Comparison of Three Treatment Regimens for Latent Syphilis of Late or Unknown Duration Using Public Health Surveillance Data

Travis John Hunt

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Committee:

Sara N. Glick

Matthew R. Golden

Lisa E. Manhart

Program Authorized to Offer Degree:

Department of Epidemiology

University of Washington

Abstract

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Travis John Hunt

Chair of the Supervisory Committee:

Sara N. Glick

Department of Medicine

Background: The CDC recommends treating latent syphilis of late/unknown duration (LSUD) with three doses of intramuscular benzathine penicillin G (BPG) or twenty-eight days of oral doxycycline. This recommendation lacks high-quality evidence.

Methods: Using public health surveillance data from King County, Washington, we conducted a retrospective cohort study comparing rates of serological cure (≥2-titer RPR decline) among persons with LSUD following receipt of one of three regimens: one dose of BPG, three doses of BPG, and twenty-eight days of doxycycline. Subjects included persons diagnosed 2007-2020 with initial an RPR ≥1:2 and follow-up RPR testing 1-36 months post-treatment. We stratified initial RPRs into high- and low-titer (≥1:32, <1:32) and compared outcomes using Cox proportional hazards.

Results: The study population included 761 persons with median time from treatment to last RPR/serological cure of 219 days (IQR 114-488). Among high-titer persons, serological cure occurred in 36 (88%) of 41, 330 (88%) of 376, and 58 (88%) of 64 receiving single-dose BPG, three-dose BPG, and doxycycline, respectively. Among low-titer persons, serological cure occurred in 4 (31%) of 13, 114 (49%) of 235, and 14 (47%) of 30 receiving single-dose BPG, three-dose BPG, and doxycycline, respectively. Controlling for initial RPR, serological cure did not differ between high-titer persons receiving one- and three-dose BPG (aHR: 0.89; 95% CI: [0.63, 1.26]) or one-dose BPG and twenty-eight days of doxycycline (aHR: 1.03; 95% CI: [0.68, 1.58]).

Conclusions: Serological outcomes in high-titer LSUD following one dose of BPG, three doses of BPG, and twenty-eight days of doxycycline are similar.

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Authors: Travis J. Hunt, MD[1,2], Anna Berzkalns, MPH[3], Chase A. Cannon, MD, MPH[1,3], Tim W. Menza, MD, PhD[1,3], Julia C. Dombrowski, MD, MPH[1,2,3], and Matthew R. Golden, MD, MPH[1,2,3]

[1]Department of Medicine, University of Washington, Seattle, Washington, USA.

[2]Department of Epidemiology, University of Washington, Seattle, Washington, USA.

[3]HIV/STI/HCV Program, Public Health-Seattle & King County, Seattle, Washington, USA

Corresponding Author:

Travis J. Hunt, MD

1959 NE Pacific St. Box 356423

Seattle, WA 98195

Email: thunt91@uw.edu; Phone: 206-685-4456; Fax: 206-616-3892

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Summary:

For high-titer latent syphilis of late or unknown duration (RPR ≥1:32), serological response did not differ between persons receiving one or three doses of benzathine penicillin G.

Abstract:

Background: The CDC recommends treating latent syphilis of late/unknown duration (LSUD) with three doses of intramuscular benzathine penicillin G (BPG) or twenty-eight days of oral doxycycline. This recommendation lacks high-quality evidence.

Methods: Using public health surveillance data from King County, Washington, we conducted a retrospective cohort study comparing rates of serological cure (≥2-titer RPR decline) among persons with LSUD following receipt of one of three regimens: one dose of BPG, three doses of BPG, and twenty-eight days of doxycycline. Subjects included persons diagnosed 2007-2020 with initial an RPR ≥1:2 and follow-up RPR testing 1-36 months post-treatment. We stratified initial RPRs into high- and low-titer (≥1:32, <1:32) and compared outcomes using Cox proportional hazards.

