Improved Diagnostic Accuracy of Group A Streptococcal Pharyngitis With Use of Real-Time Biosurveillance

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Background: Clinical prediction rules do not incorporate real-time incidence data to adjust estimates of disease risk in symptomatic patients.

Objective: To measure the value of integrating local incidence data into a clinical decision rule for diagnosing group A streptococcal (GAS) pharyngitis in patients aged 15 years or older.

Design: Retrospective analysis of clinical and biosurveillance predictors of GAS pharyngitis.

Setting: Large U.S.-based retail health chain.

Patients: 82 062 patient visits for pharyngitis.

Measurements: Accuracy of the Centor score was compared with that of a biosurveillance-responsive score, which was essentially an adjusted Centor score based on real-time GAS pharyngitis information from the 14 days before a patient's visit: the recent local proportion positive (RLPP).

Results: Increased RLPP correlated with the likelihood of GAS pharyngitis ($r^2 = 0.79$; $P < 0.001$). Local incidence data enhanced diagnostic models. For example, when the RLPP was greater than 0.30, managing patients with Centor scores of 1 as if the scores were 2 would identify 62 537 previously missed patients annually while misclassifying 18 446 patients without GAS pharyngitis. Decreasing the score of patients with Centor values of 3 by 1 point for an RLPP less than 0.20 would spare unnecessary antibiotics for 166 616 patients while missing 18 812 true-positive cases.

Limitations: Analyses were conducted retrospectively. Real-time regional data on GAS pharyngitis are generally not yet available to clinicians.

Conclusion: Incorporating live biosurveillance data into clinical guidelines for GAS pharyngitis and other communicable diseases should be considered for reducing missed cases when the contemporaneous incidence is elevated and for sparing unnecessary antibiotics when the contemporaneous incidence is low. Delivering epidemiologic data to the point of care will enable the use of real-time pretest probabilities in medical decision making.

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For communicable diseases, the risk for infection depends on local incidence (1, 2). However, clinicians rarely can access those data at the point of care and do not use formal quantitative approaches to adjust estimates of disease probability based on local incidence (3). The maturation of real-time infectious disease surveillance systems (3–7), coupled with the increased adoption of electronic health records, offers opportunities to improve clinical decision making by incorporating up-to-date information about local disease incidence into decision support algorithms. Even for such diseases as influenza, for which robust surveillance exists and results are widely publicized, there are no quantitative, automated methods to adjust decision support with real-time incidence data (8). In this study, we evaluated use of real-time biosurveillance data for the care of adults and older adolescents with pharyngitis.

Group A streptococcal (GAS) pharyngitis is the most common bacterial form of acute pharyngitis, with 600 million cases occurring annually worldwide (9). The disease occurs across the age spectrum, with a peak incidence in school-aged children (age 5 to 15 years). Timely antibiotic treatment reduces acute rheumatic fever, suppurative complications, symptom duration, missed work and school days, and transmission (10). Because physical examination is an unreliable method to diagnose GAS pharyngitis, the American College of Physicians (ACP) and the Centers for Disease Control and Prevention (CDC) advocate using the Centor score to classify GAS pharyngitis risk in adults (11, 12). Clinicians assign the Centor score (0 to 4) according to the following criteria: 1 point each for presence of exudates, history of fever, presence of swollen anterior cervical lymph nodes, and absence of cough. Despite evidence-based guidelines, patients with pharyngitis are often misclassified, leading to inappropriate antibiotics for those with viral disease and undertreatment of those with bona fide GAS pharyngitis. The empirical strategy proposed by the ACP leads in some cases to unnecessary antibiotic prescription (13, 14) and contributes to antimicrobial resistance.

Cases of GAS pharyngitis occur sporadically, with spatial and temporal fluctuations in incidence and occasional outbreaks (15–18), reflecting the dynamic epidemiologic nature of causative strains (19). Even when guidelines are followed, the accuracy of rapid GAS pharyngitis testing is

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Context

The Centor score is commonly used to assess the risk for group A streptococcal pharyngitis in individual patients by determining the presence or absence of specific symptoms and signs.

Contribution

Modifying the Centor score by adding biosurveillance data on the local incidence of group A streptococcal pharyngitis improved diagnostic accuracy of the score.

Caution

The study was conducted among older adolescents and adults presenting to retail pharmacy clinics. Patients suspected of having sepsis were not included.

Implication

Incorporation of biosurveillance data can improve clinical decision making for a common infectious disease and reduce unnecessary use of antibiotics.

—The Editors

affected by the pretest probability of disease, which is related to the likelihood of exposure. In temperate climates, GAS pharyngitis may peak in the winter and early spring (16), but clinicians lack accurate methods to recognize the onset, duration, or magnitude of local outbreaks from year to year.

