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MAJOR ARTICLE

Comparing 7-Day Versus 6–8-Day Penicillin Treatment Intervals Among Pregnant People With Syphilis of Late or Unknown Duration: No Difference Found in Incidence of Congenital Syphilis

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Background. Guidelines recommend that pregnant patients with syphilis of late/unknown duration be treated with benzathine penicillin G, dosed as 3 weekly intramuscular injections (BPGx3) given ideally at strict 7-day intervals. Given limited pharmacokinetic data, it is unknown whether more flexible BPG treatment intervals might be effective in preventing congenital syphilis (CS).

Methods. We used California surveillance data to identify birthing parent/infant dyads wherein the pregnant parent had syphilis of late/unknown duration between January 1, 2016 – June 30, 2019. We divided the dyads into 3 groups based on prenatal treatment: (1) BPGx3 at strict 7-day intervals, (2) BPGx3 at 6-8 day intervals, and (3) no/inadequate treatment. We then compared CS incidence among infants in each group.

Results. We analyzed 1,092 parent/infant dyads: 607 (55.6%) in the 7-day treatment group, 70 (6.4%) in the 6–8 day treatment group, and 415 (38.0%) in the no/inadequate treatment group. The incidence proportion of infants meeting CS criteria in each group was, respectively, 5.6%, 5.7%, and 36.9%. Compared with BPGx3 at 7-day intervals, the odds of CS were 1.0 [95% CI 0.4–3.0] in the 6–8 day group and 9.8 [95% CI 6.6–14.7] in the no/inadequate treatment group.

Conclusions. Prenatal BPGx3 at 6–8 days was no more likely to lead to CS in infants than 7-days. These findings hint that 6-8-day intervals might be adequate to prevent CS among pregnant people with syphilis of late/unknown duration. Consequently, it is possible that CS evaluation beyond an RPR at delivery may be unnecessary in asymptomatic infants whose parents received BPGx3 at 6–8 days.

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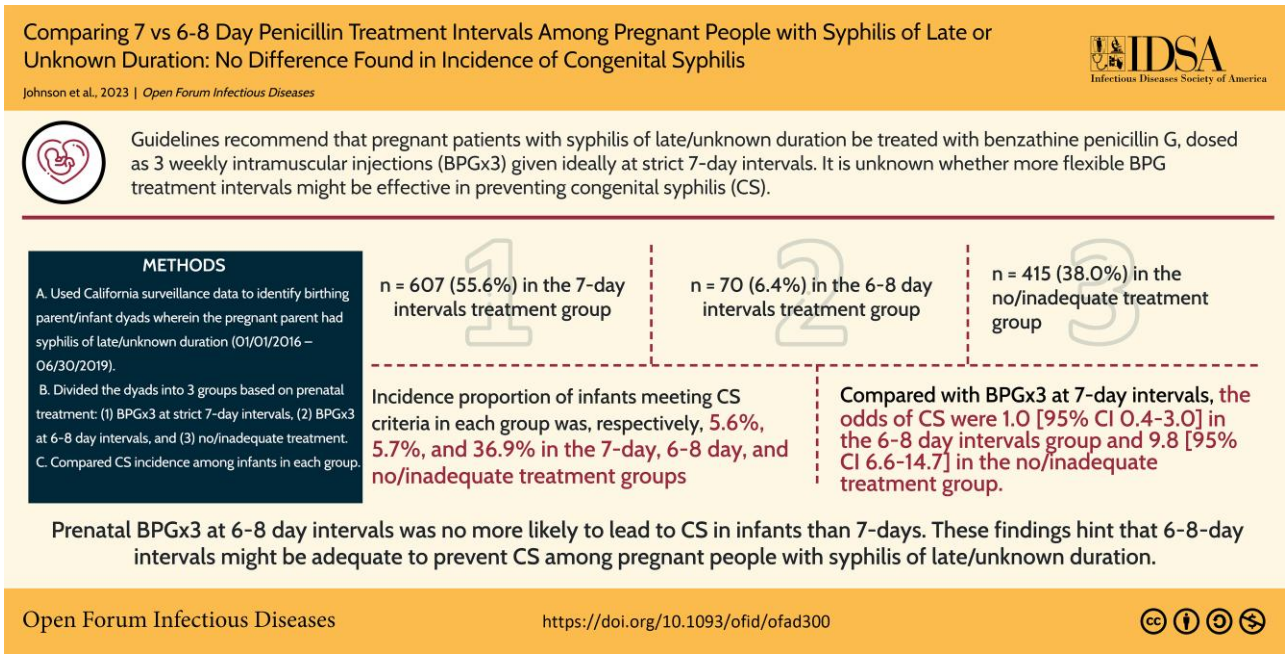
Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/comparing-7-vs-6-8-day-penicillin-treatment-intervals-among-pregnant-people-with-syphilis-of-late-or-unknown-duration-no-difference-found-in-incidence-of-congenital-syphilis

