Foundation Merieux #1

Nov 11-13, 2015

Pertussis in Young Infants

Mattel Children's Hospital at UCLA

The Continuing Problem of Early Diagnosis in Very Young Infants

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The Continuing Problem of Missed and Delayed Diagnosis and Treatment of Pertussis in Young Infants*

* New Title

Mattel Children's Hospital at UCLA

Pertussis Facts*

- *Bordetella pertussis* contains many antigens (toxins) that participate in the infectious process. All of these toxins interfere with the innate immune response.
- In contrast with the contributors to the infectious process, clinical illness is due to just two factors:
  * PT causes severe disease in infants.
  * The cause of cough (“cough toxin”) is unknown.

* Cherry J.D. and Paddock C.D. Expert Rev. Vaccines. 2014; 13: 1115-1123.

Pertussis in Young Infants

- Initially infant looks deceptively well;coryza,sneezing,clearing throat,no fever,mild cough
- Paroxysmal stage:gagging,gasping,eye bulging,bradycardia,cyanosis,vomiting
- Leukocytosis with lymphocytosis
- Apneic episodes
- Seizures
- Respiratory distress
- Pneumonia
- Adenovirus or RSV coinfection can confuse picture

Categories Relating to Pertussis in Young Infants

- Diagnosis missed.
- Diagnosis delayed.
- Risk factors for infection.
- Risk factors for death.
- Prevention of severe disease.
- Prevention of death.

Diagnosis Missed

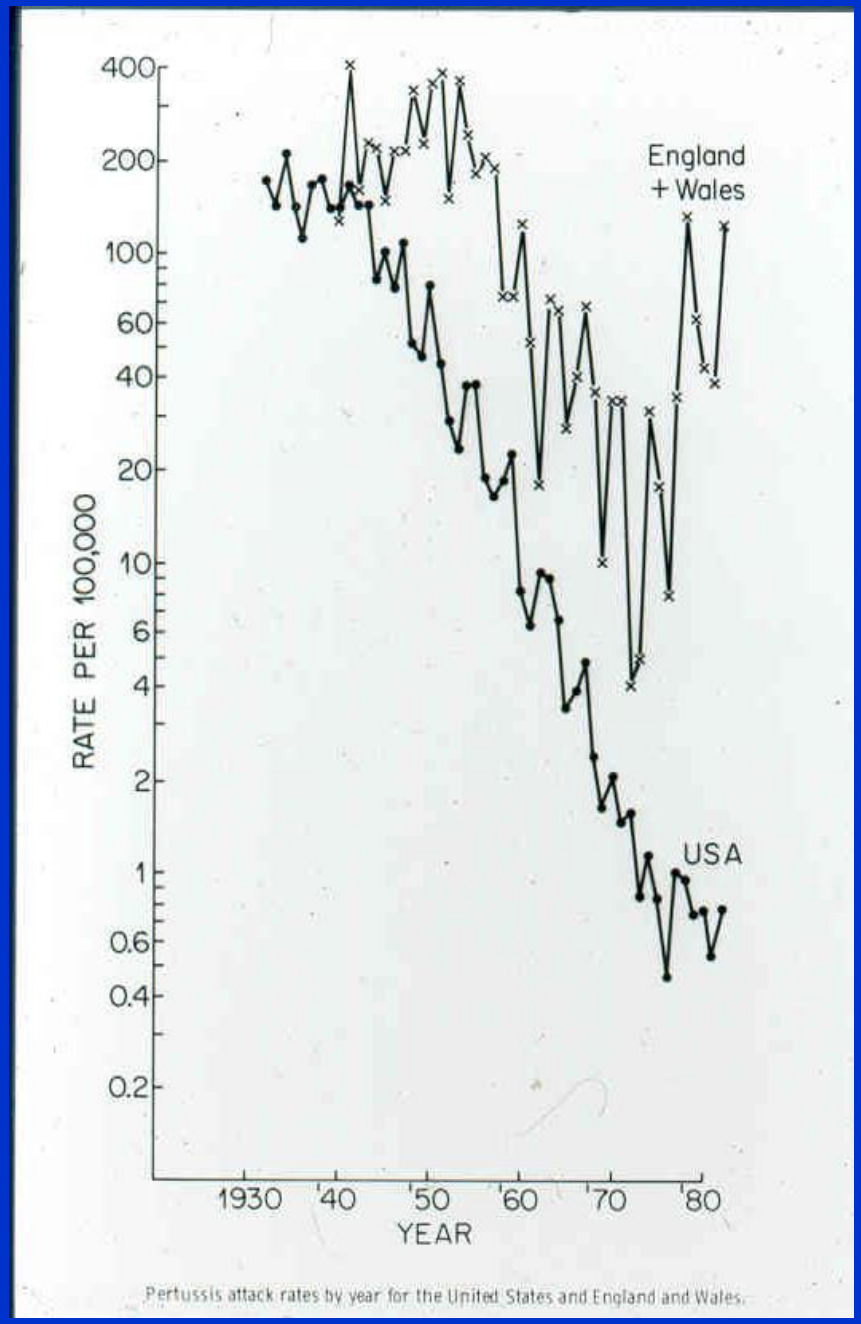
CURRENT PROBLEMS IN PEDIATRICS®

Volume XIV Number 2 February 1984

THE EPIDEMIOLOGY OF PERTUSSIS AND PERTUSSIS IMMUNIZATION IN THE UNITED KINGDOM AND THE UNITED STATES: A COMPARATIVE STUDY

James D. Cherry, M.D.

YEAR BOOK MEDICAL PUBLISHERS, INC.
Chicago



Pertussis attack rates by year for the United States and England and Wales.

