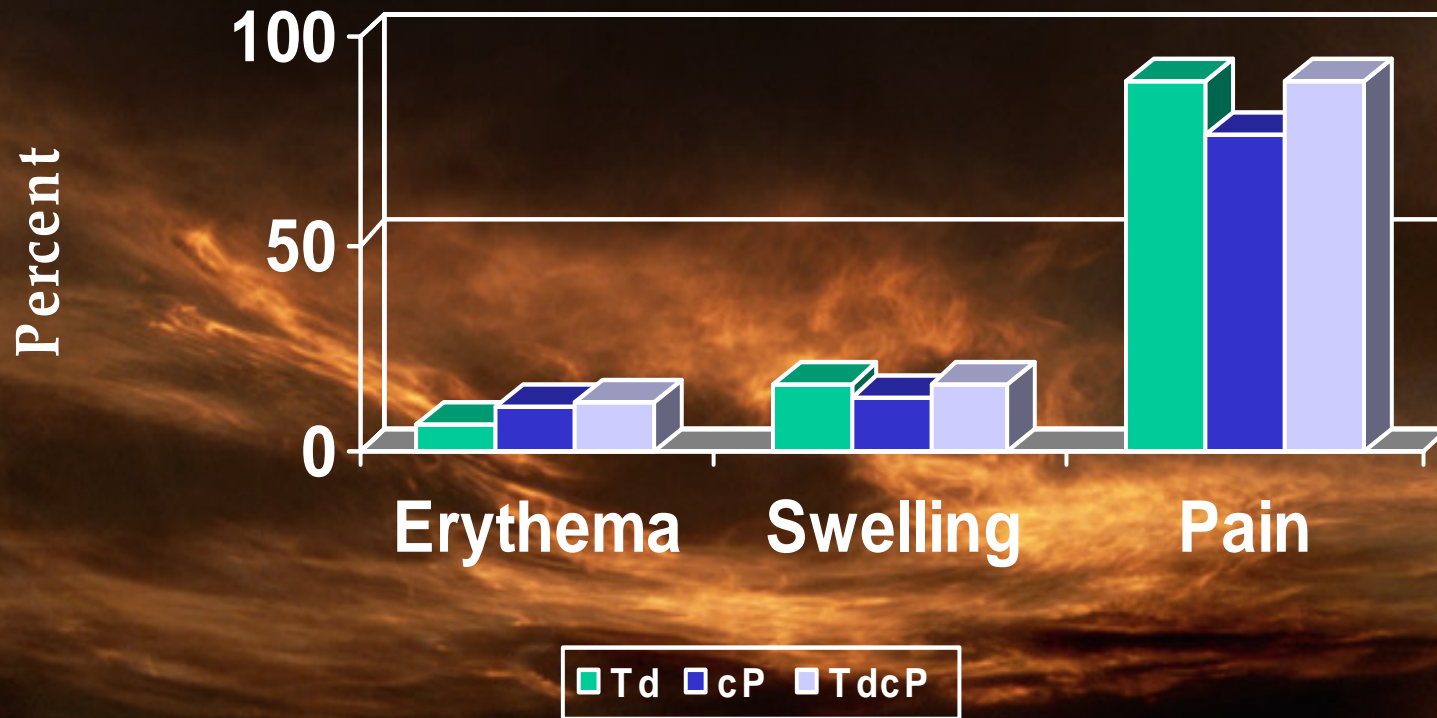
Aventis Pasteur

- pertussis toxoid (PT) 2.5  g
- filamentous hemagglutinin (FHA) 5  g
- Fimbriae 2 + 3 (FIM) 5  g
- Pertactin (PRN) 3  g
- Tetanus toxoid (T) 5 Lf
- Diphtheria toxoid (d) 2 Lf
- aluminum phosphate 1.5 mg
- 2-phenoxyethanol 0.6%