Results: The study population included 761 persons with median time from treatment to last RPR/serological cure of 219 days (IQR 114-488). Among high-titer persons, serological cure occurred in 36 (88%) of 41, 330 (88%) of 376, and 58 (88%) of 64 receiving single-dose BPG, three-dose BPG, and doxycycline, respectively. Among low-titer persons, serological cure occurred in 4 (31%) of 13, 114 (49%) of 235, and 14 (47%) of 30 receiving single-dose BPG, three-dose BPG, and doxycycline, respectively. Controlling for initial RPR, serological cure did not differ between high-titer persons receiving one- and three-dose BPG (aHR: 0.89; 95% CI: [0.63, 1.26]) or one-dose BPG and twenty-eight days of doxycycline (aHR: 1.03; 95% CI: [0.68, 1.58]).

Conclusions: Serological outcomes in high-titer LSUD following one dose of BPG, three doses of BPG, and twenty-eight days of doxycycline are similar.

Key Words: Latent syphilis, treatment, high RPR

Introduction:

The United States syphilis epidemic is accelerating, with increasing rates in heterosexual women and a rising proportion of syphilis classified as latent syphilis of late or unknown duration (LSUD).[1,2] Centers for Disease Control and Prevention (CDC) guidelines recommend treating LSUD with three weekly intramuscular doses of benzathine penicillin G (BPG) or twenty-eight days of doxycycline.[3] The recommendation to use three doses of BPG instead of the single dose used in early syphilis is based largely on the observation that *Treponema pallidum* replicates more slowly in late latent infection than in early infection and the unproven supposition that this difference impacts treatment efficacy.[4,5,6] Similarly, data comparing penicillin to doxycycline in the treatment of LSUD are limited.[7,8]

Treating all persons with LSUD with three weekly doses of BPG imposes a significant burden on patients, the healthcare system, and health departments, and completion rates with this regimen are low.[9] Because the criteria for classifying latent syphilis as early require a documented fourfold (or two-titer) increase in reactive plasma reagin (RPR) compared to testing performed in the prior year, a history of clearly identifiable symptoms of primary or secondary syphilis, or the diagnosis of early syphilis in a sex partner, many recently acquired latent infections are classified as LSUD by default.[3] Given the known association of higher RPR titer with early (versus late) infection, as well as animal model data demonstrating that VDRL titers decline over time in the absence of treatment, it seems likely that many high-titer LSUD cases are actually early infections.[10, 31s, 32s, 33s] Importantly, the value defining what qualifies as a "high" initial RPR varies in medical literature, with initial RPRs of $\geq$1:32 and $\geq$1:64 considered "high-titer" and associated with cure in various studies.[6,11] Insofar as early latent syphilis infections are classified as LSUD due to lack of information for exact staging, this

misclassification likely leads to many patients receiving more BPG doses than necessary, and some authorities have questioned the value of LSUD as clinical classification to guide therapy, proposing that RPR titer might be a better criterion for classifying stage of infection and determining treatment.[1,12-14] Moreover, the definition of late is somewhat arbitrary, as illustrated in the variance between treatment guidelines, with the World Health Organization, Australian, and UK guidelines defining late latent syphilis as infections diagnosed more than 2 years after acquisition, and the CDC and European guidelines defining late latent infections as those diagnosed more than a 1 year following acquisition.[3,15-18] These differences lack strong, evidence-based justifications and affect treatment recommendations.

While our sexual health clinic and medical providers in King County, WA typically follow CDC guidelines in the management of syphilis, in some instances persons diagnosed with LSUD receive a single dose of BPG and do not return for additional treatment. Our public health program previously looked at a small sample of 25 persons diagnosed with LSUD from 2021 to 2023 who only received one dose of BPG to inform decisions on how much effort to invest into outreach to promote completion of three-dose regimens in nonpregnant persons who do not return for recommended second and third doses of BPG treatment. To better address the question of whether a single dose of BPG might lead to equivalent serological response in the treatment of higher-titer LSUD, we used public health surveillance data that include reported RPR test results to compare serological responses among persons receiving a single dose of BPG intramuscularly, three weekly doses of BPG intramuscularly (CDC-recommended therapy), and 28 days of doxycycline for the treatment of LSUD.