Cherry 1984

Reported Infant Pertussis Deaths in England and Wales vs the U.S. 1979-81

- Reported infant deaths in England and Wales were 32; this 6-fold less than in the U.S.
- During 1979-81 in England and Wales deaths due to other respiratory infections increased.
- From the above I calculated that there were an additional 362 infants deaths due to pertussis in England and Wales

Pertussis Deaths Signed Out as SIDS

- Nicol A and Gardner A. Arch.Dis. Child. 1988;63:41-7. Did an analysis similar to mine but included SIDS. They found some pertussis deaths signed out as SIDS; 66-306.
- Landgren et al. Similar findings in Sweden and Norway. Eur J Peds.1997;156: 404-9.
- Heininger U. et al, Controlled study; no SIDS pertussis association. Peds. 2004;114:e9-e15

Diagnosis Delayed

2010 Pertussis Deaths

- Case 1: February 2010
  - Previously healthy, Hispanic female, Los Angeles County
  - Household members with cough illness, however, mom stated they became ill after infant became ill
  - Lived with mother, father, 3 siblings, uncles, aunts, and 2 cousins
  - Symptom onset age 3 weeks
  - Seen by healthcare provider 3 times in 3 days prior to admit; pertussis not considered by provider
  - Admitted from ER after 3 day history of fever, cough, and respiratory distress
  - Transferred from community hospital to children's hospital PICU for intubation
  - WBC 47,500; 65% lymphocytes
  - Pulmonary HTN, partial exchange transfusion, ECMO

2010 Pertussis Deaths, continued

- Case 2: April 2010
  - Previously healthy, Hispanic female, San Bernadino County
  - Lived with mother, brother, sister (grandmother babysat)
  - Symptom onset age 12 days; mother URI/cough 1 week prior
  - Seen in community hospital ER 5 days later, post-tussive vomiting noted, but diagnosed with viral URI and discharged home – pertussis not considered
  - Seen in community hospital ER one week later after developing apnea and cyanosis; transferred from ER to children's hospital PICU; intubation, ECMO
  - Admission WBC 33,900
  - Pulmonary HTN, renal failure
  - Intracranial hemorrhage on day 30 of ECMO → ECMO discontinued → seizures → hemodynamic instability → death

2010 Pertussis Deaths, continued

- Case 3: April 2010
  - Previously healthy, Hispanic female, Fresno County
  - Lived with mom, dad, sister – no daycare
  - Father had cough illness for several weeks
  - Cough onset at age 5 weeks, one week prior to admission
  - Seen in ER 4 days prior to admission with cough, post-tussive vomiting and cyanosis; pertussis not considered - discharged home
  - Seen in ER 4 days later and admitted
  - Hospitalized in children's hospital for one week before transfer to PICU and intubation
  - WBC 80,000; pulmonary HTN - single volume exchange transfusion done
  - Transferred to second children's hospital PICU for ECMO, but not done due to multiorgan failure

2010 Pertussis Deaths, continued

- Case 4: May 2010
  - Hispanic male, Stanislaus County
  - Lived with father, mother, 3 siblings – no daycare
  - Mother had history of cough
  - At age 6 days, hospitalized x 24 hours for hyperbilirubinemia; cough onset day after discharge
  - 10 days later, admitted from ER to community hospital where pertussis was not considered at time of admit; condition worsened shortly after admission → transferred after admission to children's hospital PICU for intubation and ECMO x 7 days
  - Initial WBC 69,000 with 34% lymphocytes; second WBC 90,700 with 26% lymphocytes
  - Pulmonary HTN, disseminated intravascular coagulation, multiorgan failure

2010 Pertussis Deaths, continued

- Case 5: May 2010
  - Previously healthy, Hispanic male, LA County
  - Lived with mother, 2 siblings (grandmother babysat)
  - No identified ill contacts
  - Cough onset at age 7 weeks, 2 days prior to admit from ER, pertussis not considered at time of admit; transferred from floor to PICU on day of admit after condition worsened
  - Admission WBC 33,420; 58% lymphocytes → WBC 100,540; 25% lymphocytes → had two single volume exchange transfusions
  - Pulmonary HTN, profound hypoxemia and hypotension from myocardial suppression and ARDS with acute renal failure

2010 Pertussis Deaths, continued

- Case 6: July 2010
  - Previously healthy, Hispanic female, LA County
  - Lived with mother, father, MGM, and two siblings
  - No identified ill contacts
  - Cough onset at age 6 weeks; during the next 8 days until her death, she was seen by her primary care provider x 3 and in an ER x 1 before the second ER visit that led to her admission – pertussis was not considered; she was almost immediately transferred to a PICU after admission and died the next day
  - WBC 131,000 with 35% lymphocytes

2010 Pertussis Deaths, continued

- Case 7: July 2010
  - Hispanic male, San Diego County
  - Lived with mother and vaccinated 7 year old sibling
  - No identified ill contacts (mother with cough?)
  - Cough onset at 19 days of age; one week history of mild cough, URI symptoms PTA
  - Circumoral cyanosis, increasing respiratory rate and work of breathing on day of admission
  - Seen in ER (O2 sat 86%) and admitted; initial diagnosis bronichiolitis, but pertussis in the differential
  - ECMO → intracranial hemorrhage → death 8 days after admission

Risk Factors for Infection

- A family member with an afebrile cough illness which in undiagnosed or misdiagnosed.
- Large family and extended family.
- Being Hispanic.