Keywords. congenital syphilis; sexually transmitted infections (STIs); syphilis in pregnancy; syphilis prevention; syphilis treatment intervals.

Congenital syphilis (CS) is a serious public health threat in the United States. CS rates have risen dramatically from historic lows in the late 20th century, with the 2020 national CS rate (57.3 cases per 100 000 live births) representing a 254% increase compared with 2016 [1]. Similarly, in California—which, as of 2020, had the second-highest number of CS cases in the country [1]—CS cases rose by >200% between 2015 and 2019 [2].

CS can be associated with significant morbidity and mortality, with abnormal signs and symptoms including severe anemia, thrombocytopenia, jaundice, rash, bone deformities, neurologic manifestations (eg, meningitis, blindness, and deafness), and even prenatal or perinatal complications (eg, prematurity, low birth weight, miscarriage, stillbirth, or neonatal death) [3–5]. Vertical transmission can occur during any stage of syphilitic infection [4, 6] and—left untreated—up to 40% of infants born to pregnant people with syphilis may be stillborn or die shortly after birth [7]. However, CS is preventable; nearly 100% of cases can be averted if prenatal syphilis is treated early enough during pregnancy [4].

Appropriate prenatal treatment may also reduce the need for invasive workup among infants. Many infants with in utero syphilis exposure appear asymptomatic at birth [8], rendering CS diagnosis difficult by examination alone. While dark-field microscopy, immunohistochemistry, special stains, or molecular methods can confirm CS [9], these tests are rarely performed in clinical practice and range in sensitivity. Reactive syphilis serologic results are also challenging to interpret in infants, since parental IgG antibodies cross the placenta [9]. For these reasons, infant management often relies on assessment of prenatal treatment adequacy. Infants with normal physical examination findings and nontreponemal antibody titers ≤4-fold those of their birthing parent—but whose parent received inadequate syphilis treatment in pregnancy—are still recommended to undergo evaluation, including cerebrospinal fluid (CSF) analysis, complete blood cell count, and long-bone radiography [9].

Defining treatment adequacy for syphilis in pregnancy is thus essential for both preventing CS and minimizing the need for invasive diagnostic tests. The Centers for Disease Control and Prevention (CDC) recommends that pregnant patients with syphilis of late latent or unknown duration (late or unknown duration) receive benzathine penicillin G (BPG) in 3 weekly intramuscular injections of 2.4 million units (BPGx3), optimally spaced at 7-day intervals and initiated ≥30 days before delivery to treat the parental infection and prevent CS [9]. However, strict 7-day intervals are not always feasible, and data are lacking to inform clinical management or assess infant outcomes at delivery when pregnant patients receive BPGx3 at intervals other than 7-days.

Because subtherapeutic penicillin levels may be permissible to treat syphilis of late or unknown duration if not sustained

for >24–30 hours [10], we hypothesized that infants born to birthing parents treated with BPGx3 at 6–8-day intervals (initiated ≥30 days before delivery) would be no more likely to meet CS criteria than those treated at 7-day intervals. If true, these findings could have important implications, hinting that: (1) prenatal 6–8-day treatment intervals may be adequate to prevent CS among pregnant patients with syphilis of late or unknown duration, and (2) CS diagnostic testing beyond a rapid plasma reagin (RPR) titer may be unnecessary in otherwise asymptomatic infants whose birthing parents received BPGx3 at more flexible 6–8-day intervals (without evidence of parental reinfection or treatment failure).

