Children's Hospital Boston Emergency Medicine and Informatics Program

Harvard Medical School

How Real-Time Biosurveillance Can Help Clinical Practice

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Grand Rounds

Health Sciences Informatics

Johns Hopkins University

Baltimore, MD

Disclosures

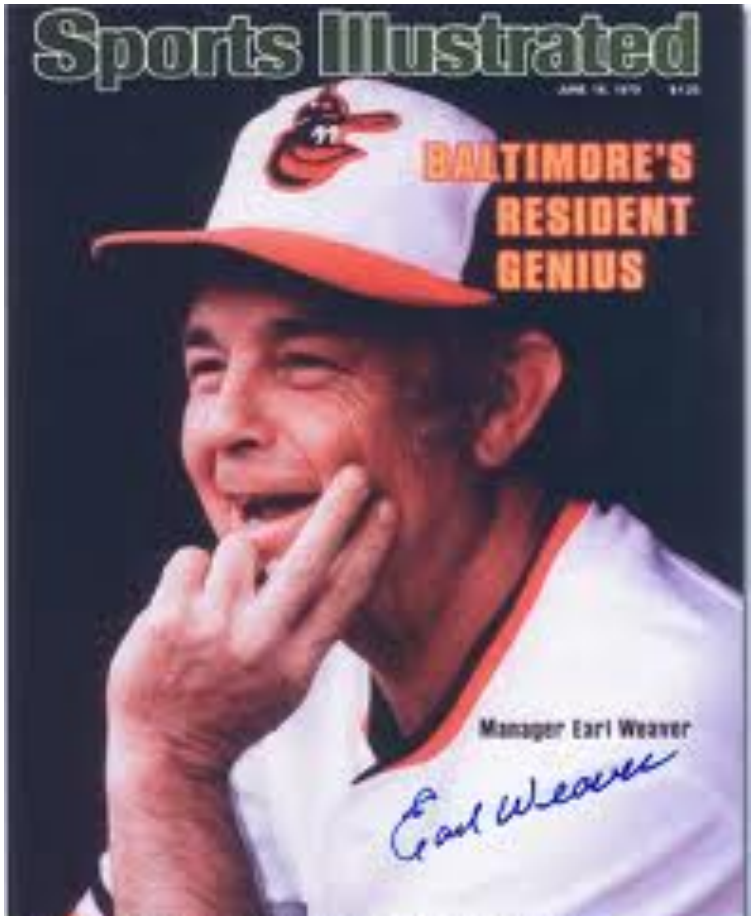
Andrew Fine, MD, MPH has no financial relationship with any commercial interest.

Objectives

1. Understand the value of biosurveillance as a predictor of communicable disease

2. Describe the incorporation of biosurveillance into a clinical prediction model for strep throat at the point of care

3. Describe the incorporation of biosurveillance data into a prediction model for strep throat for use by patients prior to a clinical encounter


Sports Illustrated
BALTIMORE'S RESIDENT GENIUS
Manager Earl Weaver
Earl Weaver

Topics

Clinical prediction rules

Bacterial meningitis
Pertussis
Facial Palsy
Strep throat

Clinical Prediction

- Outcome not known at presentation
- Physicians have difficulty estimating risks
- Tendency to over-estimate likelihood of rare events
  - Adults undergoing head computed tomography (CT) scans
  - MD pretest probability of significant CT findings: 33%
  - Actual incidence of significant CT findings: 5%

Clinical Prediction Rules

- Combine history, physical exam, and laboratory data to estimate probability of an outcome
- Can also suggest next course of management
- Designed to assist NOT replace decision-making

Whooping Cough Epidemic in New York

Number of Deaths from the Disease Have Almost Doubled—Board of Health Figures Show Its Ravages—Dangerous to Grown Up People as Well as Infants—In the Suburbs.

NEW YORK and its suburbs are in the grasp of whooping cough, that dread disease of children. Doctors at the Health Board say it amounts almost to an epidemic—an epidemic which might be prevented if people would but take the proper precaution. They say that many of the children now suffering from the disease and some of those who have died might not have been sick were it not for the prevalent but nevertheless unreasonable idea which prevails that a child must have the disease some time, and hence might as well be exposed to the contagion first as last. Never was there such a dangerous doctrine, say the Health Board men; that the less a child is exposed to any disease the better for the child.

by eliminating the microbe of whooping cough and suggesting means for its cure. For at the present time the cause of the disease is not known, nor is there any specific remedy. The Health Board has conducted research work to the end of finding out the origin of the disease, and so also have students at some of the big medical schools, but without result.

Not knowing what they are fighting, it is difficult for the physicians to outline a definite course of treatment. In addition they are hampered by the old-fashioned notion of the necessity for every child having the disease, which is often furthered by the action of mothers who deliberately expose their children to its virulence. Dr. Walter Bensel of the Health Board denounced this

down under it. Sleep is apt to be lost and the restlessness that takes its place adds to the debilitating effect. Then the child is apt to lose one or more of its daily meals, which still further completes the prostration. So that when the child is attacked by bronchitis or the bronchial-pneumonia that often follows whooping cough, the poor little sufferer is in no physical condition to withstand it, and so succumbs.

PROPER TREATMENT.

"As to treating the disease, there is almost nothing that can be done. Some physicians recommend and administer a sedative to relieve the violence of the paroxysm, but the sedative, on the other hand, is apt to destroy the appetite, and therefore increase the general weak-

***New York Times*, July 13, 1902**

Approaches to an Infant with a Cough

Case: 7 m.o. presents to the ED with 2 days of cough, low-grade fever.

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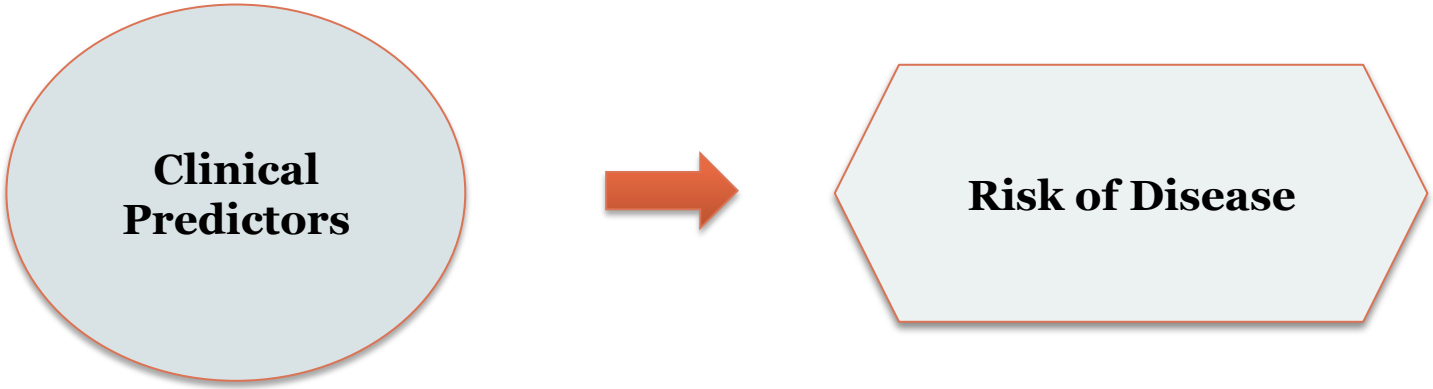
3) Epidemiologic Context: The clinician enters the symptoms into an on-line calculator, which automatically incorporates real-time biosurveillance data quantifying the recent local pertussis incidence; estimates the child's pertussis risk at 24%.

Epidemiology Adds Important Context

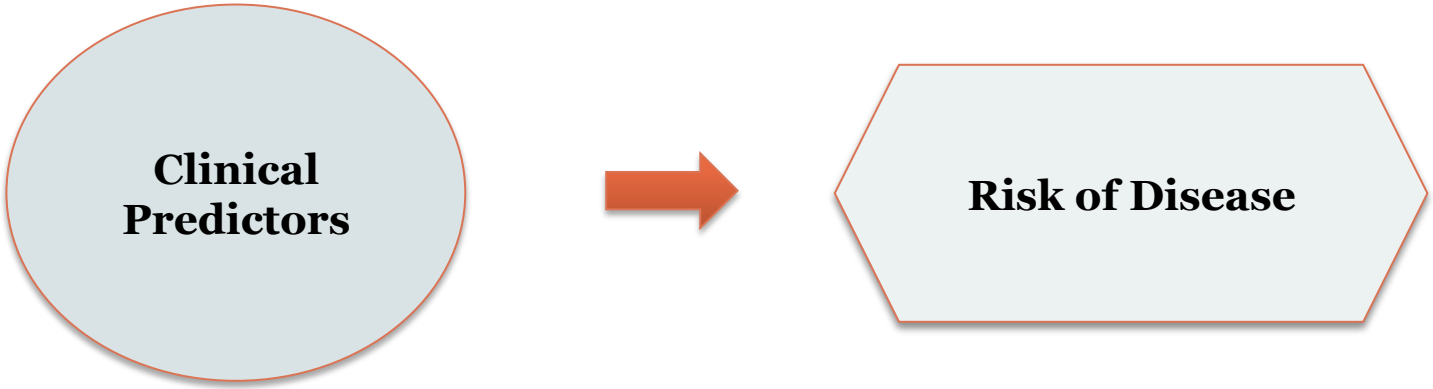
- Risk of disease depends on exposure to others who are infected
- Risk of exposure depends on local disease incidence
- *Can the integration of real-time epidemiology improve the accuracy of clinical prediction rules?*

Standard Approach

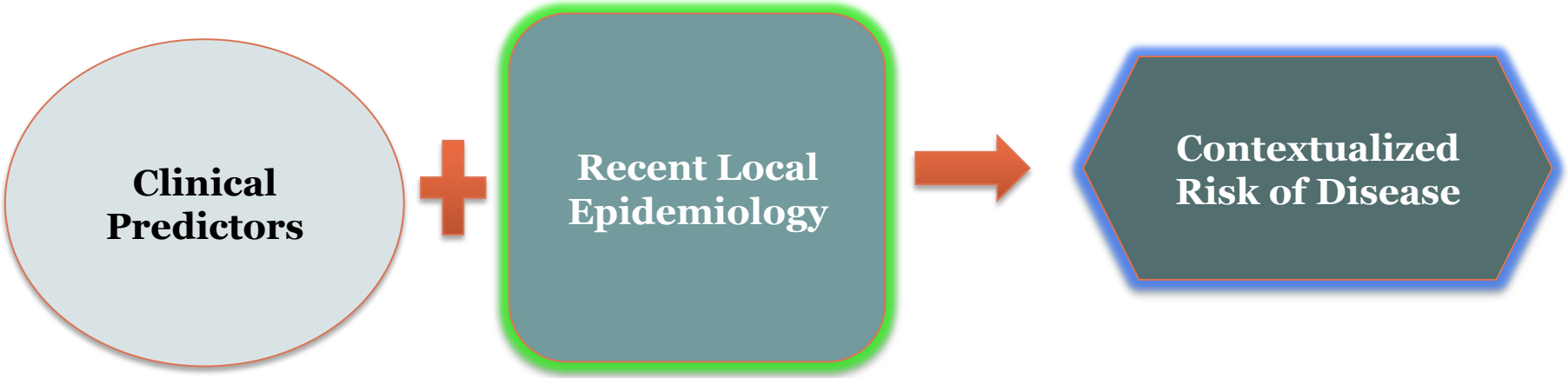


Novel Approach

Standard Approach



Novel approach



Epidemiologic Context: Examples

Disease	Approach
Meningitis	*Internal hospital data*
Pertussis	*Statewide public health data*
Facial palsy	*CDC county-level incidence data*
Pharyngitis	*National retail health data*