Risk Factors for Death

Background

- *B. pertussis* can cause severe illness and death in young infants (associated with extreme leukocytosis)
- Ten deaths in California in 2010
- Education program
- Suggested early PICU care with Rx for extreme leukocytosis
- Planned to evaluate leukodepletion Rx

Our Efforts in California in 2010

- Contacted all AAP, AAFP and ER physicians.
- Offered 24/7 phone avaliability, presened a description of infant pertussis and presented how to do pertussis culture/PCR.
- The AAP mailer went out a second time from CDPH.

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Characteristics of Severe *Bordetella pertussis* Infections Among Infants ≤ 90 Days of Age Admitted to Pediatric Intensive Care Units- Southern California, September 2009-June 2011*

* Murray, E.L. et al. Journal of the Pediatric Infectious Diseases Society. 2013;2: 1-6

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Methods

- All 31 infants ≤90 days with pertussis, admitted to PICUs at our 5 centers
- Records abstracted and merged with CDPH registry
- Compared the 8 more severe cases (death and/ or pulmonary hypertension) with the 23 less severe cases
- Statistics: Fisher's exact test was used to compare proportions between severe vs less severe groups. The t test or Kruskal-Wallis test was used to compare means or medians respectively, depending on the normality as determined by the Shapiro-Wilk test. Kaplan-Meier methods were used to estimate time to event medians that were compared with the log rank test
- Internal review board approval was obtained from all participating hospitals and CDPH

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Results

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White blood cell counts

	More severe *B. pertussis* infection (N = 8)		Less severe *B. pertussis* infection (N = 23)		P-value
	n	%	n	%	
Peak WBC*					
N	8		22		<0.01
Mean	74,200		26,900		
Median	74,100		24,200		
Range	40,700–102,000		10,200-55,200		
WBC ≥30,000*†	8	100	8	36	<0.01
Onset to WBC ≥30,000 (days)					
N	8		22		<0.01
Mean	5.1		22.2		
Median	3.0		Not reached		
Range	0–14		6-61+		
≥50% increase in WBC in 24 hours‡	4	50	0	0	0.01

*** One child did not have a WBC available**
† Only includes infants whose WBC exceeded 30,000
‡ Calculation required at least 2 WBC, so infants with 0 or 1 WBC were excluded

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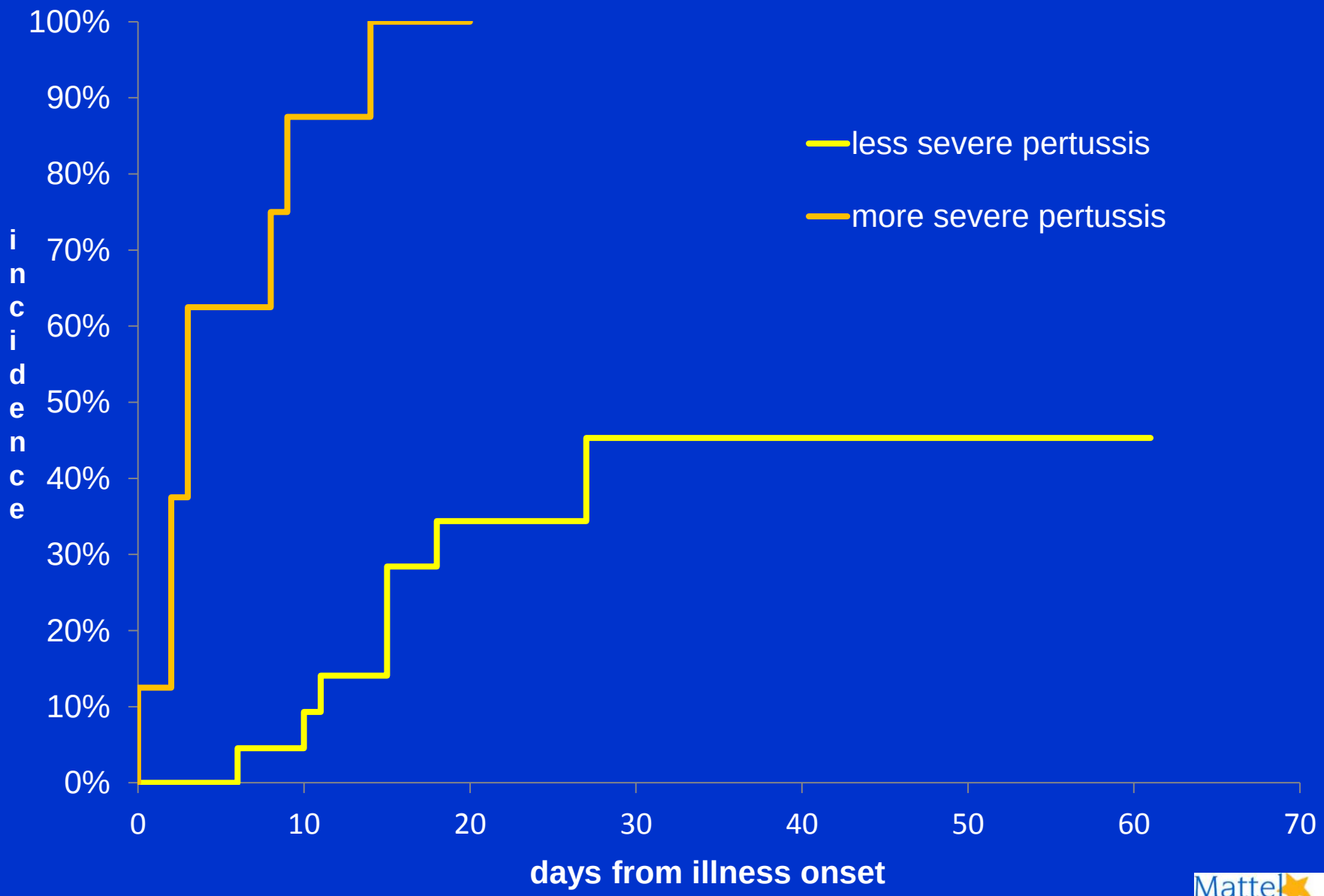
Days from illness onset to White Blood Cell count > 30,000