Materials and Methods:

We conducted a retrospective cohort study of persons diagnosed with LSUD using public health surveillance data to assess the association of the receipt of different antibiotic treatment regimens with a two-titer (or fourfold) decline in RPR following treatment, a widely used serological marker of cure.[3,19] Subjects included persons with LSUD reported to Public Health – Seattle & King County between 2007 and 2020 with an initial RPR ≥1:2 and any follow-up RPR reported in the 1 to 36 months following treatment initiation. Syphilis is a reportable infection in Washington state, and laboratories are required to report syphilis serological test results and submit specimens to the Washington State Department of Health for confirmatory testing. Disease Intervention Specialists (DIS) routinely investigate syphilis cases to determine the stage of syphilis and treatment status and, as resources permit, provide partner services. Treatment information is recorded in a public health database of all reported syphilis cases. Using these data, we compared serological response to three treatment regimens: one dose of BPG, three weekly doses of BPG, and twenty-eight days of doxycycline 100mg twice daily.

We stratified our analyses into high-titer and low-titer initial RPR categories based on the hypothesis that high-titer LSUD infections are often early infections for which single-dose BPG is the accepted treatment. Based on our programs' prior preliminary analysis of 25 cases, the consideration of both 1:32 and 1:64 as "high-titer" RPRs associated with serological cure in the literature, and nonsignificant exploratory X^2 results using both breakpoints not supporting reason to favor one breakpoint over the other, we elected to use a threshold of ≥1:32 for the study analysis to include the largest number of persons diagnosed with high-titer LSUD.[6,9] Our study analysis did not include the 25 persons diagnosed with LSUD used in the preliminary analysis.

We used Cox proportional hazards to compare regimens, controlling for initial RPR titer, and defined time-to-event as time-to-final-RPR, determining final RPR as the first RPR with two-titer decline relative to the initial RPR or as the most recent RPR within 36 months of treatment, if the participant did not experience two-fold RPR decline—whichever was sooner.

For sensitivity analyses, we first stratified our Cox proportional hazards analysis to separately look at outcomes in persons with initial follow-up data within 180 days. We undertook this analysis to diminish the potential impact of bias related to differences in people who did and did not return for testing within recommended intervals and in recognition of how RPR titers may decrease over time even in the absence of treatment.[20,21] Second, to address the potential impact of confounding, we used inverse probability weighting. This approach estimates the probability that subjects received different treatments based on observed covariates and then weights observations based on these probabilities. In effect, the application of these weights to the study population creates a pseudo-population in which confounders are equally distributed across treatment groups. Covariates used in this analysis included initial RPR titer, HIV status, race, ethnicity, and age as a binary variable of <35 years or ≥35 years. Analyses were performed in Stata BE 18. This study did not require IRB review per Common Rule criteria as confirmed via the University of Washington Human Subjects Research Determination worksheet.

Results:

Medical providers and laboratories reported a total of 1,449 persons diagnosed with LSUD during the study period, of which 790 met our initial study inclusion criteria. Among the 659 excluded persons, 529 did not have a follow-up RPR in Washington state within 3 years of

treatment and 287 had an RPR that was 1:1 or nonreactive, with 157 excluded on both criteria. We excluded an additional 39 persons, including 12 who had follow-up RPRs without preceding treatment and 27 who received 2 BPG injections or received fewer than 28 days of doxycycline. Thus, the final study population included 761 persons who received 1 dose of BPG (n = 54), 3 weekly doses of BPG (n = 611), or 28 days of doxycycline 100mg twice daily (n = 96). The median age of study subjects was 35 years (IQR 28-47), 62% were cisgender men who have sex with men (MSM), and 38% were living with HIV (Table 1). Median time-to-final-RPR was 219 days (IQR 114-488). For comparison, of the 372 persons with an initial RPR of 1:2 or greater who were excluded solely due to lack of retesting within 3 years, 33 received 1 dose of BPG, 281 received three weekly doses of BPG, and 44 received 28 days of doxycycline (n =358). The remaining 14 received 2 BPG injections or fewer than 28 days of doxycycline. Demographics of persons who did not undergo retesting varied significantly compared to the study population in terms of race, ethnicity, HIV status, sexual behavior, and syphilis history (S1 Table 1).