In this study, we compared the diagnostic accuracy of the Centor score adjusted with real-time contemporaneous data on local disease incidence (biosurveillance) with that of the Centor score alone to identify GAS pharyngitis. We limited the clinical analysis to patients aged 15 years or older, for whom the Centor score and ACP guidelines are intended.

METHODS

Participants and Setting

We retrospectively analyzed data collected from patients tested for GAS pharyngitis when they presented with pharyngitis to MinuteClinic, a large, national retail health chain with more than 500 sites in 26 states (20–23). MinuteClinic provided data for the following periods: 1 October 2006 to 6 February 2008 and 14 August 2008 to 31 October 2008. Patients were included if they presented with a primary symptom of pharyngitis and were tested for GAS pharyngitis or if they had symptoms of pharyngitis and were tested for GAS pharyngitis. MinuteClinic practice is to care only for patients who do not appear septic. Patients could contribute more than 1 encounter. We did not exclude patients who were pregnant, were known to have been treated for streptococcal pharyngitis in the prior month, were already receiving antibiotics, or had comorbid diseases.

Nurse practitioners or physician assistants routinely collected a consistent set of historical and physical examination elements stored in a common database across all locations. These providers have demonstrated greater than 99% adherence to an established acute pharyngitis protocol: the "Strep Pharyngitis Algorithm" from the Institute for Clinical Systems Improvement (24). According to this algorithm, providers collect structured data on signs and symptoms, obtain rapid GAS pharyngitis tests for all patients with pharyngitis (with confirmatory testing for those who have negative results), and treat only those with positive results. The data set was limited to patients with complete information for the following variables: visit date, MinuteClinic location, age, signs and symptoms included in the Centor score, and test results.

Test Methods

All sites used the Clinical Laboratory Improvement Amendments–waived QuickVue In-Line Strep A test (Quidel, San Diego, California). The confirmatory test was a throat culture (42%) or streptococcal DNA probe (58%). Patients were considered positive for GAS pharyngitis if the rapid or confirmatory test result was positive (25).

Statistical Analysis

Statistical analysis was restricted to the 9 MinuteClinic markets with at least 7000 patient visits each for pharyngitis over the study period, encompassing 132 821 patient encounters across 6 states (Georgia, Indiana, Maryland, Minnesota, North Carolina, and Tennessee). For clinical analyses, we included visits from patients at least 15 years of age ($n = 82\,062$), with two thirds ($n = 54\,981$) selected randomly for derivation and the rest ($n = 27\,081$) for validation. We included data from patients younger than age 15 years ($n = 50\,759$) when calculating the overall local incidence data because these patients contribute to the epidemiologic context of the clinically analyzed population.

To enable integration of contemporaneous, local epidemiologic data on GAS pharyngitis, we created a biosurveillance variable reflecting disease incidence called *recent local proportion positive* (RLPP). This moving window was defined as follows: RLPP = number of patients testing positive for GAS pharyngitis in market A in the previous 14 days/total number of patients tested for GAS pharyngitis in market A in previous 14 days.

To calculate the 14-day RLPP for a patient seen on 15 October 2007, for example, we divided the number of positive GAS pharyngitis test results by the number of GAS pharyngitis tests sent in that market from 1 to 14 October 2007. We calculated 3-, 7-, and 14-day RLPPs and compared them by using Pearson correlation coefficients.

Patients were grouped by Centor score (0 to 4) and RLPP (in intervals of 0.01). For example, we calculated the proportion of patients with a Centor score of 2 who tested positive for GAS pharyngitis when the RLPP was 0.30. We performed this calculation for all combinations of Centor scores (0 to 4) and RLPPs (0.10 to 0.40) when at least 40 patients shared a combination. For each Centor score, we plotted the proportion of patients testing positive as a

Table 1. **Clinical Characteristics of Patients Presenting With Pharyngitis to the Retail Health Clinics (Derivation Set = 54 981 Patient Visits)**

Characteristic	Overall (n = 54 981)	Patients Positive for GAS Pharyngitis (n = 13 823)	Patients Negative for GAS Pharyngitis (n = 41 158)
Women, %	68	66	68
Mean age (median [interquartile range]), *y*	33.5 (33 [24–41])	33.2 (33 [25–40])	33.5 (33 [24–41])
Age group, %			
15–18 y	13	10	14
19–39 y	58	64	56
40–59 y	26	24	26
>60 y	3	2	3
Fever, %	31	45	26
Swollen anterior cervical lymph nodes, %	61	77	55
Absence of cough, %	68	76	66
Tonsillar exudates, %	22	40	16
Distribution by Centor score*, %			
0	8	3	10
1	33	18	38
2	34	34	35
3	18	31	14
4	6	15	3

GAS = group A streptococcal.
* To calculate the Centor score for a patient who presents with acute pharyngitis, 1 point is given for each of the following items: presence of tonsillar exudates, history of fever, presence of swollen anterior cervical lymph nodes, and absence of cough (11).

function of RLPP. Linear regression was used to determine the strength of association between RLPP and GAS pharyngitis positivity for each Centor score, and the Pearson coefficient was used for correlation.