Epidemiologic Context: Examples

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Clinical Case

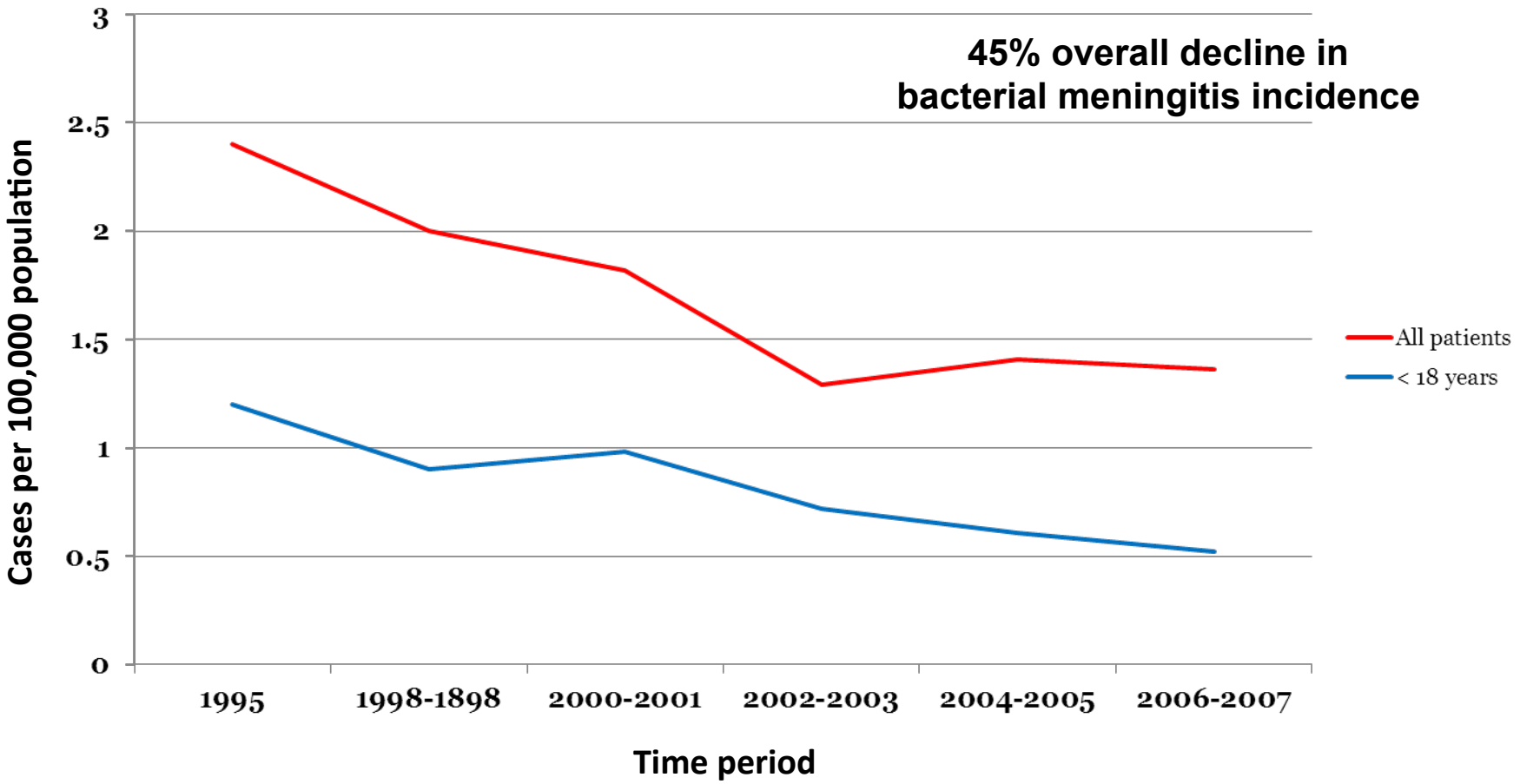
4 yo M presents w/ 3 days of headache, photophobia

- Exam: Stiff neck
- Labs:
  - Peripheral ANC 8,000 cells/mm^3
  - Lumbar puncture (LP)
    - Cerebrospinal (CSF) WBC 1,000 cells/mm^3 [40% polymorphonuclear (PMN) and 50% mononuclear cells]
    - CSF protein 65 mg/dL and CSF glucose 45 mg/dL
    - CSF Gram Stain negative
- What would you do?

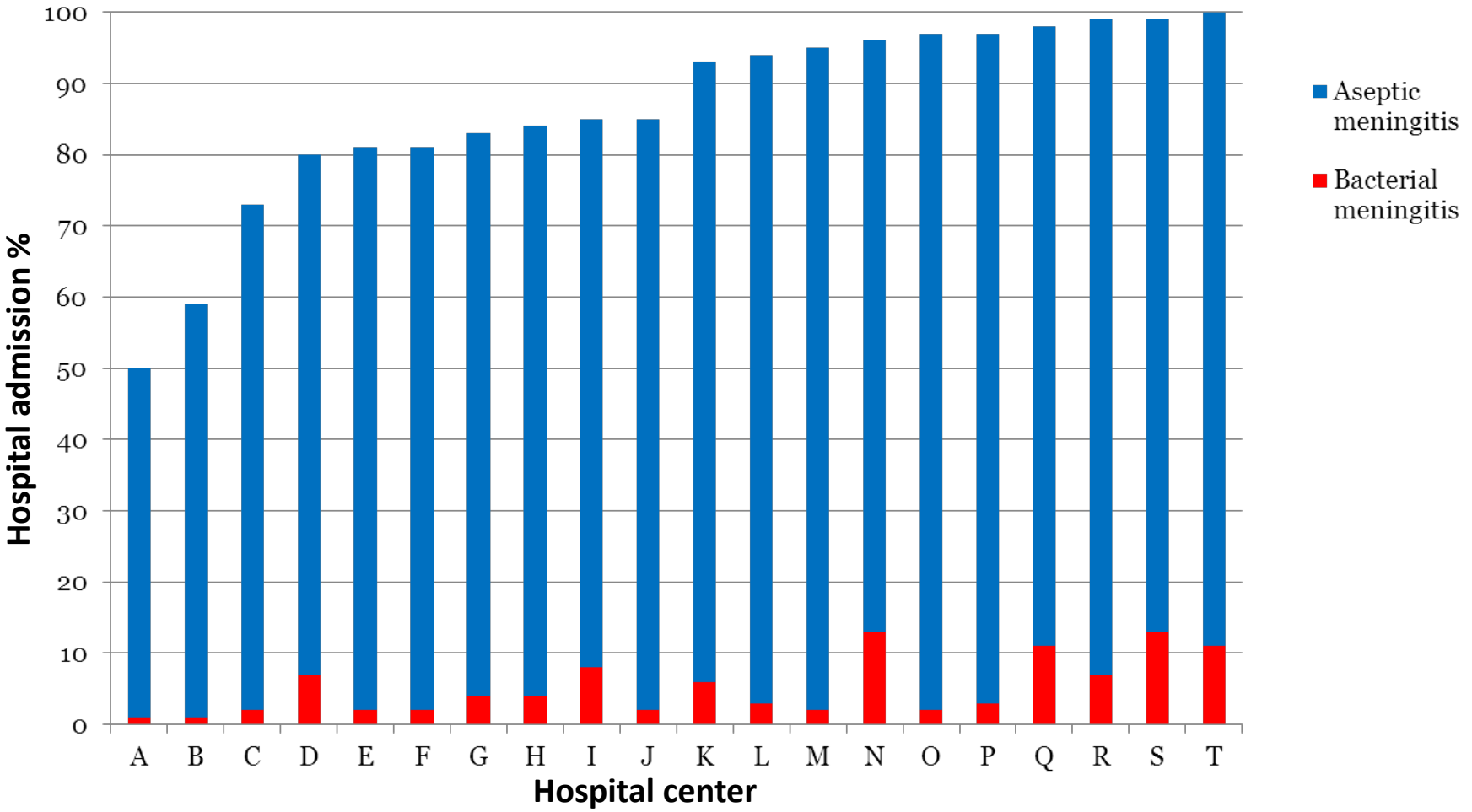
Meningitis

- Most children with CSF pleocytosis have aseptic, not bacterial, meningitis
  - Bacterial meningitis → parenteral antibiotics
  - Aseptic meningitis → supportive care
- Challenge to promptly identify those children with bacterial meningitis without over treating those with aseptic meningitis

Bacterial Meningitis Incidence



Hospital Admission Rates



The Bacterial Meningitis Score

1. Positive CSF Gram stain
2. CSF ANC $\geq$ 1000 cells/mm^3
3. CSF protein $\geq$ 80 mg/dL
4. Peripheral ANC $\geq$ 10,000 cells/mm^3
5. History of seizure at or prior to presentation

No predictors → very low-risk
One or more predictors → not low-risk

Nigrovic et al, JAMA, 2007.

Proof of Concept: Meningitis

- Bacterial meningitis score – based on clinical factors and test results
- Add "epidemiologic context" for each patient
- Factor in # of recent aseptic meningitis cases at Children's Hospital Boston Emergency Department
- Measure the effect on model performance

Meningitis with Epidemiologic Context

Metric	Bacterial Meningitis Score	Epidemiologic Context Model
Sensitivity	98	98
Specificity	72	81

- Identified 47 additional of aseptic meningitis
- Missed no additional bacterial meningitis cases
- Local data source to incorporate context

Meningitis Take Home Point

- Proof of concept
- Integrating epidemiology adjusts the rule and improves its performance
- Explore other diseases where context would matter