Of 483 persons with an initial RPR $\geq$1:32, serological cure occurred in 36 (88%) of 41 persons who received 1 dose of BPG, 330 (88%) of 376 who received 3 doses of BPG, and 58 (88%) of 66 who received doxycycline (p=1.00). Controlling for initial RPR, serological cure did not differ significantly between persons receiving 1 and 3 doses of BPG (hazard ratio: 0.89; 95% CI: [0.63, 1.26]) or between persons receiving 1 dose of BPG and 28 days of doxycycline (hazard ratio: 1.03; 95% CI: [0.68, 1.58]); (Figure 1). Median time-to-final-RPR was 175 days (IQR 98-361).

Among 278 persons with an initial RPR <1:32, 4 (31%) of 13 treated with 1 dose of BPG, 114 (49%) of 235 treated with 3 doses of BPG, and 14 (47%) of 30 treated with doxycycline had serological cure (p=0.458); (Table 2). Serological cure did not differ

significantly between persons receiving 1 and 3 doses of BPG (hazard ratio: 0.69; 95% CI: [0.25, 1.86]) or between persons receiving 1 dose of BPG and 28 days of doxycycline (hazard ratio: 0.94; 95% CI: [0.28, 3.13]); (Figure 2). Median time-to-final-RPR was 377 days (IQR 181-748).

For sensitivity analyses for both high- and low-titer LSUD, adjusted hazard ratios for persons who had repeat RPR follow-up within 180 days did not differ significantly between regimens (S1 Table 2). Using inverse probability weighting for high-titer LSUD, average treatment effects on number of days until cure were similar between treatment regimens, crossing the null in each instance, though with wide confidence intervals (S1 Table 3). For low-titer LSUD, there were very few persons who received only a single dose of BPG, so we did not employ inverse probability weighting due to concern for accuracy.

Discussion:

In this retrospective cohort study, we found that one dose of BPG, three weekly doses of BPG, and twenty-eight days of doxycycline resulted in identical levels of serological response among persons treated for high-titer LSUD. We observed somewhat greater variation in the occurrence of serological cure among persons with low-titer LSUD treated with different regimens. Although not significantly different, this statistical finding was based on small numbers with notably low serological cure rates across all treatments. These findings suggest that a single dose of BPG may be sufficient in patients with high-titer LSUD.

Data on the optimal therapy for LSUD are largely observational.[22-25] To our knowledge, only one randomized trial comparing different syphilis treatment regimens has included patients with LSUD, and that trial enrolled only 12 persons with LSUD.[26] However, prior studies have found that rates of serological response are lower in persons with lower initial RPRs – a finding

consistent with our observations – and in persons with later stages of syphilis.[27,28] Retreatment of persons with late latent syphilis who do not have a serological response to therapy at 12 months does not appear to improve serological outcomes, suggesting that more intensive penicillin therapy may not be significantly better.[29]

Our finding that one and three doses of BPG leads to equivalent levels of serological response in high-titer LSUD could reflect the fact that many of these patients actually have early syphilis but are classified as LSUD due to the stringency of criteria or lack of complete information required for classifying infections as early latent syphilis. RPR titers in untreated persons decline over time, and high titer is consequently associated with early infection, though there is substantial overlap of the distribution of pre-treatment RPR titers between early and late infection.[10] Alternatively, they may reflect equivalence of single- and three-dose BPG therapies in high-titer late latent infection.