We considered the ACP guideline recommending that patients with a Centor score of 1 should not be tested or treated for GAS pharyngitis, those with a score of 2 should be tested and treated only if they test positive, and those with a score of 3 should be treated empirically (1 of 2 ACP options). For patients with a Centor score of 1 or 2, we evaluated a biosurveillance-responsive score constructed by adding 1 point to the score of patients when the RLPP exceeded the following thresholds: 0.20, 0.25, 0.30, and 0.35. When the RLPP exceeded the threshold and triggered an increase in the score, we calculated the number of patients in that group who would be correctly and incorrectly reclassified as positive for GAS pharyngitis. The assumption is that testing is 80% sensitive and 95% specific (26). We subtracted the number incorrectly reclassified from the number correctly reclassified to determine the net reclassification; we then divided the net reclassification by the number of patients to determine the net percentage reclassification at each RLPP threshold. To facilitate comparison across the different RLPP thresholds, we calculated the number of patients reclassified correctly and incorrectly for hypothetical cohorts of 1000 patients. To determine the number needed to test to identify each additional case of GAS pharyngitis, we divided the additional number of patients tested by the additional number correctly reclassified as positive for GAS pharyngitis at each threshold.

We calculated national estimates of the number of patients for whom management would have been different with use of the biosurveillance-responsive approach compared with the traditional Centor score approach. To calculate the national effect on an estimated 10.5 million annual national pharyngitis visits (27), we extrapolated the relevant distributions from the MinuteClinic data for age (62% of patients were ≥15 years of age), Centor score (32% of patients had a Centor score of 1), and RLPP (21% of patients presented when the RLPP exceeded 0.30). We examined the effect of reducing the score by 1 point for patients with a Centor score of 2 or 3 if the RLPP was below the following thresholds: 0.15, 0.20, and 0.25. We calculated the number of patients and number per 1000 who were correctly and incorrectly reclassified as negative for GAS pharyngitis, the net number and net percentage reclassified, and the estimated number of patients nationally whose management would have been altered. The Children's Hospital Boston Committee on Clinical Investigation approved this database analysis. We performed statistical analyses by using JMP software, version 8 (SAS Institute, Cary, North Carolina).

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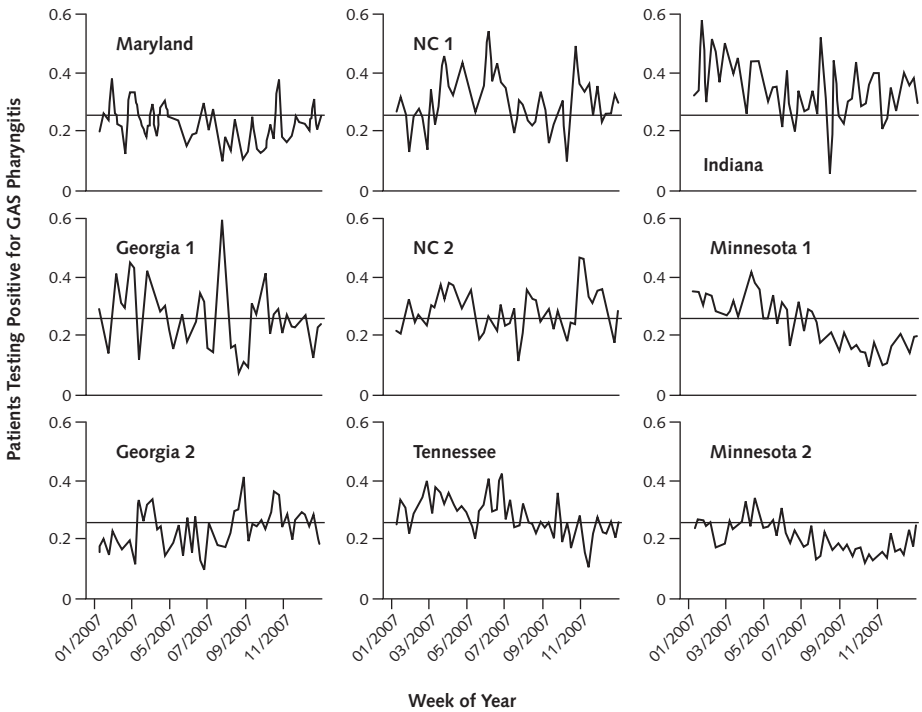
RESULTS

Table 1 shows patient characteristics for the derivation set (n = 54 981), including distribution by sex, age, clinical findings, and Centor score. Two thirds of patients had Centor scores of 1 or 2, and 68% of patients were female.

