Frequency and Characteristics of Biological False-Positive Test Results for Syphilis Reported in Florida and New York City, USA, 2013 to 2017

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ABSTRACT Discordant syphilis test results, with a reactive nontreponemal test and nonreactive treponemal test are usually considered biological false-positive test results (BFPs), which can be attributed to other conditions. Syphilis surveillance laws mandate laboratory reporting of reactive syphilis tests, which include many BFPs. We describe the frequency of BFPs, titer distributions, and titer increases from reported test results in Florida and New York City (NYC). Reactive nontreponemal tests for individuals with at least one nonreactive treponemal test and no reactive treponemal test were extracted from sexually transmitted disease (STD) surveillance systems in Florida and NYC from 2013 to 2017. Characteristics of individuals with BFPs were analyzed after selecting the observation with the highest titer from each individual. We next considered all results from individuals to characterize persons who had a 4-fold titer increase between successive nontreponemal tests. Among 526,540 reactive nontreponemal tests, there were 57,580 BFPs (11%) from 39,920 individuals. Over 90% ($n = 52,330$) of BFPs were low titer ($\leq 1:4$), but 654 (1%) were high-titer BFPs ($\geq 1:32$). Very high-titer ($\geq 1:128$) BFPs were more common among individuals over 60 years of age (odds ratio [OR], 2.68; 95% confidence interval [CI], 1.22 to 5.91). A 4-fold increase in titer was observed among 1,863 (14%) individuals with more than one reported BFP. Most BFPs detected by surveillance were low titer, but some were high titer and some had a 4-fold increase in titer. Review of patient histories might identify underlying conditions contributing to these high and rising titers.

KEYWORDS biological false positive, epidemiology, nontreponemal, public health, surveillance studies, syphilis

Syphilis is a notifiable disease in all states (1). State and local laws require health care providers to report diagnoses and for laboratories to report reactive syphilis test results to their state or local public health department. Reactive results of both treponemal tests (such as enzyme immune assay [EIA], *Treponema pallidum* particle agglutination assay [TP-PA], or fluorescent treponemal antibody absorption [FTA-ABS]) and nontreponemal tests (such as the rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL] test) are considered indicative of syphilis (past or present) (1, 2). Nontreponemal tests detect anticardiolipin antibodies and are not specific to syphilis (3, 4). Specimens with a reactive nontreponemal result and a nonreactive treponemal test result are considered biological false positives (BFPs) and make up 14 to 40% of reactive nontreponemal tests, depending on the prevalence of syphilis (1, 5).

Previous studies explored the frequency of BFPs in the general population (0.14% to 0.59%) (6–8). Syphilis BFPs have been associated with several patient characteristics, such as female sex, older age, intravenous drug use, and pregnancy (although this may

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just reflect frequent screening of pregnant women) (6–10). Medical conditions such as autoimmune disorders, including systemic lupus erythematosus (SLE), cancers, malaria, other treponemal infections, human immunodeficiency virus (HIV) infection, and hepatitis C infections, have been associated with increases in BFPs (6, 7, 9–13).

Studies of BFPs have been based on general population syphilis testing, which identified a few hundred BFPs, or testing of specific populations with even fewer BFPs (6, 8, 9, 12, 14). These studies found that most BFPs have low titers ($\leq 1:4$), and the nontreponemal tests often revert to nonreactive without intervention (7, 15). The largest general population study is from a university hospital, where testing of 300,000 serum samples yielded 726 BFPs with titers of $\geq 1:4$, including 86 BFPs with titers of $\geq 1:32$ (16). The causes of high-titer BFPs were not reported. Other reports of high-titer BFPs include an individual with SLE (1:128), a patient with lymphosarcoma (1:256), an individual with autoimmune hemolytic anemia (1:512), and an individual with Waldenström's macroglobulinemia (1:32,000) (6, 17–19). Syphilis surveillance provides a unique opportunity for identifying BFPs, because all reactive nontreponemal tests are reported and reports include many BFPs from the general population.

BFPs can create challenges and inefficiencies for syphilis surveillance and diagnosis. Changes in nontreponemal test titers are used to monitor response to treatment and to detect reinfection (20). For a person with past infection, a two-dilution or more increase in nontreponemal titers is considered indicative of reinfection (21). Nontreponemal titer increases that were thought to be unrelated to reinfection have been observed among individuals with HIV infection (2, 22). Titer increases of two dilutions or more have not been reported in previous studies of BFPs except for one patient with Waldenström's macroglobulinemia, whose titer increased from 1:8,192 to 1:32,000 (17).