We also observed similar rates of serological response across treatment regimens in patients with low-titer LSUD. However, our sample size for this population – particularly persons with low-titer LSUD treated with only one dose of BPG – was small. Cure rates were low for all three regimens in this population and, although not significantly different, were lowest in the single-dose BPG group. Given our small sample size, we believe that the absence of a significant difference between treatment regimens among patients with low-titer LSUD should be interpreted with caution and more data are needed on this subject.

This study has several key limitations. First and foremost, we do not know that a two-titer RPR decrease is always indicative of microbiological cure, and it is possible that microbiological cure rates differ among persons with good serological response who are treated with different regimens. Serological response is an accepted marker of cure in current clinical practice, and

monitoring late manifestations of syphilis as an outcome is impractical. Additionally, this study is observational, not a randomized clinical trial, and is consequently subject to bias and confounding. Factors not routinely collected across all studied years in the public health surveillance data set – particularly substance use, housing status, poverty, and history of incarceration – may have affected who received the different treatment regimens and which patients did not receive serological follow-up. Although we did not observe differences in treatment regimens in our inverse probability analysis, we cannot eliminate the possibility of residual confounding by key social determinants of health. This analysis also would have benefited from a comparison to a cohort of untreated LSUD with observed follow-up RPRs. However, within our included population, we only identified 12 such persons who had at least 3 months of follow-up time prior to receiving treatment, of which only 2 remained untreated for more than one year. Lastly, in agreement with the case definition of LSUD employed by the National Notifiable Disease Surveillance System (NNDSS) of CDC, our study population groups people with late latent syphilis with people who have latent syphilis of unknown duration. In our experience, very few cases can be clearly defined as having late latent syphilis, and we were not able to define a meaningful number of such cases through our surveillance system. It is possible that such cases would have a different response to treatment than what we observed.[30]

In conclusion, we found that 1 dose of BPG, 3 doses of BPG, and 28 days of doxycycline were associated with identical levels of serological response among patients with LSUD and an RPR $\geq$1:32. Although these observational data do not provide the strength of evidence of a randomized controlled trial, we believe they should be reassuring to clinicians and public health authorities that one dose of BPG is likely sufficient to treat this group of patients. Our clinic and public health program continue to recommend standard of care regimens to all patients to LSUD,

but we also offer patients with high-titer LSUD the option of receiving a single dose of BPG with 28 days of doxycycline, acknowledging that many patients will not complete all 28 days of doxycycline. We suggest offering patients this regimen when a medical provider or the patient is concerned that adherence to weekly benzathine may be unlikely. The inclusion of the doxycycline in this regimen reflects our continued uncertainty about single-dose benzathine penicillin in the treatment of LSUD and our desire to exercise an abundance of caution in the absence of long-term clinical follow-up data and findings from a randomized controlled trial. With this approach, we do not invest scarce clinic and public health resources into attempting to ensure that all patients with high-titer LSUD return to clinic for doses 2 and 3 of BPG, and we do not routinely seek to restart treatment in nonpregnant people who received a single dose and have had an appropriate RPR titer decline. How to best treat LSUD is an important, understudied area of clinical STI research, and there is interest in examining treatment regimens that require less follow-up.[34s] A large, randomized controlled trial would ideally be undertaken to determine whether a single dose of BPG is sufficient to treat LSUD.

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Table 1: Characteristics of persons with LSUD treated with 1 BPG dose, 3 weekly BPG doses, or 28 days of oral doxycycline in King County, WA, 2007-2020