Results: Demographics and Baseline Characteristics

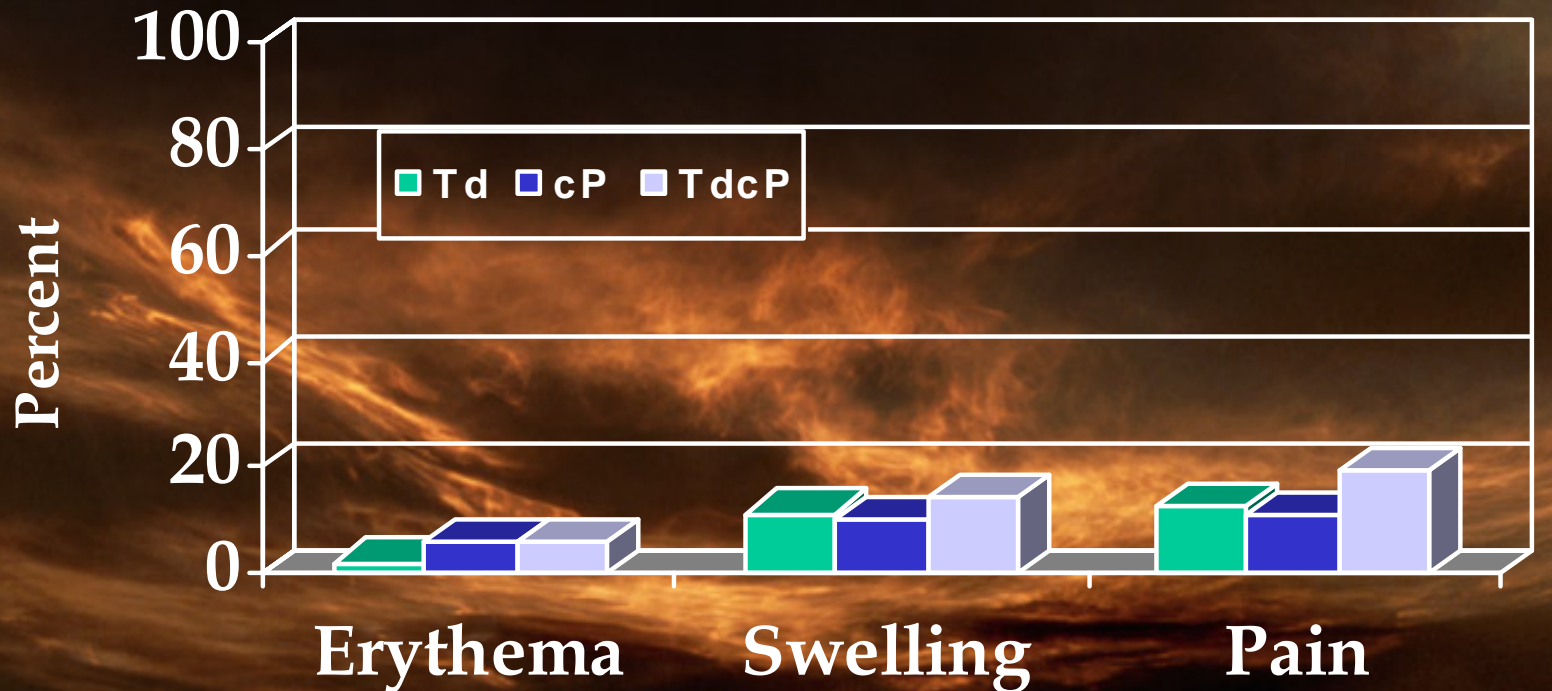
- 149-151 participants per study group
 - Td
 - aP
 - TdaP (3 lots)
- 68% females
- mean age 33.7 years
 - range 12.0-54.7 years
 - 12.3% adolescents

