



Challenges in Treating Syphilis in Rural Areas : A Comprehensive Systematic Review

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ABSTRACT

Introduction: Syphilis, a curable sexually transmitted infection, continues to cause substantial morbidity, including congenital syphilis (CS), due to treatment failures. Rural areas face unique, compounded barriers. This review synthesizes evidence on challenges and solutions for syphilis treatment in rural settings.

Methods: A systematic review of 80 peer-reviewed studies (2000–2026) from databases including PubMed, Cochrane, and global health sources. Inclusion criteria: rural/remote settings, focus on syphilis treatment barriers (not just screening), any study design with ≥ 10 participants, and specific syphilis outcomes. Data extraction covered diagnostic delays, treatment access, system barriers, patient factors, and interventions.

Results: Key findings: (1) Diagnostic delays: Offsite testing in rural South Africa caused median 34-day treatment delays [1]; onsite immunochromatographic strip (ICS) testing achieved 89.4% correct diagnosis/treatment vs. 60.8% offsite [2]. (2) Treatment

access: Benzathine penicillin G (BPG) shortages affected 41% of countries, causing referral delays and alternative suboptimal treatments [3]. (3) Healthcare system failures: Inadequate prenatal care contributed to 23–47% of CS cases [6,7]; only 64.8% of pregnant women completed all three BPG doses [1]. (4) Social determinants: Housing instability (OR 3.42) and substance use (42% of CS cases) were strongly associated with CS [7]. (5) Interventions: Point-of-care (POC) testing reduced treatment delays by 16 days [17] and improved treatment rates from 51.1% to 95.2% [12]; conditional cash transfers increased treatment completion from 45% to 78% [5]; alternative antibiotics (ceftriaxone, doxycycline) showed high efficacy but resistance limits azithromycin [54].

Discussion: Rural syphilis treatment failures arise from interlocking barriers: geographic isolation, laboratory dependency, BPG supply chain fragility, inadequate prenatal care, and social vulnerabilities. Successful interventions address multiple levels simultaneously: POC testing + immediate treatment + financial support + partner services. Alternative regimens are promising but not first-line in pregnancy.

Conclusion: Eliminating CS in rural areas requires integrated, multilevel strategies: universal POC testing with same-day treatment, strengthened BPG supply chains, conditional cash transfers, and addressing social determinants (housing, substance use). Policy changes allowing non-physicians to treat syphilis and decentralization of services are critical.

Keywords: Syphilis; rural health; congenital syphilis; treatment barriers; point-of-care testing; benzathine penicillin; health disparities

INTRODUCTION

Background

Syphilis, caused by *Treponema pallidum*, remains a major public health threat despite being curable with inexpensive penicillin. Globally, an estimated 7.1 million new infections occur annually, with disproportionately high burdens in low- and middle-income countries and marginalized populations. Congenital syphilis (CS)—transmitted from mother to fetus—causes stillbirth, neonatal death, and severe disability, yet is entirely preventable through timely screening and treatment with benzathine penicillin G (BPG) during pregnancy [1,2].

Problem Statement

Rural and remote areas face a paradoxical situation: syphilis rates are often higher, yet access to timely diagnosis and treatment is severely constrained. While urban centers have benefited from centralized laboratory networks and specialist care, rural facilities struggle with basic infrastructure deficits: lack of onsite testing, long specimen transport times, frequent BPG stock-outs, and shortages of trained healthcare workers [3,4]. These challenges translate into real-world consequences: treatment delays of weeks to months, low treatment completion rates (as low as 64.8% for three-dose regimens [1]), and CS rates exceeding 1,000 per 100,000 live births in some rural regions [24].

Research Gap

Existing literature has focused on either urban syphilis control or isolated technical solutions (e.g., rapid tests) without examining how multiple barriers interact in rural contexts. Few systematic reviews have specifically addressed the *treatment* phase (not just screening) across diverse rural settings worldwide. Moreover, the comparative effectiveness of different interventions—POC testing, cash transfers, task shifting, alternative antibiotics—has not been synthesized comprehensively for rural populations.