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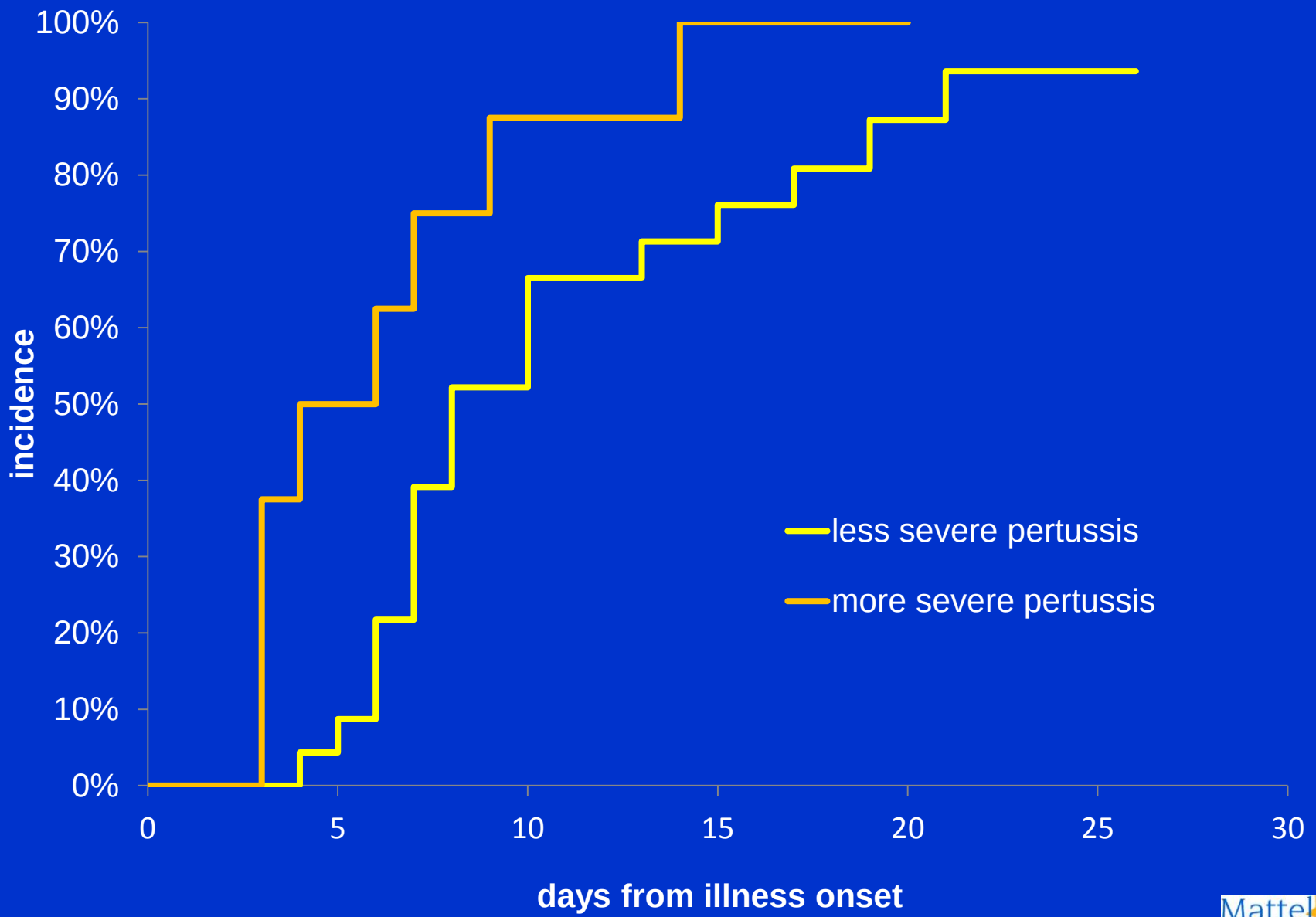
Heart rate measurements

	More severe *B. Pertussis* infection (N = 8)		Less severe *B. Pertussis* infection (N = 23)		P-value
	n	%	n	%	
Maximum heart rate					<0.01
Mean	210.8		188.5		
Median	209.5		193.0		
Range	183–238		148–212		
Heart rate ≥170/minute	8	100	20	87	0.55
Onset to heart rate ≥170/minute (days)					
N	8		23		<0.01
Mean	6.1		10.9		
Median	5.0		8.0		
Range	3–14		4–26+		

Days from illness onset to heart rate > 170



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Respiratory rate measurements

	More severe *B. pertussis* infection (N = 8)		Less severe *B. pertussis* infection (N = 23)		P-value
	n	%	n	%	
Maximum respiratory rate					<0.01
Mean	104.5		70.5		
Median	97.5		67.0		
Range	76–158		42–128		
Respiratory rate ≥70/minute	8	100	10	43	<0.01
Onset to respiratory rate ≥70/minute (days)					
N	8		23		<0.001
Mean	6.9		21		
Median	6.5		27		
Range	2–15		7–61+		

