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Late latent syphilis treatment:
Clinician perspectives of the current three-dose benzathine penicillin G regimen and the implementation of a single-dose regimen

Collaboration for Evidence, Research and Impact in Public Health

We acknowledge that this research has taken place on Country across Western Australia and pay our respects to Elders past and present. Our research team is based in Boorloo (Perth) on the lands of the Whadjuk Noongar people, who have been custodians of this boodjar since time immemorial.

We acknowledge all Traditional Custodians and their continuing connection to culture, community, land, sea and rivers.

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Funding: through a grant received by University of Western Australia from the Commonwealth represented by Department of Health.

Suggested citation: Collaboration for Evidence, Research and Impact in Public Health (CERIPH). (2024). *Late latent syphilis treatment: Clinician perspectives of the current three-dose benzathine penicillin G regimen and the implementation of a single-dose regimen*. CERIPH, Curtin University: Bentley, Western Australia.

ISBN: 978-0-6486452-4-5

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Executive Summary

Background and aim

Over the last decade, syphilis cases in Australia have risen dramatically. The recommended treatment regimen for late latent syphilis (defined as an infection acquired more than two years prior to diagnosis or of unknown duration) requires three intramuscular (IM) injections of benzathine penicillin G (BPG) at a dosage of 2.4 million units (MU) (1.8 grams), delivered at one-week intervals. However, low completion rates of this three-dose BPG regimen have prompted clinical trials investigating the pharmacoequivalence, safety, and feasibility of a single, high-dose subcutaneous BPG infusion compared to the established three-dose regimen. This study aimed to identify sexual health clinicians' perspectives of barriers to, and enablers of, late latent syphilis treatment completion under the current three-dose BPG regimen; and training needs for healthcare providers and service resource implications associated with the potential introduction of a single-dose treatment regimen.

Methods

Study participants were private and public sector clinicians with experience treating patients with late latent syphilis in the past two years in Australia. Participants were invited to complete an online questionnaire. The questionnaire was informed by the findings of a systematic review and included three main sections: primary place of employment and syphilis treatment experience, barriers to and enablers of syphilis treatment completion of the three-dose BPG regimen, and training needs and service resource implications associated with the potential introduction of a single-dose BPG regimen.

Descriptive statistics were used to analyse the multiple-choice questions examining the effect of factors related to the completion of the three-dose. The responses to the open-ended questions were analysed using content analysis whereby each qualitative response was split into phrases and coded using Peh's conceptual model of factors identified as influencing medication adherence.

Findings

This study assessed clinicians' perspectives of the current three-dose BPG regimen and the

under-trial single high-dose BPG regimen for late latent syphilis treatment. The clinicians nominated a range of barriers to completion of the current three-dose BPG regimen, which included limited understanding of treatment by patients, inflexibility in treatment dosing, and pain from the IM injections. The majority of clinicians reported that they would support a single-dose BPG regimen, if this regimen was supported by evidence, as they saw this approach as a way to improve treatment completion. To support the successful implementation of the one-dose treatment regimen, the clinicians called for both online and on-demand clinical training and consideration of costs related to staff capacity and expertise, equipment, transport and storage requirements of the medication, and documented updated treatment guidelines.

Background

In Australia, syphilis is a notifiable sexually transmissible infection (STI).[1] Notifications of rates of syphilis cases in Australia per 100,000, increased four-fold from 6.0 in 2011 to 24.3 in 2022,[2, 3] and in 2023 there were 6,443 syphilis cases identified.[4] However, the evidence on the proportion of late latent syphilis cases (positive syphilis test without the presence of any clinical signs or symptoms; acquired two years or unknown duration before the diagnosis) among the total number of syphilis cases in Australia is limited. Statistics from Queensland show that 33.9% (370) of syphilis notifications in 2022 were late latent cases, and late latent syphilis notifications increased from 154 cases (4.2 per 100,000 population per year) in 2001 to 370 cases (7.1 per 100,000 population per year) in 2022.[5] In Victoria, among women diagnosed with syphilis at a health centre, the proportion of late latent syphilis cases increased from 36.4% (12 cases) in 2015-2017 to 60.9% (42 cases) in 2018-2020.[6]

Treatment for late latent syphilis currently requires three intramuscular (IM) injections of 2.4 million units (MU) (1.8 grams) of benzathine penicillin G (BPG) delivered at weekly intervals.[7] However, since the completion rate of all three BPG injections is low,[8, 9] clinical trials have been conducted to examine the pharmaco-equivalence, safety, and feasibility of subcutaneous (SC) infusion of a single high dose of 7.2 MU BPG, compared to the injection of three doses of 2.4 MU of BPG (7.2 MU in total).[10-16] In a randomised crossover study with 15 healthy adult participants receiving 1.2 MU of BPG intramuscularly or subcutaneously for either the first or second dose, it was reported that the principal absorption half-life was significantly longer in the SC injection than the IM injection.[12] Similarly, the prolonged elevated serum penicillin concentration was observed in a trial of 24 participants who received 3.6 or 7.2 or 10.8 MU of BPG as a single SC infusion co-administered with lignocaine, a local anaesthetic, at the umbilical region of the abdomen.[10, 14, 15] These participants reported transient and mild reactions at the infusion site.[10, 11, 14, 15] Currently, a clinical trial is being undertaken to examine the safety and tolerability of a single SC of 7.2 MU BPG co-administered with lignocaine at the buttock for the treatment of syphilis.[16]