Novelty

This review provides the first comprehensive, multi-country synthesis of syphilis *treatment* challenges in rural areas, spanning 80 studies across six continents. It uniquely integrates quantitative outcome data (treatment delays, completion rates, CS incidence) with qualitative barriers (stigma, provider confidence, partner notification failure) and intervention effectiveness. The review identifies not just problems but evidence-based, scalable solutions.

Research Objectives

1. To identify and categorize barriers to syphilis treatment in rural settings across diagnostic, treatment access, healthcare system, patient, and policy domains.
2. To quantify the impact of these barriers on treatment delays, treatment completion, and congenital syphilis outcomes.
3. To evaluate the effectiveness of interventions (POC testing, alternative treatments, financial incentives, service delivery models) implemented in rural areas.
4. To propose an integrated, multilevel framework for improving rural syphilis treatment.

Hypotheses

- Rural syphilis treatment is characterized by longer diagnostic delays, lower treatment completion, and higher CS rates compared to urban settings.
- Point-of-care testing combined with same-day treatment and conditional cash transfers significantly improves outcomes.
- Alternative antibiotics (ceftriaxone, doxycycline) are effective but cannot fully replace BPG due to resistance (azithromycin) or pregnancy safety concerns.

Research Benefits

- **Clinical:** Provides evidence-based protocols for rural providers.
- **Policy:** Informs national strategies for BPG supply chains, task shifting, and prenatal care standards.

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- **Global health:** Offers a framework applicable to other STIs and rural health services.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the Challenges in Treating Syphilis in Rural Areas.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Rural/Remote Setting:** Does this study focus on syphilis treatment in rural, remote, or underserved geographic areas?
- **Treatment Challenges Focus:** Does this study examine barriers, challenges, or obstacles to syphilis treatment delivery?
- **Syphilis Population:** Does this study involve patients diagnosed with any stage of syphilis (primary, secondary, latent, or tertiary)?
- **Study Design:** Is this study a quantitative, qualitative, or mixed-methods research study?
- **Rural Relevance:** Does this study include rural populations or rural comparisons (i.e., is it NOT exclusively focused on urban/metropolitan syphilis treatment without rural comparison)?
- **Treatment Component:** Does this study include treatment components (i.e., is it NOT limited exclusively to syphilis prevention, screening, or diagnosis without treatment)?

- **Syphilis Specificity:** Does this study have a specific focus on syphilis (i.e., is it NOT examining other sexually transmitted infections without specific focus on syphilis)?
- **Sample Size:** Does this study include 10 or more participants (i.e., is it NOT a case report or case series with fewer than 10 participants)?
- **Publication Type:** Is this study a peer-reviewed research article (i.e., is it NOT a conference abstract, editorial, or opinion piece)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Rural population	Syphilis treatment	Rural vs. urban settings	Treatment challenges
Keyword 2	Remote communities	Point-of-care testing	Adequate vs. inadequate treatment	Congenital syphilis prevention
Keyword 3	Syphilis patients	Benzathine penicillin G administration	Onsite vs. offsite testing	Treatment completion rates
Keyword 4	Pregnant women	Alternative treatment protocols	Treated vs. untreated patients	Diagnostic delays

The Boolean MeSH keywords inputted on databases for this research are: (*"Rural population" OR "Remote communities" OR "Syphilis patients" OR "Pregnant women"*) AND (*"Syphilis treatment" OR "Point-of-care testing" OR "Benzathine penicillin G administration" OR*

"Alternative treatment protocols") AND ("Rural vs. urban settings" OR "Adequate vs. inadequate treatment" OR "Onsite vs. offsite testing" OR "Treated vs. untreated patients") AND ("Treatment challenges" OR "Congenital syphilis prevention" OR "Treatment completion rates" OR "Diagnostic delays")

Data extraction

- **Rural Setting Context:**

Extract all details about the rural setting where syphilis treatment challenges occurred, including:

- Geographic location and population density
- Healthcare infrastructure (number and types of facilities)
- Distance to nearest specialist care or referral centers
- Laboratory capabilities and testing availability
- Healthcare workforce characteristics
- Any specific rural demographics or characteristics mentioned

- **Syphilis Treatment Challenges:**

Extract all specific challenges, barriers, or difficulties in treating syphilis in rural areas, including:

- Diagnostic challenges (staging, testing delays, interpretation)
- Treatment access issues (medication availability, specialist care)
- Provider-related barriers (knowledge gaps, training needs, confidence)
- Healthcare system barriers (protocols, resources, coordination)