Epidemiologic Context Approach

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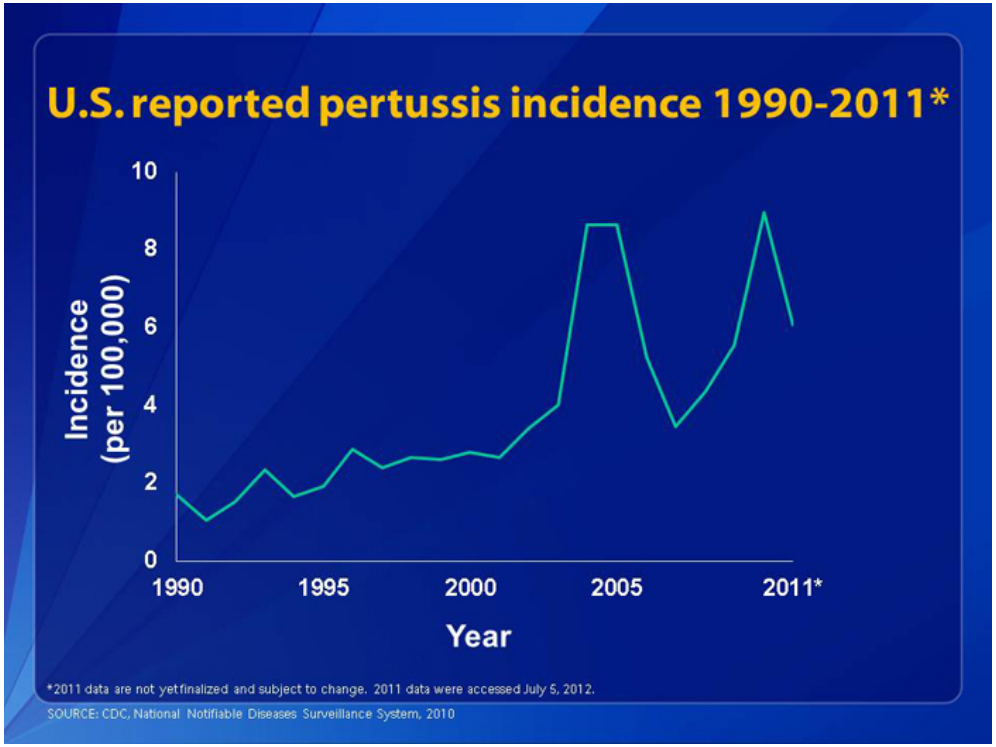
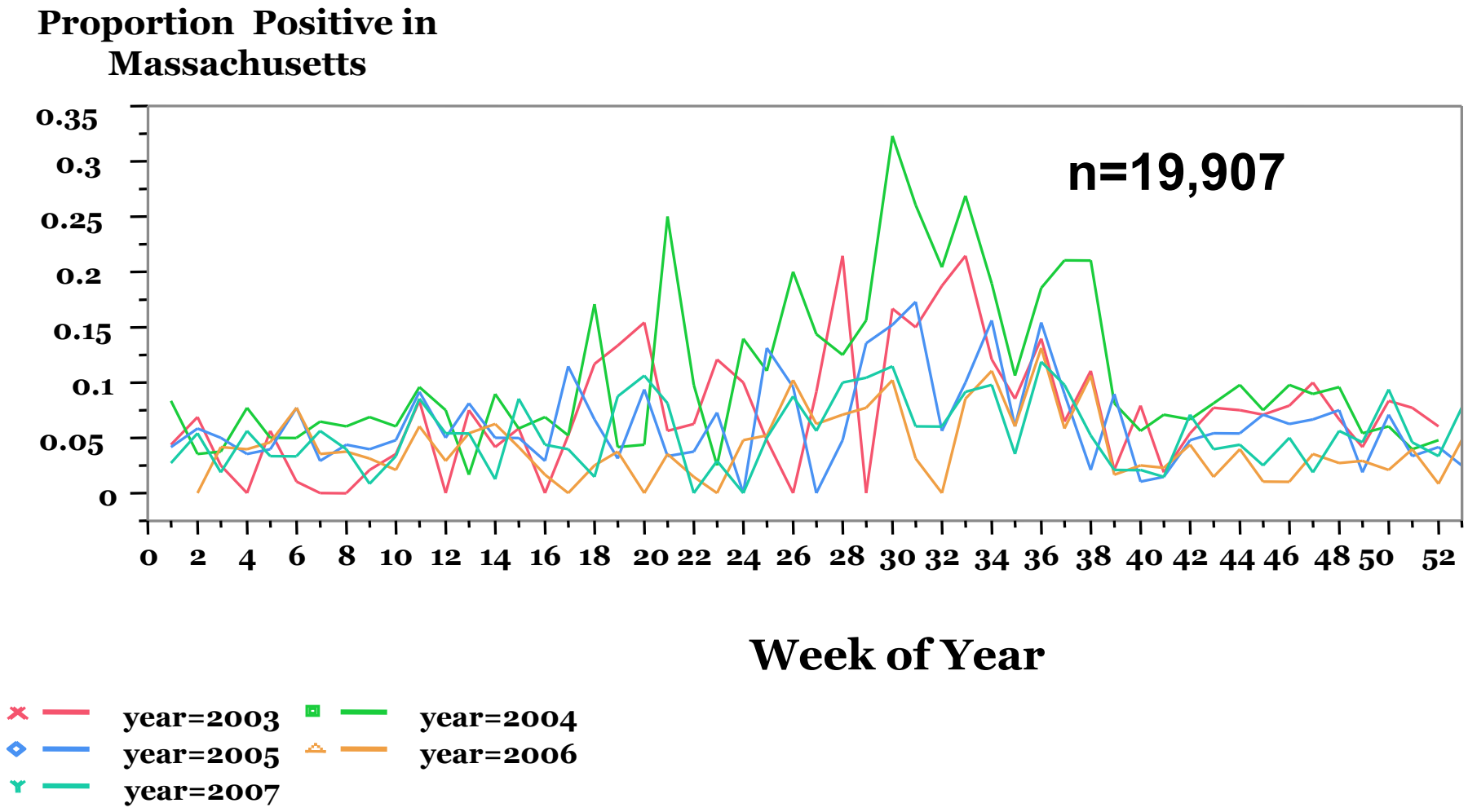
Bordetella Pertussis

- Incidence
- Impact
- Difficult to diagnose early
- Delayed test results
- Outbreaks have temporal and geographic variability



Centers for Disease Control and Prevention

Pertussis Weekly Proportion Positive,2003-07



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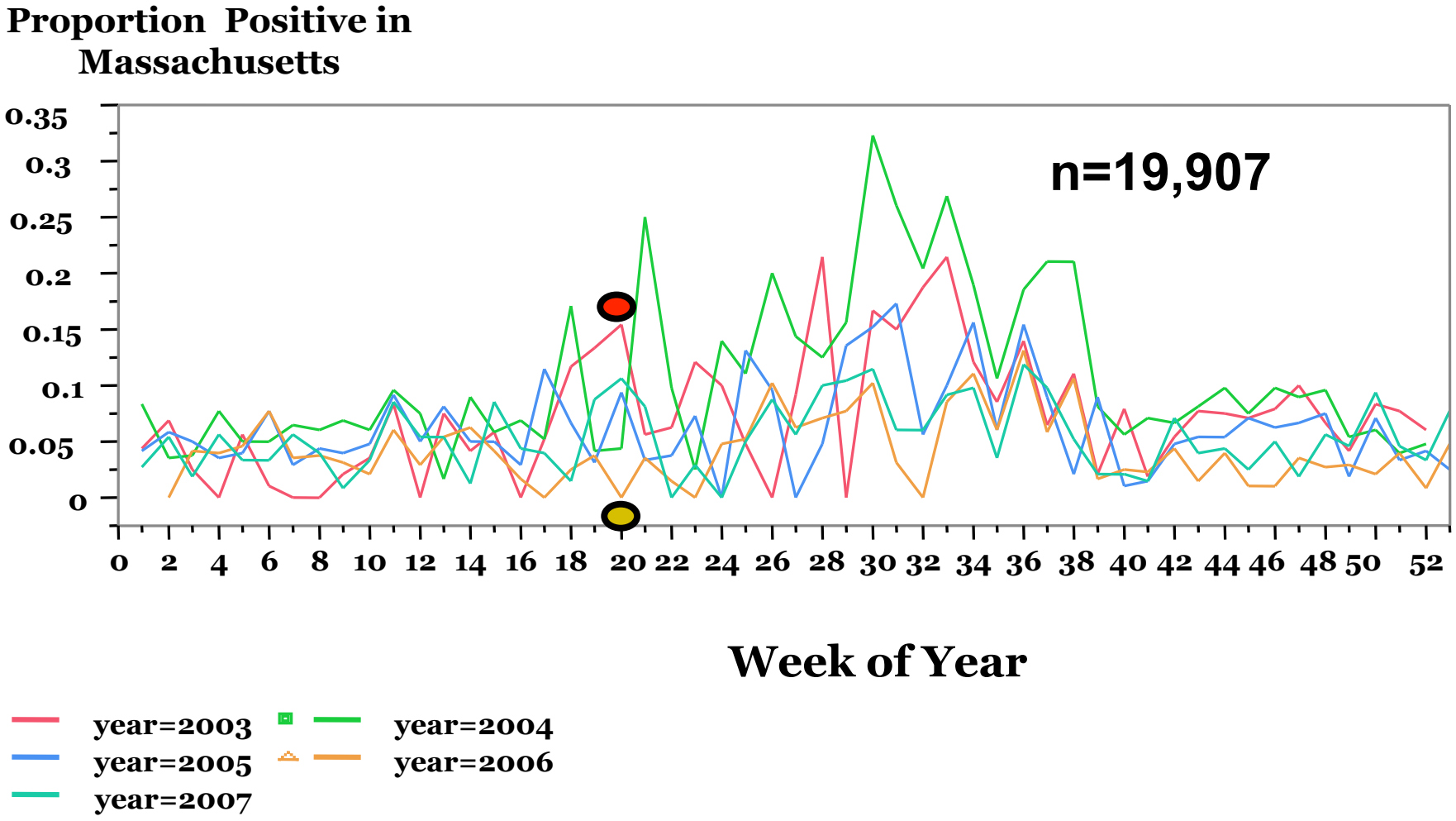

Prediction Models for Pertussis in Infants

"Clinical model"

Predictor	AOR (95% CI)	P value
Cyanosis	6 (3-13)	<0.0001
Cough >= 1 week	3 (1-7)	0.004
Absence of fever	7 (1-118)	0.02

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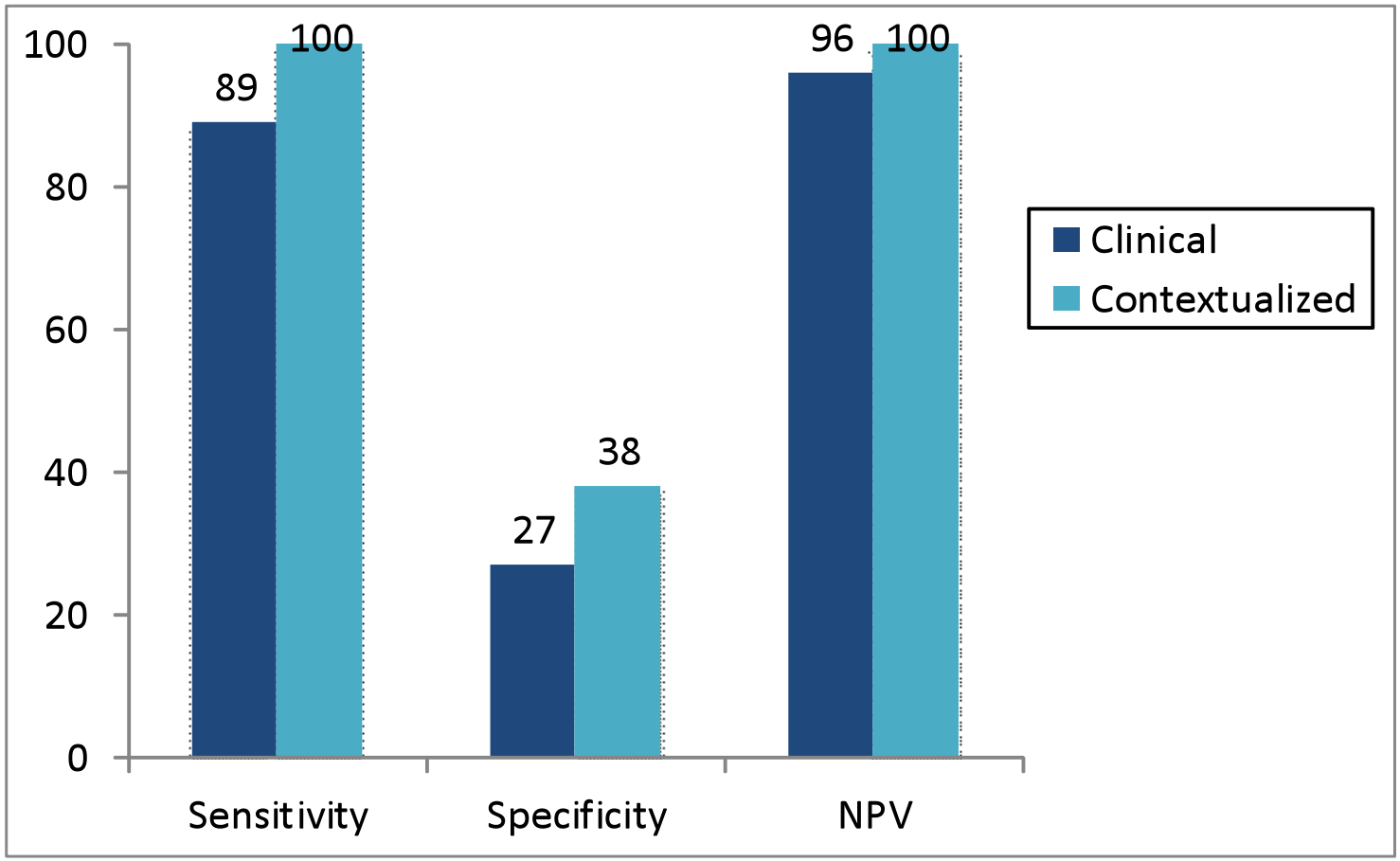
Cough >= 1 week	3 (1-7)	0.004
Absence of fever	7 (1-118)	0.02