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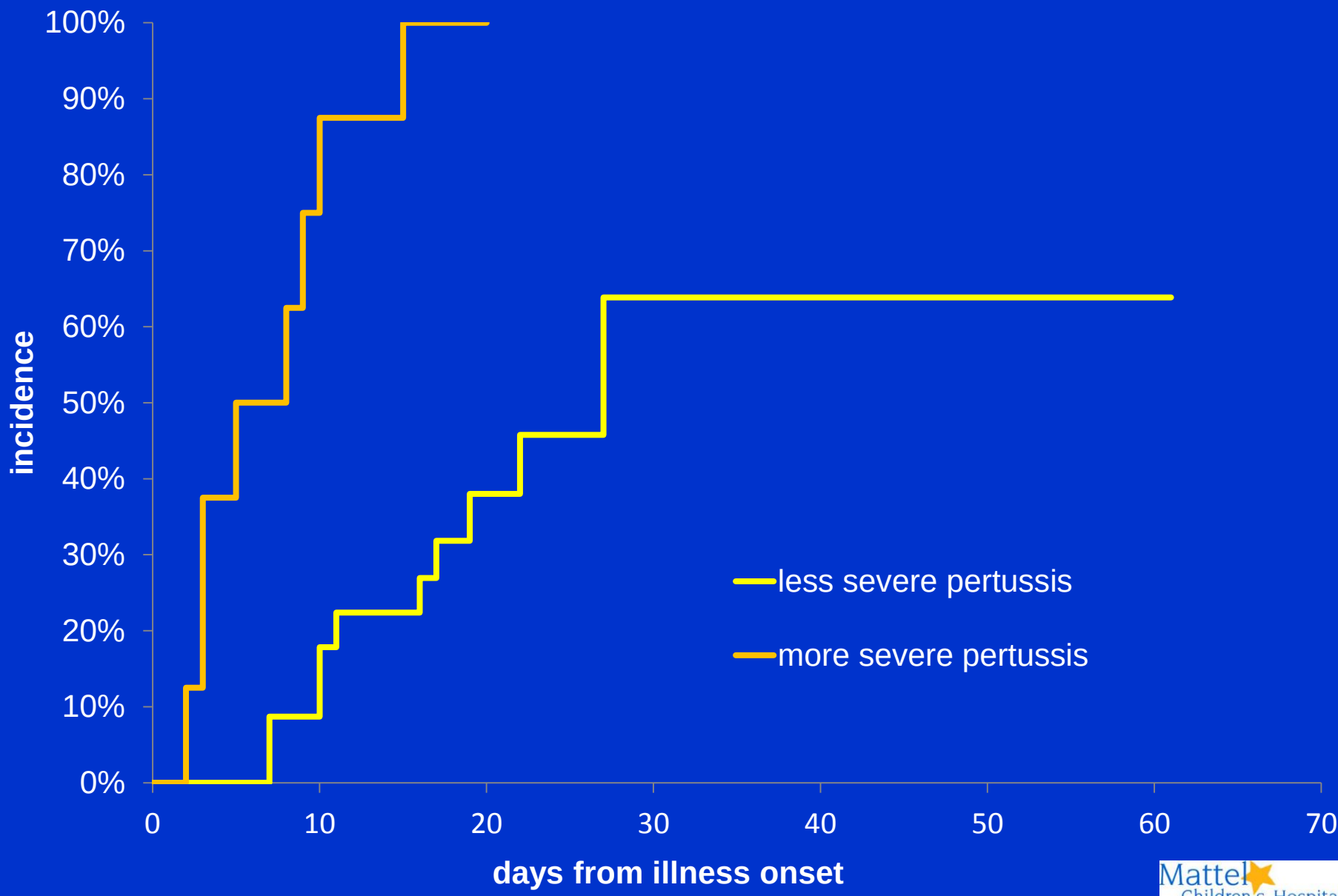
Days from illness onset to respiratory rate > 70



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Complications

	More severe *B. pertussis* infection (N=8)		Less severe *B. Pertussis* infection (N=23)		P-value
	n	%	n	%	
Complications					
Seizure	3	38	1	4	0.04
Hypotension/Shock	4	50	0	0	<0.01
Renal Failure	3	36	0	0	0.01
CXR-confirmed pneumonia	8	100	10	43	0.01
Onset to CXR-confirmed pneumonia (days)					
N	8		22		<0.01
Mean	6.5		21.1		
Median	5.0		23		
Range	2–14		6–61+		