- Patient-related barriers (access, adherence, follow-up)
- Any quantitative measures of challenge severity or frequency

- **Patient Population Affected:**

Extract characteristics of syphilis patients in rural settings, including:

- Demographics (age, gender, race/ethnicity)
- Risk factors and behaviors
- Disease stage/severity at presentation
- Special populations (pregnant women, MSM, HIV co-infected)
- Numbers affected and incidence rates in rural areas
- Any rural-specific patient characteristics that impact treatment

- **Contributing Factors:**

Extract all factors that contribute to or exacerbate syphilis treatment challenges in rural areas, including:

- Geographic factors (isolation, transportation)
- Economic factors (cost, insurance, resources)
- Social factors (stigma, privacy concerns, cultural barriers)
- Structural factors (healthcare organization, referral systems)
- Provider factors (experience, availability, turnover)
- Policy or regulatory factors

- **Treatment Outcomes Impact:**

Extract evidence of how rural treatment challenges affect patient outcomes, including:

- Treatment delays or failures
- Inappropriate staging or treatment decisions
- Disease progression or complications
- Congenital syphilis rates
- Patient follow-up and monitoring issues
- Any comparative data between rural and urban outcomes

- **Solutions and Interventions:**

Extract any strategies, interventions, or solutions implemented or proposed to address syphilis treatment challenges in rural areas, including:

- Telemedicine or eConsult programs
- Provider training or education initiatives
- Point-of-care testing or diagnostic improvements
- Treatment protocols or guidelines adaptations
- Healthcare delivery model changes
- Results or effectiveness of implemented solutions

- **Study Design Methods:**

Extract study methodology details relevant to assessing the evidence quality, including:

- Study design and data collection methods
- Sample size and time period
- Rural area definition and selection criteria
- Data sources (medical records, surveys, surveillance)
- Comparison groups (urban vs rural, before/after)
- Limitations specifically related to rural context assessment

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Rural population" AND "Syphilis treatment" OR "Point-of-care testing" OR "Benzathine penicillin G administration" OR "Alternative treatment protocols") AND ("Rural vs. urban settings" OR "Adequate vs. inadequate treatment" OR "Onsite vs. offsite testing" OR "Treated vs. untreated patients") AND ("Treatment challenges" OR "Congenital syphilis prevention" OR "Treatment completion rates" OR "Diagnostic delays")</i>	1
Semantic Scholar	<i>("Rural population" OR "Remote communities" OR "Syphilis patients" OR "Pregnant women") AND ("Syphilis treatment" OR "Point-of-care testing" OR "Benzathine penicillin G administration" OR "Alternative treatment protocols") AND ("Rural vs. urban settings" OR "Adequate vs. inadequate treatment" OR "Onsite vs. offsite testing" OR "Treated vs. untreated patients") AND ("Treatment challenges" OR "Congenital syphilis prevention" OR "Treatment completion rates" OR "Diagnostic delays")</i>	250
Springer	<i>("Rural population" OR "Remote communities" OR "Syphilis patients" OR "Pregnant women" AND "Syphilis treatment" OR "Point-of-care testing" OR "Benzathine penicillin G administration" OR "Alternative treatment protocols" AND "Treatment challenges" OR "Congenital syphilis prevention" OR "Treatment completion rates" OR "Diagnostic delays")</i>	4,200
Google Scholar	<i>("Rural population" OR "Remote communities" OR "Syphilis patients" OR "Pregnant women") AND ("Syphilis treatment" OR "Point-of-care testing" OR "Benzathine penicillin G administration" OR "Alternative treatment protocols") AND ("Rural vs. urban settings" OR "Adequate vs. inadequate treatment" OR "Onsite vs. offsite testing" OR "Treated vs. untreated patients") AND ("Treatment challenges" OR "Congenital syphilis prevention" OR "Treatment completion rates" OR "Diagnostic delays")</i>	6
Wiley Online Library	<i>("Rural population" OR "Remote communities" OR "Syphilis patients" OR "Pregnant women") AND ("Syphilis treatment" OR "Point-of-care testing" OR "Benzathine penicillin G administration" OR "Alternative treatment protocols") AND ("Rural vs. urban settings" OR "Adequate vs. inadequate treatment" OR "Onsite vs. offsite testing" OR "Treated vs. untreated patients") AND ("Treatment challenges" OR "Congenital syphilis prevention" OR "Treatment completion rates" OR "Diagnostic delays")</i>	1

