Arizona Epi-Aid:

Increasing Use of Serology in Pertussis Diagnosis

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Pertussis in Arizona

- **Pertussis increase in 2011**
  - USA: decrease in pertussis compared with 2010
  - Arizona: 59% increase compared with 2010
  - Incidence in AZ increased from 8.3 to 10.1/100,000 persons

- **First pertussis death since 2009**
  - Neonate with symptom onset at 7 days
  - Parents had paroxysmal cough 2 weeks prior to delivery
  - Neonate initially diagnosed with upper respiratory tract infection
  - Died after a one month admission

Call for Epi-Aid

- **Maricopa County**
  - Many suspected pertussis cases tested using serology
    - 90% of suspected cases over a 6 month period
- **Rationale**
  - Arizona has increasing number of serology tests for pertussis
  - Potential for serology as a tool in pertussis diagnosis
    - Further investigation needed: validity and impact on surveillance and case investigation

Epi-Aid Objectives

1. Assess the use of serology for pertussis diagnosis

2. Assist with guidance on pertussis case prioritization for investigation and test recommendations

3. Development of educational tools for providers

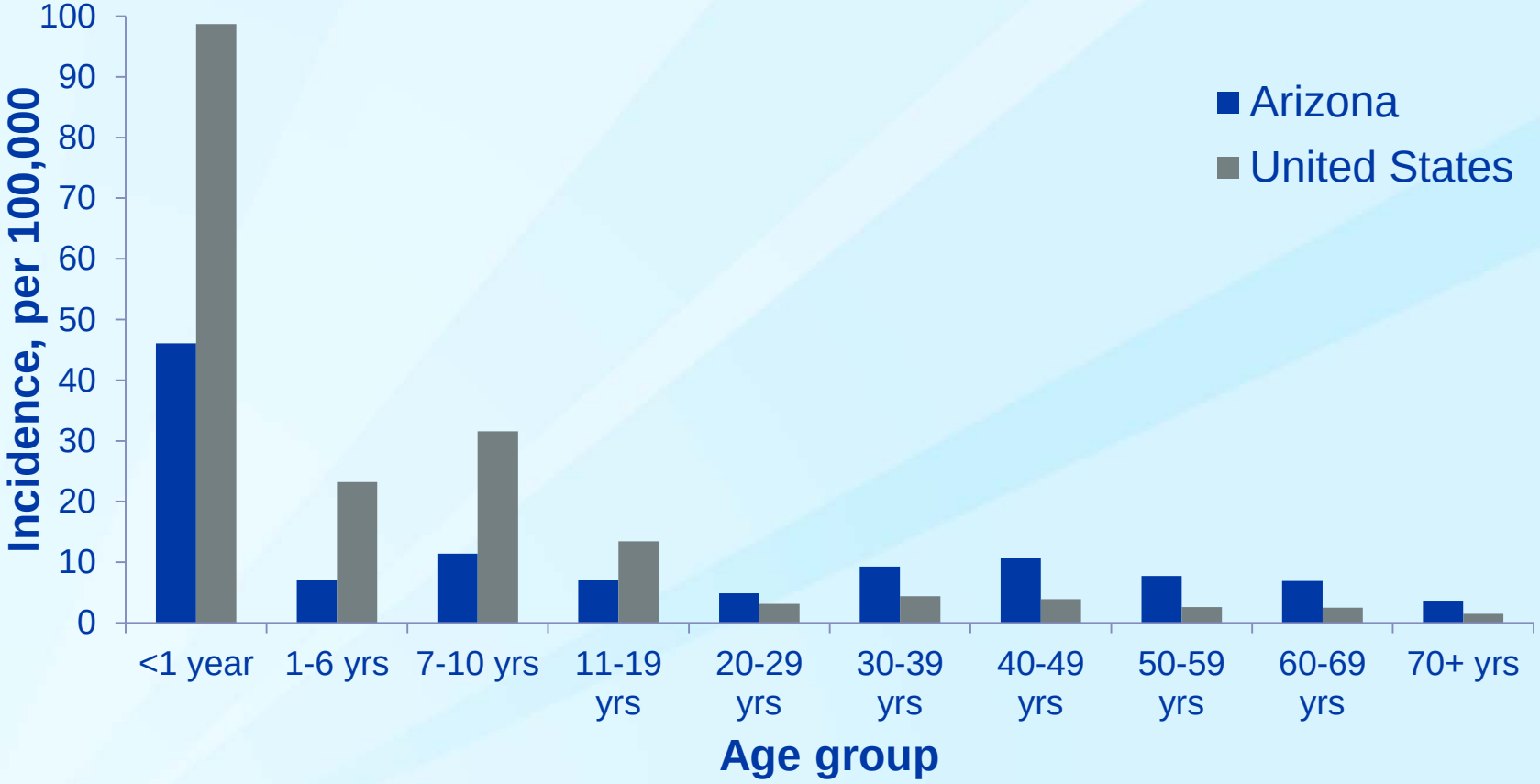
Outline

- Background
  - Epidemiology and reported pertussis test choice
  - Diagnostic Testing
- Methods and Results
- Conclusions
- Recommendations