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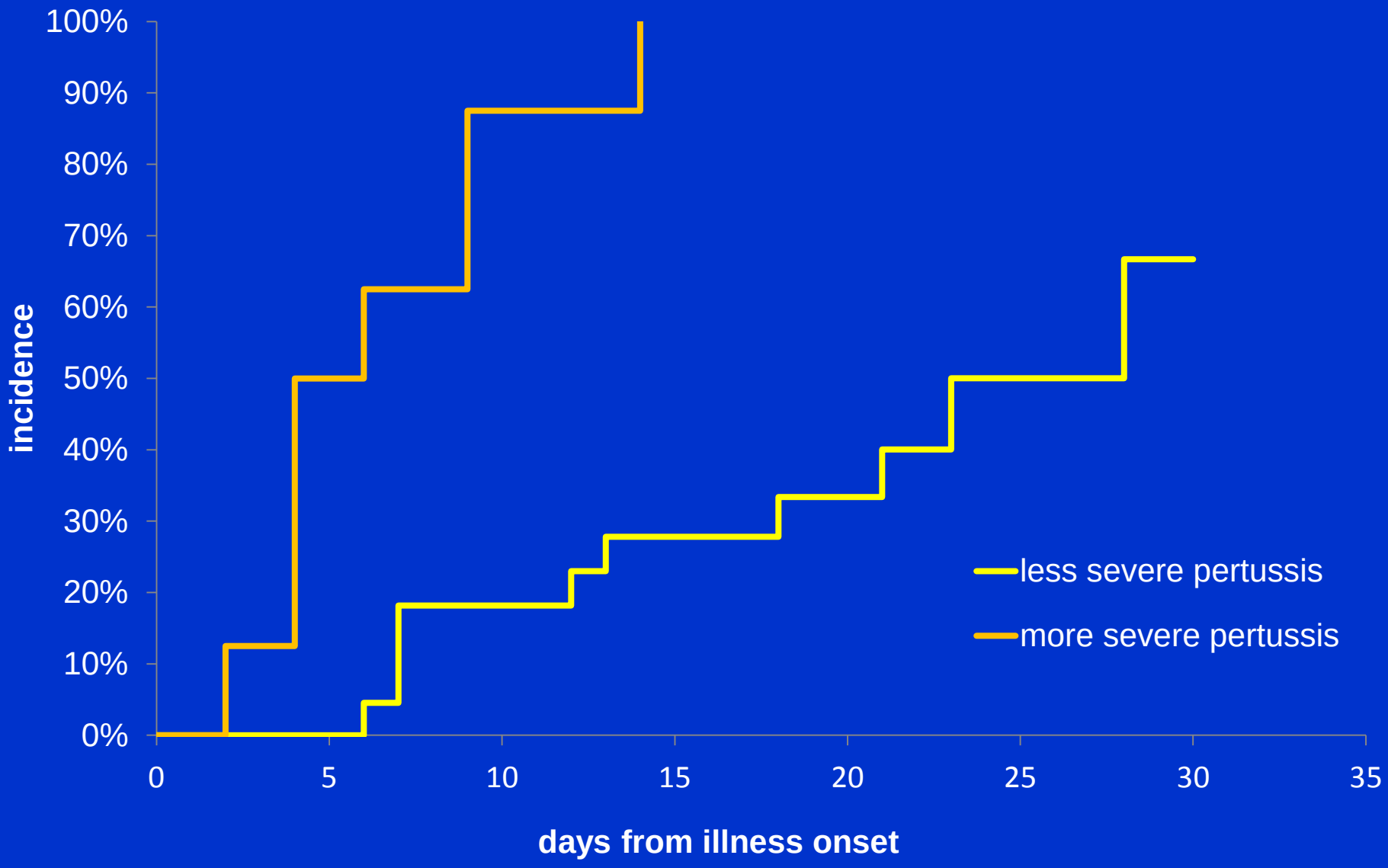
Days from illness onset to x ray confirmed pneumonia



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Procedures

	More severe *B. pertussis* infection (N=8)		Less severe *B. pertussis* infection (N=23)		P-value
	n	%	n	%	
Procedures					
Intubated	6	75	2	9	<0.01
Exchange transfusion	6	75	0	0	<0.001
Maximum FiO_2†					
N	6		2		<0.01
Mean	0.88		0.55		
Median	0.90		0.55		
Range	0.70–1.0		0.55–0.55		

† Only includes infants who were intubated (N = 8)

Summary

- Our study is unique: all PICU ≤90 days, therefore all severe
- We attempted to gain insight in risk factors for a very severe disease
- No differences found in demographics or health care indicators
- More severe had higher mean and median WBC and more rapid rise
- More severe had higher mean and median heart rates and shorter time interval in reaching rate ≥ 170/ min.
- Similar findings for respiratory rates
- More severe group all had pneumonia with a shorter time period to pneumonia onset

Risk Factors Associated With infants Deaths From Pertussis: A Case-Control Study

Kathleen Winter, Jennifer Zipprich, Kathleen Harriman K, Erin Murray, Jeffery Gornbein J, Sandra Jo Hammer, Nava Yaganeh, Kristina Adachi, and James Cherry

Clinical infectious Diseases 2015; 61(7):1099-106

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Methods

- Case-control study: 53 fatal pertussis cases from 1998-2010 in California matched to 183 nonfatal hospitalized pertussis cases <120 days of age
  - Matched on county and nearest onset date
- Complete hospital and ER medical records obtained; abstracted data on symptoms, diagnostic testing, treatment, medical care prior to hospitalization, medical history, breastfeeding and vaccination status
- Cases and controls matched to birth records to obtain data on birth weight, gestational age, Hispanic ethnicity, race, maternal age and parity
- Cases and controls matched to CA Immunization Registry to supplement vaccination history information

Table 1. Maternal and infant characteristics

	Deaths (N=53)		Non-Deaths (N=183)		
	No. of Patients*	Value (percent)	No. of Patients*	Value (percent)	P-value
Infant Characteristics					
Birth weight (median)	49	3084.0 grams	176	**3263.0 grams**	**0.003**
Gestational age (median)	50	266.0 days	165	**273.0 days**	**0.012**
Age at onset of symptoms (median)	53	29.0 days	183	**47.0 days**	**<0.001**
Symptoms					
Paroxysmal cough	47	**30 (64)**	177	154 (87)	**0.002**
Vaccination history					
Any DTaP	52	2 (4)	180	**28 (16)**	**0.033**
DTaP >=7 days prior to onset	52	2 (4)	180	23 (13)	0.077
DTaP >=14 days prior to onset	52	2 (4)	180	19 (11)	0.175

* The numbers of subjects for whom data were available

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Table 2. Clinical course of illness and treatment characteristics