Figure 1. **Proportion of cases positive for GAS pharyngitis, by study week for 9 locations.**



The x-axis represents the time from 1 January 2007 to 31 December 2007, and the y-axis is the weekly proportion of cases positive for GAS pharyngitis. Each graph shows the proportion of patients who tested positive each week in 1 of 9 markets. The axes have been standardized to allow comparison across markets. The horizontal line is the average across all markets (0.25) and is provided for reference and to facilitate comparison. The hash marks on the x-axis display bimonthly intervals. GAS = group A streptococcal; NC = North Carolina.

Thirteen percent of the patients were 15 to 18 years of age. Most patients (91%) had a single encounter, and 7% had 2 encounters. In the validation set, the distribution of patients was the same as in the derivation set for age, sex, presence of fever, presence of swollen anterior cervical nodes, absence of cough, presence of tonsillar exudates, and distribution of Centor score. The median number of patients tested per month was 7289 (interquartile range, 4365 to 8602). With regard to volume over time, 29 826 patients were tested in the first quarter of the study, 32 143 in the second, 36 156 in the third, and 34 696 in the fourth. The number of patient visits for the entire study population was as follows: Georgia 1 (n = 7777), Georgia 2 (n = 9797), Maryland (n = 9720), North Carolina 1 (n = 12 236), North Carolina 2 (n = 10 122), Indiana (n = 8901), Tennessee (n = 15 365), Minnesota 1 (n = 30 391), and Minnesota 2 (n = 27 972).

The proportion of all patients testing positive varied across time and location, demonstrating no obvious predictable season for GAS pharyngitis (**Figure 1**). For example, during the week of 24 December 2007, the proportions positive were below 20% in 3 markets, 20% to 29% in 4, and greater than 30% in 2. The 3-, 7-, and 14-day RLPPs were strongly correlated (14 vs. 7: $r^2 = 0.79$, $P < 0.001$; 7 vs. 3: $r^2 = 0.63$, $P < 0.001$; 14 vs. 3, $r^2 = 0.48$, $P < 0.001$); thus, we used the 14-day RLPP for subsequent analyses because it provides a realistic time frame to generate reliable, contemporaneous local data on GAS pharyngitis.

Overall, 25% of all patients tested positive for GAS pharyngitis in the derivation and validation sets, greater than the 17% in the original Centor study (11) but similar to findings in Wigton and colleagues' validation study (26%) (28). For patients with Centor scores of 1 to 4, the proportion testing positive is lowest when the RLPP is low and increases with rising RLPP (P values for slopes < 0.001). **Figure 2** illustrates the proportion testing positive plotted by RLPP, grouped by Centor score. Each point on the graph represents a group of patients with an identical Centor score–RLPP dyad. Overall, a patient with a Centor score of 3 is more likely than a patient with a Centor score of 2 to test positive for GAS pharyngitis (43% to 25%), but this changes under particular epidemiologic conditions. To illustrate, 350 of 1053 (33% [95% CI, 30% to 36%]) patients with a Centor score of 2 test positive when the RLPP is greater than 0.35, compared with 109 of 328 (33% [CI, 28% to 38%]) with a Centor score of 3 when the RLPP is less than 0.15. The **Appendix Figure** (available at www.annals.org) shows a similar graphical distribution for the same analysis with use of the validation set.

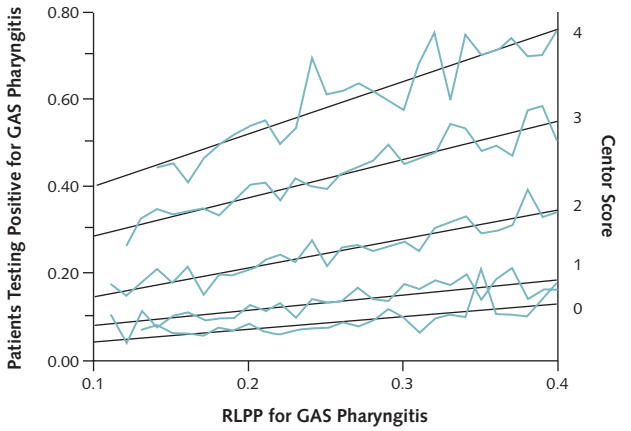
We measured the effect of adding 1 point to a Centor score of 1 when the RLPP exceeded specific thresholds. Hypothetically, testing 1000 patients when the RLPP is greater than 0.30, for example, would correctly reclassify 139 and incorrectly reclassify 41 patients as positive, a ratio exceeding 3:1 (**Table 2**). GAS = group A streptococcal; RLPP = recent local proportion positive.