In the event that the new single high-dose BPG regimen is found to be safe and has

pharmaco-equivalence to the three-dose regimen, understanding the factors influencing the completion of the current three-dose regimen, and the factors to be considered in the implementation of a single-dose regimen requires further investigation to inform clinical service delivery. This study aimed to identify sexual health clinicians' perspectives of barriers to, and enablers of, late latent syphilis treatment completion under the current three-dose BPG regimen; and training needs for healthcare providers and service resource implications associated with the introduction of a single-dose treatment regimen.

Methods

Study participants were clinicians with experience treating patients with late latent syphilis in the past two years. Clinicians were recruited from the private sector (private and not-for-profit sexual health clinics from all states and territories in Australia), and the public sector (public sexual health clinics in Armadale Health Service, Fiona Stanley Hospital, Fremantle Hospital, and Royal Perth Hospital). The proposed sample size was 50 (25 clinicians from the public sector and 25 from the private sector). Recruitment occurred from late 2023 to early 2024. This research received ethics approval from the South Metropolitan Health Service Human Research Ethics Committee (RGS6273) and Curtin University Human Research Ethics Committee (HRE2023-0576).

Recruitment

Recruitment strategies for clinicians from the private and public sectors deviated due to different ethical governance processes. To recruit clinicians working within the private sector, email invitations were sent to managers or information desks of sexual health clinics. Clinics that did not respond to the email invitations were followed up with a phone call (states and territories other than the state of Western Australia, and country region of Western Australia) and in-person (Perth Metropolitan Area). Within the public sector, recruitment materials were sent by the study team to contacts located within the Perth health services, to be forwarded to relevant clinicians on behalf of the study team. These contacts were asked to send a follow-up email two weeks prior to the survey closing. To ensure only eligible clinicians completed the survey, the first two questions screened out clinicians who were not currently working in Australia and those who did not treat any late latent syphilis cases during the two-year period prior to the survey.

Questionnaire

The questionnaire was informed by the findings of a systematic review of the literature[17] that identified barriers to and enablers of late latent syphilis treatment completion under the current three-dose regimen. The questionnaire included three main sections: primary place of employment and syphilis treatment experience, barriers to and enablers of syphilis treatment completion of the three-dose BPG regimen, and training needs and service

resource implications associated with the potential introduction of a single-dose BPG regimen. The questionnaire is included in Appendix A.

Data Analysis

The survey data were exported from Qualtrics to Microsoft Excel and the Statistical Package for Social Sciences version 29 (SPSS v29).[18] Descriptive statistics were used to describe the clinicians and analyse the multiple-choice question listing factors related to the completion of the three-dose regimen. The response options of 'minor effect', 'moderate effect' and 'major effect' were combined to create a new group called 'some effect' [response category 'I don't know' was not included in the final calculation for each response]. This new category was used to calculate the proportion of clinicians that reported the factor had an effect on treatment completion.

The proportion of clinicians who commented that each factor could have some effect on treatment completion was calculated as follows.

$$n\_some\ effect = n\_minor\ effect + n\_moderate\ effect + n\_major\ effect$$

$$proportion\_some\ effect = \frac{n\_some\ effect}{(n\_no\ effect + n\_some\ effect)}\ \%$$

The responses to the open-ended questions were analysed using content analysis whereby each qualitative response was split into phrases and coded using Peh's conceptual model of factors identified as influencing medication adherence and are presented in Table 1.[19] The phrases were coded as factor example(s), which were then grouped into factors, under the five dimensions of Peh's conceptual model, namely, condition, medication, healthcare system/healthcare providers, patients, and socioeconomic. Counts were undertaken for each code and proportions were calculated for each dimension. De-identified quotes were used in the data presentation.

Table 1. Conceptual model of factors contributing to medication adherence: From Peh et al.[19]