Epidemiology and Test Choice

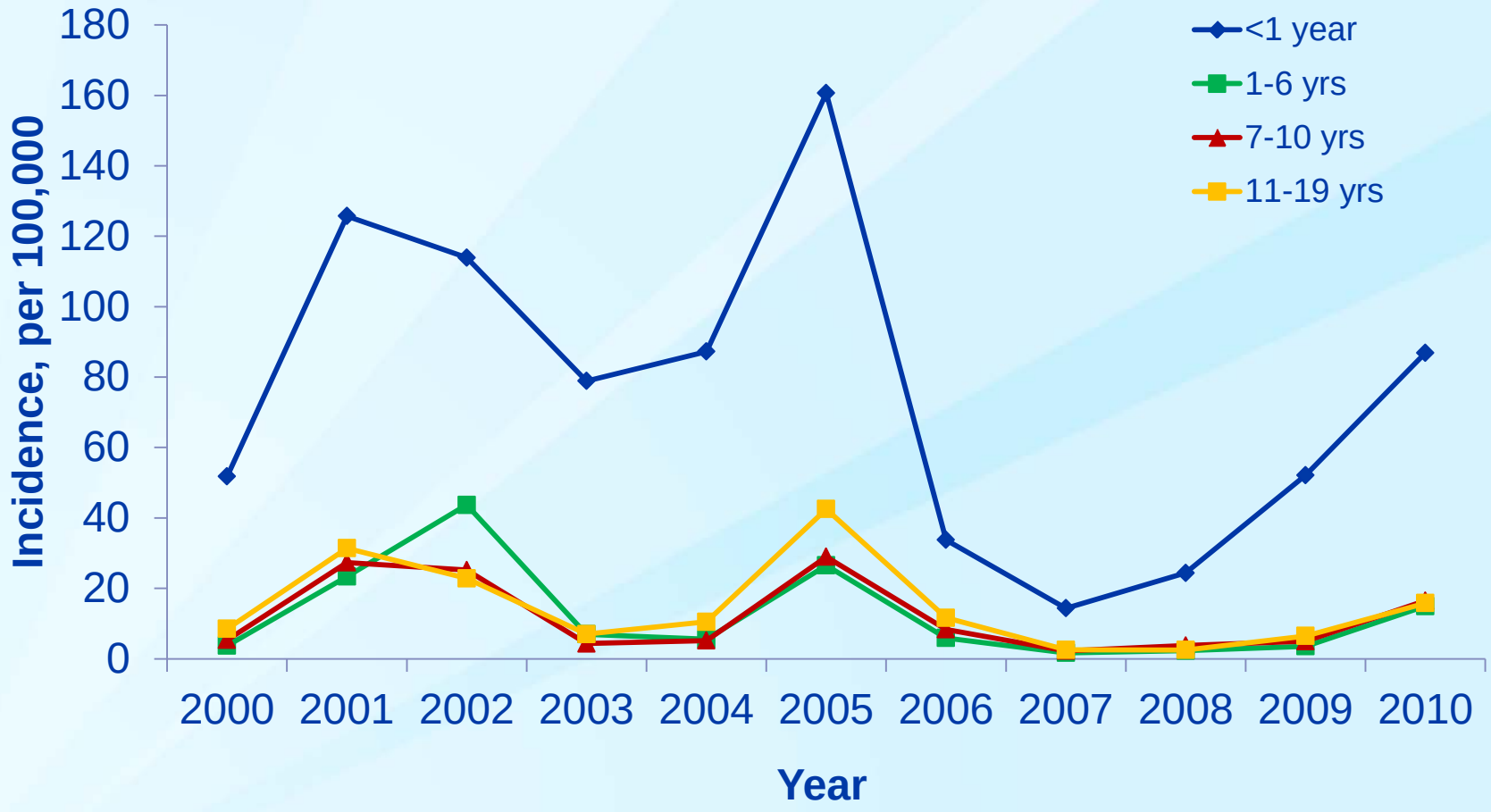
BACKGROUND

Incidence of Reported Pertussis in Arizona and the United States, 2010, NNDSS



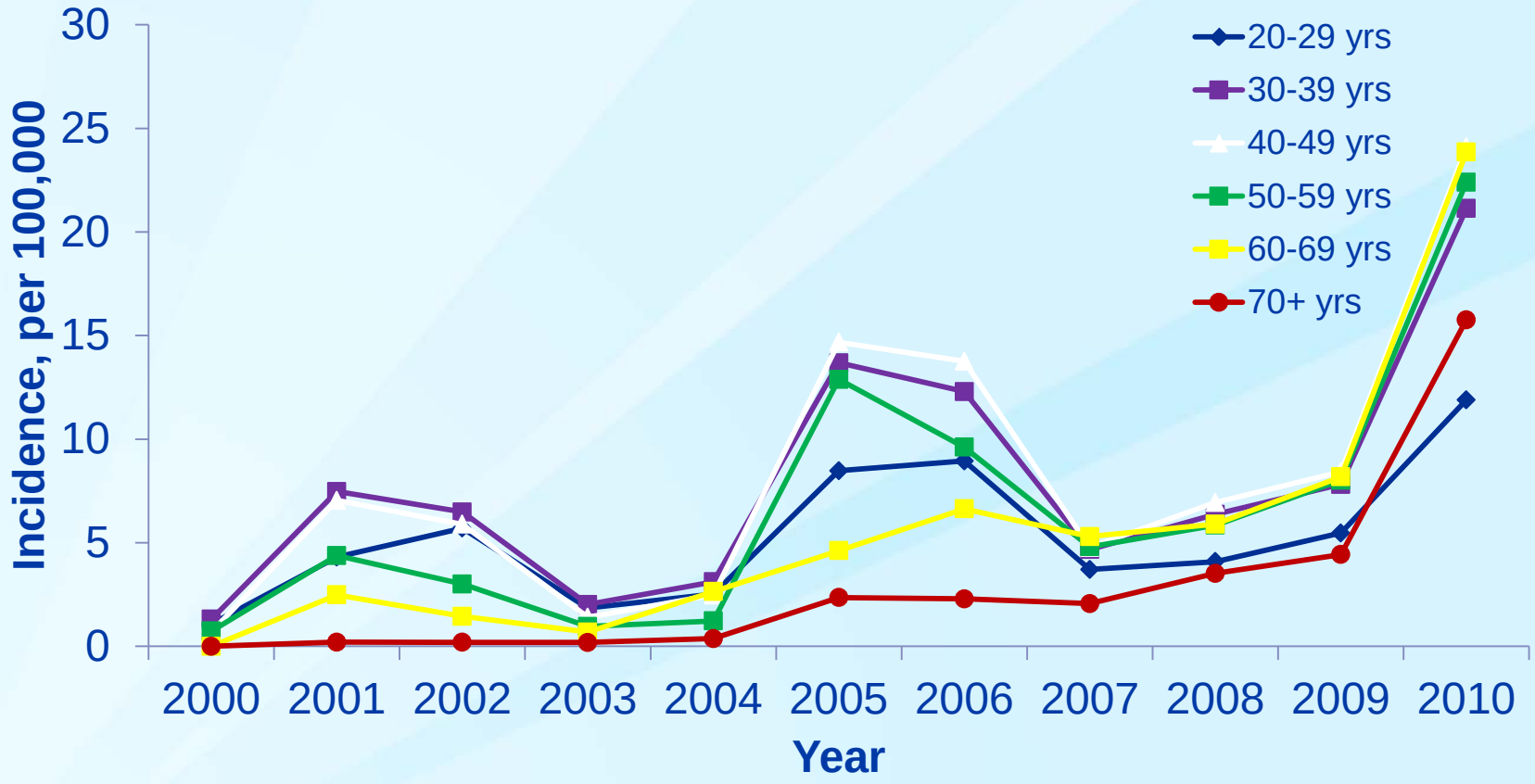
* Source: CDC, National Notifiable Diseases Surveillance System