Variable	N=761	%[1]
Age Range in Years		
18-24	101	13%
25-34	261	34%
35-44	172	23%
45-54	149	20%
55+	78	10%
Race		
White	375	49%
Black	116	15%
American Indian/Alaska Native	10	1%
Asian	59	8%
Native Hawaiian/Other Pacific Islander	14	2%
Other	43	6%
Unknown/Missing	144	19%
Ethnicity		
Hispanic/Latinx	135	18%
Non-Hispanic/Latinx	504	66%
Unknown/Missing	122	16%
Gender and Sexual Behavior		
Cisgender MSM[2]	479	-
Cisgender MSW[3]	57	-
Cisgender Women, All	128	-
Cisgender Men with Unknown Gender of Sex Partners	104	-
Transgender/Nonbinary/Genderqueer[4]	1-9	-
HIV status		
HIV+	290	38%
HIV-	305	40%
Unknown	166	22%
Syphilis History		
Prior Syphilis	144	19%
No prior syphilis	617	81%
Prior Syphilis Stage		
Primary	22	15%
Secondary	37	26%
Early Latent	50	35%
Late/Unknown Duration	34	24%
Missing	1	0%

1. Rounded to nearest whole percentage
2. MSM = men who have sex with men
3. MSW = men who have sex with women
4. Demographic values <10 suppressed

Table 2: Serological cure of persons diagnosed with LSUD stratified by initial RPR titer and treatment received in King County, WA, 2007-2020

High-Titer Treatment (1:32+)	**No Two-Titer Drop (n=59)**	**Two-Titer Drop (n=424)**	**95% CI for Cure**
BPG IM once	5 (12%)	36 (88%)	74-96%
BPG IM for three weeks	46 (12%)	330 (88%)	84-91%
Doxycycline 100mg twice daily for 28 days	8 (12%)	58 (88%)	78-95%
Low-Titer Treatment (<1:32)	**No Two-Titer Drop (n=146)**	**Two-Titer Drop (n=132)**	**95% CI for Cure**
BPG IM once	9 (69%)	4 (31%)	9-61%
BPG IM weekly for 3 weeks	121 (51%)	114 (49%)	42-55%
Doxycycline 100mg twice daily for 28 days	16 (53%)	14 (47%)	28-66%
All Titers, Combined	**No Two-Titer Drop (n=205)**	**Two-Titer Drop (n=556)**	**95% CI for Cure**
BPG IM once	14 (26%)	40 (74%)	60-85%
BPG IM weekly for 3 weeks	167 (27%)	444 (73%)	69-76%
Doxycycline 100mg twice daily for 28 days	24 (25%)	72 (75%)	65-83%

Figure 1: Kaplan-Meier Estimates of Time-To-Cure by Treatment Regimen for High-Titer LSUD