METHODS

Inclusion and Exclusion Criteria

We used California sexually transmitted disease (STD) surveillance data to identify dyads of birthing parent–infant wherein the parent was reported to public health as having syphilis of late or unknown duration while pregnant, including at the time of delivery, between 1 January 2016 and 30 June 2019. In accordance with CDC STD surveillance definitions [11], pregnant patients were considered to have syphilis of late or unknown duration if they had no clinical or serologic evidence of having newly acquired syphilis within the last 12 months and either (1) no history of prior syphilis, with currently reactive treponemal and nontreponemal serologic results, or (2) a history of prior syphilis with a 4-fold rise in nontreponemal titers (RPR or VDRL, without evidence of this increase lasting <2 weeks). California providers and laboratories are required to report all syphilis and CS cases to health authorities [12, 13].

We included all California birthing parent–infant dyads reported using the centralized state surveillance system, which excludes individuals residing in San Francisco or Los Angeles (which report syphilis and CS cases using a separate system). We also excluded dyads in which the birthing parent was diagnosed with neurologic, ocular, or otic syphilis, because treatment for these conditions differs from that for syphilis of late or unknown duration. Birthing parents who did not have a documented reactive RPR or VDRL titer during pregnancy or at delivery were ineligible, since in utero syphilis transmission is less likely to occur in the absence of reactive nontreponemal serologic results [14]. Finally, we excluded dyads in which the parent had a known diagnosis of adequately treated syphilis before pregnancy and had only stable, low-level reactive nontreponemal titers during pregnancy (ie, consistent with serofast status).

Individual birthing parents were eligible to be included in our analysis more than once—as part of separate dyads—if they were reported as having new diagnoses of syphilis of late or unknown duration (with reactive nontreponemal serologic results) during >1 pregnancy or had a multiple-gestation pregnancy within the study dates.

Defining Treatment Intervals and CS Diagnoses

We divided eligible dyads into 3 groups—those in which the parent received (1) prenatal BPGx3 at strict 7-day intervals initiated ≥30 days before delivery; (2) prenatal BPGx3 at 6–8-day intervals (wherein no interval fell outside 6–8 days), initiated ≥30 days before delivery; or (3) no or inadequate treatment. Inadequate treatment was defined as any of the following: a non-BPG antibiotic, an incorrect dosage or formulation of BPG, BPGx3 at intervals outside 6–8 days, <3 doses of BPG before delivery, or BPG initiated <30 days before delivery.

CS cases were defined using a combination of STD surveillance and clinical criteria [9, 11]. Infants were considered to have confirmed or probable CS if they (1) had laboratory evidence of CS, with *Treponema pallidum* identified in a clinical sample by darkfield microscopy, polymerase chain reaction, or immunohistochemistry/special stains; (2) were reported as syphilitic stillbirths; or (3) had a reactive nontreponemal test result, along with CS findings at physical examination or radiography, a reactive CSF VDRL result, or an otherwise-unexplained elevated CSF white blood cell (WBC) count or protein level in a nontraumatic lumbar puncture (defined as WBC count >15/μL or CSF protein level >120 mg/dL [11] in a CSF sample with a red blood cell count <500/μL). Outside of surveillance criteria, infants were also classified as CS cases clinically if they had a nontreponemal titer 4-fold higher than their birthing parent at delivery.

Statistical Analyses

We first summarized characteristics of parent-infant dyads. For birthing parents, these characteristics included age, race/ethnicity, human immunodeficiency virus (HIV) status, weeks of gestation at time of syphilis diagnosis and treatment, highest nontreponemal titer in pregnancy, receipt of prenatal care (yes or no), and trimester of first prenatal care (if received). Nontreponemal (RPR/VDRL) titers were grouped into higher (≥1:32) and lower (<1:32) categories, as characterized in the 2021 CDC sexually transmitted infection (STI) treatment guidelines [15], since higher titers in pregnancy are more likely to result in vertical transmission [16]. For infants, characteristics included vital status (alive or stillbirth/neonatal death), sex assigned at birth, gestational age at birth, birth weight, and nontreponemal titers at birth.