	Deaths (N=53)		Non-Deaths (N=183)		
	No. of Patients*	Value (Percent)	No. of Patients*	Value (Percent)	P-value
Course of illness					
Pulse rate, highest (median)	53	**208 bpm**	172	170 bpm	**<0.001**
Pulse oxygen, lowest (median)	52	**67.0%**	170	86.0%	**<0.001**
WBC count, highest (median)	53	**84,900 cells/mm^3**	170	19,400 cells/mm^3	**<0.001**
Among unvaccinated only‡	50	**85,600 cells/mm^3**	153	19,700 cells/mm^3	**<0.001**
Lymphocyte count, highest (median)	51	**30.7**	161	13.0	**<0.001**
WBC ≥30,000 cells/mm^3	52	**51 (98)**	167	**34 (20)**	**<0.001**
Days to WBC 30 threshold (median)	51	6.0 days	34	9.5 days	0.055
Pulmonary hyptertension	53	**34 (64)**	180	2 (1)	**<0.001**
Seizures	52	**17 (33)**	180	5 (3)	**<0.001**
Encephalitis	53	**8 (15)**	180	2 (1)	**<0.001**
Pneumonia	53	**51 (96)**	160	58 (36)	**<0.001**
Treatment					
Received macrolide antibiotics	53	45 (85)	180	**174 (97)**	**0.002**
Days to macrolide initiation (median)	43	0 days	172	1.0 days	0.308
Received steroids	53	**27 (51)**	177	41 (23)	**<0.001**
Received sildenafil	53	4 (8)	182	4 (2)	0.079
Received Nitric Oxide	53	**32 (60)**	182	3 (2)	**<0.001**
Intubated	53	**52 (98)**	183	11 (6)	**<0.001**
Received exchange transfusion	53	**11 (21)**	183	0 (0)	**<0.001**
ECMO†	52	**17 (33)**	181	1 (1)	**<0.001**

*The numbers of subjects for whom data were available

†Extra Corporeal Membrane Oxygenation

‡ Excludes all subjects vaccinated >14 days prior to illness onset

Table 3. Illness Characteristics; controlling for patient characteristics - Multivariate-stepwise logistic model regression*

	Odds Ratio Estimate	95% Wald Confidence Interval	p-value
Birth weight	0.998	(0.997-0.999)	0.006
Highest WBC count‡	1.059	(1.033-1.085)	<0.001
Pulmonary HTN	30.315	(4.084-225.017)	0.001
Seizure	4.204	(0.652-27.089)	0.131

*variables for selection included birthweight, gestational age, age at symptom onset, receipt of DTaP vaccine, highest WBC count, highest pulse, lowest pulse oxygen, paroxysmal cough, posttussive vomit, pulmonary hypertension, seizure, encephalitis, pneumonia

† Concordance statistic = 98.2

‡ per 1,000 units

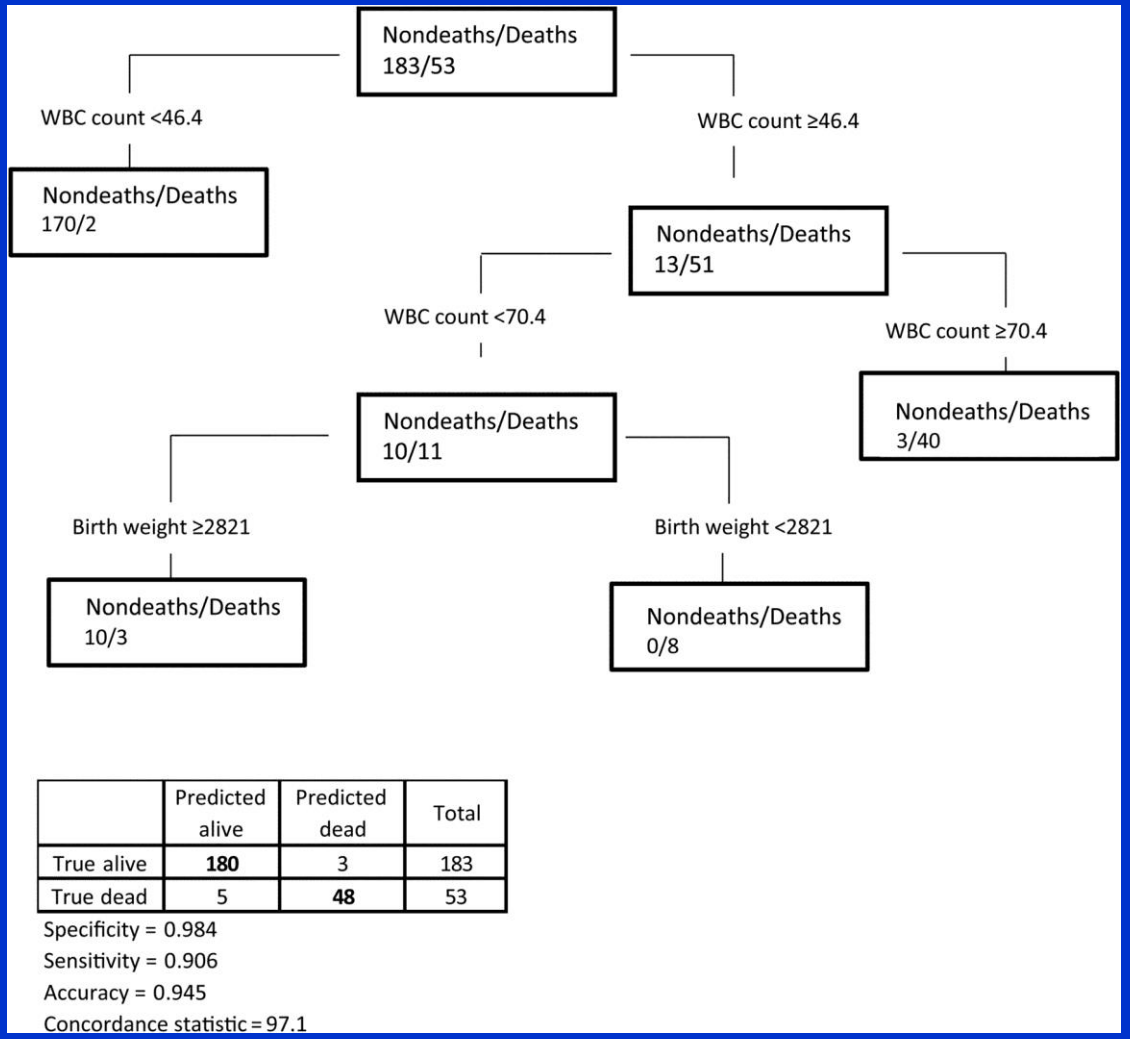
Table 4. Treatment Characteristics; controlling for patient characteristics - Multivariate- stepwise logistic model regression*