"Contextual model"

Predictor	AOR (95% CI)	P value
Cyanosis	7 (3-16)	<0.0001
Recent weekly incidence	6 (2-13)	0.0001
Cough > = 1 week	3 (2-8)	0.005

State-level Pertussis Data Improves Model



p=0.04	p<0.001	p=0.02

Pertussis Take Home Points

- Statewide public health data source
- Information about patients of all ages applied to predict pertussis in infants
- Real-time biosurveillance could improve management of a difficult to diagnose vaccine preventable disease

Epidemiologic Context Approach

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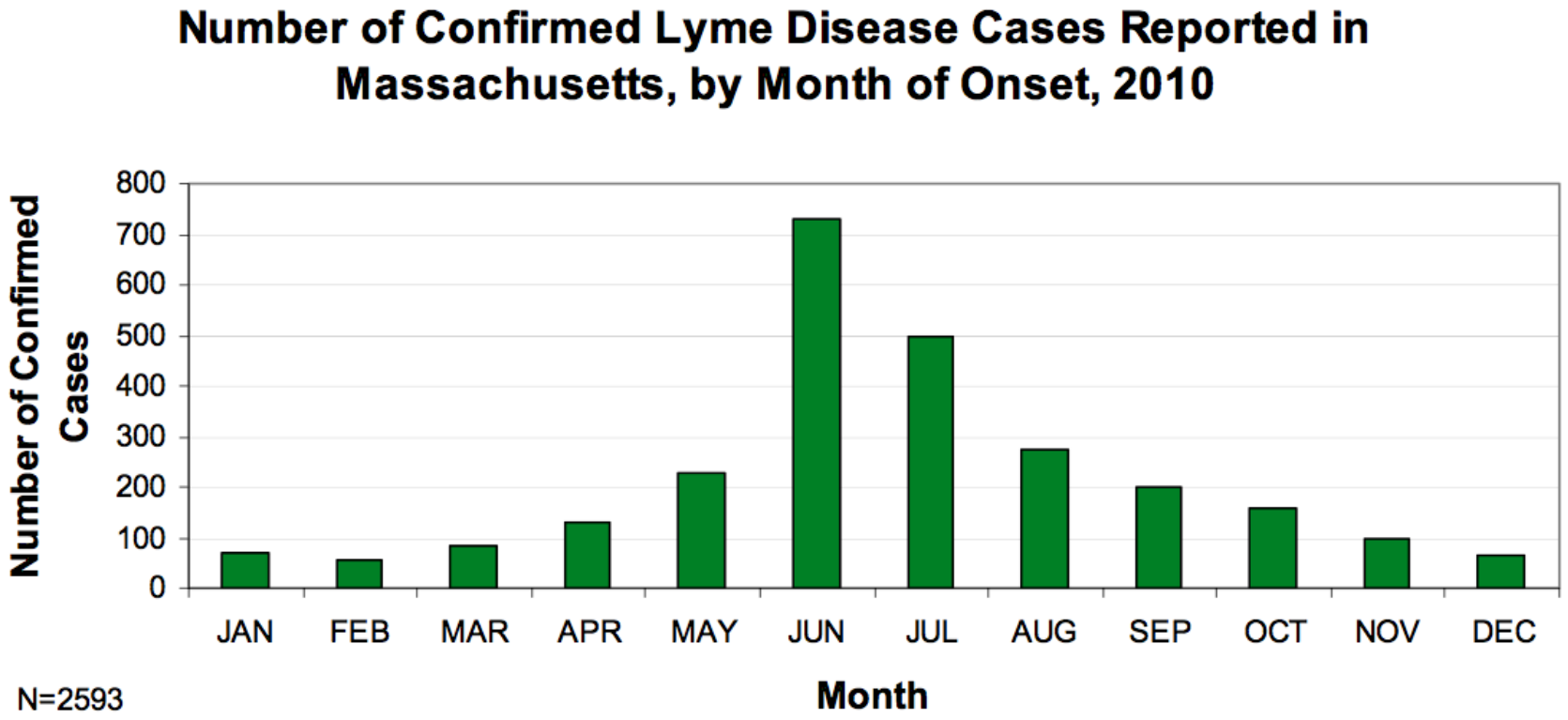
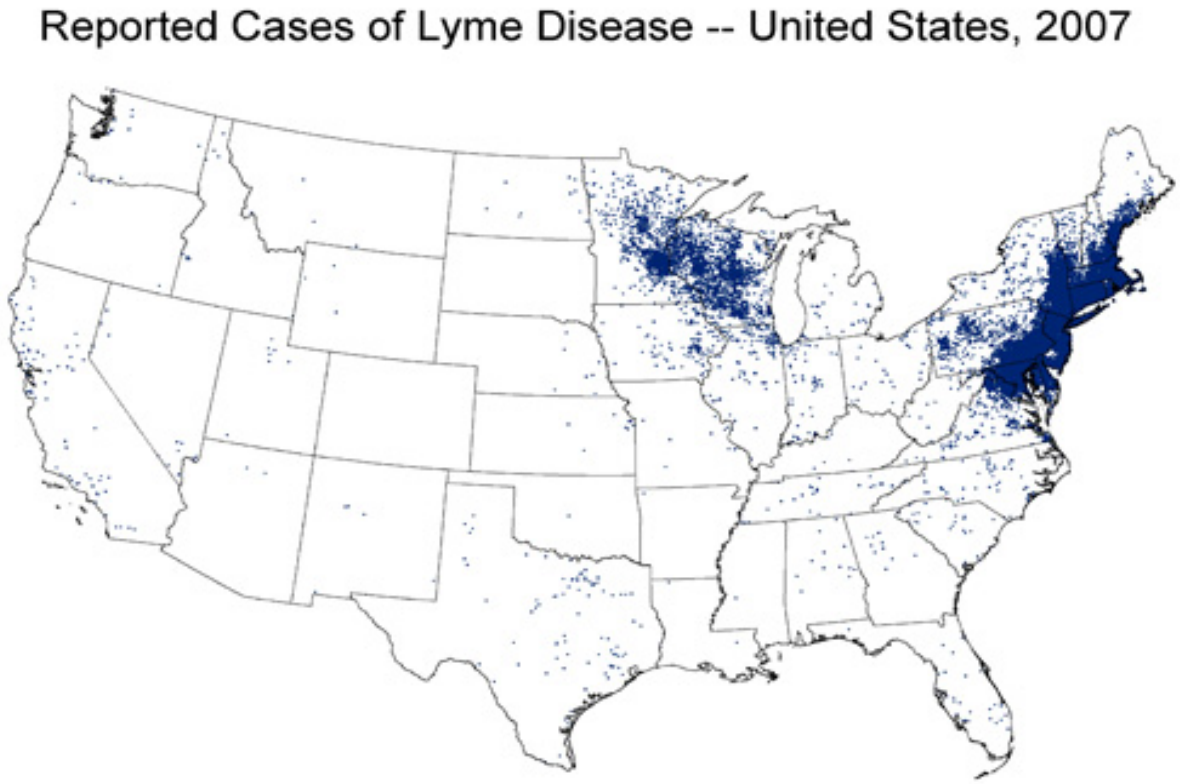
Location Location Location…

- Facial palsy presents diagnostic challenge
- Differentiate early disseminated Lyme from other etiologies
- Delayed test results