In this study, we aimed to describe the frequency of BFPs among serologic test results reported to two large STD prevention programs. We assessed the distribution of BFP titers over time and the association between demographics and high-titer BFPs and measured the frequency of 4-fold titer increases among persons with BFPs.

MATERIALS AND METHODS

Reported reactive nontreponemal tests were deduplicated based on specimen collection date and titer value and extracted for each year from 2013 to 2017 from the Florida Department of Health and New York City Department of Health and Mental Hygiene surveillance systems. We defined BFPs as reactive nontreponemal tests from an individual with at least one reported nonreactive treponemal test and no reported reactive treponemal tests in their serological history through 2017. Syphilis BFP results were compared against the total number of reactive treponemal tests from 2013 to 2017. Syphilis BFPs were further stratified by nontreponemal titer value, nontreponemal test type, reporting site, and year of specimen collection.

We first limited each individual to only one BFP by selecting the highest titer during the study period or, if of equivalent value, the most recently reported titer to create a database where each person was linked to only one BFP. We extracted nontreponemal specimen collection date, nontreponemal titer, reported sex of the individual, reported pregnancy status (using the pregnancy status on the corresponding syphilis event), reported HIV status at the time of the nontreponemal test, and age in years at specimen collection date. In addition, for those with more than one reactive nontreponemal test, we compared titers to determine the frequency of reported 4-fold or greater increases from sequential titers. Individuals with more than one BFP were stratified into those with no 4-fold titer increases and those with one or more 4-fold titer increases in their reported nontreponemal tests. Time (in days between tests) was calculated for the most recent 4-fold titer increase.

Titer values were categorized as low titer ($\leq 1:4$), medium (1:8 or 1:16), high (1:32 or 1:64), and very high ($\geq 1:128$) groups. Reactive titers without quantitation were excluded from categorization. Individuals with high titer, including very high titer, and very high titer BFPs were compared separately to individuals with low and medium titer BFPs combined. Syphilis BFP titer categories and 4-fold titer increases were stratified by site, sex, pregnancy status, HIV status, and age to calculate odds ratios and 95% confidence intervals using Open Source Epidemiologic Statistics for Public Health. This project was reviewed by the Centers for Disease Control and Prevention and was determined to be an activity that is not human subject research (no. 7160).

RESULTS

From 2013 to 2017, there were 526,540 deduplicated, reactive nontreponemal tests (204,423 in Florida and 286,117 in New York City [NYC]), including 57,580 (11%) BFPs (28,183, or 12%, in Florida and 29,397, or 10%, in NYC) from 39,920 individuals. Rapid plasma reagin (RPR) was the test type reported for 99.5% (57,240 out of 57,548) of BFPs.

TABLE 1 Frequency and distribution of nontreponemal titers among individuals with biological false-positive syphilis serology in Florida and New York City, 2013 to 2017

Location and yr	Nontreponemal titer											Total
	Reactive, no quantitation	1:1	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	
New York City total	179	17,110	6,472	3,150	1,531	657	206	73	13	3	3	29,397
2013	119	3,458	1,289	641	317	149	44	17	2	0	0	6,036
2014	11	3,100	1,278	666	279	129	35	9	3	1	0	5,511
2015	14	2,872	1,244	572	304	132	40	18	2	1	0	5,199
2016	14	3,386	1,374	672	335	132	45	15	5	0	2	5,980
2017	21	4,294	1,287	599	296	115	42	14	1	1	1	6,671
Florida total	1,212	14,470	6,323	3,414	1,719	689	236	81	29	8	2	28,183
2013	130	2,270	1,035	665	348	149	41	11	3	0	0	4,652
2014	231	2,886	1,184	658	343	109	27	8	7	2	1	5,456
2015	269	2,844	1,284	706	360	139	54	24	11	3	1	5,695
2016	285	3,049	1,531	839	398	177	76	31	3	1	0	6,390
2017	297	3,421	1,289	546	270	115	38	7	5	2	0	5,990
All sites total	1,391	31,580	12,795	6,564	3,250	1,346	442	154	42	11	5	57,580

The proportion of reactive nontreponemal tests that were BFPs was fairly consistent by site and year, ranging from 9.5% to 12.4%.