Local Adverse Events



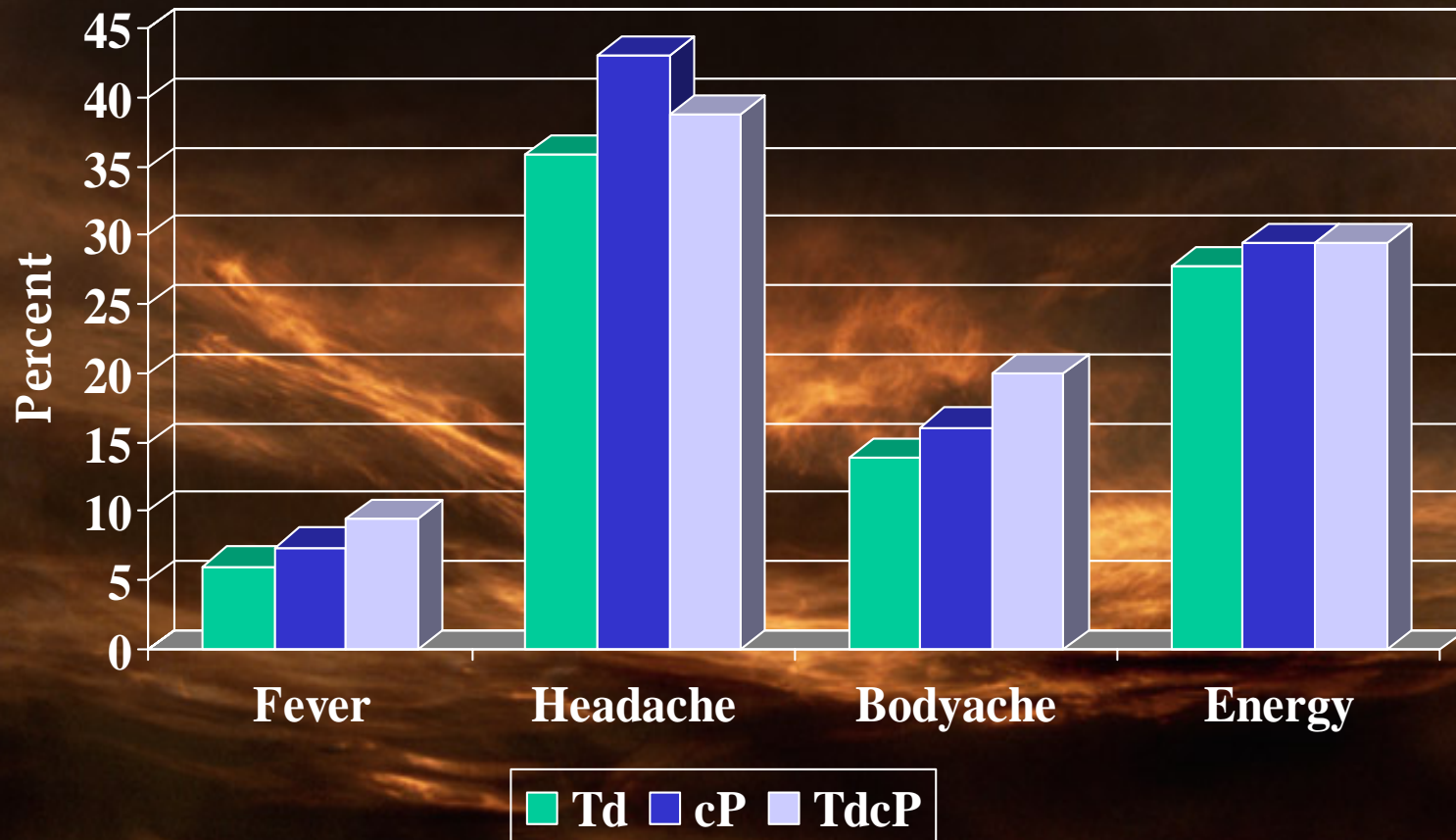
Halperin Vaccine 2000

Local Adverse Events

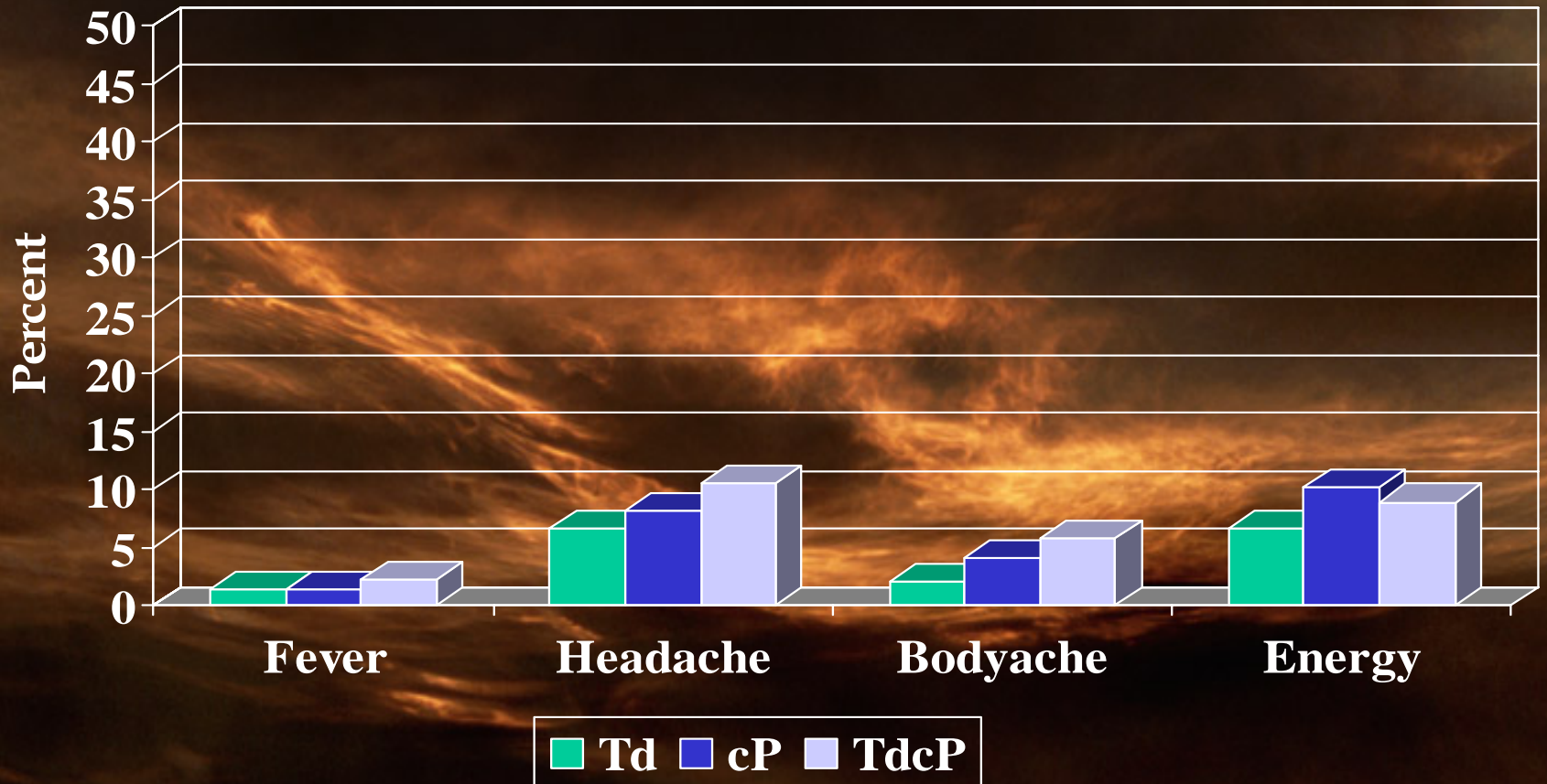


Significant Local Adverse Event

Systemic Adverse Events



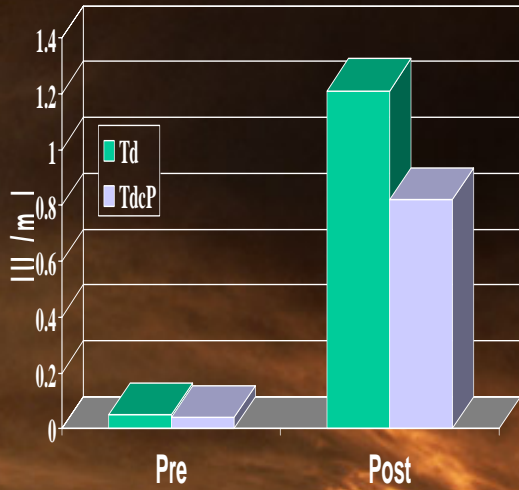
Systemic Adverse Events



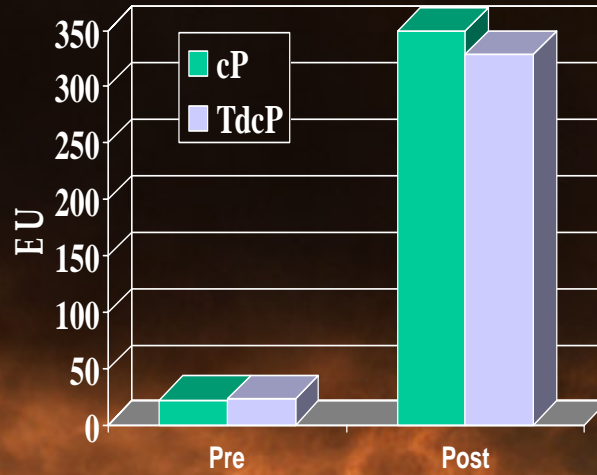
Significant Systemic Event

Antibody Response

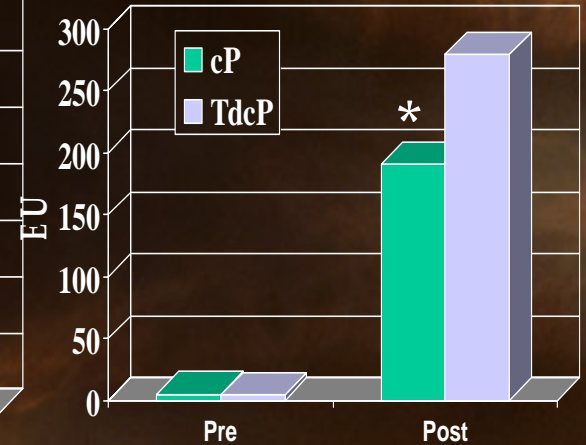
Dip
GMT



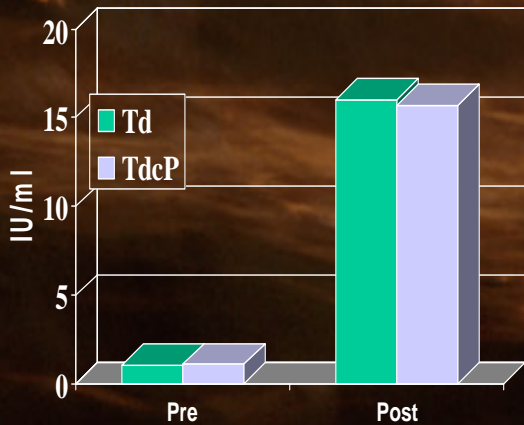
FHA
GMT



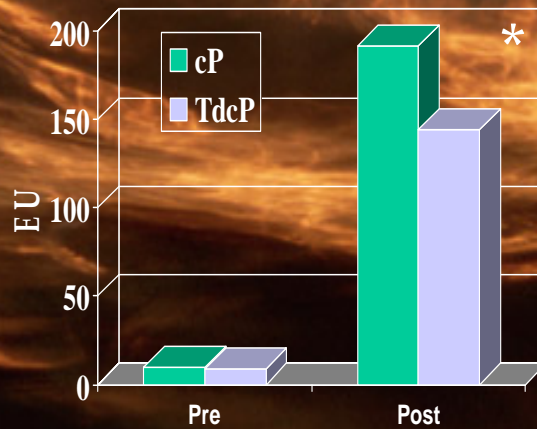
PRN
GMT



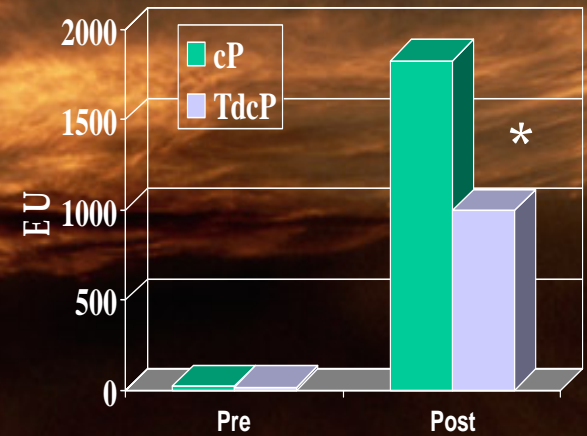
Tet
GMT



PT
GMT



FIM
GMT



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

GMT EU/ml after indicated vaccine

Antigen	2, 4, 6 mo		TdaP		TdaP-IPV	
	Sweden I	Sweden II	Adolescents	Adults	Adolescents	Adults
