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Use of the Historical Limits Method to Detect Increases in Primary and Secondary Syphilis, Arizona 2011–2014:

An Exploratory Study

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Abstract

Background: Increasing numbers of reported primary and secondary (P&S) syphilis cases in the United States suggest the need for improved surveillance methods. An outbreak detection method using reported syphilis test results, which can be counted before the conclusion of a syphilis case investigation, could lead to timelier outbreak detection.

Methods: The historical limits comparison method was used to compare the number of positive rapid plasma reagin results reported during 2011–2014 with data for the preceding 3 years. An outbreak alert was generated when the monthly count of positive rapid plasma reagin quantitative results was greater than the historical mean plus 2 standard deviations for 2 consecutive months.

Results: Three outbreak alerts occurred during 2011–2014. The first alert occurred in December 2012 in Maricopa County (Phoenix area). Primary and secondary cases subsequently increased from 10 in January 2013 to 15 in March followed by 5 months of consecutive increases. A second alert was generated for Maricopa County in May 2014. Primary and secondary cases increased from 20 in May to 42 in July 2014. Reported cases remained elevated for approximately 7 months after the second alert. In December 2013, an outbreak alert occurred for Pima County (Tucson area). The number of reported P&S syphilis cases in Pima County increased from 6 in February to 15 in March. Counts of reported cases remained elevated for approximately 6 months after the alert.

Conclusions: Use of historical limits comparison method based on syphilis laboratory results can provide an outbreak alert before increases in reported cases of P&S syphilis.

Despite the proliferation of various disease outbreak detection systems, no system has been optimized for the detection of outbreaks of primary and secondary (P&S) syphilis. Syphilis investigations and case classification are time intensive, resulting in a lag in case reporting to

the health jurisdiction.¹ This lag in data reporting can result in delays of outbreak detection. Because, laboratory reporting of positive values frequently precedes case classification and reporting, a surveillance system that uses positive serologic tests for syphilis may help overcome the challenge of using syphilis case reporting in outbreak detection.

Since 2009, the Arizona Department of Health, Sexually Transmitted Disease Control Program (AZSTDP) has used a syphilis outbreak detection system based on a historical limits comparison method (HLCM)² to monitor reported syphilis-related laboratory results. The system monitors positive rapid plasma reagin (RPR) quantitative results received via electronic laboratory reporting, faxes, and mail. The AZSTDP HLCM compares the number of reported positive quantitative laboratory results in the chosen month with historical positive syphilis laboratory data from preceding years. Herein, we describe the use of the HLCM to monitor positive RPR values in the 2 most populous counties in Arizona: Maricopa County and Pima County. In addition, we describe the detection of outbreaks or P&S syphilis that occurred during 2012–2014, in Pima County and Maricopa County, AZ using this method.

METHODS

Syphilis Case Reporting and Case Investigation

Syphilis case investigations usually begin in 1 of 3 ways: (1) a medical provider in Arizona reports a diagnosis of syphilis to the AZSTDP (reporting is required within 5 business days of diagnosis³); (2) a laboratory reports test results, without a matched provider case report, that meet the AZSTDP requirements for investigation; (3) infected contacts are elicited during a contact investigation. Upon initiation of a case investigation a field record is created within the state AZSTDP surveillance system (Patient Reporting Investigating Surveillance Manager (PRISM), Tallahassee, FL). A submitted case report or received laboratory result is not counted as a case by the surveillance system until the investigation is concluded. Final case classification as P&S is determined by provider report of symptoms consistent with P&S or interview of cases and documented history of symptoms at the time of diagnosis. At this point, the field record creation date is used as the report date for the case within PRISM. For this HLCM, P&S cases were used for comparison with positive syphilis RPR results.

Laboratory Reporting and Selection of Positive Syphilis RPR Results

Laboratories in Arizona report positive syphilis RPR results to the AZSTDP within 5 business days of result.³ These positive RPR results are entered into PRISM. Approximately 15% of positive syphilis laboratory results are received via electronic laboratory reporting with the remainder received via hardcopy through fax and mail or through online portals provided by the performing laboratory.