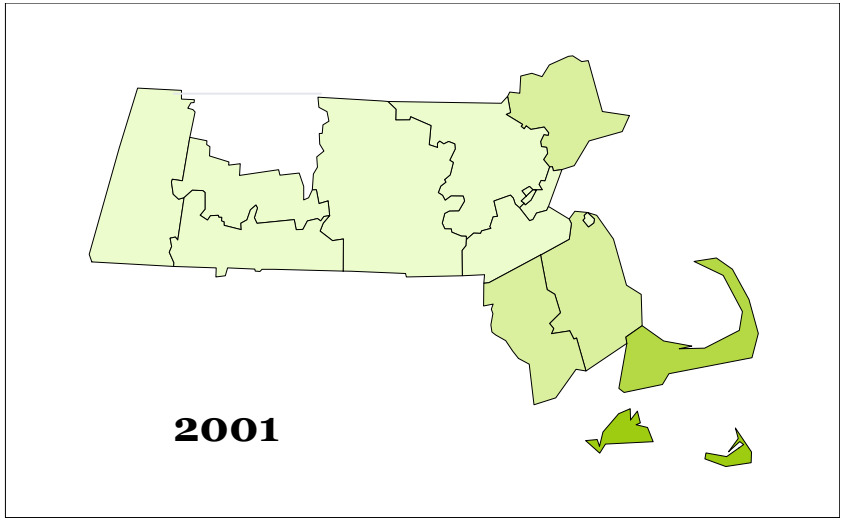
Seasonal Variation

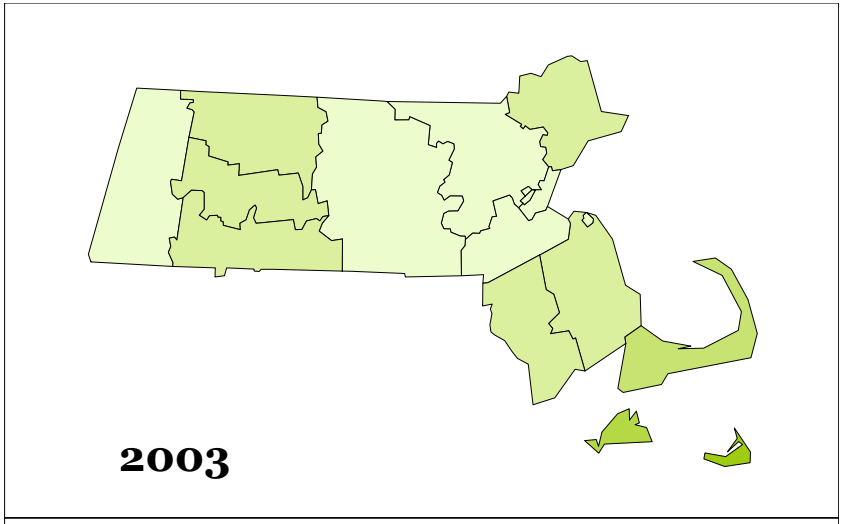


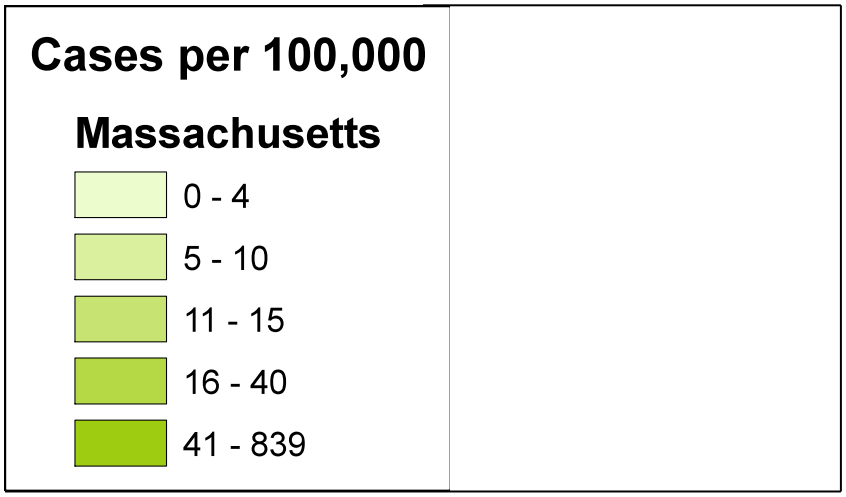
Geographic Variation of Lyme Disease

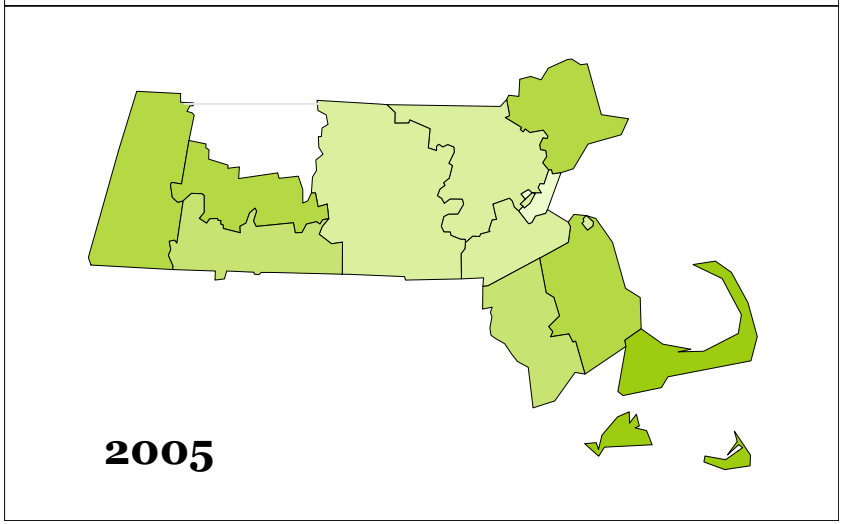


Lyme Incidence by County, 2001-05









Logistic Regression: "Clinical" model

Predictor	AOR (95% CI)	P value
Headache	4 (2-8)	<0.0001
Fever	3 (2-7)	0.0017

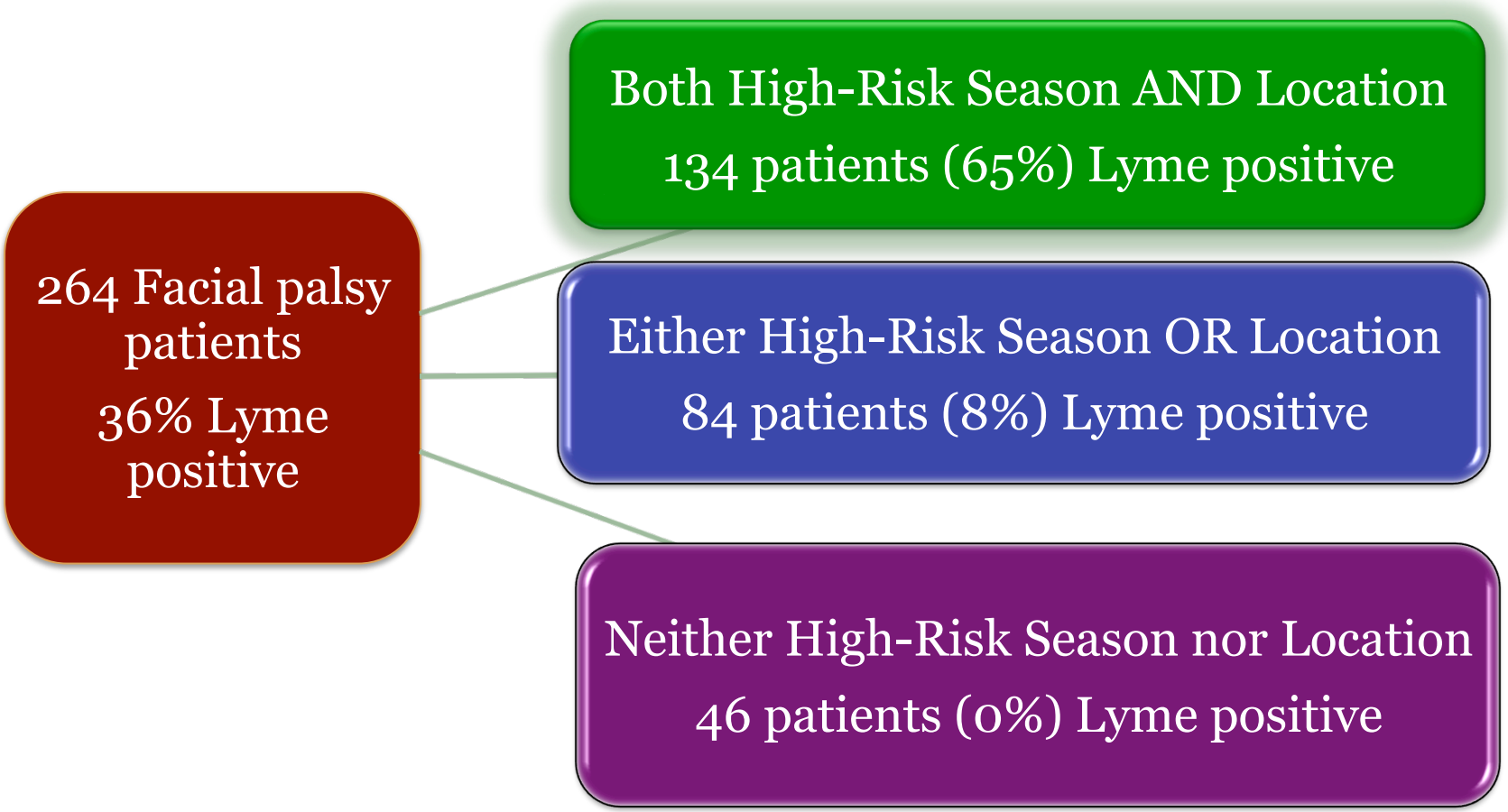
Logistic Regression: "Epidemiologic" model

Predictor	AOR (95% CI)	P value
Lyme season	25 (9-107)	<0.0001
3 year incidence in home county	20 (7-68)	<0.0001

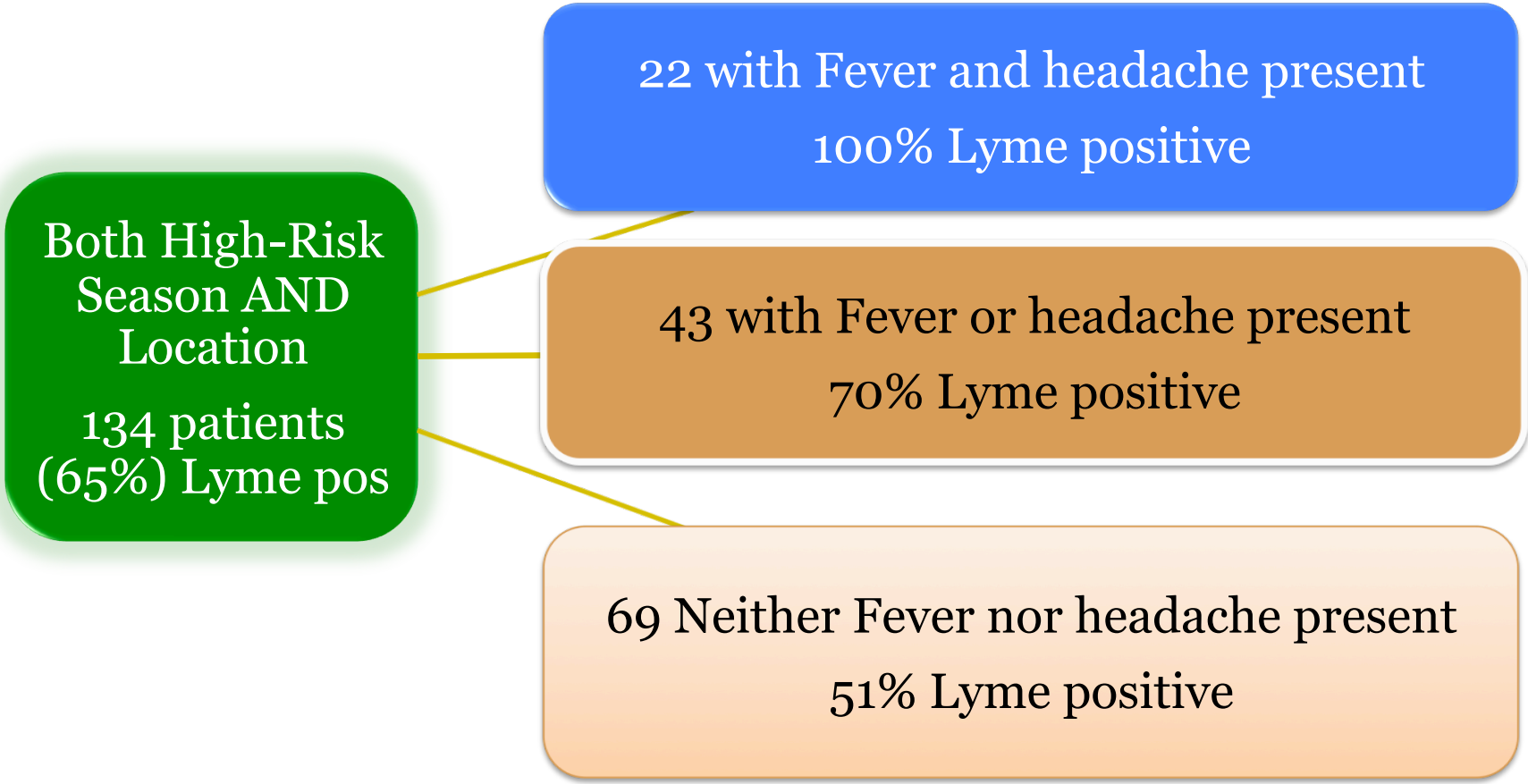
Logistic Regression: "Contextualized" model

Predictor	AOR (95% CI)	P value
Lyme season	25 (8-113)	<0.0001
3 year incidence in home county	18 (7-69)	<0.0001
Fever	4 (2-11)	0.007
Headache	3 (1-6)	0.009

Epidemiologic Conditions Help Identify Lyme



Symptoms Help Further Identify Lyme



Facial Palsy Take Home Points

- Timing and location are important predictors of etiology of facial palsy
- Especially when combined with clinical predictors