Incidence of Reported Pertussis in Arizona, by Pediatric and Adolescent Age-Groups, 2000-2010



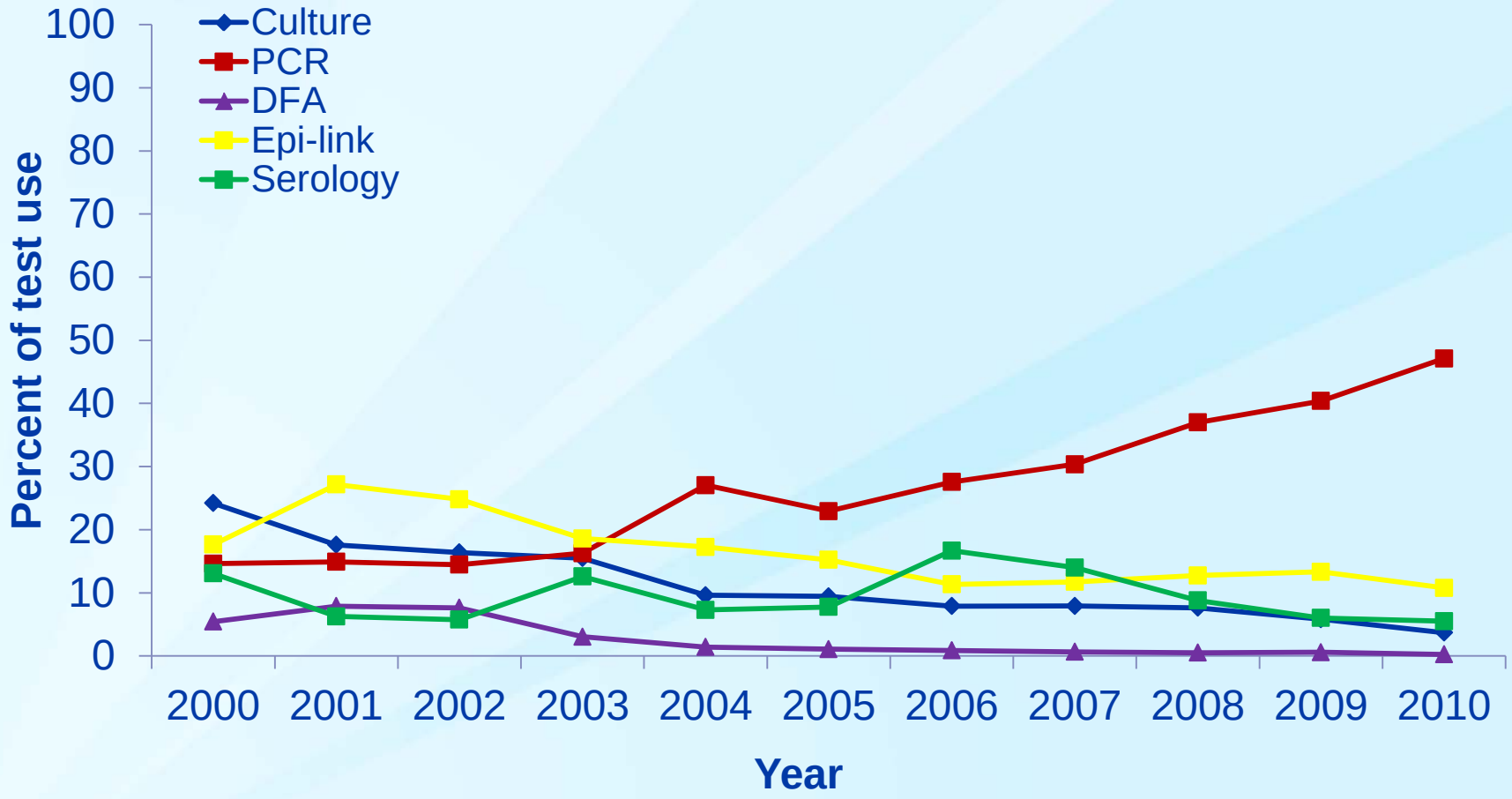
* Source: Medsis and pre-Medsis databases

Incidence of Reported Pertussis in Arizona, by Adult Age-Groups, 2000-2010



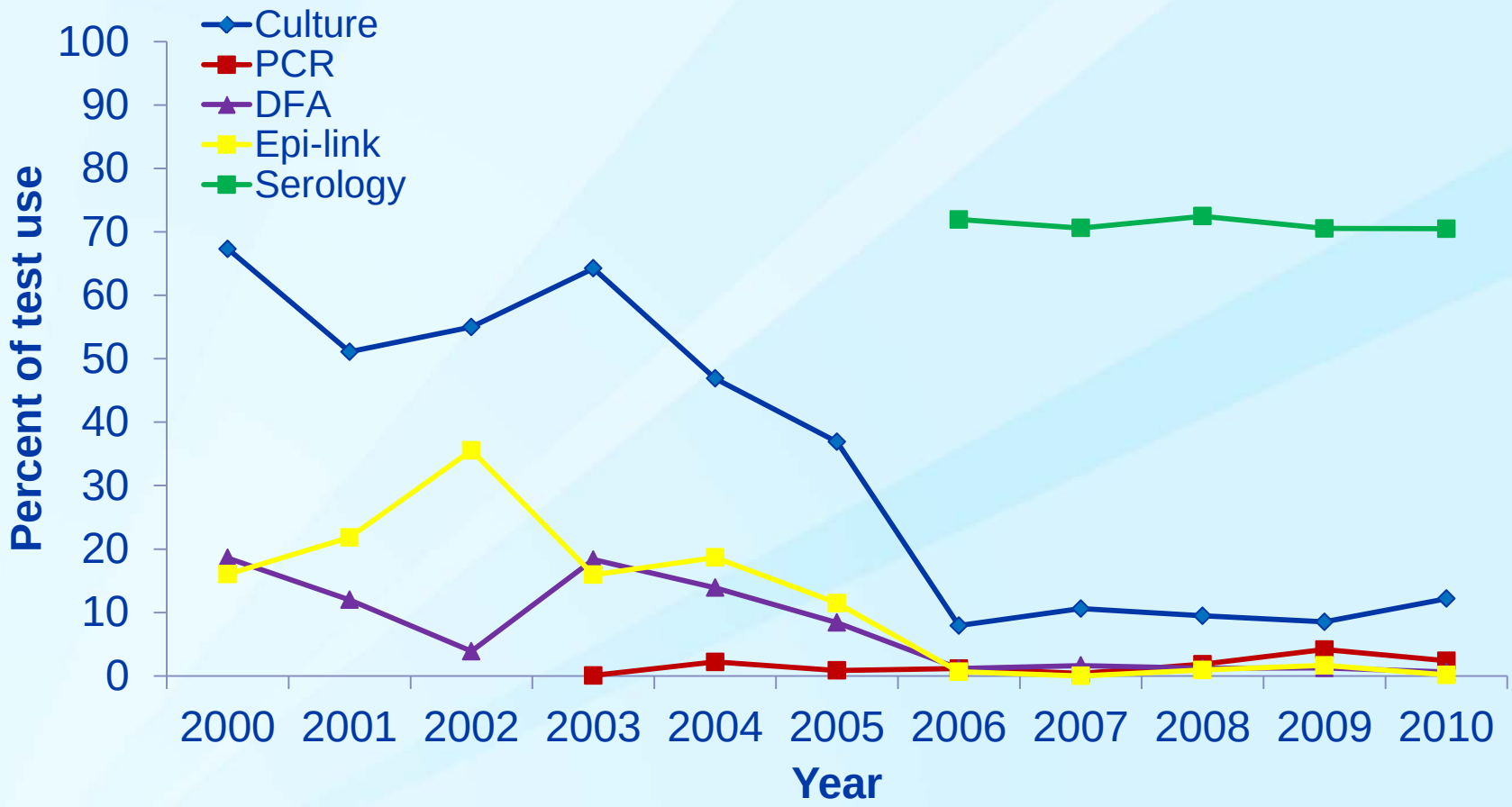
* Source: Medsis and pre-Medsis databases