To select the parameters to use for HLCM we used Pearson correlation coefficient⁴ to identify a correlation between values of positive RPR titer results per month and number of P&S syphilis cases reported in that same month. Two correlation coefficients were calculated. A coefficient of $r = 0.64$ ($P < 0.0001$) was calculated when comparing the count of all quantitative positive RPR results (RPR titer 1:1) received per month to the number of

P&S syphilis cases reported per month. A coefficient of $r = 0.43$ ($P < 0.0001$) was calculated when comparing the number of quantitative RPR titer results greater than or equal to 1:8 received per month to the number of P&S syphilis cases reported per month. The RPR values 1:1 were chosen for inclusion in the HLCM because of the larger calculated coefficient.

To avoid isolated 1-month increases in RPR counts possibly caused by reporting aberrations, it was decided that 2 consecutive months where RPR results exceeded the mean plus 2 standard deviations would constitute an outbreak alert.

Historical Limits Analysis

The AZSTDP HLCM process consisted of 5 steps: (1) positive syphilis RPR data were imported in line-listed format into SAS Software v.9.3 (Cary, NC); (2) a frequency analysis was performed to count the positive RPR results per month for the current year and each month in the corresponding 3-month periods in the previous 3 years; (3) the mean for each historical and current data point was calculated; (4) a SAS Proc SGPLOT was performed to visualize the output; (5) the HLCM is run in SAS once monthly and interpreted by a state-based AZSTDP epidemiologist.

An outbreak alert occurs when the following condition is met for 2 consecutive months:

$$X_0 > \mu + 2\sigma_x$$

Where X_0 is the number of reported positive RPR results in the current month, and μ and σ_x are the mean and standard deviation of the historical positive RPR data. This method uses monthly data from three 3-month periods (the current month, the preceding month, and the subsequent month) in the corresponding months from the preceding 3 years; for a total of 9 data periods (Fig. 1).

RESULTS

Maricopa County

Historical Limits Alert—Maricopa County experienced 2 outbreak alerts; one in 2012 and another in 2014. The first outbreak alert occurred in December 2012 based on the positive RPR counts in the months of October ($N = 436$ RPRs) and November 2012 ($N = 388$ RPRs) (Fig. 2). After this alert, the count of P&S syphilis cases recorded per month gradually increased from 10 in January 2013 to 13 in April and 25 in July. No other outbreak alerts were recorded in 2013 for Maricopa County. The second alert occurred in May of 2014 based on the positive RPR counts in the months of March ($N = 415$ RPRs) and April ($N = 424$ RPRs). After the outbreak alert generated in May 2014, signals continued consecutively from June to September (Fig. 2). These signals coincided with ever increasing P&S syphilis case counts in the same period.

Syphilis Cases Reported to ADHS by Maricopa County—After the first outbreak alert, case counts increased from a 2-year low of 10 in December 2012 to 15 cases in months

February and March 2013 followed by increases to 25 and 26 cases in July and August. Beginning in February 2013, P&S syphilis cases in Maricopa County remained higher than 15 per month through December 2013. Overall, in the first half of 2013, 81 cases of P&S syphilis were reported with another 130 cases reported in the second half (Fig. 2).

The second alert in May 2014, reflecting RPR counts in the months March and April, preceded 4 continuous months of increasing P&S syphilis case counts. In the 3 years (2011–2013) before this outbreak alert, Maricopa County had never recorded more than 30 P&S syphilis cases in a single month. After the May 2014 alert, the number of reported P&S syphilis cases exceeded 30 per month for the rest of the year. In the first 4 months of 2014, 96 P&S syphilis cases were reported compared with 313 during the rest of the year (Fig. 2).

Pima County

Historical Limits Alert—In December 2013, the HLCM for Pima County issued an alert based on RPR results in October ($N = 87$) and November ($N = 79$) (Fig. 3). Subsequently, in April 2014, an increase in reported P&S syphilis cases was noted from 6 in February to 15 in March (Fig. 3). Thus, the HLCM outbreak alert occurred 4 months before the increase in reported P&S syphilis cases in Pima County.