Epidemiologic Context Approach

Disease	Approach
Meningitis	*Internal hospital data*
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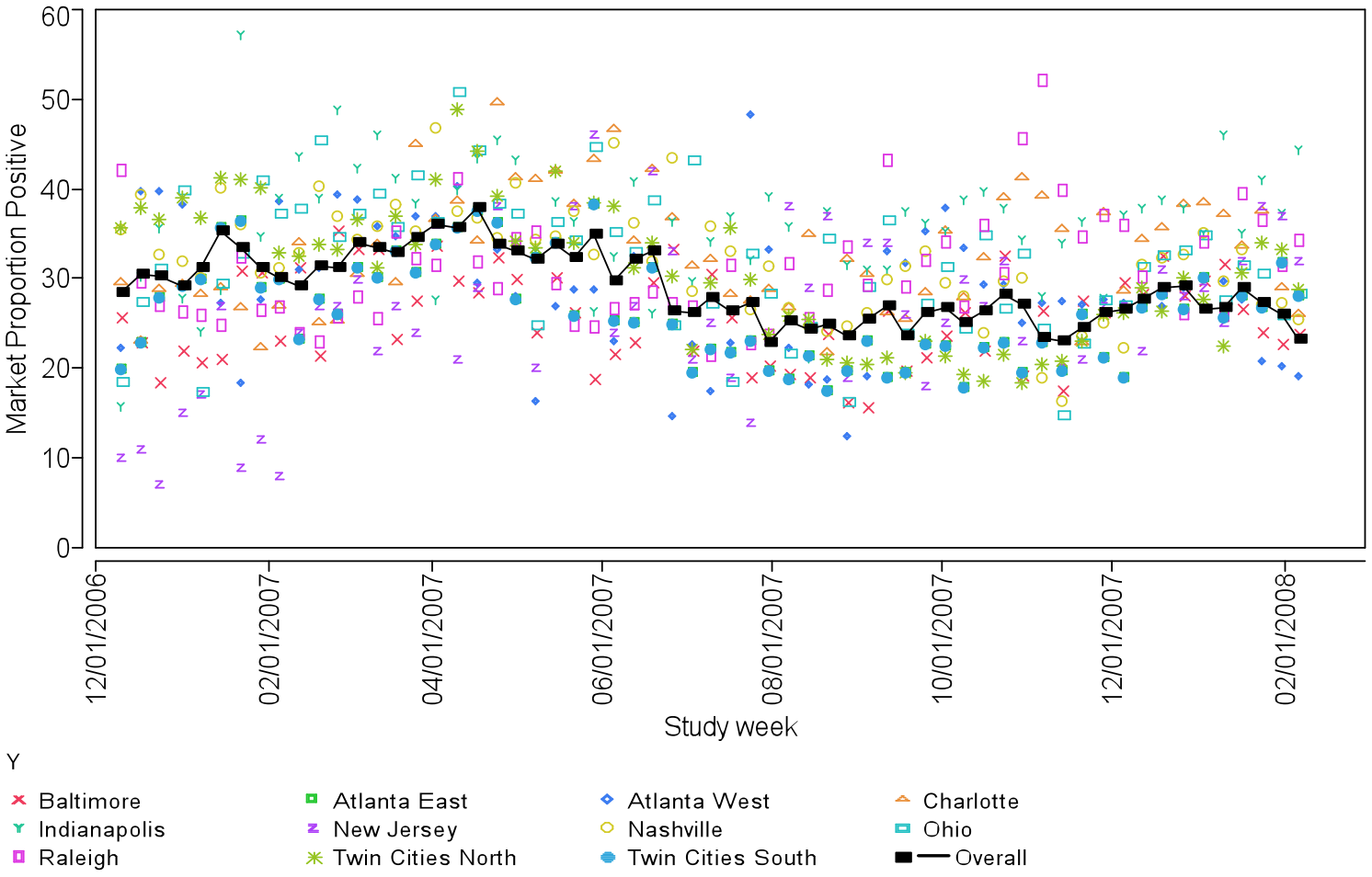
Group A Streptococcal Pharyngitis

- Most common cause of bacterial pharyngitis
- Importance of timely antibiotics

- Subtle diagnostic changes improve public health
  - Increase case detection
  - Reduce unnecessary antibiotics (mostly viral)

Strep Variation by Time and Location



Centor Score

- Fever
- Absence of cough
- Tonsillar exudates
- Swollen, tender anterior cervical lymph nodes

Centor Score	Strep positive (%) n=286
0	3
1	7
2	15
3	32
4	56

GAS Probability and Management (Adults*)

Centor score	CDC Guideline
0	Do not test, Do not treat
1	Do not test, Do not treat
2	Treat if rapid test positive
3	Option 1: Treat if rapid test positive Option 2: Treat empirically
4	Treat empirically

Integrate Recent Local Strep Data into Score

Retail clinics (500, 25 states)

- Geographic variation
- Real-time data entry into template forms
- Clinical algorithms followed closely by NPs and PAs
- Minimal free text
- >238,656 patients tested for strep ~ 1 year
- Able to calculate Centor
- Test All

Methods (1)

- Subjects – patients who presented to retail clinic with sore throat and were tested for strep, 9/06-2/08
- Analysis restricted to 9 locations with >7000 visits for pharyngitis
- 132,821 visits in 6 states (GA, IN, MD, MN, NC, TN)
  - Excluded secondary visits, patients on abx in previous month
- 110,208 age >=3 years

Methods (2)

- Derivation/Validation set – 2/3, 1/3 random split
- Data elements
  - Age
  - Visit Date
  - Clinic location
  - Clinical signs and symptoms
  - Pharyngitis test results
  - Composite variable (to reflect local incidence)

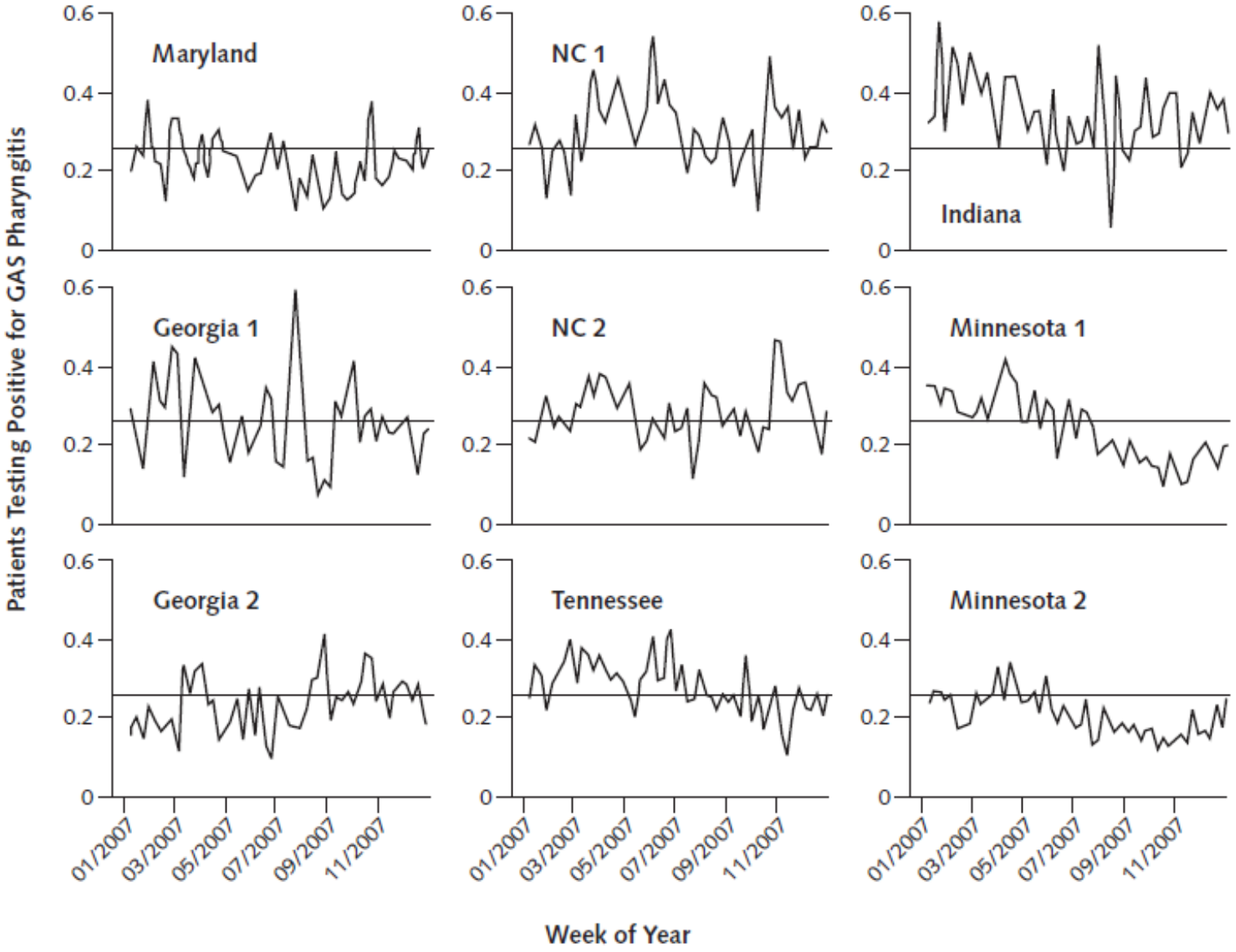
Recent Local Proportion Positive (RLPP)

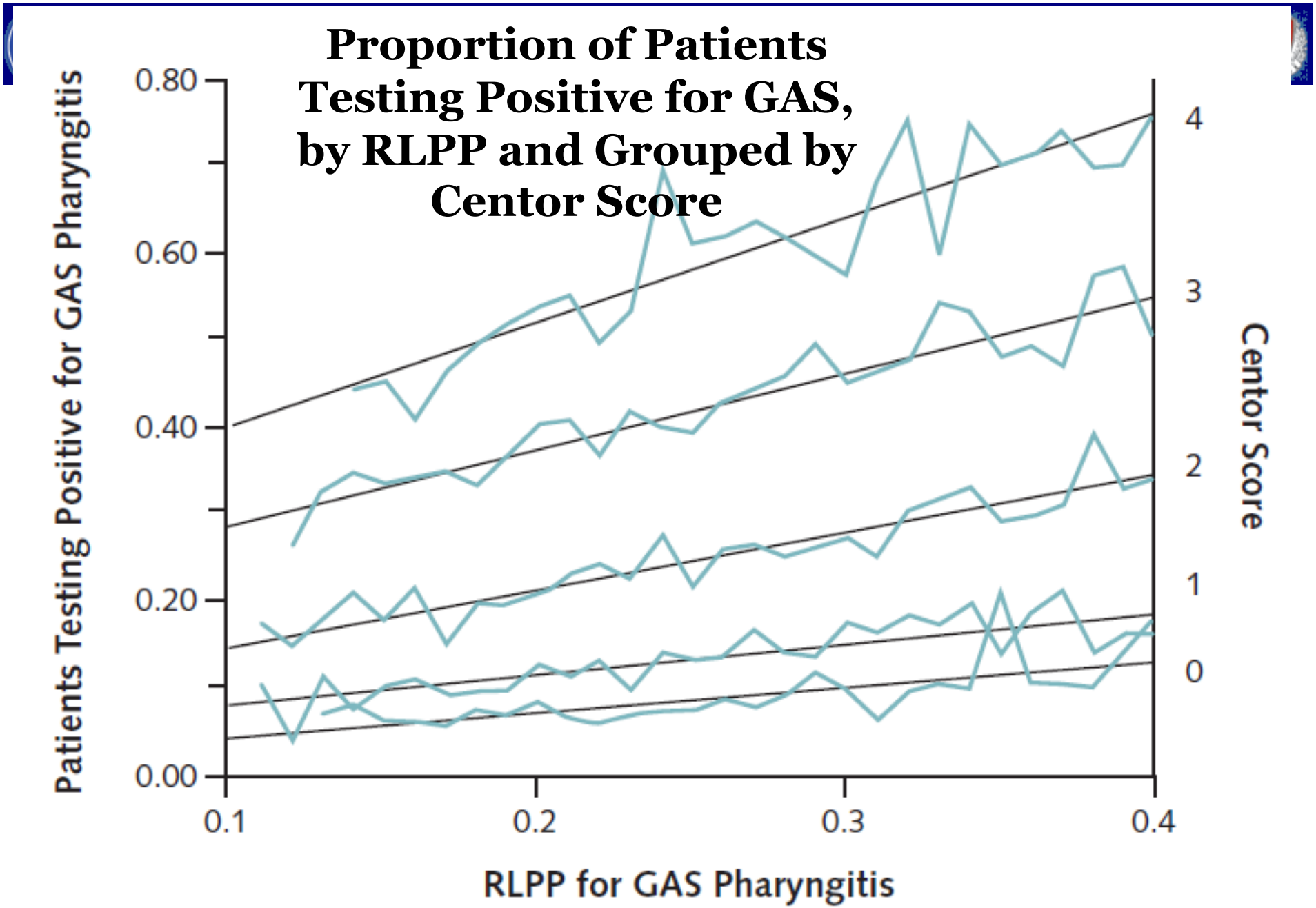
- Moving window measures proportion of patients testing positive prior to each date in each location
- For a patient presenting in Baltimore on Dec 15