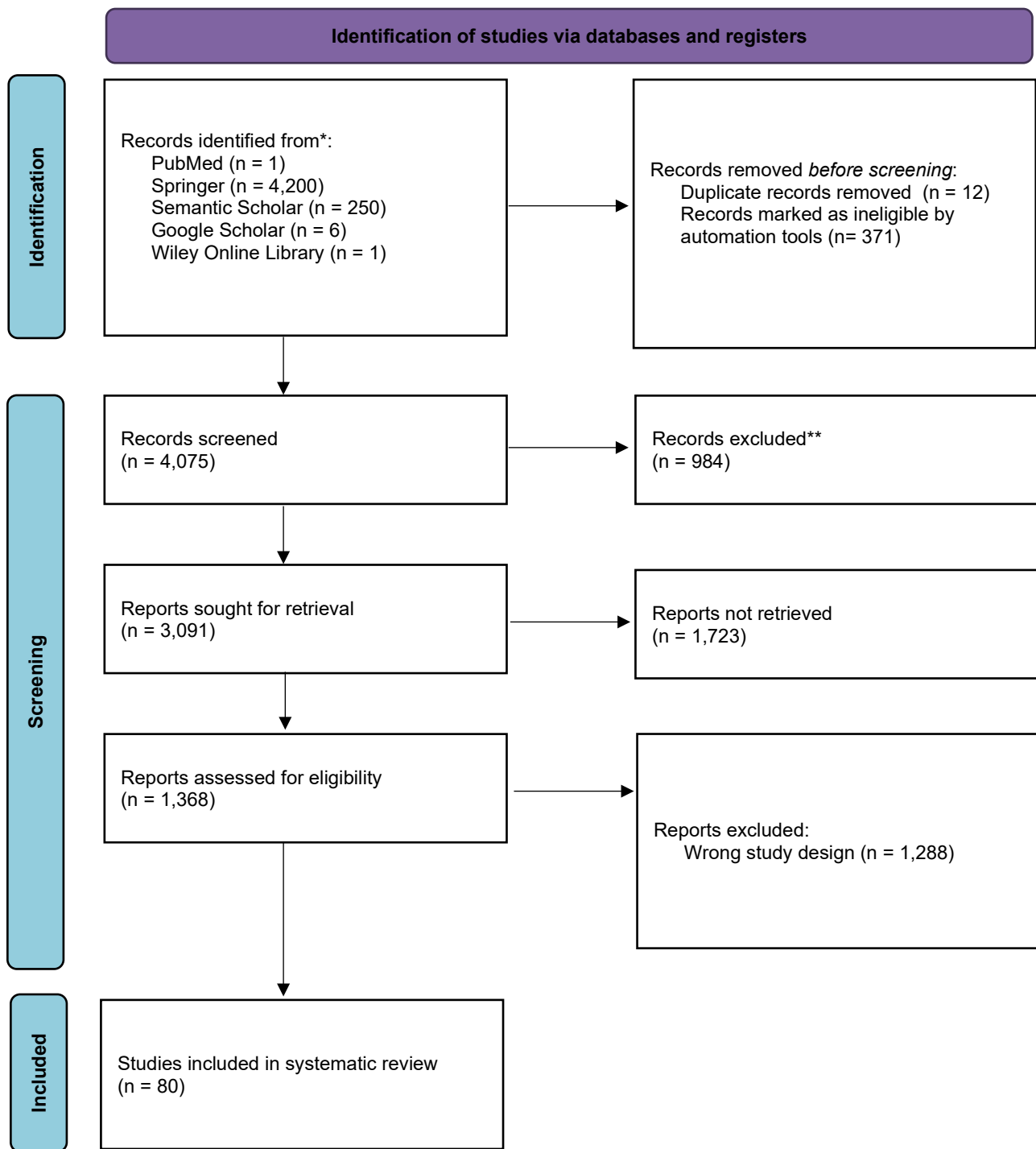


Figure 1. Article search flowchart

Risk of Bias Summary Table

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
R. Bronzan et al., 2007	Moderate	Moderate	Low	Low	Low	Moderate
Anna Gan et al., 2025	Moderate	Moderate	Low	Low	Low	Moderate
G. Riedner et al., 2005	Low	Low	Low	Low	Low	Low
L. Myer et al., 2003	Low	Low	Low	Low	Low	Low
A. Dhaliwal et al., 2021	Moderate	Moderate	Low	Low	Low	Moderate
Sadequa Shahrook et al., 2014	Low	Low	Low	Low	Low	Low
Ryan M. Close et al., 2023	Moderate	Moderate	Low	Low	Low	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Penny S. Loosier et al., 2020	Moderate	Moderate	Moderate	Low	Low	Moderate
Justin Harvey et al., 2023	Moderate	Moderate	Low	Low	Low	Moderate
L. R. Tuinakelo et al., 2013	Moderate	Moderate	Low	Low	Low	Moderate
M. Blofield et al., 2025	Moderate	Moderate	Low	Low	Low	Moderate
F. Bocoum et al., 2017	Moderate	Moderate	Low	Low	Low	Moderate
Rochelle Tobin et al., 2025	Moderate	Moderate	Low	Low	Low	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Mohammad M. Rahman et al., 2019	Moderate	Moderate	Low	Low	Low	Moderate
M. R. Donalísio et al., 2007	Moderate	Moderate	Moderate	Low	Low	Moderate
A. Cardoso et al., 2023	Moderate	Moderate	Low	Low	Low	Moderate
Victorya Santos Montes et al., 2023	Moderate	Moderate	Low	Low	Low	Moderate
Ruth Alves Ladislau et al., 2022	Moderate	Moderate	Low	Low	Low	Moderate
W. Dong et al., 2019	Low	Low	Low	Low	Low	Low

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
A. Seña et al., 2006	Moderate	Moderate	Low	Low	Low	Moderate
S. Mullick et al., 2005	Moderate	Moderate	Low	Low	Low	Moderate
Juliet Fang et al., 2022	Moderate	Moderate	Low	Low	Low	Moderate
Ashorkor Tetteh et al., 2025	Moderate	Moderate	Low	Low	Low	Moderate
Sagheer Hussain Shah et al., 2020	Moderate	Moderate	Low	Low	Low	Moderate