Syphilis Cases Reported to ADHS by Pima County—In 2013, there were only 6 or fewer P&S syphilis cases per month in Pima County. However, after the outbreak alert in December, cases increased from March through September 2014, there were 10 or more reported cases per month 6 times. Monthly case counts exceeded 15 during 4 of these. Signals continued for the months of May to December 2014. Overall, 55 cases of P&S syphilis were reported in Pima County in 2013, and 142 cases were reported in 2014 (Fig. 3).

False-Positive Alerts—Four outbreak alerts in 3 other Arizona counties (2 in Apache County, 1 in La Paz County, 1 in Yavapai County) occurred that were not followed by an increase in P&S syphilis cases within the next 6 months (data not shown). These counties have relatively small populations, low number of positive RPR test results, and low P&S syphilis prevalence.

Sensitivity and Positive Predictive Value—The 3 outbreak alerts described herein were counted as true-positive results. Inspection of the data revealed an increase in cases in Maricopa County from April 2012 to October 2012 that did not result in an outbreak alert (Fig. 2). The lack of an alert before or during this increase was considered a false-negative alert for the purpose of calculating sensitivity. With 3 true-positive results and 1 false-negative alert, the sensitivity of the HLCM in Arizona counties was 75%.

The 3 true-positive alerts and 4 false-positive alerts generated by the HLCM resulted in a calculated positive predictive value (PPV) of 43%.

DISCUSSION

The HLCM has been previously used for disease outbreak detection.^{5,6} Because Arizona is a border state, has a history of high syphilis rates, and includes groups (minorities, drug users, men who have sex with men) that are disproportionately affected by syphilis, Arizona meets the Centers for Disease Control and Prevention definition of a possible syphilis reemergence area.⁷ Recognizing that delays in case reporting and case investigation can result in delays in identification of P&S case increases, the AZSTDP implemented HLCM protocols. The HLCM tracks positive RPR results and reported P&S syphilis cases in tandem to anticipate case increases based on positive syphilis laboratory results. With the implementation of HLCM in Arizona for P&S syphilis surveillance, parameters were set for identifying increases in positive syphilis test results before an increase in the number of reported P&S cases. In addition, positive RPR results and reported P&S syphilis cases were tracked alongside and reviewed routinely by an epidemiologist. Implementation of the HLCM by the AZSTDP provided state epidemiologists with outbreak alerts before 2 sharp sustained increases in cases in Maricopa County (Phoenix Area), along with an outbreak alert approximately 4 months before a large increase in reported cases in Pima County (Tucson Area).

In Maricopa County, the December 2012 outbreak alert preceded a 7-month period in which the count of reported cases steadily increased. This outbreak alert heralded a 2-year continuous increase in P&S syphilis cases. In the 7 months after the second outbreak signal, Maricopa County recorded over 30 P&S syphilis cases each month. Over the previous 4 years, only once had there been a month with a reported case count of 30.³ At the time of this alert, reports from disease investigation specialists and data from epidemiologic curves based on case counts had already informed public health officials of an increase in reported syphilis cases. However, the alert forecasted the continued increase in cases in the following months.

Two consecutive outbreak signals occurred in October and November 2013 for Pima County. Four months later, the number of reported P&S syphilis cases in Pima County nearly tripled and remained at above average monthly counts for the next 7 months. This warning allowed state epidemiologists to notify the county of a possible increase in cases. Additionally, state epidemiologists were able to begin preparing epidemiologic profiles, background information and presentations for the affected county so that all of the information would be readily available should the alert represent a continued increase in cases.

There are limitations to the use of this method.⁸ Delays in the accumulation and data entry of positive RPR results can result in false-negative results. Clusters or aberrations in the historical data points can reduce the ability of the HLCM to detect aberrations in the future by increasing false-negative errors. For example, an aberration in historical data could be caused by a short-term syphilis screening program active in a given month. The Arizona Department of Health, Sexually Transmitted Disease Control Program does not currently correct for this limitation. Any change in procedure that causes the count of RPR tests to be higher in the historical data compared to the current count will increase these errors. Conversely, a change that causes the count of reported RPR tests in the historical data to be