Reported Diagnostic Test Use for Pertussis Cases, US, 2000-2010



* Source: NNDSS

Reported Diagnostic Test Use for Pertussis Cases, Arizona, 2000-2010



* Source: Medsis and pre-Medsis databases

Pertussis Diagnostic Testing

BACKGROUND

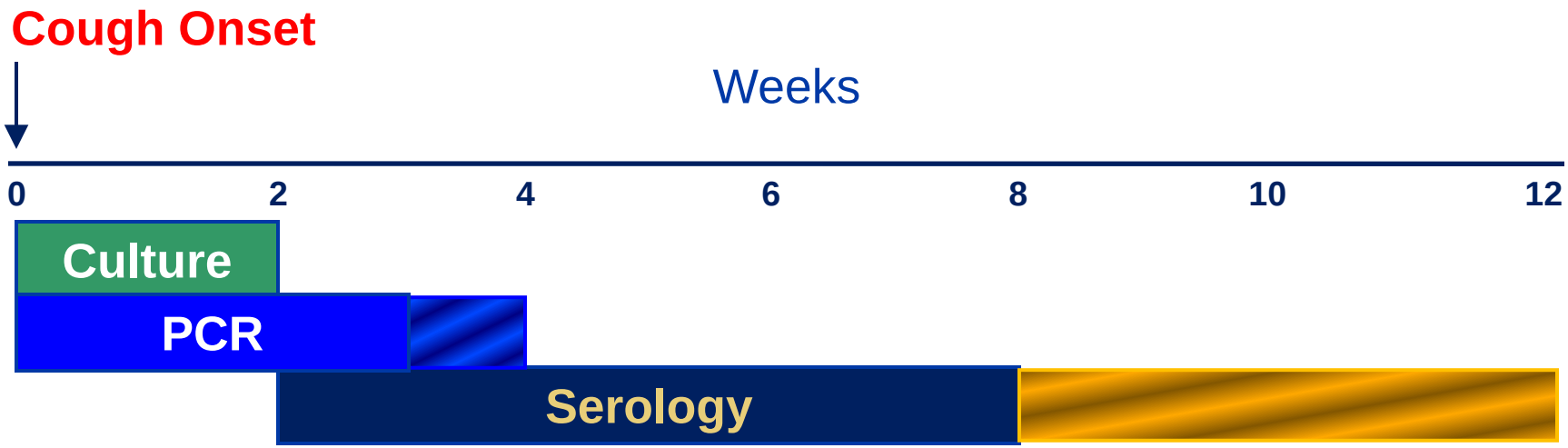
CSTE Case Definition for Pertussis

- **Clinical case definition:**
  - Cough > 2 weeks AND
  - paroxysms, inspiratory whoop, or post-tussive vomiting

Case Classification

Probable	Confirmed
- Meets clinical case definition	- Culture positive - PCR + clinical case definition - Epi link + clinical case definition

Optimal Timing for Pertussis Diagnostic Testing



Source: http://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-confirmation.html
Menzies et al. Clinical and Vaccine Immunology, 2009.

Serology Testing for Pertussis

- **Commercial assays**
  - Clinical accuracy not well defined
  - Study examining usefulness underway
- **Frequency of specimen collection**
  - Acute and convalescent vs. single
- **Antigen and antibody class**
  - Anti-PT IgG
- **Vaccination status**
  - Anti-PT IgG, ≥6 months post vaccination

Menzies et al. Clinical and Vaccine Immunology, 2009.
Pawloski et al. Clinical and Vaccine Immunology, 2012.
Riffelmann et al. Journal of Clinical Microbiology, 2010.
Pawloski et al. American Society for Microbiology, Poster Presentation, 2012.