We used χ^2 tests to compare characteristics between dyads in which the parent received prenatal BPGx3 at 7-day versus 6–8-day intervals. We then calculated CS incidence proportions among dyads wherein the parent was treated at 7-day versus 6–8-day intervals (with incidence proportion defined as the number of infants who met CS criteria divided by the total number of infants within each treatment group). Finally, we built unadjusted logistic models to estimate the odds of CS

Table 1. Baseline Characteristics of 1092 Birthing Parent–Infant Dyads With Prenatal Syphilis of Late or Unknown Duration by Treatment Interval, California, 1 January 2016 to 30 June 2019

Characteristic	Inadequate Treatment (n = 415)[a]		BPGx3 at Strict 7-d Intervals (n = 607)[a]		BPGx3 at 6–8-d Intervals (n = 70)[a]		*P* Value (7-d vs 6–8-d Intervals)
	No.	%	No.	%	No.	%	
Parental characteristics							
Age, median (IQR), y	28 (25–33)		27 (23–32)		27 (22–32)		.85
Race and ethnicity							.59
Hispanic	187	47.0	335	59.0	35	52.2	
White	131	32.9	121	21.3	14	20.9	
Black	53	13.3	73	12.9	12	17.9	
Asian	14	3.5	20	3.5	2	3.0	
Other[b]	13	3.3	19	3.4	4	6.0	
Unknown[c]	17	…	39	…	3	…	
Received any prenatal care[d]							.09
Yes	174	43.4	587	97.7	65	94.2	
No	227	56.6	14	2.3	4	5.8	
Unknown	14	…	6	…	1	…	
Timing of initial prenatal care							.10
Trimester 1	34	26.2	230	58.4	23	47.9	
Trimester 2	44	33.9	130	33.0	23	47.9	
Trimester 3	52	40.0	34	8.6	2	4.2	
Unknown	44	…	193	…	17	…	
No prenatal care	241	…	20	…	5	…	
Length of gestation at syphilis diagnosis, median (IQR), wk	30.5 (22.0–35.2)		12.9 (8.8–21.0)		14.4 (9.6–21.7)		.31
Length of gestation at syphilis treatment, median (IQR), wk	32.9 (26.3–36.3)		15.7 (10.9–23.7)		16.1 (11.5–22.6)		.98
Highest RPR titer							.52
Low (<1:32)	191	46.9	326	53.8	36	51.4	
High (≥1:32)	206	50.6	271	44.7	34	48.6	
Reactive	10	2.5	9	1.5	0	0.0	
Unknown	8	…	1	…	0	…	
HIV status							.15
Positive	3	0.9	2	0.4	1	1.9	
Negative	872	99.1	507	99.6	52	98.1	
Unknown	100	…	98	…	17	…	
Infant characteristics							
Gestational age at birth, median (IQR), wk	37 (34–39)		39 (38–40)		39 (37–40)		.14
Sex assigned at birth							.14
Male	214	52.1	325	53.5	31	44.3	
Female	197	47.9	282	46.5	39	55.7	
Unknown	4[e]	…	0	…	0	…	
Birth weight, median (IQR), g	2910 (2242–3310)		3303 (2945–3650)		3189 (2850–3560)		.08
RPR titer (serum/cord blood)							.77
Low (<1:32)	215	58.4	411	71.1	51	77.3	
High (≥1:32)	77	20.9	11	1.9	1	1.5	
Reactive	11	17.7	11	1.9	1	1.5	
Not reactive	65	3.0	145	25.1	13	19.7	
Unknown	47	…	29	…	4	…	
Vital status							.09
Alive	376	90.6	603	99.3	68	97.2	
Stillbirth or neonatal death	39	9.4	4	0.7	2	2.8	

Abbreviations: BPGx3, benzathine penicillin G in 3 weekly injections of 2.4 million units, given ≤30 days before delivery; HIV, human immunodeficiency virus; IQR, interquartile range; RPR, rapid plasma regain.

[a]Data represent no. and % of birthing parents or infants, unless otherwise identified as median (IQR).

[b]"Other" includes other, multirace, and American Indian/Alaska Native.

[c]Unknown values throughout Table 1 were not included in statistical calculations and are thus not reported in the percentage breakdowns within each category presented.

[d]Prenatal care defined as having at least one prenatal care visit.

[e]All with unknown sex were stillborn.

Table 2. Incidence Proportions of Congenital Syphilis by Treatment Status of Birthing Parents With Syphilis of Late or Unknown Duration Diagnosed During Pregnancy—California, 1 January 2016 to 30 June 2019

CS in Infants	Inadequate Treatment (n = 415)	BPGx3 at Strict 7-d Intervals (n = 607)	BPGx3 at 6–8-d Intervals (n = 70)	*P* Value (7-d vs 6–8-d Intervals)
Infants meeting CS criteria, no.	153	34	4	…
Infants not meeting CS criteria, no.	262	573	66	…
CS incidence proportion, %	36.9	5.6	5.7	.97

Abbreviations: BPGx3, benzathine penicillin G in 3 weekly injections of 2.4 million units, given ≤30 days before delivery; CS, congenital syphilis.