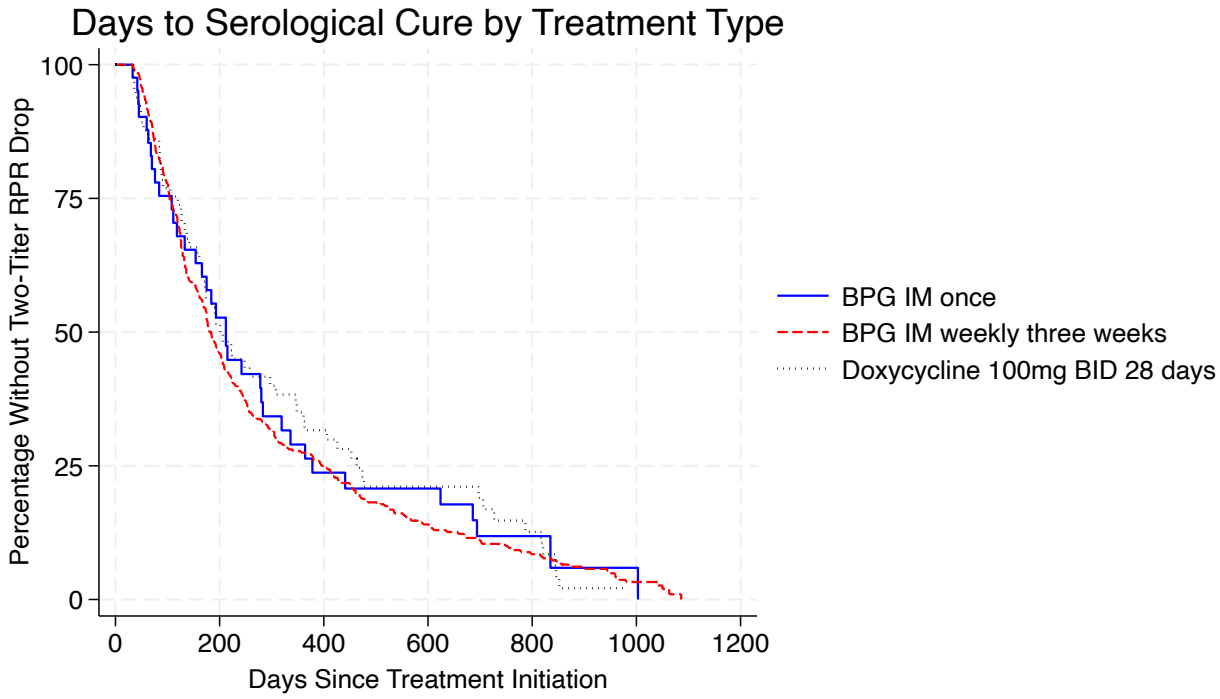
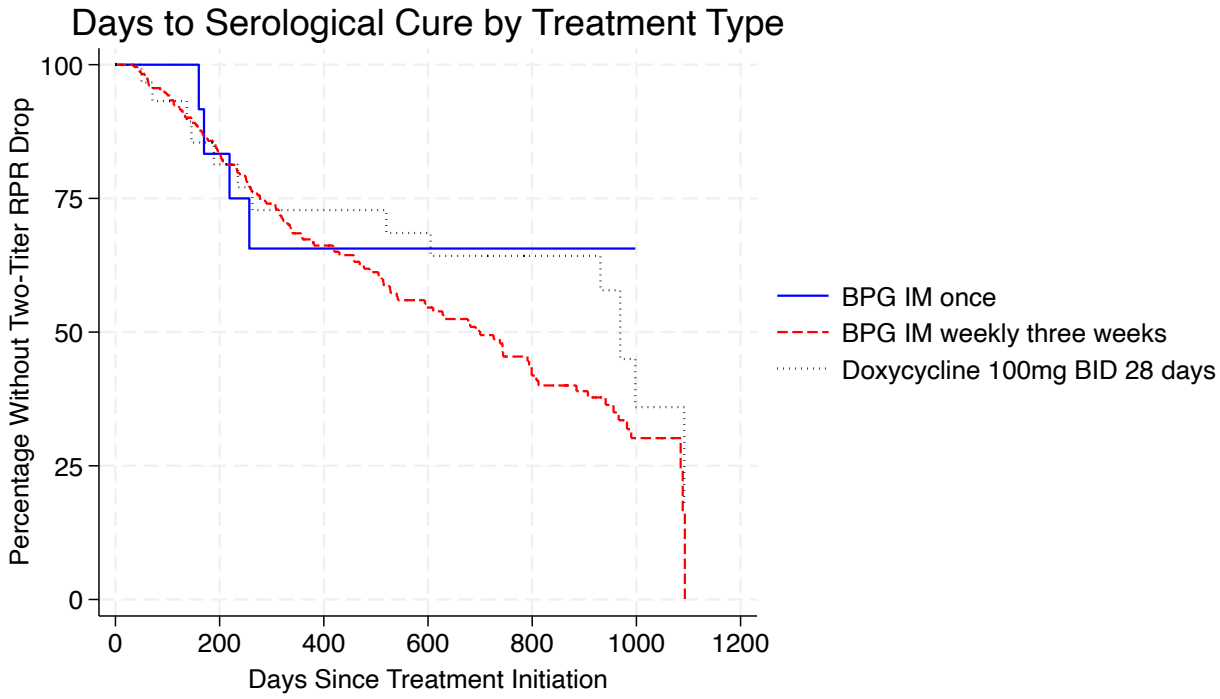


Figure 2: Kaplan-Meier Estimates of Time-To-Cure by Treatment Regimen for Low-Titer LSUD