Objective 1: Assess the use of serology as a pertussis diagnostic

METHODS AND RESULTS

Methods: Objective 1

- **Assess the use of serology as method of pertussis diagnosis**
  - **Obtain detailed information from commercial labs serving AZ**
  - Request results from main commercial labs serving Arizona and perform chart review
  - Informal interviews with providers to discuss reasoning behind pertussis diagnostic test choices

Commercial Lab Diagnostic Tests

	Kit	Test	Antigens
Arup	Savyon ELISA	IgG	FHA and PT
	Immunoblot	IgM	FHA and PT
		IgA	FHA and PT
LabCorp	Savyon ELISA	IgG	FHA and PT
		IgM	FHA and PT
		IgA	FHA and PT
Focus	Multi-analyte Immunodetection	IgG	FHA or PT
		IgA	FHA or PT

Methods: Objective 1

- **Assess the use of serology as method of pertussis diagnosis**
  - Obtain detailed information from commercial labs serving Arizona
  - **Request results from main commercial labs serving Arizona and perform chart review**
    - **Clinical scenario prompting test order**
    - **Clinical scenario and test result**
    - **Appropriateness of test order (ie timing of test, age of patient)**
  - Informal interviews with providers to discuss reasoning behind pertussis diagnostic test choices

Sampling Scheme

Commercial Lab Results (381 practices, 3381 patients)

Restriction to Metro Phoenix Area

High Ordering Practices

Adult (≥20 patients)
Mixed
Pediatric (>1 patient)

Low Ordering Practices

Adult (≤5 patients)
Pediatric (1 patient)

All pediatric practices

Systematic random sampling of adult and mixed practices

Goal Sample: 156 practices, 1061 patients

Characteristics of the Attained Sample

	N	% of goal sample attained
Practice Type	91	58%
High ordering	61	80%
Low ordering	30	38%
Adult	33	42%
Mixed	37	74%
Pediatric	21	78%
Total Subjects	834	79%
Adult	692	79%
Child*	142	89%

* Child: 10 years of age or less

Generalizability of Attained Sample

	Percentage		Chi-square
	Frame (n=2362)	Attained sample (n=834)	
Overall Test Result**			
Positive	59	56	0.25
Negative	41	44	
Age group			
Adult	98	83	<0.0001
Child*	2	17	
Lab			
Arup	54	54	0.81
LabCorp	46	46	
Ordering Practice Type			
High	63	94	<0.0001
Low	14	6	
Mid-range	23	0	
Sex			
Male	34	35	0.75
Female	66	65	

* Child: 10 years of age or less

** Overall test result: positive = one or more positive tests; negative = all negative tests

Demographics

	N=807	Percentage
Sex		
Male	273	35
Female	533	65
Age group		
Adult	672	83
Child*	135	17
Lab		
Arup	433	57
LabCorp	374	43
Overall Test Result**		
Positive	454	56
Negative	353	44

* Child: 10 years of age or less

** Overall test result: positive = one or more positive tests; negative = all negative tests

Practice, Provider and Visit Type

	N=807	Percentage
Ordering Practice Type		
High	788	94
Low	46	6
Practice Type		
Adult	325	40
Adult and Pediatric (Mixed)	451	56
Pediatric	31	4
Provider type		
MD	361	46
DO	184	24
PA	135	17
NP	98	13
Other (NMD)	3	0.3
Visit Type		
ER	8	1
Outpatient	790	99

Cough Symptoms

	N=807	Percentage
Cough		
Positive	747	93
Cough Type		
Dry	223	28
Productive	209	26
Not in record/Unknown	372	46
Cough Duration (at time of test, days)		
Mean	76	
Median	30	
Range	1-3823	
Timing of test in relation to cough duration		
<14 days	146	18
≥14 days	457	57
not collected	204	25

Other Symptoms

	N=807	Percentage
Paroxysms		
Not in record	750	93
Whoop		
Not in record	781	97
Post-tussive vomiting		
Negative	141	18
Not in record	624	78
Apnea		
Not in record	772	96
Fever		
Negative	332	41
Positive	156	19
Not in record	317	39

Pertussis and Other Diagnoses

	N	Percent
Diagnosed with pertussis		
No	252	31
Yes	121	15
Not in record	431	54
Tested specifically for pertussis immune status		
No	579	71
Yes	47	6
Not in record	182	23
Coccidioidomycosis Testing		
Negative Result	472	69
Positive Result	12	2
Not Ordered	110	16
Not in record	92	13

Comparison of Adults and Children

	Adult Percentage (N=672)	Child* Percentage (N=135)
Timing of test in relation to cough duration		
<14 days	17	26
≥14 days	58	50
timing not collected	25	24
Overall Test Result**		
Positive	60	36
Negative	40	64