Table 3. Unadjusted Logistic Model Predicting Odds of Congenital Syphilis by Birthing Parent's Treatment Regimen—California, 1 January 2016 to 30 June 2019

Parental Treatment	Unadjusted OR (95% CI)
BPGx3 at 7-d intervals	Reference
BPGx3 at 6–8-d intervals	1.0 (.4–3.0)
Inadequate treatment	9.8 (6.6–14.7)

Abbreviations: BPGx3, benzathine penicillin G in 3 weekly injections of 2.4 million units, given ≤30 days before delivery; CI, confidence interval; OR, odds ratio.

by prenatal treatment regimen. All statistical tests were performed using SAS software, version 9.4 (SAS Institute). This project was given a nonresearch determination by the California Health and Human Services Agency's Committee for the Protection of Human Subjects. Formal patient consent was not deemed necessary as this study used only deidentified, surveillance-level data originally collected for the purposes of public health.

RESULTS

Study Population

Within the study dates, 1173 diagnoses of late or unknown duration syphilis during pregnancy were reported, resulting in 1092 dyads (93.1%) eligible for our analysis (Supplementary Figure 1). Of these, 607 (55.6%) received BPGx3 at strict 7-day intervals, 70 (6.4%) received BPGx3 at 6–8-day intervals, and 415 (38.0%) received no or inadequate prenatal treatment.

Sociodemographic and Clinical Characteristics of Birthing Parents

There were no significant differences ($P > .05$) (Table 1) between birthing parents treated with BPGx3 at 7-day versus 6–8-day intervals when comparing age (median age, 27 years in both groups), race/ethnicity (59.0% vs 52.2% Hispanic), or HIV status (99.6% vs 98.1% HIV negative), respectively. The 7-day and 6–8-day BPG groups were also alike ($P > .05$) in receipt of prenatal care (97.7% and 94.2%, respectively, received at least some), trimester of first prenatal care (first trimester for 58.4% vs 47.9%), and highest nontreponemal titers in pregnancy (53.8% vs 51.4% with RPR/VDRL titers <1:32; 44.7% vs 48.6% with titers ≥1:32).

The 415 birthing parents who received no or inadequate syphilis treatment were like those in the 7-day and 6–8-day groups in age (median age 28), race/ethnicity (47.0% Hispanic), and HIV status (99.1% HIV negative) but were less likely to receive prenatal care (56.6% received none) and had syphilis diagnosed later in pregnancy (at a median of 30.5 weeks' gestation, compared with 12.9 and 14.4 weeks in the 7-day and 6–8-day groups, respectively). Most (59.5%) of the birthing parents in the no/inadequate treatment group had not received any syphilis treatment before delivery (Supplementary Table 1).

Infant Clinical Characteristics

Infants born to parents treated with BPGx3 at 7-day intervals were similar to those born to parents treated at 6–8-day intervals ($P > .05$; Table 1) in vital status (99.3% and 97.2% live births, respectively), median gestational age at birth (39 weeks), median birth weight (3303 and 3189 g), and nontreponemal syphilis serologic results at birth (71.1% and 77.3% with RPR/VDRL titers <1:32; 1.9% and 1.5% with titers ≥1:32). In contrast, infants born to birthing parents who received no or inadequate prenatal treatment had higher death rates (9.4% stillbirth/neonatal deaths), lower median birth weights (2940 g), and higher RPR/VDRL titers (20.9% ≥1:32). There were 191 infants in our analysis (including 16 syphilitic stillbirths and 1 neonatal death) who met criteria for CS, including 34 (18%) in the 7-day group, 4 (2%) in the 6–8-day group, and 153 (80%) in the no/inadequate treatment group (Table 2).

CS Incidence

The incidence proportions of CS in the 7-day, 6–8-day, and no/inadequate treatment groups were 5.6%, 5.7%, and 36.9% respectively (Table 2). There was no difference in CS incidence proportion between the 7-day and 6–8-day groups by χ^2 analysis ($P = .97$; Table 2). In unadjusted logistic regression (Table 3)—with 7-day intervals as the reference—the odds ratio for CS incidence was 1.0 (95% confidence interval, .4–3.0) in the 6–8-day group and 9.8 (6.6–14.7) in the no/inadequate treatment group.