PT	49.4	51.6	181	139	172	115
FHA	39.1	57.0	333	333	243	229
PRN	116	134	362	269	253	210
FIM	351	352	1471	930	1199	633

Aventis Pasteur Ltd

NIAID Multicenter Study: US

- Prospective, randomized controlled trial
- ~2700 adolescents and adults enrolled
 - GlaxoSmithKline aP (PT, FHA, PRN)
 - Hepatitis A vaccine control
- Prospective surveillance for cough illness
- Laboratory confirmation of cases (culture, PCR, serology)
- Pa vaccine was effective in preventing culture/PCR positive pertussis in adolescents and adults

Ward et al. 2001



NATIONAL CONSENSUS CONFERENCE ON PERTUSSIS

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Goals of the Pertussis Control Strategy

- To decrease morbidity and mortality from pertussis across the entire life span
 - Protection of adolescents and adults is a worthy goal for the benefit of these cohorts themselves
 - It is not clear whether a collateral benefit of protection of infants would be achieved
 - Priority
 - Improve control in infants and young children.
 - Control pertussis in adolescents (by use of universal adolescent immunization).
 - Develop and implement effective strategies for control of pertussis in adults.

Extending Pertussis Immunization to Adolescents and Adults

- Is there a disease of sufficient frequency to be prevented? • Yes
- Is the disease of sufficient severity to warrant prevention? • Yes
- Are there any other reasons to immunize? • Yes/maybe
- Is there a safe and effective vaccine? • Yes
- Can the program be implemented? • Yes
- Would immunization be cost **effective**? • Unknown

Summary

- Pertussis occurs in adolescents and adults
 - the illness is under-diagnosed and under-reported
 - the spectrum of illness varies widely; the burden of disease is substantial but not precisely established
 - safe, immunogenic, and effective vaccines are available for use in adolescents and adults

Conclusions and Recommendations

- Pertussis is an increasing problem in adolescents and adults in Canada
- The true disease burden is not known because the distribution of cases along the spectrum of disease severity has not been established
- Adult formulation acellular pertussis vaccines are underutilized in Canada
- Routine immunization of adolescents should be implemented; better data on the burden of disease in adults may support routine adult immunization