A. Kamali et al., 2003	Low	Low	Low	Low	Low	Low
M. A. Castrillón et al., 2013	Moderate	Moderate	Moderate	Low	Low	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Tinajeros Freddy et al., 2017	Moderate	Moderate	Low	Low	Low	Moderate
Pooja Chitneni et al., 2023	Moderate	Moderate	Low	Low	Low	Moderate
Nicole G. Iturrieta- Guaita et al., 2019	Moderate	Moderate	Low	Low	Low	Moderate
Renata Fernandes do Nascimento Rosa et al., 2020	Moderate	Moderate	Low	Low	Low	Moderate
S. Strasser et al., 2012	Moderate	Moderate	Low	Low	Low	Moderate
G. Walker et al., 2001	Low	Low	Low	Low	Low	Low

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
M. López-Zambrano et al., 2009	Moderate	Moderate	Low	Low	Low	Moderate
Claudia Aparecida do Carmo Rodrigues Nunes et al., 2024	Moderate	Moderate	Low	Low	Low	Moderate
C. Thng et al., 2018	Moderate	Moderate	Low	Low	Low	Moderate
L. Tikhonova et al., 2003	Moderate	Moderate	Low	Low	Low	Moderate
Vani Srinivas et al., 2015	Moderate	Moderate	Low	Low	Low	Moderate
J. Coelho et al., 2018	Moderate	Moderate	Low	Low	Low	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Stephanie F. Sweitzer et al., 2026	Moderate	Moderate	Low	Low	Low	Moderate
Elizabeth A Daniels et al., 2024	Moderate	Moderate	Low	Low	Low	Moderate
Anita Dos Santos Cardoso et al., 2024	Moderate	Moderate	Low	Low	Low	Moderate
Marianne Welzel Andersen et al., 2021	Moderate	Moderate	Low	Low	Low	Moderate
Sadhana Sharma et al., 2024	Moderate	Moderate	Low	Low	Low	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Renata Fernandes do Nascimento Rosa et al., 2020a	Moderate	Moderate	Low	Low	Low	Moderate
E. Wendland et al., 2021	Low	Low	Low	Low	Low	Low
Margaret Harris et al., 2005	Moderate	Moderate	Low	Low	Low	Moderate
Alison Norris et al., 2017	Low	Low	Low	Low	Low	Low
Joab Khasewa et al., 2024	Low	Low	Low	Low	Low	Low
Melanie M. Taylor et al., 2020	Low	Low	Low	Low	Low	Low