* Child: 10 years of age or less

** Overall test result: positive = one or more positive tests; negative = all negative tests

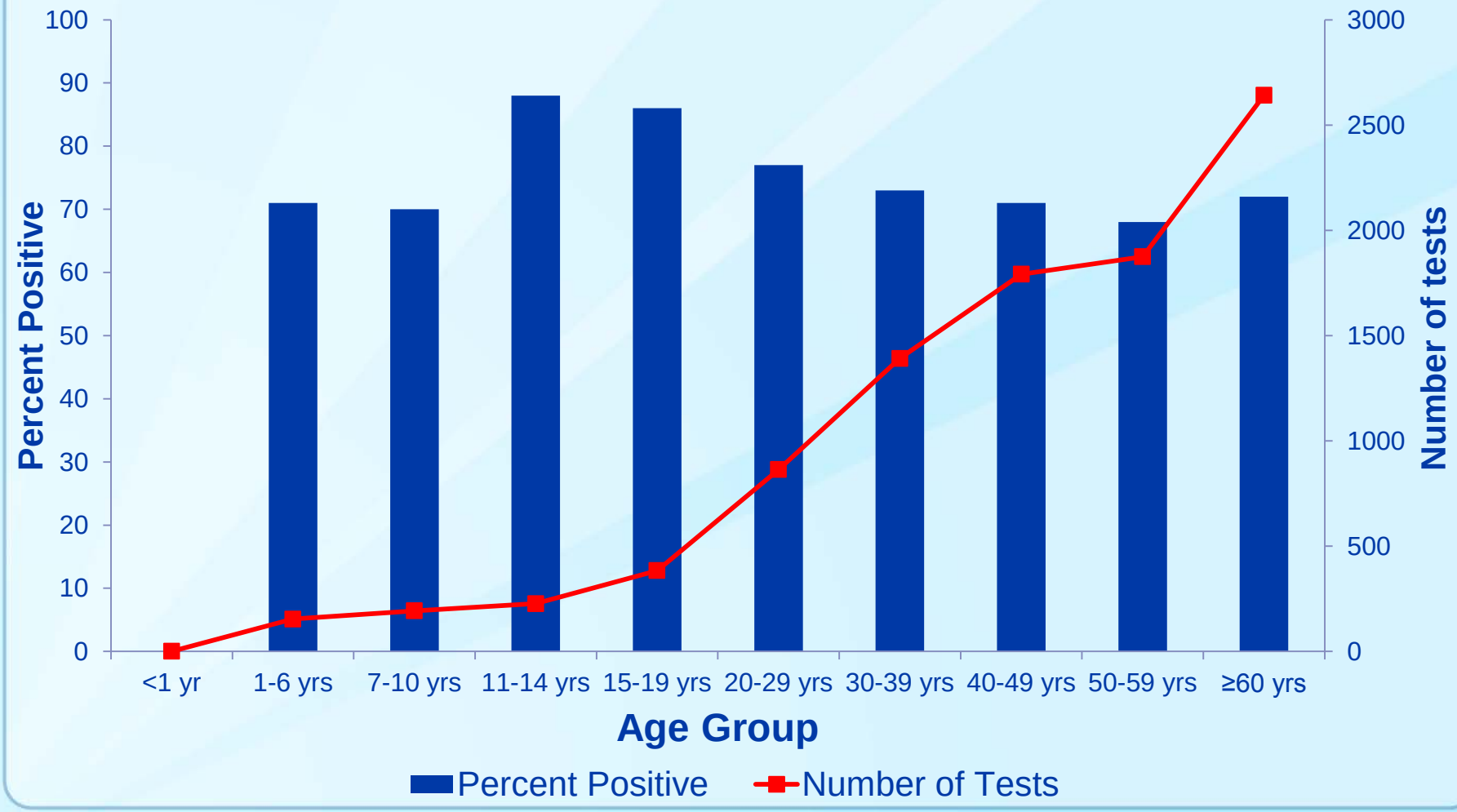
Pertussis Tests Ordered

		N=7588	Percentage
LabCorp	B. pertussis DFA	88	1
	B. pertussis Culture	6	0.07
	B. pertussis PCR	148	2
	B. pertussis IgA Ab	522	7
	B. pertussis IgG Ab	1149	15
	B. pertussis IgM Ab	1183	15
Arup	B. pertussis DFA	1	0.01
	B. pertussis Culture	1	0.01
	B. pertussis PCR	1	0.01
	B. pertussis IgA Ab	1414	19
	B. pertussis IgG Ab	1571	20
	B. pertussis IgM Ab	1504	20

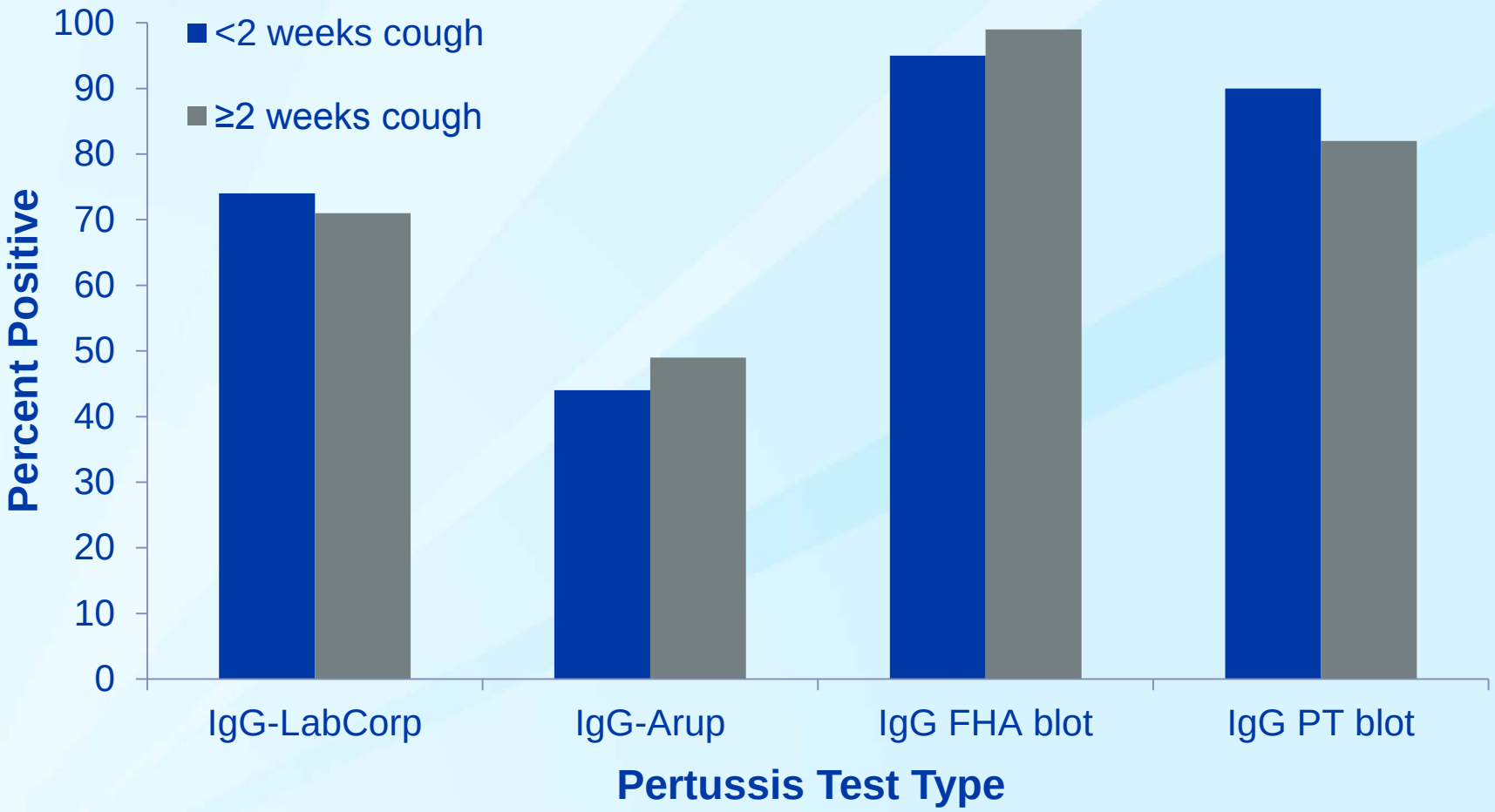
Positive Pertussis Tests

		N Positive	Percent Positive
LabCorp	B. pertussis IgA Ab	99	19
	B. pertussis IgG Ab	801	70
	B. pertussis IgM Ab	334	28
Arup	B. pertussis IgA Ab	249	18
	B. pertussis, IgA Immunoblot FHA	149	73
	B. pertussis, IgA Immunoblot PT	50	24
	B. pertussis IgG Ab	722	46
	B. pertussis, IgG Immunoblot FHA	559	98
	B. pertussis, IgG Immunoblot PT	472	82
	B. pertussis IgM Ab	345	23
	B. pertussis, IgM Immunoblot FHA	2	1
	B. pertussis, IgM Immunoblot PT	5	2