Peh's Dimensions	Factors	Factor examples
Condition	Disease control	▪ Symptoms ▪ Complications ▪ Severity ▪ Acute events/deterioration ▪ Impact on lifestyle
	Disease characteristics	▪ Cognitive deficit ▪ Symptom bother ▪ Consequence
	Patient-specific	▪ Co-morbidities ▪ time since diagnosis ▪ declining health
Medication	Medication regimen	▪ Complexity ▪ Dosage ▪ Type ▪ Pill burden ▪ Interference in routine ▪ Clarity of instructions on the label ▪ Regimen familiarity
	Medication effects	▪ Side effects ▪ Safety ▪ Efficacy ▪ Benefits ▪ Patient experience
	Medication properties	▪ Cost ▪ Physical properties ▪ Formulation
Healthcare system/ healthcare provider	Healthcare provider characteristics	▪ Relationship ▪ Communication ▪ Trust in provider ▪ Clinical care ▪ Ability to relate ▪ Provision of training/follow-up ▪ Prescription practice ▪ Patient education
	Healthcare system-related factors	▪ Access ▪ Provider continuity ▪ Cost ▪ Drug supply ▪ Regulation processes ▪ Quality of health services ▪ Information support ▪ Insurance coverage
Patient	Cognitive and psychological factors	▪ Perceptions ▪ Beliefs ▪ Concerns

Peh's Dimensions	Factors	Factor examples
		▪ Knowledge/ health literacy ▪ Emotions ▪ Motivations/ goals
	Behavioural factors	▪ Organisation ▪ Planning ▪ Lifestyle
	Priorities	▪ Quality of life ▪ Other competitive needs
	Non-modifiable characteristics	▪ Demographics ▪ Experience ▪ Type of user ▪ Physical factors
	Family/ caregiver characteristics	▪ Hesitancy ▪ Support ▪ Relationship
Socio-economic	Social/environmental factors	▪ Social context ▪ Interaction ▪ Support ▪ Culture, language ▪ Stigma, norms ▪ External influences ▪ Sociodemographic ▪ Promotional prompts ▪ Environment
	Lifestyle factors	▪ Alcohol ▪ Drug use
	Economic factors	▪ Income ▪ Education ▪ Occupation ▪ Living condition ▪ Insurance

Results

A total of 62 potential clinician respondents accessed the online survey, 27 were excluded and the remaining 35 were included in the analysis. The number of excluded responses and reasons for exclusion are listed in Table 2.

Table 2. Reasons for respondent exclusion from the study (n=27)

Reasons for exclusion	n (%)
Not eligible	11 (40.7)
Signed in and left	9 (33.3)
Consent was provided but no other responses to the questionnaire	5 (18.5)
Consent was not provided	2 (7.4)

The clinicians' primary place of employment and experience providing syphilis treatment are presented in Table 3. More than half of the clinicians (51.4%; n=18) worked in the public sector, with most primarily based within hospitals (48.6%; n=17) or specialist sexual health clinics (37.1%; n=13). When asked to estimate the number of patients with late latent syphilis they had treated in the past two years, 60.0% (n=21) had treated between one and five patients. Less than half (42.9%; n=15) reported that all of their late latent syphilis patients in the past two years had completed a full course of three-dose BPG regimen. Among these 15 clinicians, six (40.0%) reported that there had been patients who did not complete the three-dose BPG over the course of their career, while five clinicians (33.3%) reported that they were not able to recall any three-dose BPG regimen incompletions.

Table 3. Clinician location and experience with three-dose BPG treatment over time

		n (%)*
Public or private sector	Public	18 (51.4)
	Private	17 (48.6)
Primary place of employment	Private general practice	5 (14.3)
	Hospital	17 (48.6)
	Specialist sexual health clinic	13 (37.1)

		n (%)*
Estimated number of patients treated using a 3-dose BPG regimen in the past 2 years	1-5	21 (60.0)
	6-10	7 (20.0)
	11-15	1 (2.9)
	16-20	2 (5.7)
	21-25	-
	26-30	2 (5.7)
	More than 30	2 (5.7)
Estimated percentage of treatment completion in the past 2 years	1-20%	1 (2.9)
	21-40%	1 (2.9)
	41-60%	8 (22.9)
	61-80%	3 (8.6)
	81-99%	7 (20.0)
	100%	15 (42.9)
Experience of treatment incompletion over the course of their career (N=15)	Yes	6 (40.0)
	No	2 (26.7)
	I cannot recall	5 (33.3)

*(n=35) unless otherwise specified

Factors influencing incompletion of the three-dose BPG regimen

Twenty-six clinicians reported that some of their late latent syphilis patients that they had treated over the last two years had not completed the three-dose BPG treatment. The factors most frequently rated by the clinicians as having some effect on treatment incompletion were '*Lack of flexibility in treatment dosing*' (100%; n=25), *'Limited patient understanding of the importance of treatment compliance'* (100%; n=26), *'Pain associated with injections'* (96.0%; n=24), '*Instability in patients' life circumstances'* (95.8%, n=23), and *'Competing demands on patients' time'* (92.0%; n=23) (Table 4). The least frequently reported factors to have some effect on treatment incompletion were *'Allergic reaction to treatment'* (20.8%; n=5), *'Treatment costs'* (40.0%; n=10), *'Lack of staff knowledge of appropriate syphilis treatment'* (40.0%; n=10), and *'Lack of staff knowledge of appropriate follow-up processes'* (41.7%; n=10).