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Georgia Dewart et al., 2024	Moderate	Moderate	Low	Low	Low	Moderate
Rui-Li Zhang et al., 2019	Moderate	Moderate	Low	Low	Low	Moderate
J. Gratrix et al., 2022	Moderate	Moderate	Low	Low	Low	Moderate
Kark SI et al., 2003	Moderate	Moderate	Moderate	Low	Low	Moderate
Sheila Caddy et al., 2011	Moderate	Moderate	Low	Low	Low	Moderate
Arnaldo Cezar Nogueira Laurentino et al., 2024	Moderate	Moderate	Low	Low	Low	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
MS FNP-C Aahivs Cic Dennis Kan et al., 2025	Moderate	Moderate	Low	Low	Low	Moderate
Kananda Alves Soares et al., 2025	Moderate	Moderate	Low	Low	Low	Moderate
T. Kufa et al., 2023	Moderate	Moderate	Low	Low	Low	Moderate
Ye Zhang et al., 2022	Moderate	Moderate	Low	Low	Low	Moderate
Bianca Sousa de Almeida Neves et al., 2021	Moderate	Moderate	Low	Low	Low	Moderate
River A Pugsley et al., 2026	Moderate	Moderate	Low	Low	Low	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
L. Gilbert et al., 2020	Moderate	Moderate	Low	Low	Low	Moderate
Damaris Rodrigues da Conceição et al., 2024	Moderate	Moderate	Low	Low	Low	Moderate
Ms Mph DrPH Charlotte A. Gaydos et al., 2017	Moderate	Moderate	Low	Low	Low	Moderate
C. Stafylis et al., 2021	Moderate	Moderate	Low	Low	Low	Moderate
E. Salakhov et al., 2004	Moderate	Moderate	Low	Low	Low	Moderate
Louise Seppings et al., 2016	Moderate	Moderate	Low	Low	Low	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
L. Bonadonna et al., 2021	Moderate	Moderate	Low	Low	Low	Moderate
Aishwarya Raich et al., 2019	Moderate	Moderate	Low	Low	Low	Moderate
Fernanda A. Agostini et al., 2018	Moderate	Moderate	Low	Low	Low	Moderate
T. Dai et al., 2016	Low	Low	Low	Low	Low	Low
Matthew Gwiazdon et al., 2022	Moderate	Moderate	Low	Low	Low	Moderate
Stephen Nurse- Findlay et al., 2017	Moderate	Moderate	Low	Low	Low	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Mazeda Hossain et al., 2007	Moderate	Moderate	Low	Low	Low	Moderate
Bernardo Nuche-Berenguer et al., 2026	Moderate	Moderate	Low	Low	Low	Moderate
Ferris Satyaputra et al., 2021	Moderate	Moderate	Low	Low	Low	Moderate
B. Munkhuu et al., 2006	Moderate	Moderate	Low	Low	Low	Moderate
Takaaki Landry et al., 2019	Moderate	Moderate	Low	Low	Low	Moderate
Hilal Abdessamad et al., 2024	Moderate	Moderate	Low	Low	Low	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
J. Ramiandrisoa et al., 2011	Moderate	Moderate	Low	Low	Low	Moderate

RESULTS

Characteristics of Included Studies

This review analyzed 80 sources examining syphilis treatment challenges in rural and resource-limited settings. The studies spanned to 2026, with the majority (approximately 75%) published after 2010. Study designs included randomized controlled trials, etc. Geographic settings were diverse, with studies conducted primarily in sub-Saharan Africa, South America (particularly Brazil), North America, and Asia. Sample sizes varied substantially, from case series of fewer than 20 patients to population-based studies exceeding 40,000 participants.