Because the updated 2021 CDC STI treatment guidelines state that BPG intervals beyond 9 days are not acceptable in pregnancy [17] (implying that intervals of up to 9 days may be permissible), we also performed a sensitivity analysis among birthing parents in our study who received at least 1 of 3 BPG injections at a 9-day interval, initiated >30 days before delivery

(with no intervals falling outside 6–9 days). In this very small group of 5 dyads, 2 of 5 infants (40% of) met CS criteria.

DISCUSSION

In this analysis of >1000 birthing parent–infant dyads, we observed no difference in CS incidence when parents were treated with BPGx3 at strict 7-day versus more flexible 6–8-day intervals. These findings were not due to other differences between the infants whose parents were treated with BPG at 7 vs 6-8 day intervals—there were none ($P > .05$) when comparing infant vital status, gestational age at birth, gestational age at syphilis diagnosis and treatment, birth weight, or RPR/VDRL titers. In contrast, CS incidence was >9 times higher among infants whose parents received no or inadequate prenatal syphilis treatment.

Our results have implications for clinical and public health practice. They provide new evidence that more flexible 6–8-day intervals for prenatal treatment of late or unknown duration syphilis may be adequate to prevent CS. Data regarding appropriate BPG intervals in pregnancy are otherwise minimal, limited primarily to pharmacologic studies that do not assess CS prevention. In nonpregnant people, such pharmacologic studies suggest that 7–9-day BPG intervals achieve uninterrupted serum penicillin levels at the desired concentrations (0.03 IU/mL or 0.018 μg/mL [10, 18]) throughout the treatment period for syphilis of late or unknown duration [19]. In pregnancy, however, physiologic changes—such as increased blood volume, cardiac output, renal blood flow, creatinine clearance, and total body water, combined with decreased plasma protein concentrations—are likely to result in lower serum penicillin concentrations [20]. Indeed, in one pharmacokinetic study of penicillin levels in pregnant patients (all at 38–39 weeks' gestation), 36% of participants (9 of 25) already had subtherapeutic penicillin levels exactly 7 days after a BPG injection of 2.4–million units [20].

Yet pharmacokinetic data may not always translate directly to clinical reality. For nonpregnant people, national STI treatment guidelines suggest—based on clinical experience—that treatment intervals of up to 10–14 days might be acceptable treatment for late or unknown duration syphilis [15]. The same flexibility is not extended to pregnant patients, in whom strict 7-day treatment intervals are still preferred. The updated 2021 CDC STI treatment guidelines state that pregnant patients who have delays in BPG injections beyond 9 days should repeat the full course of therapy, but they do not comment on whether there is evidence to support these longer treatment intervals (likely owing to existing gaps in the literature). While our numbers are relatively small, our analysis hints that pregnant patients treated at 6–8-day intervals may be no more likely to deliver infants meeting criteria for CS than those treated at strict 7-day intervals.

In contrast, though our numbers were much too small to draw conclusions, nearly half (40%) of infants born to parents treated with BPGx3 with at least one 9-day interval met CS criteria, preliminarily hinting that these longer treatment intervals may be less effective in preventing CS (see Supplementary Table 2 for details of the 5 parent-infant dyads who received BPGx3 with at least one 9-day interval, initiated ≥30 days before delivery, with no intervals given outside 6–9 days). Much more robust studies, ideally using national data to allow for much larger sample sizes, would be needed to formally evaluate the effectiveness of 9-day treatment intervals.

Based on our findings, clinicians and public health practitioners may wish to consider defining 6–8-day intervals as adequate for CS prevention among pregnant patients with syphilis of late or unknown duration. This change could have important implications for patients, providers, and public health STD control programs. From a patient/provider perspective, more flexible 6–8-day treatment intervals could better accommodate the realities of syphilis treatment in the United States today, when transportation barriers, missed appointments, clinic hours, patient work and travel schedules, and other structural obstacles [21] can routinely impede successful treatment completion (particularly if strict 7-day BPG intervals are required). Acceptance of 6–8-day treatment intervals during pregnancy within national STI treatment guidelines could also mean that fewer asymptomatic infants would be recommended for invasive CS diagnostic testing—including blood sampling, lumbar punctures, and radiography—based on inadequate prenatal treatment alone.