	Odds Ratio Estimate	95% Wald Confidence Interval	p-value
Intubation	317.187	(37.477->999.99)	<0.001
Nitric oxide	4.444	(1.043-18.945)	0.044

*variables for selection included birthweight, gestational age, age at symptom onset, receipt of DTaP vaccine, steroid use, macrolide antibiotics, nitric oxide, ECMO, intubation

† Concordance statistic = 94.1

Classification tree of illness characteristics predictive of death due to pertussis.



	Predicted alive	Predicted dead	Total
True alive	**180**	3	183
True dead	5	**48**	53

Specificity = 0.984
Sensitivity = 0.906
Accuracy = 0.945
Concordance statistic = 97.1

Kathleen Winter et al. Clin Infect Dis. 2015;cid.civ472

Conclusions

Among young infants hospitalized with pertussis:

- Prompt initiation of macrolide antibiotic therapy was protective against death
- Younger infants and those with low birth weight have higher odds of death; LBW <2800g a predictor of death
- Elevated WBC count, particularly >46K, is an important predictor of death
  - WBC counts should be monitored and consideration of aggressive clinical treatments when rapid rise is observed
- All fatal cases were intubated
- PHTN, seizures, pneumonia and encephalitis more common among deaths; more data needed to know if nitric oxide increases risk of death
  - “life saving” efforts - ECMO, exchange transfusion may be initiated too late
- DTaP may protect against high WBC counts and death
  - Three studies indicate that accelerating first dose is helpful

Exchange Blood Transfusion in the Management of Severe Pertussis in Young Infants

D.Nieves et al. PIDJ.2013;32:698-699

TABLE 1. Selected Findings* in 10 Infants Preceding Exchange Transfusion in the Management of Pertussis

Category	Death					Survival				
Case Number	1	2	3	4	5	6	7	8	9	10
Age (wk)	8	3	8	4	6	9	2	14	7	5
WBC count peak†	76	62	100	65	83	102	74	82	75	91
Clinical manifestations										
Seizures	o	o	o	o	o	+	+	o	o	+
Pneumonia	+	+	+	+	+	+	+	+	o	+
Pulmonary hypertension	+	+	+	+	+	+	+	o	o	o
Shock/hypotension	+	+	+	+	+	o	o	o	o	o
Organ failure	+	+	+	+	–	o	o	o	–	–
Interventions										
Intubated	+	+	+	+	+	+	+	+	+	+
Extracorporeal membrane oxygenation Rx	+	+	o	o	+	o	o	o	o	o
Exchange transfusion	+	+	+	+	+	+	+	+	+	+

*All findings (except death) noted before exchange transfusion.

†In thousands.

+, yes; o, no; -, not reported.

A Prospective Observational Study of Exchange Blood Transfusion in the Management of Severe Pertussis In Infants < 120 Days Old

All California hospitals with PID services and PICUs

October 2013-April 30, 2015

Mattel Children's Hospital at UCLA

Prelimenary Analysis of Cases in this Study Suggest that Misdiagnosis of Shock and Over Treatment May be a Problem

- Confusing bradycardia and apnea with shock.
- Use of pressors without evidence of hypotension.
- Use of conventional methods to treat pulmonary hypertension.

Diagnosis

Clues in the Clinical Dx of Pertussis in Young Infants

- They have a cough illness without fever.
- They don't have wheezing unless there is a concomitant viral infection.
- They have a rapidly rising WBC count with a lymphocytosis. Therefore do a WBC count on all infants with a new afebrile cough illness.
- Most often there is an adult family member with an afebrile cough illness.

Clues in the Clinical Dx of Pertussis in Older Children,Adolescents and Adults

- Lack of fever
- Lack of a truly productive cough
- WBC,ESR and CRP normal
- Feeling of a choking sensation
- Cough worse at night; need to sleep sitting up
- Sweating episodes
- Normal between coughing episodes

Treatment

Treatment

- In young infants, it is imperative to do a WBC count when initially seen and to monitor the WBC, and pulse and respiratory rates at frequent intervals
- A subset of infants should receive early exchange transfusion and non-aggressive PICU care
- To be successful exchange transfusion must be done before hypotension/shock and organ failure
- Exchange transfusion should be better than leukofiltration

Treatment

- **Children**
- Azithromycin = 10 mg/kg on day 1 and 5 mg/kg on days 2-5 as a single dose/day

Why Hospitalize Infants

- Assess progression/cadence of illness (in particular monitor WBC count)
- Assess life-threatening events
  - Severity/number paroxysms
  - Ability self-rescue
- Prevent or treat complications
- Be able to do exchange transfusion before shock/hypotension or organ failure
- Educate parents in care/course

What Can Be Done?

- Dx and Rx pertussis (particularly in young infants).
- Educate those who care for adults that pertussis is common in adults, usually misdiagnosed and it can be prevented to some degree by Tdap.
- Promote cocooning around infants and most importantly administer Tdap to all pregnant women with each pregnancy.
- Rather than Td give Tdap every 10 years.
- Lower the start date of DTaP to 6 weeks.

Questions/Comments