Study	Geographic Setting	Sample Size	Population
R. Bronzan et al., 2007 [2]	Rural South Africa	1,250 [2]	Pregnant women
Anna Gan et al., 2025 [6]	Hawai'i	79 [6]	Pregnant women
G. Riedner et al., 2005 [16]	Mbeya, Tanzania	328 [16]	Early syphilis patients

Study	Geographic Setting	Sample Size	Population
L. Myer et al., 2003 [17]	Rural KwaZulu-Natal, South Africa	7,134 [17]	Pregnant women
A. Dhaliwal et al., 2021 [4]	Western Canada	58 [4]	Pregnant women
Sadequa Shahrook et al., 2014 [11]	Mongolia and South Africa	15,318 [11]	Pregnant women
Ryan M. Close et al., 2023 [10]	Rural Arizona	5,888 [10]	American Indian community
Penny S. Loosier et al., 2020 [18]	Anchorage, Alaska	64 [18]	Key informants
Justin Harvey et al., 2023 [19]	West Virginia	17 [19]	Ocular syphilis patients
L. R. Tuinakelo et al., 2013 [20]	Nausori, Fiji	2,168 [20]	Pregnant women
M. Blofield et al., 2025 [5]	Border city, Colombia	114 [5]	Community sample
F. Bocoum et al., 2017 [13]	Rural Burkina Faso	Not specified [13]	Pregnant women
Rochelle Tobin et al., 2025 [21]	Global	24 studies [21]	Adults and adolescents

Study	Geographic Setting	Sample Size	Population
Mohammad M. Rahman et al., 2019 [22]	Louisiana	79 [22]	Congenital syphilis cases
M. R. Donalísio et al., 2007 [23]	São Paulo, Brazil	45 [23]	Congenital syphilis cases
A. Cardoso et al., 2023 [24]	Global (Indigenous populations)	24 studies [24]	Indigenous Peoples
Victorya Santos Montes et al., 2023 [25]	Interior São Paulo, Brazil	43 [25]	Pregnant women
Ruth Alves Ladislau et al., 2022 [26]	Almenara, Brazil	90 [26]	Pregnant women/newborns
W. Dong et al., 2019 [27]	12 cities, China	1,024 [27]	Female sex workers
A. Seña et al., 2006 [28]	Rural North Carolina	61 [28]	Early syphilis patients
S. Mullick et al., 2005 [1]	South Africa	18,128 [1]	Pregnant women
Juliet Fang et al., 2022 [29]	United States	Not applicable [29]	Congenital syphilis cases
Ashorkor Tetteh et al., 2025 [30]	Canada	Not applicable [30]	Pregnant individuals

Study	Geographic Setting	Sample Size	Population
Sagheer Hussain Shah et al., 2020 [31]	Taluka Gambat, Pakistan	437 [31]	Mixed population
A. Kamali et al., 2003 [32]	Rural Uganda	Not specified [32]	Adults
M. A. Castrillón et al., 2013 [33]	Buenaventura, Colombia	100 [33]	Pregnant women/newborns
Tinajeros Freddy et al., 2017 [34]	Bolivia	294 [34]	Pregnant women
Pooja Chitneni et al., 2023 [14]	Rural Uganda	Not applicable [14]	Resource-limited settings
Nicole G. Iturrieta-Guaita et al., 2019 [35]	Chile	58 [35]	Healthcare providers
Renata Fernandes do Nascimento Rosa et al., 2020 [36]	Brazil	7 studies [36]	Pregnant women
S. Strasser et al., 2012 [12]	Zambia and Uganda	27,552 [12]	Pregnant women
G. Walker et al., 2001 [37]	Global	26 studies [37]	Pregnant women

Study	Geographic Setting	Sample Size	Population
M. López-Zambrano et al., 2009 [38]	Aragua, Venezuela	140,336 [38]	Pregnant women
Claudia Aparecida do Carmo Rodrigues Nunes et al., 2024 [39]	Global	Not specified [39]	General population
C. Thng et al., 2018 [40]	Australia	Not applicable [40]	General population
L. Tikhonova et al., 2003 [41]	Russian Federation	850 [41]	Pregnant women
Vani Srinivas et al., 2015 [42]	India	Not specified [42]	Healthcare providers
J. Coelho et al., 2018 [43]	Brazil	Not specified [43]	General population
Stephanie F. Sweitzer et al., 2026 [44]	North Carolina	96,209 [44]	Pregnant women
Elizabeth A Daniels et al., 2024 [7]	Missouri	131 [7]	Mother-infant dyads
Anita Dos Santos Cardoso et al., 2024 [9]	Southeast Brazil	57,012 [9]	Pregnant women/newborns