By extrapolation, we estimated that approximately 449 908 of the 10.5 million pharyngitis visits per year would occur among persons 15 years of age or older, with a Centor score of 1 when the RLPP exceeded 0.30. The biosurveillance approach for guiding the care of these patients would identify 62 537 additional GAS pharyngitis cases in the United States annually and lead to treatment of an additional 18 446 patients without GAS pharyngitis. The number needed to test to detect each additional case of GAS pharyngitis is 7.2. **Appendix Table 1** (available at www.annals.org) displays the corresponding analyses for the validation set: 60 048 additional cases would be identified, and 18 103 patients without GAS pharyngitis would be treated. In the validation set, the number needed to test is 7.4.

We examined outcomes generated by adding 1 point to the Centor score of adults and older adolescents with a score of 2 (n = 18 942) at specific RLPP cutoffs (**Table 2**). Increasing the score incrementally when the RLPP is greater than 0.30 and empirically treating a simulated cohort of 1000 of these patients would correctly reclassify 62 but incorrectly reclassify 657 patients as positive. Through extrapolation, this approach correctly identifies 29 450 additional GAS pharyngitis cases in the United States annually, but at a cost of inappropriately treating 312 077 patients without GAS pharyngitis.

Next, we tabulated outcomes generated by subtracting 1 point from the Centor score of all adults and older adolescents with a score of 3 (n = 10 056) or 2 (n = 18 942) at defined RLPP cutoffs (**Table 3**). Testing 1000 hypothetical patients with a score of 3 when the RLPP is less than 0.20, rather than treating them empirically, would correctly reclassify 620 but incorrectly reclassify 70 patients as negative. In the United States, this could spare antibiotics for 166 616 patients (5 million doses) while missing only 18 812 cases annually. **Appendix Table 2** (available at www.annals.org) shows the corresponding data from the validation set: A total of 169 637 patients would be spared antibiotics, whereas 17 632 patients would be missed.

Figure 2. **Proportion of patients testing positive for GAS pharyngitis, by RLPP and grouped and labeled by Centor score.**



Each line represents patients with the same Centor score across varying RLPPs. The proportion of patients who tested positive increases both as the clinical score and the RLPP increase. The Pearson coefficient was used to measure the strength of correlation. The r^2 values, representing the proportion of the variation in GAS pharyngitis positivity that can be attributed to the RLPP, are 0.81 ($P < 0.001$) for a Centor score of 4, 0.86 ($P < 0.001$) for a Centor score of 3, 0.86 ($P < 0.001$) for a Centor score of 2, 0.70 ($P < 0.001$) for a Centor score of 1, and 0.47 ($P < 0.001$) for a Centor score of 0. The slopes of the lines for Centor scores of 4, 3, 2, 1, and 0 are 1.21, 0.88, 0.64, 0.37, and 0.29, respectively. Each data point represents a median of 223 patients (range, 41 to 1152 patients; interquartile range, 115 to 518 patients). GAS = group A streptococcal; RLPP = recent local proportion positive.

Table 2. **Reclassification Accuracy of Adjusted Centor Score Resulting From Increasing Score by Increments of 1 Point at Different Thresholds of GAS Pharyngitis Activity***

Centor Score	RLPP Threshold	Cases Reclassified as Positive for GAS Pharyngitis			Cases Reclassified per 1000, *n*		National Estimates of Numbers Affected, *n*	
		Incorrect, *n*	Correct, *n*	Net Change, *n* (%)	Incorrect	Correct	Incorrect	Correct
1	>0.20 (n_1 = 13 056)	556	1542	985 (8)	43	118	63 647	174 658
	>0.25 (n_1 = 8796)	370	1119	749 (9)	42	127	40 058	121 129
	>0.30 (n_1 = 4355)	180	607	427 (10)	41	139	18 446	62 537
	>0.35 (n_1 = 1579)	65	216	151 (10)	41	137	7394	24 707
2	>0.20 (n_2 = 13 987)	9738	747	−8991 (−64)	696	53	1 087 646	82 824
	>0.25 (n_2 = 9583)	6555	537	−6018 (−63)	684	56	688 768	56 390
	>0.30 (n_2 = 4746)	3117	293	−2824 (−60)	657	62	312 077	29 450
	>0.35 (n_2 = 1818)	1150	122	−1028 (−57)	632	67	120 336	12 757