Table 4.Clinicians' ratings of factors that reduced treatment completion of late latent syphilis treatment regimen (N=26)

	n (%)[a]					Overall some effect n (%)[b] (excluding 'I do not know')
	No effect	Minor effect	Moderate effect	Major effect	I do not know	
Limited patient understanding of the importance of treatment compliance	-	7 (26.9)	10 (38.5)	9 (34.6)	-	26 (100)
Lack of flexibility in treatment dosing	-	1 (3.8)	12 (46.2)	12 (46.2)	1 (3.8)	25 (100)
Pain associated with injections	1 (3.8)	4 (15.4)	13 (50.0)	7 (26.9)	1 (3.8)	24 (96.0)
Competing demands on patient time	2 (7.7)	9 (34.6)	7 (26.9)	7 (26.9)	1 (3.8)	23 (92.0)
Instability in patients' life circumstances	1 (3.8)	4 (15.4)	4 (15.4)	15 (57.7)	2 (7.7)	23 (95.8)
Incomplete patient medical records e.g., contact information or treatment history	3 (11.5)	7 (26.9)	9 (34.6)	6 (23.1)	1 (3.8)	22 (88.0)
Patients' inability to access services due to transport barriers	3 (11.5)	8 (30.8)	5 (19.2)	9 (34.6)	1 (3.8)	22 (88.0)
Limited time available for staff to undertake follow-up	5 (19.2)	8 (30.8)	7 (26.9)	5 (19.2)	1 (3.8)	20 (80.0)
Treatment side-effects	5 (19.2)	13 (50.0)	5 (19.2)	1 (3.8)	2 (7.7)	19 (79.2)
Inadequate hospital/clinic follow-up systems	8 (30.8)	8 (30.8)	6 (23.1)	4 (15.4)	-	18 (69.2)
Lack of patient trust	6 (23.1)	8 (30.8)	8 (30.8)	2 (7.7)	2 (7.7)	18 (75.0)
Service wait times	9 (34.6)	10 (38.5)	4 (15.4)	2 (7.7)	1 (3.8)	16 (64.0)
Lack of support from patients' partners	9 (34.6)	6 (23.1)	4 (15.4)	5 (19.2)	2 (7.7)	15 (62.5)

	n (%)[a]					Overall some effect n (%)[b] (excluding 'I do not know')
	No effect	**Minor effect**	**Moderate effect**	**Major effect**	**I do not know**	
Patients' past experiences of syphilis and syphilis treatment	10 (38.5)	5 (19.2)	4 (15.4)	5 (19.2)	2 (7.7)	14 (58.3)
Patients do not accept syphilis diagnosis	10 (38.5)	8 (30.8)	3 (11.5)	3 (11.5)	2 (7.7)	14 (58.3)
Inadequate supply of BPG	11 (42.3)	8 (30.8)	3 (11.5)	2 (7.7)	2 (7.7)	13 (54.2)
Inadequate antenatal care (including late initiation)	7 (26.9)	5 (19.2)	4 (15.4)	3 (11.5)	7 (26.9)	12 (63.2)
Patient required to undertake spinal puncture and staging	11 (42.3)	3 (11.5)	5 (19.2)	4 (15.4)	3 (11.5)	12 (52.2)
Patient comorbidities	11 (42.3)	8 (30.8)	3 (11.5)	1 (3.8)	3 (11.5)	12 (52.2)
Lack of staff knowledge of appropriate follow-up processes	14 (53.8)	4 (15.4)	4 (15.4)	2 (7.7)	2 (7.7)	10 (41.7)
Treatment costs	15 (57.7)	6 (23.1)	1 (3.8)	3 (11.5)	1 (3.8)	10 (40.0)
Lack of staff knowledge of appropriate syphilis treatment	15 (57.7)	4 (15.4)	4 (15.4)	1 (3.8)	2 (7.7)	9 (37.5)
Allergic reaction to treatment	19 (73.1)	4 (15.4)	1 (3.8)	-	2 (7.7)	5 (20.8)

[a] number and proportions of respondents who rated each nominated factor to have no, minor, moderate, or major effect on treatment incompletions; or selected "I do not know" option.

[b] proportions of respondents who rated each nominated factor to have some effect on treatment incompletion = {(n_minor effect + n_moderate effect + n_major effect) / (n_no effect + n_minor effect + n_moderate effect + n_major effect)}%

Reasons for supporting the new single-dose BPG regimen

Most clinicians (94.3%; n=33) reported they would support the introduction of a new treatment regimen, if it were supported by evidence. Two clinicians reported that they required more information to answer the question of whether they would support the new regimen. Reasons for supporting a new single-dose BPG treatment comprised three of Peh's dimensions (medications, healthcare system/ healthcare providers, and patients) and are presented in Table 5. The most frequently expressed medication-related reasons to support the introduction of a new treatment regimen, if supported by evidence, were that the dosage would be more flexible (34%; n=18) and patient compliance would be better with the new regimen (22.6%; n=12). For example, one clinician explained, "*More convenient for patients* [and] *time saving.*" The most commonly expressed healthcare system-related reason was that the cost of the new regimen to the healthcare system would be less than that of the three-dose regimen (90%; n=9). The clinicians stated that a "*A single regimen would be more practical and would be less demanding on hospital resources*" and there would be "*Improved patient adherence,* [and] *reduction in cost to patient/health care system*."