Supplement 1: Comparison of Three Treatment Regimens for Latent Syphilis of Late or Unknown Duration Using Public Health Surveillance Data, Supplemental Tables

Table 1: Comparative Demographics of Persons Excluded Due to Lack of Follow-up

Variable	Excluded Due to Lack of Follow-up (N=358)	Included Population (N=761)
Age Range in Years (X^2 p = .054)[1]		
18-24	46 (13%)	101 (13%)
25-34	111 (31%)	261 (34%)
35-44	86 (24%)	172 (23%)
45-54	57 (16%)	149 (20%)
55+	57 (16%)	78 (10%)
Race (X^2 p < .001)[1]		
White	146 (41%)	375 (49%)
Black	72 (20%)	116 (15%)
Asian	33 (9%)	59 (8%)
Native Hawaiian/Other Pacific Islander	10 (3%)	14 (2%)
Other[2]	16 (4%)	53 (7%)
Unknown/Missing	80 (22%)	144 (19%)
Ethnicity (X^2 p < .001)[1]		
Hispanic/Latinx	62 (17%)	135 (18%)
Non-Hispanic/Latinx	202 (56%)	504 (66%)
Unknown/Missing	94 (26%)	122 (16%)
Gender and Sexual Behavior (X^2 p < .001)[1]		
Cisgender MSM[3]	150	479
Cisgender MSW[4]	61	57
Cisgender Women, All	74	128
Cisgender Men with Unknown Gender of Sex Partners	70	104
Transgender/Nonbinary/Genderqueer[5]	1-9	1-9
HIV status (X^2 p < .001)[1]		
HIV+	70 (20%)	290 (38%)
HIV-	134 (37%)	305 (40%)
Unknown	154 (43%)	166 (22%)
Syphilis History (X^2 p < .001)[1]		
Prior Syphilis	14 (4%)	144 (19%)
No prior syphilis	344 (96%)	617 (81%)
Prior Syphilis Stage (Fisher's Exact p = .82)[1]		
Primary	1 (7%)	22 (15%)
Secondary	3 (21%)	37 (26%)
Early Latent	5 (36%)	50 (35%)
Late/Unknown Duration	5 (36%)	34 (24%)
Missing	0 (0%)	1 (0%)

(1) Chi-squared and Fisher's exact tests, suppressed cells excluded (2) American Indian/Alaska Native merged into "Other" category in this table to include in X^2 rather than omit due to suppression (3) MSM = men who have sex with men (4) MSW = men who have sex with women (5) Demographic values <10 suppressed and percentages omitted to prevent back-calculation

Table 2: Cox Proportional Hazards for High- and Low-Titer LSUD, Stratified by Time to Follow-up Within 180 Days

High-Titer LSUD			
Follow-Up Time	Regimen	aHR	95% CI
≤180 days	BPG 1 vs. BPG 3	1.13	0.73, 1.76
≤180 days	BPG 1 vs Doxy 28d	1.60	0.93, 2.75
Low-Titer LSUD			
Follow-Up Time	Regimen	aHR	95% CI
≤180 days	BPG 1 vs. BPG 3	0.81	0.25, 2.60
≤180 days	BPG 1 vs Doxy 28d	0.85	0.19, 3.91

Table 3: Inverse Probability Weighting Comparison of the Effects of BPG 1, BPG 3, and Doxy 28d on Serological Outcome of High-Titer LSUD

Average Treatment Effects Comparison, Days to Cure			
Regimen	Days to Cure	95% CI	p-value
BPG 1 vs BPG 3	26 days	-83, 135	0.64
BPG 1 vs Doxy 28d	5 days	-122, 132	0.94
Primary Outcome, Mean Days to Cure			
Regimen	Mean Days to Cure	95% CI	
BPG 1	312	208, 416	
BPG 3	286	257, 315	
Doxy 28d	307	236, 379	

Supplement 2: Comparison of Three Treatment Regimens for Latent Syphilis of Late or Unknown Duration Using Public Health Surveillance Data, Supplemental References

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