Most (88.4%, 50,939/57,580) of the reported BFPs were low titer ($\leq 1:4$) (Table 1). This was similar across both sites (85.8% [24,207/28,183] for Florida and 90.1% [26,732/29,397] for NYC). Just over 1% (654/57,580) were high titer ($\geq 1:32$) BFPs, and 58 of these had very high titers ($\geq 1:128$). The 654 high-titer BFPs were from 476 individuals, and the 58 very high titers were from 46 individuals.

Among 39,920 unique individuals with BFPs, individuals with high titers (odds ratio [OR], 1.27; 95% confidence interval [CI], 1.06 to 1.52) or very high titers (OR, 2.01; 95% CI, 1.10 to 3.70) were more likely to be identified in Florida (Table 2). The proportion of BFPs that were high titer was greatest among individuals over 40 years of age, and the proportion with a very high titer was greatest among individuals over 60 years of age. However, 14 individuals with very high-titer BFPs were reported to be 18 to 29 years of age. Individuals with high- and very high-titer BFPs did not differ from individuals with low and medium titers by sex, pregnancy status, or HIV status.

In total, 13,330 individuals, across both sites had more than one reported BFP, and 1,863 (14%) of these individuals (1,043 in Florida and 820 in NYC) reported at least one 4-fold increase in their nontreponemal titers while remaining nonreactive on treponemal tests (Table 3). The time between the tests could be determined for 1,830 individuals with a 4-fold titer increase. There was a median of 497 days between tests (interquartile range [IQR], 168.5 to 1,354.5 days). However, 16.4% ($n = 302$) of the 4-fold increases were within 90 days or less. Among BFPs, 4-fold titer increase was associated with persons living with HIV (OR, 1.34; 95% CI, 1.06 to 1.70). However, this association only explains 87 (4.7%) individuals. Similarly, pregnant women with BFP had a higher likelihood of having a 4-fold increase in their titer (OR, 1.20; 95% CI, 1.02 to 1.42). Individuals with BFPs who were over 30 years of age were more likely to have 4-fold titer increases in their serological results compared to 18- to 29-year-olds.

DISCUSSION

This study is the largest single study of syphilis BFP test results. Like previous studies, we found that 11% of reactive nontreponemal tests were BFPs, and most had low-titers (7, 8, 15). About 1% of the BFPs were high- and very high-titer BFPs, and 4-fold titer increases in individuals with only BFP syphilis results were not uncommon. Although this study utilized surveillance data and did not contain medical histories of reported BFPs, we found that among individuals with BFP syphilis results, high- or very high-titer BFP results were more likely for older individuals and those in Florida (which could be related to an older population; 20.1% of the population is age ≥ 65 years in

TABLE 2 Deduplicated titers for individuals with biological false-positive syphilis serologies stratified by titer level category and demographic characteristics, Florida and New York City, 2013 to 2017^a

Characteristic	Total	Low/medium ($\leq 1:16$)	High ($\geq 1:32$) ^b	OR (95% CI)	Very-high ($\geq 1:128$)	OR (95% CI)
Total	39,775	39,299	476	–	46	–
Location						
FL	19,168	18,910	258	1.27 (1.06–1.52)	30	2.01 (1.10–3.70)
NYC	20,526	20,308	218	–	16	–
Sex						
Male	12,608	12,455	153	–	19	–
Female	27,009	26,686	323	0.99 (0.81–1.20)	27	0.66 (0.37–1.19)
Unknown/other	77	77	0	–	0	–
Pregnant						
Yes	3,253	3,212	41	1.06 (0.76–1.48)	5	1.66 (0.63–4.39)
No/unknown	23,756	23,474	282	–	22	–
HIV status						
HIV positive	1,207	1,191	16	1.11 (0.67–1.83)	2	1.45 (0.35–5.99)
No known HIV positive	38,487	38,027	460	–	44	–
Age (yrs)						
<18	1,672	1,655	17	1.26 (0.76–2.11)	0	NA
18–29	14,022	13,979	113	–	14	–
30–39	10,289	10,193	96	1.16 (0.88–1.52)	9	0.88 (0.38–2.03)
40–49	5,413	5,326	87	2.01 (1.52–2.66)	6	1.12 (0.43–2.91)
50–59	4,066	4,004	62	1.91 (1.40–2.60)	6	1.49 (0.57–3.88)
60+	4,175	4,074	101	3.05 (2.33–4.00)	11	2.68 (1.22–5.91)
Missing	57	57	0	NA	0	NA

^a–, reference group; NA, not applicable.^bThe high and very high categories were compared against medium and low categories combined.