Table 5. Clinicians' reasons for supporting a single-dose BPG regimen

Peh's dimensions	Factors and examples	Reasons for supporting the single-dose regimen [Codes of phrases]	n (%)*
Medications	Medication effects (i.e., side effects, safety, efficacy, benefits, patient experience)	Safety and side-effects	6 (11.3)
		Efficacy and effectiveness	4 (7.5)
	Medication regimen (i.e., complexity, dosage, type, pill burden, interference in routine, clarity of instructions on label, regimen familiarity)	Dosage	18 (34.0)
		Compliance or adherence	12 (22.6)
	Medication properties (i.e., cost, physical	Cost (to patient)	1 (1.9)

Peh's dimensions	Factors and examples	Reasons for supporting the single-dose regimen [Codes of phrases]	n (%)*
	properties, formulation)		
	Other	If there is evidence (not specified) Overall improvement	11 (20.8) 1 (1.9)
Healthcare system and healthcare providers	Healthcare system-related factors (i.e., access, provider continuity, cost, drug supply, regulation processes, quality of health services, information support, insurance coverage)	Cost (to healthcare system) Guidelines for treatment	9 (90.0) 1 (10.0)
Patients	Cognitive and psychological factors (i.e., perceptions, beliefs, concerns, knowledge/ health literacy, emotions, motivation/ goals)	Acceptability of treatment	1 (50.0)
	Behavioural factors (i.e., organisation, planning, lifestyle)	Lifestyle (Fly-in Fly-out workers, migrants)	1 (50.0)

Total number of clinicians who responded to this question (n=32);
* n = the number of phrases coded within each dimension; % = the proportion of each code within each dimension.

Information clinicians want on the single-dose BPG treatment regimen

The information clinicians would like regarding the single-dose BPG regimen crossed three of Peh's dimensions (medications, healthcare system/ healthcare providers, and patients) (Table 6). For the medication-related factors, the clinicians mostly wanted information about pharmacokinetic and pharmacodynamic equivalence, efficacy, and treatment outcomes (45.8%; n=22). The clinicians wanted "*Confirmation of bioequivalence*," "*Data*

showing equivalence in at least Pk-PD (pharmacokinetic and pharmacodynamic)," and "*Relative efficacy vs 3-dose regimen and rates of treatment failure*." Among healthcare system and healthcare provider-related factors, clinicians wanted to know the cost associated with this regimen, including staff time and equipment (57.1%; n=4). The clinicians expressed the need to know about the "*Efficacy, timing, cost, and accessibility… Time required and equipment required*," and "*Is it more difficult or time-consuming for staff?*" The clinicians highlighted they would like to know if the new treatment is acceptable or tolerated by the patients. Quotes included "*Treatment outcomes and patient acceptance*," and "*Efficacy, safety, tolerability*."

Table 6. Information clinicians want on single-dose BPG treatment regimen for late latent syphilis treatment

Peh's dimension	Factors and examples	Information wanted by physicians [Codes of phrases]	n (%)*
Medications	Medication effects (i.e., side effects, safety, efficacy, benefits, patient experience)	Efficacy and effectiveness Safety and side-effects Patient experience	22 (45.8) 8 (16.7) 3 (6.3)
	Medication regimen (i.e., complexity, dosage, type, pill burden, interference in routine, clarity of instructions on label, regimen familiarity)	How to administer the infusion Compliance or adherence Dosage	6 (12.5) 1 (2.1) 1 (2.1)
	Other	Need more evidence (not specified) Anything	6 (12.5) 1 (2.1)
Healthcare system and healthcare providers	Healthcare system-related factors (i.e., access, provider continuity, cost, drug supply, regulation processes, quality of	Cost (staff time and equipment) Equipment for infusion Guidelines for treatment Access to health care (structural barriers)	4 (57.1) 1 (14.3) 1 (14.3) 1 (14.3)

Peh's dimension	Factors and examples	Information wanted by physicians [Codes of phrases]	n (%)*
	health services, information support, insurance coverage)		
Patients	Cognitive and psychological factors (i.e., perceptions, beliefs, concerns, knowledge/ health literacy, emotions, motivation/ goals)	Acceptability and tolerability	6 (100.0)

Total number of clinicians who responded to this question (n=34);

*n = the number of phrases coded within each dimension; % = the proportion of each code within each dimension.