Serology Test Number and Positivity Trends, by Age Group



Percent Positive Serology Tests in Relation to Cough Duration



Current Studies in Pertussis Serology

- **Previous comparison of kits – Europe**
  - Riffelmann et al:
    - Sensitivity highest for IgG; specificity for PT only highest
    - Specificity of mixed kits (FHA and PT) poor
  - Guidelines from EU Reference Laboratories
    - PT for antigen; IgG first-choice Ab class
    - Calibration to International ELISA units

- **Current analysis of serology by CDC Pertussis Lab**
  - Kit comparison study
    - Few assay kits calibrated to reference sera
    - Sensitivity highest for IgG and lowest for IgM
    - Specificity studies in progress

Riffelmann et al. Journal of Clinical Microbiology, 2010.
Guiso et al. European Journal of Microbiology and Infectious Disease, 2011.
Pawloski et al. American Society for Microbiology, Poster Presentation, 2012.

Methods: Objective 1

- **Assess the use of serology as method of pertussis diagnosis**
  - Obtain detailed information from commercial labs serving Arizona
  - Request results from main commercial labs serving Arizona and perform chart review
  - **Informal interviews with providers to discuss reasoning behind pertussis diagnostic test choices**

Provider Interviews

- **Interviewees**
  - 3 NPs (Family Practice)
  - 1 PA (Internal Medicine/Pediatrics)
  - 4 MDs (Internal Medicine, Pediatrics, Pulmonology, Allergy/Immun.)
  - 1 NMD

- **Summary of interviews: why is serology chosen?**
  - Ease of phlebotomy versus the difficulty of NP swab
  - Lack of education
  - Barriers to PCR (supply expiration, transportation, insurance)
  - Testing for immune status
  - Would like more straight-forward guidance

Methods: Objective 2

- **Assist with guidance on pertussis case prioritization for investigation and test recommendations**
  - Based on results of data analysis and current literature

Prioritization and Test Choice

- **Prioritization of cases**
  - No clear answer for how to prioritize
    - Overall, serology tests appear to have poor specificity
  - Analyses point to need for intensive provider education

- **Test choice recommendations**
  - Data from chart review not sufficient to correlate with test result
    - Unable to recommend a particular test
  - CDC evaluation of serology assays will inform future direction

Methods and Results: Objective 3

- **Development of educational tools for providers**
  - Updating of Maricopa County Pertussis Physician Fact Sheet
  - Adaptation of CDPH informational sheet on pertussis diagnostics
  - In progress: development of easily understood graphic algorithm

Conclusions

- **Use of serology as pertussis diagnostic in Arizona**
  - PCR rarely used ; serology heavily used
  - Commercially available serology assays utilize FHA **AND** PT
  - High rate of positive serology tests
  - Inappropriate timing of test and testing for immune status

- **Guidance on case prioritization**
  - Serology assay specificity appears poor
  - No clear answer on how to prioritize or test recommendation
  - Provider education needed

- **Educational tools for providers**
  - Adaptation of information sheet and new graphic algorithm

Recommendations

- **Provider Education**
  - Encourage PCR testing
  - Emphasize appropriate timing for tests
  - Discourage testing for immune status
- **Case prioritization**
  - If possible, avoid case investigations of those tested for immune status or if timing of test is inappropriate
- **Follow-up current analysis of commercial serology assays**

Thank you!

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Epi-Aid Team

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EXTRA SLIDES

Sampling Scheme

Commercial Lab Results (381 practices, 3381 patients)

Restriction to Metro Phoenix Area
350 practices, 3196 patients

High Ordering Practices

Adult (≥20 patients)
19 prac.

All practices
RSS of +/-

Mixed
50 prac.

All practices
Adults: RSS of +/- if ≥20 patients; all patients if <20
Peds: all patients

Pediatric (>1 patient)
7 prac.

All practices and patients

Low Ordering Practices

Adult (≤5 patients)
202 prac.

Random selection of 30% of practices (60), all patients

Pediatric (1 patient)
20 prac.

All practices and patients

Goal Sample: 156 practices, 1061 patients

Characteristics of the Attained Sample

Attained sample

Practice (91)

Adult : 33 practices (336 adult pts)
17 high ordering (305 adult pts)
16 low ordering (31 adult pts)

Mixed: 37 practices (466 pts)
356 adult pts
110 pediatric pts

Pediatric: 21 practices (32 pediatric pts)
7 high ordering (17 ped. pts)
14 low ordering (15 ped. pts)

Agegroup (834)