Florida, compared to 13.6% in NYC [<https://www.census.gov/quickfacts/fact/table/FL,newyorkcitynewyork/PST045218>]). This might be explained by several possible causes of BFPs, such as autoimmune, rheumatological, cancer, or other conditions that may progress with age (6, 17, 18). These titers were identified in an age group that is not often prioritized for syphilis screening and investigation, and it would be interesting to know why they were screened for syphilis (23–25). In contrast, 14 of the very high-titer BFP syphilis results were among 18- to 29-year-old individuals. Further exploration into clinical causes of these rare syphilis BFPs could better explain these findings.

Using surveillance data to assess BFPs has several drawbacks. This approach provides very limited information on clinical context because BFPs are not investigated, as they are not considered indicative of syphilis (26, 27). Moreover, negative nontreponemal tests are not required to be reported in Florida and are only required to be reported in NYC if they are accompanied by a positive test for syphilis (such as the positive treponemal and negative nontreponemal test results that may be obtained using the reverse screening algorithm). This means that we are unable to obtain the number of syphilis tests performed, and we cannot assess the number of BFPs that reverted to negative nontreponemal tests. Finally, since most of the data came from laboratories, information on HIV and pregnancy status was often missing.

Syphilis BFP test results are primarily an issue for laboratories using the traditional syphilis testing algorithm, which starts with a nontreponemal test. The reverse algorithm, which starts with a treponemal test, should not find BFPs (4, 28, 29). The increase in BFPs in both jurisdictions from 2013 to 2017 suggests that the traditional algorithm was still commonly used. Our surveillance programs process BFPs at an annual rate near the number of reported actual cases of syphilis (5,990 BFPs and 8,859 reported infections in Florida in 2017 and 6,671 BFPs and 7,995 reported infections in NYC in

TABLE 3 Individuals with biological false-positive syphilis serologies stratified by history of 4-fold titer increases and demographic characteristics, Florida and New York City, 2013 to 2017

Characteristic	Total	No 4-fold increase ^a	4-fold increase	OR (95% CI) ^b
Location				
FL	6,924	5,881	1,043	1.21 (1.10–1.33)
NYC	6,406	5,586	820	–
All Sites	13,330	11,467	1,863	
Sex				
Male	3,409	2,936	473	–
Female	9,913	8,523	1,390	1.01 (0.90–1.13)
Unknown/other	8	8	0	
Pregnant				
Yes	1,292	1,102	190	–
No/unknown	8,487	7,421	1,066	1.20 (1.02–1.42)
HIV status				
HIV positive	491	404	87	1.34 (1.06–1.70)
No known HIV positive	12,839	11,063	1,776	–
Age (yrs)				
<18	383	344	39	0.82 (0.58–1.16)
18–29	4,381	3,849	532	–
30–39	3,699	3,125	574	1.33 (1.17–1.51)
40–49	1,893	1,643	250	1.10 (0.94–1.29)
50–59	1,453	1,208	245	1.47 (1.25–1.73)
60+	1,521	1,298	223	1.24 (1.05–1.47)

^aExcludes individuals with only one reactive biological false-positive syphilis test.^b–, Denotes reference group.

2017) (30, 31). Manually reviewing these BFPs is a burden for syphilis surveillance programs that might be addressed by using computer algorithms (20).

We could not assess the possibility that some results classified as BFPs were actually due to false-negative treponemal tests because we had no specimens available for retesting. The sensitivity of treponemal tests varies by stage (lowest in primary syphilis), but for all stages the sensitivity ranged from 90.8% to 98.5% (32). We excluded individuals who had any reactive treponemal tests during the years studied, so the number of false-negative treponemal tests in our study is likely to be small. One unique aspect of this study was our ability to identify individuals with at least one 4-fold nontreponemal titer increase. This analysis requires multiple reactive nontreponemal tests to be reported for an individual (with an increasing titer) over time. We observed that this increasing titer can occur both acutely (less than 90 days between tests) or over years. This is in contrast to the commonly observed low-titer, often transient, BFPs described in other studies (7, 15). Four-fold titer changes were common among pregnant women, persons living with HIV, and older persons, suggesting that these fluctuations were the result of other conditions that affect the production of cardiolipins, but further examination of clinical data would be required to better elucidate this possibility. Alternatively, the 4-fold BFP increases could be due to chance or laboratory variation. Understanding the causes of fluctuations in BFP titers might influence the interpretation of nontreponemal titers for persons with true-positive nontreponemal tests.

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