Considerations for successful implementation of a single-dose BPG regimen

Factors recommended by the clinicians to be considered for the successful implementation of a single-dose BPG regimen crossed three of Peh's dimensions (medications, healthcare system/ healthcare providers, and patients) (Table 8). Among the medication-related factors, the clinicians mostly recommended considering the feasibility of SC infusions in the outpatient setting and the transportability of the medicine (42.9%; n=3). Among the healthcare system and healthcare provider-related factors, clinicians suggested that cost (37.3%; n=19) and training (35.3%; n=18) should be considered to ensure the successful implementation of a new treatment regimen. It was also highlighted that there needs to be consideration of costs related to equipment, medication, medication storage, procedure rooms, and staff time spent on preparation, infusions, and observations. The clinicians explained that implementation required considerations regarding "*cost and storage of antibiotic and delivery equipment. Time required for the procedure,*" as well as "*time and staffing - as I understand it the treatment itself* [one dose] *takes about 20 minutes during which time I imagine the patient must be continuously monitored*." Another clinician indicated the need for "*sufficient resources (treatment room, nursing, etcetera).*" The

clinicians reported that training should be delivered on infusion administration, along with the safety, efficacy, and effectiveness of the new one-dose regimen and pre-infusion counselling for patients.

Table 7. Factors to be considered for successful implementation of a single-dose BPG regimen for late latent syphilis treatment

Peh's dimensions	Factors and examples	Factors to be considered [Codes of phrases]	n (%)*
Medications	Medication effects (i.e., side effects, safety, efficacy, benefits, patient experience)	Side-effects	1 (14.3)
	Medication regimen (i.e., complexity, dosage, type, pill burden, interference in routine, clarity of instructions on label, regimen familiarity)	Complexity of treatment Dosage	3 (42.9) 1 (14.3)
	Other	Need more evidence (not specified)	2 (28.6)
Healthcare system and healthcare providers	Healthcare system-related factors (i.e., access, provider continuity, cost, drug supply, regulation processes, quality of health services, information support, insurance coverage)	Cost (staff time, equipment, procedure room, and drug storage) Drug supply/availability Guidelines for treatment Access to health care (structural barriers)	19 (37.3) 7 (13.7) 6 (11.8) 1 (2.0)
	Healthcare provider characteristics (i.e., relationship, communication, trust in provider, clinical care, ability to relate, provision of training/ follow-up,	Training (efficacy and safety, pre-infusion counselling, how to administer the infusion, how to monitor the infusion)	18 (35.3)

Peh's dimensions	Factors and examples	Factors to be considered [Codes of phrases]	n (%)*
	prescription practice, patient education)		
Patients	Cognitive and psychological factors (i.e., perceptions, beliefs, concerns, knowledge/ health literacy, emotions, motivation/ goals)	Acceptability and tolerability	2 (66.7)
	Priorities (i.e., quality of life, other competitive needs)	Priorities or competing needs	1 (33.3)

Total number of clinicians who responded to this question (n=34);
* n = the number of phrases coded within each dimension; % = the proportion of each code within each dimension.

Preferred methods for learning about the new single-dose BPG regimen

More than two-thirds (65.7%; n=23) of clinicians preferred online and on-demand training to learn about a new single-dose BPG regimen, while print sources were the least preferred learning method (20.0%; n=7) (Table 7). One clinician mentioned that the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) webinars and STI guidelines website were their preferred learning method.

Table 8. Preferred learning methods for the new single-dose late latent syphilis treatment

	n (%)
Online, on-demand training	23 (65.7)
Live webinars	8 (22.9)
Face-to-face workshops	8 (22.9)
Print sources	7 (20.0)
Other	1 (2.9)

(n=35); Proportions do not add up to 100% because this is a multiple-answer option question

Discussion

This study explored factors influencing non-completion of the three-dose BPG regimen for late latent syphilis treatment with Australian sexual health clinicians. Reasons clinicians would support a one-dose BPG regimen and requirements for successful implementation were also examined.

Clinicians reported that less than half of the late latent syphilis patients they had treated in the last two years had completed the full course of the three-dose BPG regimen. This finding is not unusual as treatment completion rates in previous studies for three-dose BPG have been shown to be low. For example, in a United States (US) study reported treatment completion rate for late latent syphilis was 37.3% (n=2,003) when calculated with one-week intervals between the first and second dose and between the second and third dose, while the rate was 44.7% (n=2,402) for 7 to 14-day intervals.[8] Similarly, in a review of the completion of a three-dose BPG regimen among 186 pregnant women in South Africa reported that 64.8% (n=122) completed a three-dose BPG treatment course.[20] Among these women, almost half (49%) received the second dose more than one week after the first dose and just over one-quarter (28%) received the third dose more than one week after the second dose[20], clearly showing treatment attrition stemming from the extended regimen length and strict dosing intervals. This treatment attrition over time has also been seen in a small study conducted in Queensland, Australia, with 18 pregnant women with late latent syphilis.[9] In this study, just over three quarters (78%; n=14) completed the full treatment and the dosing intervals exceeded seven days for three of the women.[9] Currently ASHM recommends 2.4 MU of BPG given as two injections containing 1.2 MU weekly for 3 weeks, for late latent syphilis,[7] a treatment regimen that although evidence informed, may inhibit treatment completion. The high proportion of patients who do not complete the three-dose regimen suggests the need for alternative regimens to improve treatment completion rates.