GAS = group A streptococcal; RLPP = recent local proportion positive.
* Adjustment of Centor score to reclassify risk according to prior probability of disease as inferred by the RLPP. For patients with a Centor score of 1 or 2, the score was increased by an increment of 1 point when RLPP exceeded thresholds. Changing from 1 to 2 would result in testing n_1 patients for GAS pharyngitis, and changing from 2 to 3 would result in treating n_2 patients empirically.

Table 3. **Reclassification Accuracy of Adjusted Centor Score Resulting From Decreasing Score by 1 Point at Different Thresholds of GAS Pharyngitis Activity***

Centor Score	RLPP Threshold	Cases Reclassified as Negative for GAS Pharyngitis			Cases Reclassified per 1000, *n*		National Estimates of Numbers Affected, *n*	
		Incorrect, *n*	Correct, *n*	Net Change, *n* (%)	Incorrect	Correct	Incorrect	Correct
2	<0.25 (n_2 = 8746)	1498	344	−1154 (−13)	171	39	175 950	40 129
	<0.20 (n_2 = 4342)	655	176	−479 (−11)	151	41	76 433	20 753
	<0.15 (n_2 = 847)	126	35	−91 (−11)	148	41	13 741	3807
3	<0.25 (n_3 = 4334)	325	2574	2249 (52)	75	594	40 971	324 492
	<0.20 (n_3 = 2080)	145	1289	1144 (55)	70	620	18 812	166 616
	<0.15 (n_3 = 371)	25	233	208 (56)	68	627	3352	30 907

GAS = group A streptococcal; RLPP = recent local proportion positive.
* Adjustment of Centor score to reclassify risk according to prior probability of disease as inferred by the RLPP. For patients with a Centor score of 2 or 3, the score was decreased by 1 point when RLPP was below threshold. Changing from 2 to 1 would result in not testing or treating n_2 patients for GAS pharyngitis, and changing from 3 to 2 would result in testing n_3 patients and treating them if they tested positive.

DISCUSSION

We asked the question, "What if clinicians could integrate real-time incidence data into clinical decision making for patients?" Retail health data on pharyngitis were ideal to address this question because clinical scores have been validated to estimate risk for GAS pharyngitis in adults, the disease is common, disease incidence varies temporally and spatially, and MinuteClinic protocol dictates that all patients with pharyngitis undergo GAS pharyngitis testing, regardless of Centor score. We show that contextualizing the Centor score by using biosurveillance data to calculate the RLPP improves prediction of positivity for GAS pharyngitis in patients presenting with pharyngitis across all clinical risk categories and is especially important when the RLPP is very high or very low. For adults and older adolescents, adjusting management on the basis of a biosurveillance approach could improve health outcomes and efficiency of health care delivery.

The ACP/CDC recommends not testing or treating adults who are unlikely to have GAS pharyngitis (Centor score of 0 or 1). We show that adults and older adolescents with a Centor score of 0 are unlikely to have GAS pharyngitis regardless of RLPP; even when the RLPP is elevated, their risk for GAS pharyngitis rarely exceeds 15%. However, our data suggest that during times of elevated RLPP, clinicians should consider testing adults and older adolescents who have a Centor score of 1. Adding 1 point for adults and older adolescents with a Centor score of 1 offers greater overall benefit than adding 1 point to those with a score of 2. In addition, subtracting 1 point from a score of 3 when the RLPP is low spares unnecessary empirical antibiotic therapy and just slightly decreases case identification.

Practice guidelines traditionally account for clinical features, and to some extent seasonality, without regard for real-time epidemiologic data on disease incidence. Some clinicians informally incorporate epidemiologic incidence data into their heuristics for medical decision making, but a clinician's knowledge of current disease trends may be prejudiced by recent or unusual cases, leading to cognitive bias and over- or underestimation of the true incidence of disease (29, 30). The propagation of retail health clinics in geographically diverse areas provided an opportunity to evaluate how local incidence data collected by using an unbiased, robust, uniform information system can improve clinical decision making.

Developing formal guidelines for incorporating biosurveillance data into the diagnostic and treatment algorithms for GAS pharyngitis necessitates a discussion of the relative trade-offs between missed cases and overtreatment of patients without true bacterial infection. For example, increasing the Centor score by 1 would have resulted in 3.4 additional cases of GAS pharyngitis diagnosed for every additional negative patient treated. Nevertheless, the public health concern of antibiotic resistance must be weighed against the benefits of preventing complications and morbid conditions from missed cases.