lower than the current count will increase false-positive errors. Although not a drawback of the HLCM, a positive RPR laboratory result is not a confirmatory marker of syphilis infection. This test is used for syphilis screening and must be followed by a confirmatory test as well as a medical treatment history search to determine if it is a new case. A transition to the PRISM data management system from a locally developed system, as well as a transition from paper-based laboratory reporting to electronic laboratory reporting occurred during 2012 and 2013. These changes may have improved surveillance and reporting of positive RPR results. In addition, in 2011 and 2012, manual entry of data into an Excel file was part of the protocol for HLCM analysis. These factors may have influenced the data that resulted in the outbreak alert in late 2012 (Maricopa County) using current protocols. Arizona Department of Health, Sexually Transmitted Disease Control Program did not use the HLCM to look for increases in reported P&S syphilis by sex, race or age group. False-positive alerts were generated in 3 counties with small populations, few numbers of positive RPRs and low P&S syphilis incidence. Further evaluation of the HLCM is needed to determine if the current model is suitable for use using current RPR titer values (1:1) when these conditions are present. Finally, the authors acknowledge that the finding of case increases after the increases in reported positive RPR results may be due to coincidence.

The HLCM achieved a sensitivity of 75% and PPV of 43%. It should be noted that a small number of data points were used to make these calculations, and the results may not be reliable. To mitigate the effect of the low sensitivity and low PPV, all data and alerts should be reviewed by public health personnel. By reviewing the data, an epidemiologist may detect an increase in cases in a situation where the HLCM produces a false-negative result. As stated above, the false-positive alerts occurred in counties with different demographics and disease epidemiology. Apache County had a population of 71,158 in 2010, and 4 cases of P&S syphilis in 2013. La Paz County had a population of 20,489 in 2010,⁹ and 0 cases in 2013.¹⁰ Also, Yavapai had a population of 211,033 and 0 cases in 2013. The true positive counties, Maricopa and Pima, had populations of 3.8 million and 980,000 in 2010, respectively. The case counts for these counties were 213 and 55 in 2013, respectively. It is possible that the low sensitivity and PPV are the result of applying the HLCM in unfavorable conditions.

To our knowledge, this is the first reported use of syphilis serologic test results in conjunction with the HLCM for use in P&S syphilis surveillance and outbreak detection at the local health department level. Other uses of the HLCM have not included STD surveillance.^{5, 6,11,12} Methods to detect outbreaks can aid public health agencies in identifying and preventing the spread of disease. Analysis of morbidity reports and electronically reported data by outbreak detection systems can provide timely identification of these disease increases. Since 1989, the Centers for Disease Control and Prevention have presented results of the historical limits method for selected notifiable diseases, such as listeria, measles, mumps, and pertussis.¹³ In 2009, the AZSTDTP tested the HLCM method by retrospectively identifying a heterosexual outbreak of syphilis in an American Indian community.^{2,14} Our current analysis demonstrates the utility of implementing the HLCM for prospective syphilis outbreak detection in jurisdictions with high populations and rates of syphilis. Alerts generated from this surveillance allowed the AZSTDTP to begin preparing preliminary epidemiological reports on an affected county that could be used to justify

increased public health activities. Upon receiving an alert other jurisdictions using the HLCM may choose to review cases by diagnosing provider, contact medical providers about recent case increases in their practices, notify public health partners, such as HIV surveillance, update media campaigns, or assess the level of resources available for outbreak response. The Arizona Department of Health, Sexually Transmitted Disease Control Program continues to use this method to prospectively detect sharp increases in syphilis as well as gonorrhea. The simple mathematical formula and ease of interpretation of the HLCM allows for implementation at public health agencies with varying degrees of epidemiological support.

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<i>2012</i>	X_7	X_8	X_9
<i>2013</i>	X_4	X_5	X_6
<i>2014</i>	X_1	X_2	X_3
<i>2015</i>		X_0	
	Feb	Mar	Apr
	<i>Month</i>		

Figure 1.

Comparison of current month positive RPR results (X_0) with positive RPR results from the mean (μ) of the number of positive RPRs from 3 consecutive months in 3 prior years: preceding month, same month, and subsequent month.

Figure 2. Historical limits analysis of reported RPR results (1:1), and reported primary and secondary syphilis cases, Maricopa County, AZ, 2011–2014.

Figure 3.
Historical limits analysis of reported RPR results (1:1), and reported primary and secondary syphilis cases, Pima County, AZ, 2011–2014.