Overall, the majority of clinicians deemed *'Limited patient understanding of the importance of treatment compliance'* and *'Pain associated with injections'* as the main factors that negatively impacted treatment completion for the current three-dose BPG treatment regimen. Similar findings have also been reported in previous studies. Nurses interviewed in

a Brazilian study, stated that a lack of knowledge about syphilis among patients led to the refusal of screening, treatment, follow-up, and partner treatment.[22] Another small qualitative Brazilian study also with nurses reported that pain among pregnant women with syphilis from the IM BPG injection was another factor limiting the completion of the three-dose treatment regimen.[23] Recognising the adverse impact of pain, modifications in IM BPG administration have been studied to determine if variations in administering processes can reduce pain. This has included, the use of different needle sizes and co-administration of BPG along with local anaesthetics;[24] and the use of cold needle (0 – 2 degree Celsius).[25] Combined factors that can negatively impact treatment completion, could potentially be addressed through the introduction of a single-dose BPG regimen, if the evidence supports the bioequivalence.

The majority of clinicians (94.3%; n=33) reported that they would support a single-dose BPG regimen, if it was supported by evidence. Clinicians stated that this single-dose approach could improve patient compliance and treatment completion by reducing patient time commitment, pain and costs, as well as providing a more convenient treatment regimen to the patient. Financial challenges have been reported as hindering syphilis treatment, as reported in relatively small studies with pregnant women in Cambodia[26] and the US.[27]

Clinicians in this study indicated that if a one-dose regimen was supported by evidence and then implemented, it would be less demanding on medical staff and other hospital and clinical resources. However, the clinicians stated that for the implementation of this single-dose treatment approach to be successful, there would also need to be consideration of financial costs related to staff capacity and expertise, equipment, transport and storage requirements, medication supplies, and the availability of documented updated treatment guidelines. Clinicians indicated the need for adequate and appropriate online and on-demand clinical treatment training, to equip them with the knowledge and skills to better inform patients and enhance patient compliance and treatment completion.

The strengths of the current study were that the responding clinicians had recent experience of late latent syphilis treatment and involved clinicians from health facilities that either specialised or did not specialise in STI treatment. The qualitative component of the

study provided the clinicians with an opportunity to express their opinions which increased our insights into this issue, serving as a foundation for future studies. A limitation of the current study was the low number of clinicians recruited; however, consistency between participant responses was high, indicating that the findings may not have changed significantly if the sample size increased. Clinicians' responses to some open-response questions were unclear, making understanding and analysing some responses difficult.

Conclusions

This study assessed clinicians' perspectives of the current three-dose BPG regimen and the under-trial single high-dose BPG regimen for late latent syphilis treatment. The clinicians nominated a range of barriers to completion of the current three-dose BPG regimen, which included limited understanding of treatment by patients, inflexibility in treatment dosing, and pain from the IM injection. The majority of clinicians reported that they would support a single-dose BPG regimen, if this regimen was supported by evidence, as they saw this approach as a way to improve treatment completion. To support the successful implementation of the one-dose treatment regimen, the clinicians called for both online and on-demand clinical training and consideration of costs related to staff capacity and expertise, equipment, transport and storage requirements of the medication, adequate medication supplies, and documented updated treatment guidelines.

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Appendix A. Questionnaire

This online questionnaire aims to identify barriers to and enablers of late latent syphilis treatment completion under the current three-dose benzathine penicillin G (BPG) regimen (link: https://www.health.wa.gov.au/Silver-book/Notifiable-infections/Syphilis).

It also seeks to identify training needs and service resource implications associated with a potential alternative treatment regimen that is currently the subject of a clinical trial led by Professor Laurens Manning – namely, a single, high dose subcutaneous infusion of benzathine penicillin G for treatment of syphilis (The SCIP Syphilis Program).

It is anticipated that these findings will be used to support health services and interventions to improve treatment completion.

This questionnaire will take 10-15 minutes of your time to complete. You have been asked to take part as you are a clinician with experience treating patients with syphilis in Western Australia.
Responses are anonymous. No one, not even the research team will be able to identify your information.
The project is being conducted by Professor Jonine Jancey, Dr Daniel Vujcich, Professor Richard Norman, Dr Rochelle Tobin and Dr Nang Nge Nge Phoo through the Western Australian Sexual Health and Blood-borne Virus Applied Research and Evaluation Network (SiREN) and the School of Population Health, Curtin University.

The information statement here (link) contains detailed information on this study. If you have any queries, you can contact Professor Jonine Jancey via phone 08 9266 3807 (office) or email: j.jancey@curtin.edu.au.

Consent

Please review the following statements and indicate if you do, or do not, consent to participate in this study.