Limitations

Patients presenting to retail health clinics may be less acutely ill and have fewer comorbid conditions than patients with pharyngitis who present to other types of health care settings, and our findings should not be applied to individuals suspected of having sepsis. Further, although all clinical and laboratory data were collected prospectively, the analyses were conducted retrospectively. Logistic concerns must be considered when the RLPP is integrated into a clinical decision-support framework. The RLPP surveillance signal stream would weaken if clinicians tested fewer low-risk patients when the RLPP is low. To preserve the accuracy of the RLPP metric, it would be imperative to maintain a stream of data through the random, intentional testing of a threshold sample of patients weekly, regardless of Centor score and RLPP. This testing approach could provide value in disease management from the population health perspective.

Our data cannot inform the debate about the importance of the streptococcal carrier state because serologic

tests for GAS pharyngitis were not performed. In this analysis, all patients were symptomatic with pharyngitis, and this clinical presentation, coupled with positive results on GAS pharyngitis testing, is universally approached as true infection in clinical practice and decision-making algorithms. We did not have information about family or close contacts who tested positive for GAS pharyngitis, but we expect that clinicians would continue to consider this information, if available. Our analyses did not cover all regions of the country but did include 6 different states.

Although the very large sample size is a strength of our study, the dependence on multiple providers' clinical assessments may introduce some variability. However, all information was collected by nurse practitioners and physician assistants trained to evaluate pharyngitis according to a strict, computer-driven protocol. Data were not available to permit calculation of intra- or interobserver variation in the collection of clinical findings that contribute to the Centor score. We are limited by the absence of data on locations of patients' schools or jobs that might permit more refined epidemiologic modeling. Studies have shown GAS pharyngitis outbreaks differentially infecting students at different schools within a town (31). Despite these limitations, we felt that retail health data on pharyngitis provided the best available data to address the question of whether local incidence could help improve care for symptomatic patients.

Conclusions

Group A streptococcal pharyngitis occurs throughout the calendar year, and thus live biosurveillance becomes particularly helpful. Because GAS pharyngitis is a common condition affecting millions per year in the United States alone, small improvements in diagnostic accuracy have substantial impact. Incorporating real-time, biosurveillance-derived epidemiologic data into a prediction rule based on a patient's signs, symptoms, location, and timing of presentation (32–34) suggests the value of this epidemiologic analogue to personalized genomic medicine (35); with the biosurveillance model, the context, instead of being derived from one's genes, derives from a quantitative representation of the epidemiologic milieu.

Developers of future recommendations for managing GAS pharyngitis should consider incorporating real-time epidemiologic data with clinical factors. This novel approach in clinical guideline creation could help restratify risk for patients when the contemporaneous incidence of disease is very high or very low, thereby improving diagnostic accuracy. Although our study focused on GAS pharyngitis, the results may have broad implications for other communicable diseases, for which real-time biosurveillance data might be used to more accurately deduce the likelihood that a symptomatic individual has a specific disease.

The massive federal investment in health information technology (36) and the maturation of real-time biosurveillance systems present new opportunities to apply real-time epidemiology to individual patients (7). The $48 billion investment is intended to support a "learning health system" (37) with bidirectional communication between clinical and public health sites, along with delivery of clinical decision support to the point of care. Our findings suggest that this learning health system should be capacitated to link live biosurveillance data with clinical decision making.

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MANUSCRIPT PROCESSING AND TURNAROUND

Annals sends about half of submitted manuscripts for peer review and publishes about 10% of submitted material. The 2010 processing and notification turnaround time for manuscripts that were rejected without external peer review was within 1 week for more than 95% of submitted manuscripts. The processing and notification turnaround time for manuscripts that were received and rejected after external peer review was within 4 weeks for 50% and within 8 weeks for 98%.

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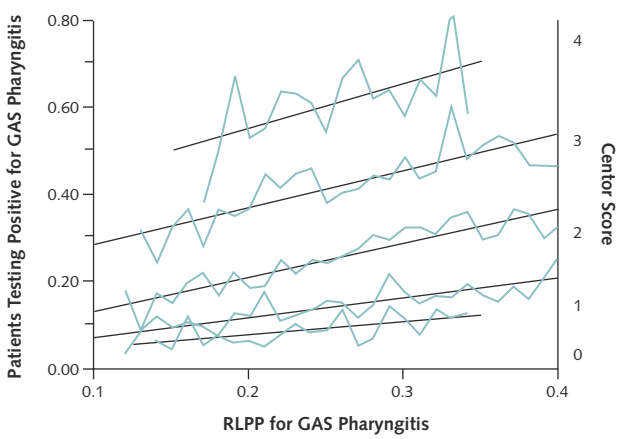
Appendix Figure. **Proportion of patients in the validation set (n = 27 081) testing positive for GAS pharyngitis, by RLPP and grouped and labeled by Centor score.**