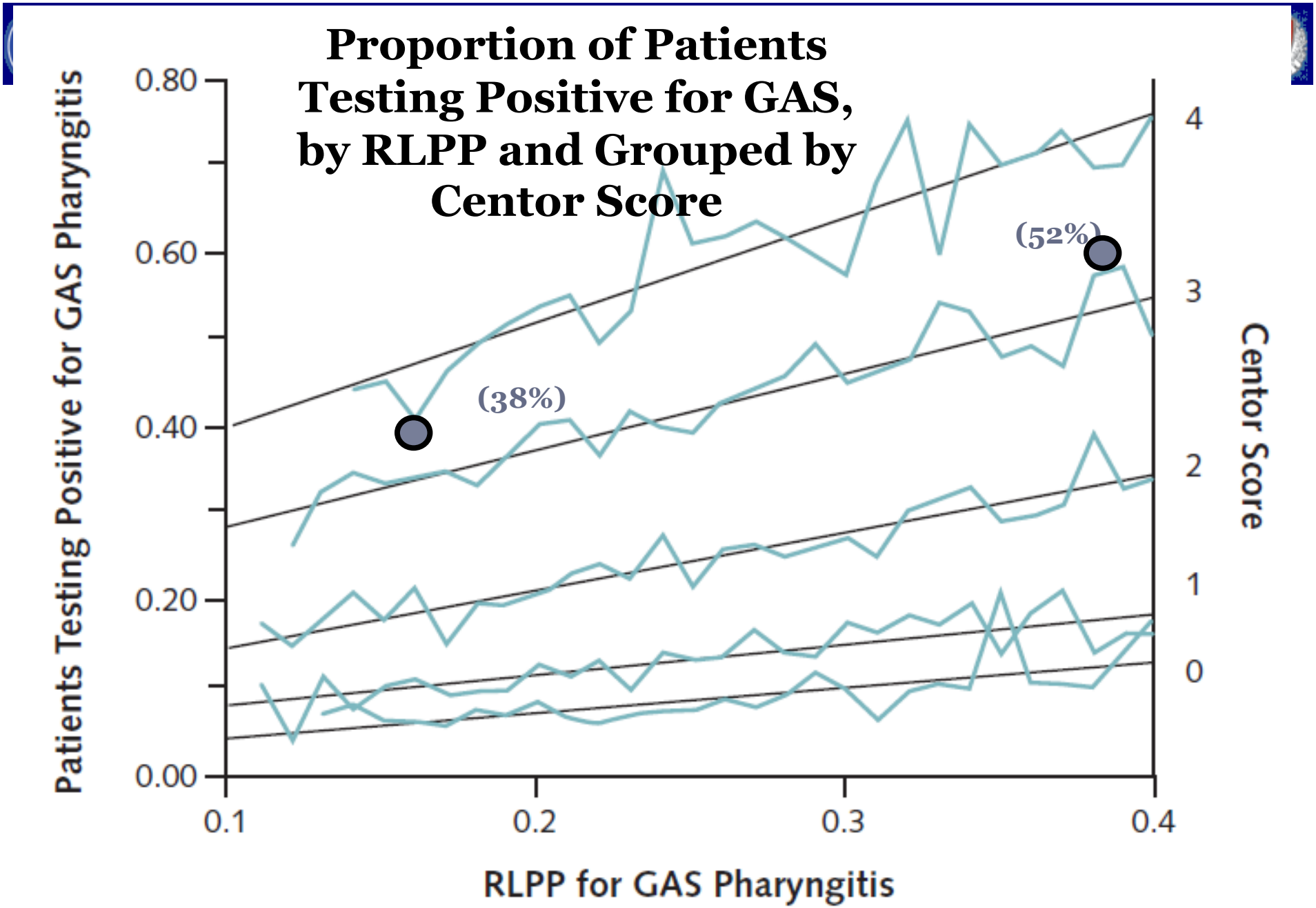
14 day RLPP (Baltimore, Dec 15) =

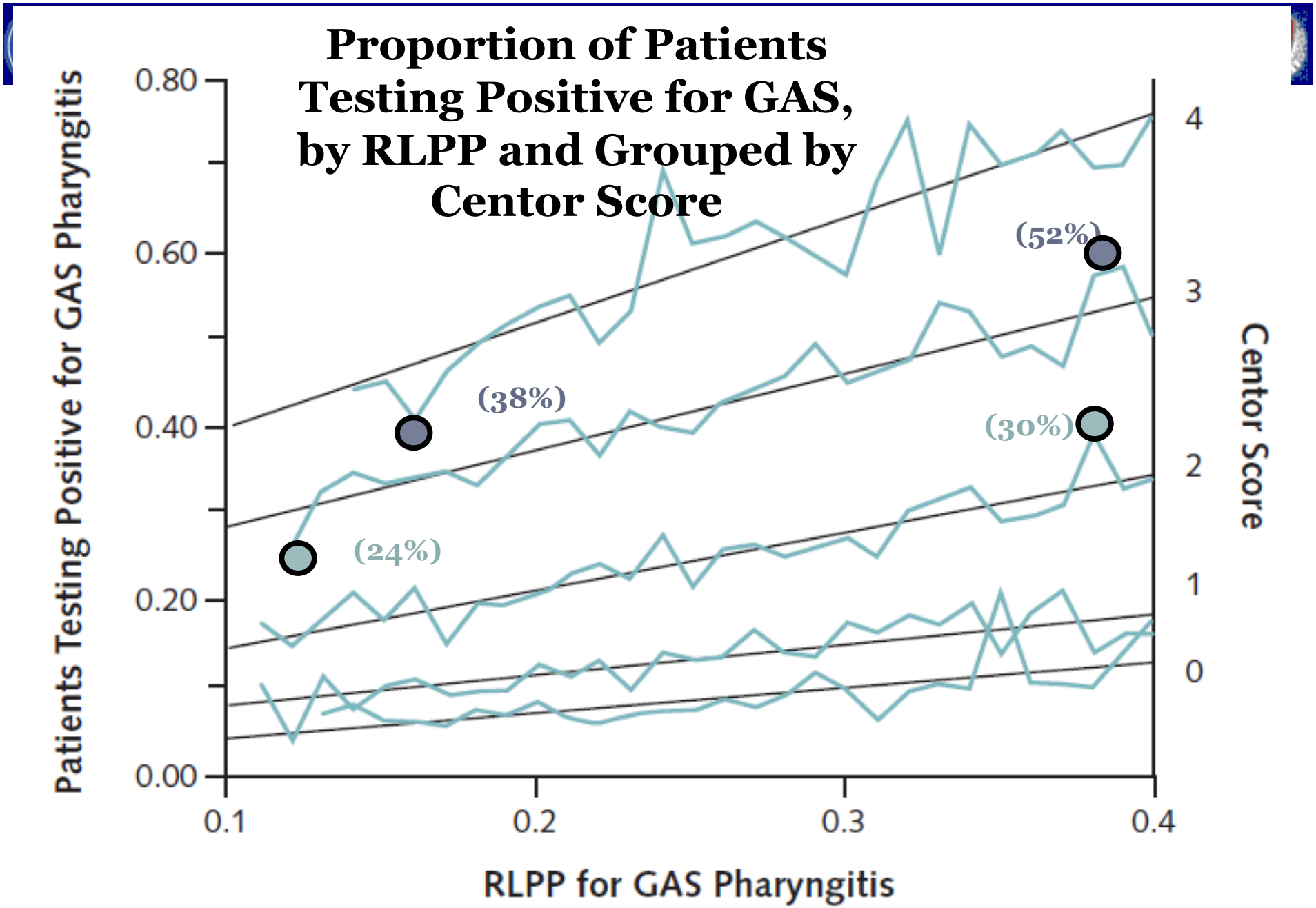
$$\frac{\text{\# of patients tested strep positive in Baltimore Dec 1-14}}{\text{total \# tested for strep in Baltimore Dec 1-14}}$$

Proportion of cases positive for GAS pharyngitis, by study week for 9 locations.




Proportion of Patients Testing Positive for GAS, by RLPP and Grouped by Centor Score
Patients Testing Positive for GAS Pharyngitis
0.80
0.60
0.40
0.20
0.00
0.1
0.2
0.3
0.4
RLPP for GAS Pharyngitis
Centor Score
4
3
2
1
0


Proportion of Patients Testing Positive for GAS, by RLPP and Grouped by Centor Score
Patients Testing Positive for GAS Pharyngitis
0.80
0.60
0.40
0.20
0.00
0.1
0.2
0.3
0.4
RLPP for GAS Pharyngitis
(38%)
(52%)
4
3
2
1
0
Centor Score