- I have read the information statement described above and I understand its contents.
- I believe I understand the purpose, extent and possible risks of my involvement in this project.
- I voluntarily consent to take part in this research project.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I understand that this project has been approved by Curtin University Human Research Ethics Committee and will be carried out in line with the National Statement on Ethical Conduct in Human Research (2007).
- I understand I will receive a copy of this Information Statement and Consent Form.

☐ I have received information regarding this research and had an opportunity to ask questions. I believe I understand the purpose, extent and possible risks of my

involvement in this project and I voluntarily consent to take part.

☐ I do not consent to take part in this study.

Questions

1) Are you a clinician currently working in Western Australia?
    - Yes
    - No

    Logic: If no– End the survey and display *"Only clinicians practising in Australia are eligible to complete this survey. We thank you for your time."*

2) How many patients with late or unknown duration syphilis do you estimate that you have **commenced** on a 3-dose benzathine penicillin G regimen in the past 2 years?
    - 0
    - 1-5
    - 6-10
    - 11-15
    - 16-20
    - 21-25
    - 26-30
    - More than 30 (open text: Please provide a number estimate)

    Logic: If 0 – End survey and display *"Only clinicians with recent experience with late or unknown duration syphilis treatment are required to complete this survey. We thank you for your time."*

3) Which of the following best describes your primary place of employment?
    - Private general practice
    - Hospital
    - Specialist sexual health clinic

4) Thinking about your patients with late or unknown-duration syphilis who commenced a 3-dose benzathine penicillin G regimen in the last 2 years, what percentage do you estimate **completed** all 3 doses of benzathine penicillin G?
    - None of my patients with late or unknown-duration syphilis have completed all 3 doses of benzathine penicillin G
    - 1-20%
    - 21-40%
    - 41-60%
    - 61-80%
    - 80-99%
    - All of my patients with late or unknown-duration syphilis have completed all 3 doses of benzathine penicillin G

Logic: If All of my patients– display the following question:
4a) Over the course of your career, have you ever had experience with patients commencing but not completing a 3-dose benzathine penicillin G regimen for treatment of late or unknown duration syphilis?

- Yes
- No
- I can't recall

Logic: If No/I can't recall– Skip to Q 7.

The following section asks questions about barriers to patients with late or unknown-duration syphilis to complete the three-dose BPG regimen.

When answering the questions please think about your patients who have commenced but not completed a 3-dose benzathine penicillin G regimen for treatment of late or unknown duration syphilis.

5) Please indicate the degree to which you believe that each of the following factors have reduced treatment completion rates among your patient sample.

	No effect	Minor effect	Moderate effect	Major effect	I don't know
Pain associated with injections					
Lack of flexibility in treatment dosing					
Treatment side-effects					
Allergic reaction to treatment					
Lack of staff knowledge of appropriate syphilis treatment					
Lack of staff knowledge of appropriate follow-up processes					
Inadequate hospital/clinic follow-up systems					
Limited time available for staff to undertake follow-up					
Inadequate supply of BPG					
Limited patient understanding of the importance of treatment compliance					
Incomplete patient medical records e.g., contact information or treatment history					
Inadequate antenatal care					

(including late initiation)					
Service wait times					
Treatment costs					
Patient required to undertake spinal puncture and staging					
Patient comorbidities					
Competing demands on patient time					
Lack of support from patients' partners					
Patients' past experiences of syphilis and syphilis treatment					
Patients do not accept syphilis diagnosis					
Lack of patient trust					
Instability in patients' life circumstances					
Patients' inability to access services due to transport barriers					

6) Are there any **other factors** that you think have had an impact on the proportion of your patients who have completed a 3-dose benzathine penicillin G regimen for treatment of late or unknown duration syphilis?
   - Yes (please describe)
   - No

Emerging research suggests that a single dose of 7.2 MU Bicillin® L-A administered by a subcutaneous infusion (lasting 10 minutes) in adults for treatment of non-*central nervous* system (CNS) syphilis infections is as effective as the current recommended treatment of three consecutive weekly intramuscular 2.4MU injections.

7) Which of the following statements best describes your current attitude to the possibility of

a single-dose treatment option for non-CNS syphilis infections?
   - I do not think a new treatment regimen is necessary (open text: Please provide your reasons)
   - I do not think a new treatment regimen would be practical (open text: Please provide your reasons)
   - I would support the introduction of a new treatment regimen if it was supported by evidence (open text: Please provide your reasons)
   - I require more information to inform my attitude to a new treatment regimen

8) What information would you like to know about this single-dose treatment option for non-CNS syphilis infections in adults? [Open text]

9) If a single-dose treatment option for non-CNS syphilis infections in adults was made available, what would be your preferred method for learning about it?

- Print resources
- Online, on-demand training
- Live webinars
- Face-to-face workshops
- Other (please specify)

10) Thinking about the clinical context in which you work, what factors would need to be considered to support the successful implementation of a single-dose treatment option for non-CNS syphilis infections in adults? [Open text]

"Thank you for completing this survey. If you would like to comment further please contact Dr Nang Nge Nge Phoo at nangngenge.phoo @curtin.edu.au"