Each line represents patients with the same Centor score across varying RLPPs. The proportion of patients who tested positive increases both as the clinical score and the RLPP increase. The Pearson coefficient was used to measure strength of correlation. The r^2 values, representing the proportion of the variation in GAS pharyngitis positivity that can be attributed to the RLPP, are 0.33 (P = 0.012) for a Centor score of 4, 0.70 (P < 0.001) for a Centor score of 3, 0.82 (P < 0.001) for a Centor score of 2, 0.68 (P < 0.001) for a Centor score of 1, and 0.35 (P = 0.005) for a Centor score of 0. The slopes of the lines for Centor scores of 4, 3, 2, 1, and 0 are 0.99, 0.80, 0.75, 0.43, and 0.28, respectively. Each data point represents a median of 140 patients (range, 45 to 555 patients; interquartile range, 82 to 290 patients). GAS = group A streptococcal; RLPP = recent local proportion positive.

Appendix Table 1. **Reclassification Accuracy of Adjusted Centor Score Resulting From Increasing Score by Increments of 1 Point at Different Thresholds of GAS Pharyngitis Activity (Validation Set)***

Centor Score	RLPP Threshold	Cases Reclassified as Negative for GAS Pharyngitis			Cases Reclassified per 1000, *n*		National Estimates of Numbers Affected, *n*	
		Incorrect, *n*	Correct, *n*	Net Change, *n* (%)	Incorrect	Correct	Incorrect	Correct
1	>0.20 (n_1 = 8681)	373	974	601 (7)	43	112	63 118	164 401
	>0.25 (n_1 = 3827)	160	504	344 (9)	42	132	39 543	124 277
	>0.30 (n_1 = 1734)	72	236	164 (9)	41	136	18 103	60 048
	>0.35 (n_1 = 633)	26	91	65 (10)	41	144	7171	25 186
2	>0.20 (n_2 = 9378)	9738	747	−8990 (−64)	710	50	1 125 725	79 276
	>0.25 (n_2 = 4145)	6555	537	−6018 (−63)	657	62	668 146	63 052
	>0.30 (n_2 = 1969)	3117	293	−2824 (−60)	635	66	302 485	19 988
	>0.35 (n_2 = 772)	1150	122	−1028 (−57)	630	67	119 019	12 658

GAS = group A streptococcal; RLPP = recent local proportion positive.
* Adjustment of Centor score to reclassify risk according to prior probability of disease as inferred by the RLPP. For patients with a Centor score of 1 or 2, the score was increased by an increment of 1 point when RLPP exceeded threshold. Changing from 1 to 2 would result in testing n_1 patients for GAS pharyngitis, and changing from 2 to 3 would result in treating n_2 patients empirically.

Appendix Table 2. **Reclassification Accuracy of Adjusted Centor Score Resulting From Decreasing Score by Increments of 1 Point at Different Thresholds of GAS Pharyngitis Activity (Validation Set)***

Centor Score	RLPP Threshold	Cases Reclassified as Negative for GAS Pharyngitis			Cases Reclassified per 1000, *n*		National Estimates of Numbers Affected, *n*	
		Incorrect, *n*	Correct, *n*	Net Change, *n* (%)	Incorrect	Correct	Incorrect	Correct
2	<0.25 (n_2 = 4395)	722	175	−548 (−12)	164	40	169 260	41 283
	<0.20 (n_2 = 2179)	330	88	−242 (−11)	152	41	75 765	20 436
	<0.15 (n_2 = 388)	49	16	−33 (−8)	126	42	11 391	3797
3	<0.25 (n_3 = 2169)	165	1275	1110	76	588	42 039	325 246
	<0.20 (n_3 = 1044)	69	663	594 (57)	66	635	17 632	169 637
	<0.15 (n_3 = 201)	12	134	122 (61)	60	666	2907	32 268

GAS = group A streptococcal; RLPP = recent local proportion positive.
* Adjustment of Centor score to reclassify risk according to prior probability of disease as inferred by the RLPP. For patients with a Centor score of 2 or 3, the score was decreased by 1 point when RLPP was below threshold. Changing from 2 to 1 would result in not testing or treating n_2 patients for GAS pharyngitis, and changing from 3 to 2 would result in testing n_3 patients and treating them if they tested positive.