Proportion of Patients Testing Positive for GAS, by RLPP and Grouped by Centor Score
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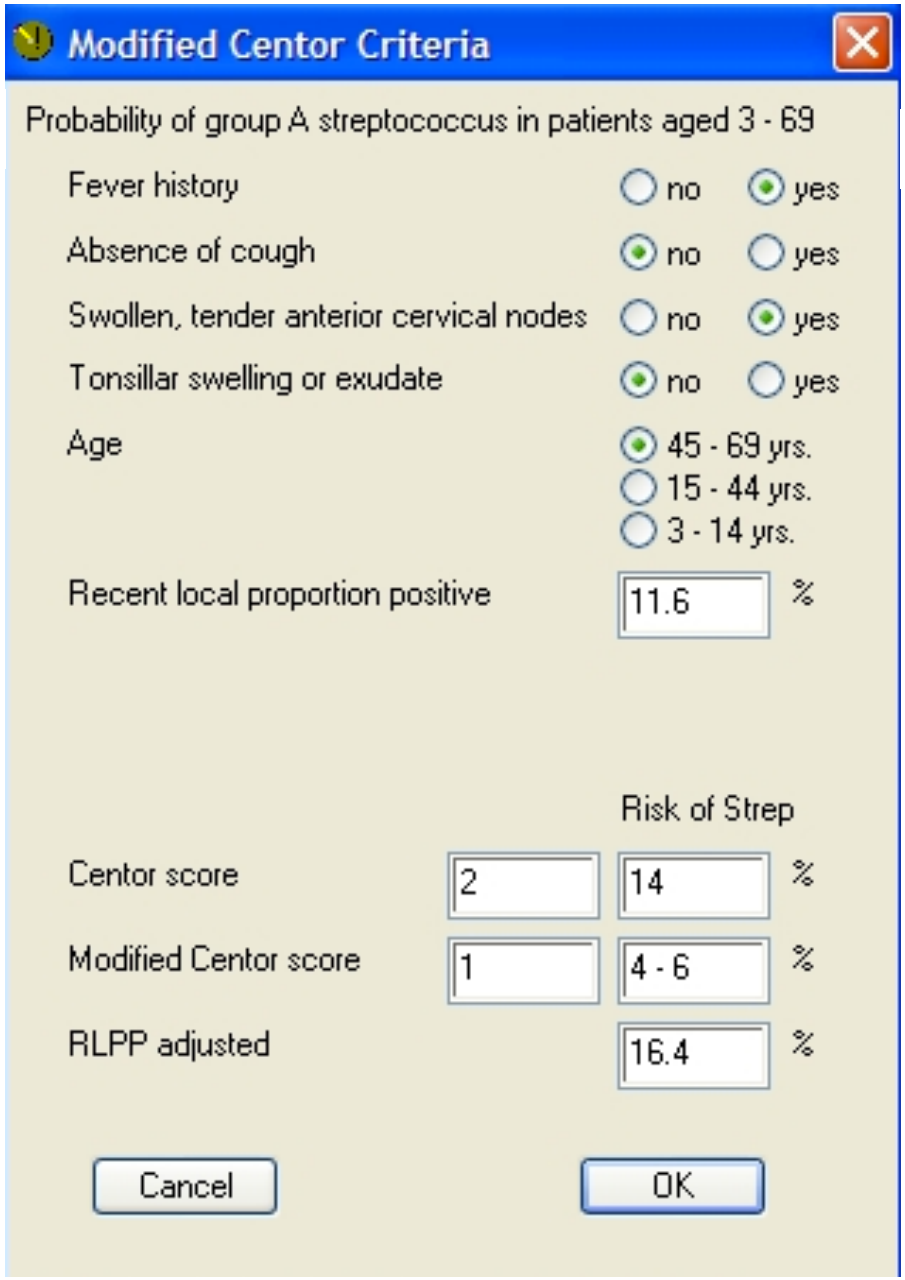
0.80
0.60
0.40
0.20
0.00
0.1
0.2
0.3
0.4
RLPP for GAS Pharyngitis
Centor Score
4
3
2
1
0
(52%)
(38%)
(30%)
(24%)

Pharyngitis Case

- 19 yo M with pharyngitis with:
  - cough (0)
  - fever (1)
  - no exudate (0)
  - no cervical adenopathy (0)
- Centor score =1 (CDC/ACP - no test, no treat)
- RLPP = 0.38 (elevated), so add 1 point to score
- Adjusted score =2 (CDC/ACP – test, treat if positive)


Modified Centor Criteria
Probability of group A streptococcus in patients aged 3 - 69
Fever history
no
yes
Absence of cough
no
yes
Swollen, tender anterior cervical nodes
no
yes
Tonsillar swelling or exudate
no
yes
Age
45 - 69 yrs.
15 - 44 yrs.
3 - 14 yrs.
Recent local proportion positive
11.6
%
Risk of Strep
Centor score
2
14
%
Modified Centor score
1
4 - 6
%
RLPP adjusted
16.4
%
Cancel
OK

Barriers for Clinicians → Home Score

- Could we bring the model to the patient?

GAS probability and Management

Centor score	ACP/CDC Guideline
0	Do not test, Do not treat
1	Do not test, Do not treat
2	Treat if rapid test positive
3	Option 1: Treat if rapid test positive Option 2: Treat empirically
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GAS probability and Management

Centor score	ACP/CDC Guideline
0	Do not test, Do not treat
1	Do not test, Do not treat

Can we identify low-risk patients and reduce emergency and outpatient visits that do not require antibiotics?

Pharyngitis Scores

	Centor	McIsaac	Clinical Biosurveillance Score
Fever	✔	✔	✔
Absence of cough	✔	✔	✔
Age		✔	
Ant Cervical adenopathy	✔	✔	✔
Exudate	✔	✔	✔
Biosurveillance			✔

Pharyngitis Scores

	Centor	McIsaac	Clinical Biosurveillance Score	Home score
Fever	✔	✔	✔	
Absence of cough	✔	✔	✔	
Age		✔		
~~Anterior Cervical LAD~~	✔	✔		
~~Exudate~~	✔	✔	✔	
Biosurveillance			✔	

Can history and biosurveillance, without physical exam, predict strep throat?

Objective

- To derive and validate a home score, assignable by the patient, to guide whether a visit is necessary for evaluation of pharyngitis

Dependent and Independent Variables

- Dependent variable
  - Strep test result
- Independent variables
  - Demographic, historical, epidemiologic variables
  - NOT Physical exam
  - 16 home score candidate predictors considered

- age, gender
- absence of cough
- "hurts to swallow"
- history of fever
- exposure to strep throat
- stomach ache
- difficulty sleeping
- ear pain, post nasal discharge
- hoarseness, headache
- nausea, vomiting
- lack of rhinorrhea
- RLPP

Calculation of Home score

- Logistic regression results used to estimate probability (0-100) of strep throat: HOME SCORE
- For each home score (0-100), we calculated the percent of patients who actually tested strep positive
- Compared the home score to percent positive
- Repeated with validation set

Hypothetical Cohorts of 1000 patients

- Chose a range of low-risk thresholds (10, 15, 20) at which patient would not need testing
- At these defined low-risk thresholds, we calculated:

1. Number of visits saved
2. Additional cases missed vs. standard approach
3. Number visits saved per missed case

Extrapolated National Impact

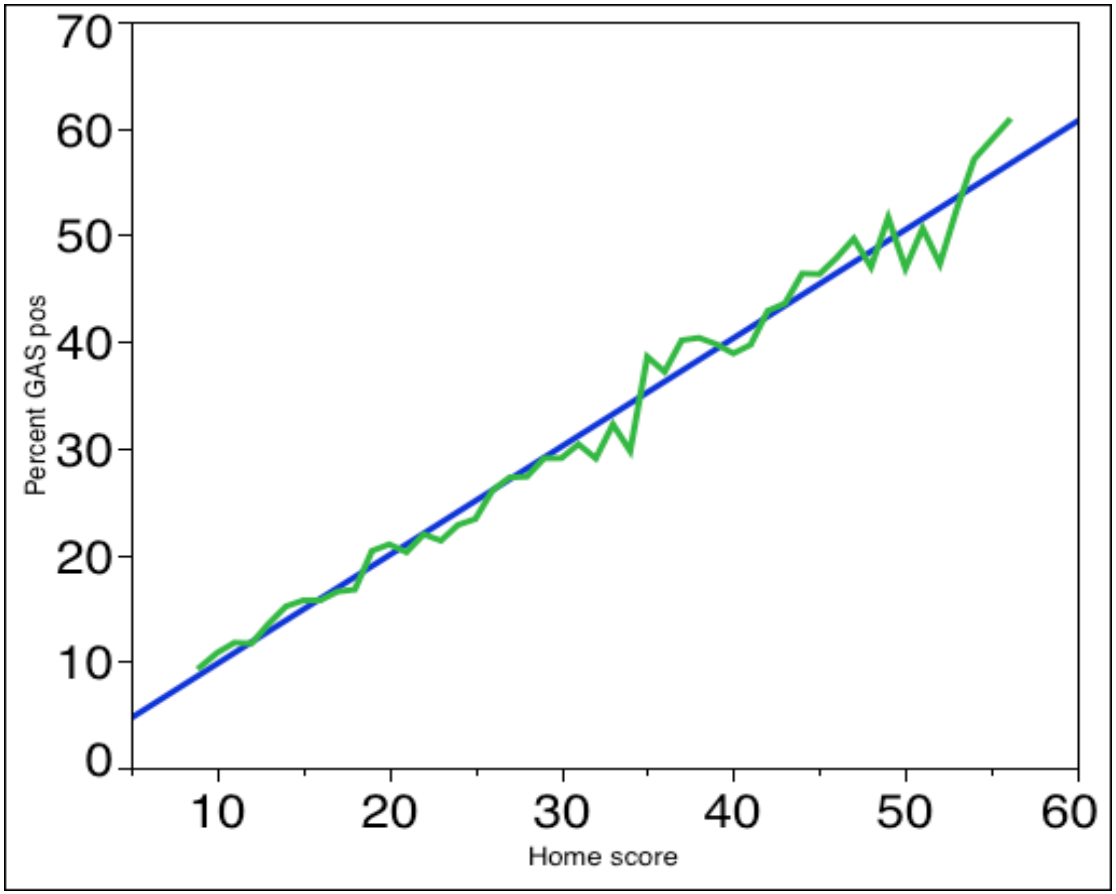
- Extrapolated to 12 million annual pharyngitis visits
- Assumed 80-90% sensitivity and 95% specificity
- Calculated potential savings based on CMS costs: strep test ($17); walk-in visit ($56-114)

Results: Logistic Regression >=15 years (n=48,089)

Predictor	Odds ratio	95% CI
Fever	2.43	(2.33-2.54)
Absence of cough	1.71	(1.63-1.80)
RLPP	1.04*	(1.04-1.04)

***1.04 per unit change in RLPP**

% Strep Positive by Home Score



Linear fit: Percent GAS pos = -0.40 + 1.02*Home score. RSquare =0.98.

Outcomes when home score identifies "low risk" (n= 48,089)

Home score threshold	Outcomes of patients in derivation set		Outcomes of patients per 1000 patients		National estimates of outcomes		Visits saved per missed case
	Visits saved (correctly classified negative)	Added cases missed vs. Centor	Visits saved (correctly classified negative)	Additional cases missed vs. Centor approach	Visits saved (correctly classified negative)	Additional cases missed vs. Centor	
<=10 (n=1535)	**1374**	**53**	**29**	**1.1**	**230,000**	**8500**	**27**
<=15 (n=9061)	4947	374	103	7.8	780,000	61,000	13
<=20 (n=21630)	18,157	1963	378	41	2.9 million	320,000	9

$17-30 M annual cost savings, or $2000-3500 saved for each case of missed GAS

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Model Performance to Predict GAS

Model	AUC
Centor	0.70
McIsaac	0.70
Clinical biosurveillance	0.72
Home score	0.65

Pharyngitis Take Home Points

- Epidemiologic context is important for common conditions as well
- Recent incidence can help adjust risk of Strep throat

Conclusions

1. *Epidemiologic Context* is an important predictor of communicable diseases.
   - Knowledge of recent local disease trends is important in accurately predicting the risk of disease in an individual patient.

Conclusions

1. *Epidemiologic Context* is an important predictor of communicable diseases.

2. Using a biosurveillance approach may improve health outcomes and efficiency of care delivery
   - By prompting clinicians to consider testing for uncommon diseases when the incidence is elevated (pertussis)
   - By encouraging clinicians to withhold interventions for common diseases when the incidence is very low (strep throat)

Conclusions

1. *Epidemiologic Context* is an important predictor of communicable diseases.

2. Using a biosurveillance approach may improve health outcomes and efficiency of care delivery

3. Infrastructure exists to foster 3 way communication between patients, providers and public health
   - Like our York colleague, we hope to bring real time data to bear on medical decision making for patients.

Thanks

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