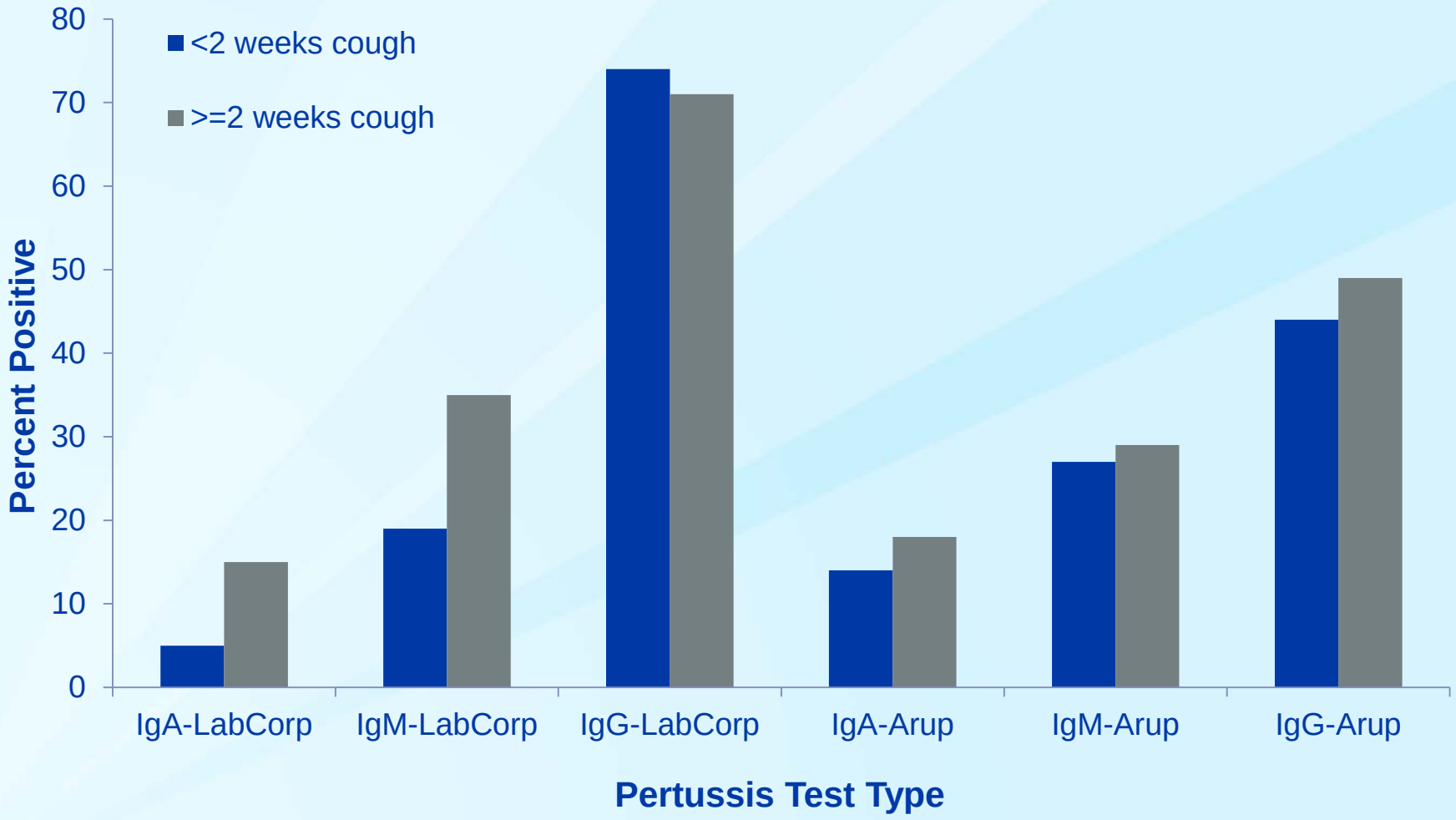
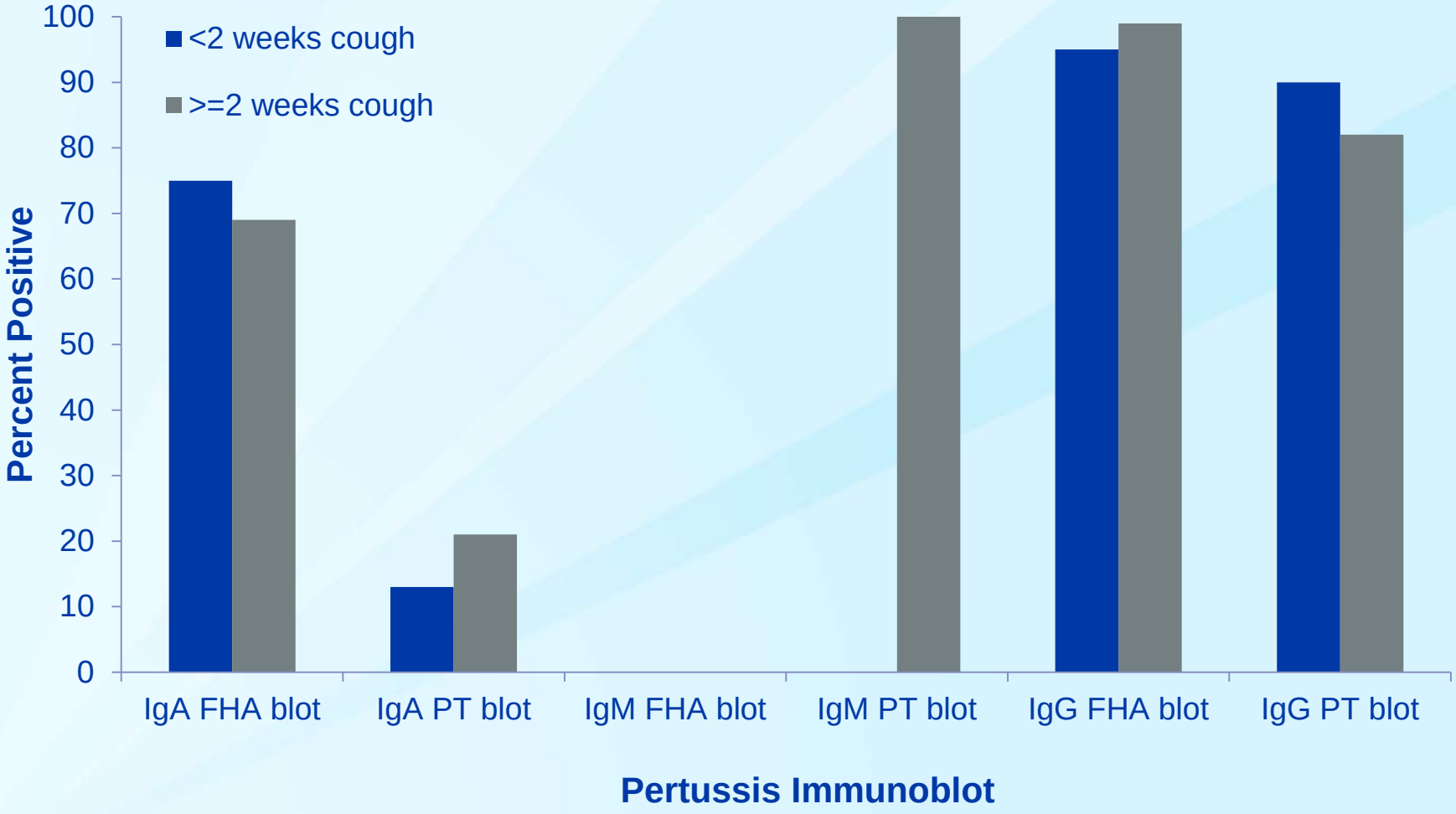
Adult : 692 patients
Child* : 142 patients

Overall Test Result**

Positive: 469 patients
Negative: 365 patients

* Child: 10 years of age or less
** Overall test result: positive = one or more positive tests; negative = all negative tests

Percent Positive ELISA in Relation to Cough Duration



Percent Positive Immunoblots in Relation to Cough Duration