From a public health perspective, acceptance of 6–8-day intervals as adequate could further allow public health STD control programs to focus limited time and resources elsewhere, rather than on retreating patients who initially received BPGx3 at 6–8 days. Importantly, because the odds of giving birth to an infant with CS were nearly 10 times higher among birthing parents who received no or inadequate syphilis treatment in pregnancy (the majority of whom also received no prenatal care), our results—like those of many other studies [22–27]—suggest that the goal of CS prevention might best be achieved by engaging out-of-care pregnant patients in prenatal care and working to ensure appropriate and timely syphilis testing and treatment during pregnancy. Finally, because United States cities and states currently determine for themselves which BPG intervals are considered adequate in pregnancy, acceptance of BPGx3 at 6–8 days as a national treatment standard could facilitate consistent CS surveillance criteria application and case counting nationwide.

Our analysis has several limitations. First, this was a retrospective observational study. Although birthing parents in the 7-day and 6–8-day BPG treatment groups were similar, this was not a randomized trial—which cannot be conducted owing to ethical concerns, given that 7-day treatment intervals are

indicated during pregnancy. There were fewer patients (n = 70) in the 6–8-day group, and we were underpowered to detect a significant difference ($\beta = .8$; $\alpha = .05$) in CS incidence. This is a limitation of public health surveillance data for a low-incidence disease like CS, when randomized trials are not possible. Relatedly, because only 5 pregnant patients received BPGx3 with at least one 9-day interval, initiated ≥30 days from delivery (with no intervals outside 6–9 days), our study was also underpowered to assess the adequacy of 9-day intervals for CS prevention. We urge more robust data collation across multiple jurisdictions to evaluate the impact of alternative treatment regimens (potentially including both 6–8-day and 6–9-day treatment intervals) on CS incidence.

Second, although adjusted regression models could have provided more robust evidence of the effectiveness of BPGx3 at 6–8-day intervals for CS prevention, such models would have become quickly oversaturated (and provided unstable estimates), again owing to the relatively small number of pregnant patients in this group. A small sample size also precluded more complicated multifactorial analyses to adjust for unmeasured differences in characteristics of birthing parents—particularly social determinants of health—in each treatment group. Third, because our analysis relied heavily on surveillance criteria (which are more sensitive than specific [27]) to identify CS cases, it is possible that noninfected infants were included in our analysis. We do not suspect, however, that this limitation would have differentially affected infants treated at 6–8- versus 7-day intervals, since surveillance criteria were applied uniformly regardless of treatment group. We also do not know why 38 infants in our analysis met CS criteria despite having received prenatal treatment at 7-day or 6–8-day intervals (Supplementary Table 3), though we suspect this is more likely due to parental reinfection or a transient rise in RPR/VDRL titers at delivery than to treatment failures, which are rare [28].

As noted above, since many of these infants met CS surveillance criteria owing to their reactive RPR result combined with the relatively nonspecific finding of elevated CSF protein level or WBC count, it is also possible that some of these infants were not truly infected with CS. Further study—including more detailed collection and analysis of medical records combined with larger sample sizes—would be needed to evaluate whether CS infant surveillance criteria should be revised to remove the elevated CSF protein level or WBC count (in isolation) from the surveillance case definitions for CS among infants with reactive RPR titers. Finally, because our analysis focused on CS prevention among infants, we did not assess parental treatment adequacy. Further study would be needed to determine whether syphilitic cure (ie, a 4-fold decline in RPR/VDRL titers within 24 months after treatment) was achieved among pregnant patients treated at 6–8-day intervals.

In conclusion, treatment of syphilis at 6–8-day intervals during pregnancy may potentially be sufficient to prevent CS. While larger studies are needed to confirm our findings, our preliminary results suggest that more flexible 6–8-day treatment intervals may have the potential to (1) obviate the need for invasive diagnostic testing among otherwise asymptomatic infants whose birthing parents received BPGx3 at 6–8-day intervals and (2) allow limited public health resources for STD control to be directed elsewhere, rather than ensuring that pregnant patients with syphilis of late or unknown duration who received BPGx3 at 6–8-day intervals be brought back into care for retreatment at strict 7-day intervals.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: no reported conflicts.

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