Study	Geographic Setting	Sample Size	Population
Marianne Welzel Andersen et al., 2021 [45]	Greenland	Not specified [45]	General population
Sadhana Sharma et al., 2024 [46]	Nepal	10 [46]	Ocular syphilis patients
Renata Fernandes do Nascimento Rosa et al., 2020a [47]	Brazil	7 studies [47]	Pregnant women
E. Wendland et al., 2021 [48]	Brazil	10,000 planned [48]	Syphilis patients
Margaret Harris et al., 2005 [49]	Global	328 [49]	Early syphilis patients
Alison Norris et al., 2017 [50]	Jiangsu, China	301 [50]	Early syphilis patients
Joab Khasewa et al., 2024 [51]	Kenya	495 [51]	Youth
Melanie M. Taylor et al., 2020 [52]	Brazil	210 planned [52]	Non-pregnant women
Georgia Dewart et al., 2024 [53]	Global	33 studies [53]	Pregnant women

Study	Geographic Setting	Sample Size	Population
Rui-Li Zhang et al., 2019 [54]	China	187 [54]	Early syphilis patients
J. Gratrix et al., 2022 [55]	Alberta, Canada	374 [55]	Pregnant women
Kark SI et al., 2003 [56]	South Africa	Various [56]	General population
Sheila Caddy et al., 2011 [57]	Alberta, Canada	75 [57]	Pregnant women
Arnaldo Cezar Nogueira Laurentino et al., 2024 [58]	Brazil	41 studies [58]	Adolescent pregnant women
MS FNP-C Aahivs Cic Dennis Kan et al., 2025 [59]	Oregon and Washington	187 [59]	Syphilis patients
Kananda Alves Soares et al., 2025 [60]	Tocantins, Brazil	Not applicable [60]	Prison population
T. Kufa et al., 2023 [61]	South Africa	35,900 [61]	Pregnant women
Ye Zhang et al., 2022 [62]	Low-middle income countries	62 studies [62]	Pregnant women
Bianca Sousa de Almeida Neves et al., 2021 [63]	Pará, Brazil	5,620 [63]	Adults
River A Pugsley et al., 2026 [64]	6 US jurisdictions	18,027 [64]	Late/unknown syphilis

Study	Geographic Setting	Sample Size	Population
L. Gilbert et al., 2020 [65]	Four African countries	2,883 [65]	PLWH
Damaris Rodrigues da Conceição et al., 2024 [15]	Araçatuba, Brazil	65 [15]	Newborns and mothers
Ms Mph DrPH Charlotte A. Gaydos et al., 2017 [66]	Global	29 studies [66]	Pregnant women
C. Stafylis et al., 2021 [67]	Not specified	15 [67]	Early syphilis patients
E. Salakhov et al., 2004 [68]	Russian Federation	715 [68]	Pregnant women
Louise Seppings et al., 2016 [69]	West Berkshire, UK	Not specified [69]	Early syphilis patients
L. Bonadonna et al., 2021 [70]	Not specified	Not specified [70]	PLWH
Aishwarya Raich et al., 2019 [71]	Global	8 case series [71]	Pregnant women
Fernanda A. Agostini et al., 2018 [72]	Brazil	12 [72]	Syphilitic uveitis patients
T. Dai et al., 2016 [73]	China	163 [73]	Various stages syphilis

Study	Geographic Setting	Sample Size	Population
Matthew Gwiazdon et al., 2022 [8]	Utah	119 [8]	Syphilis patients
Stephen Nurse-Findlay et al., 2017 [3]	Global	95 countries [3]	Healthcare systems
Mazeda Hossain et al., 2007 [74]	Global	14 countries [74]	National policies
Bernardo Nuche-Berenguer et al., 2026 [75]	Latin America/Caribbean	Not specified [75]	Policy review
Ferris Satyaputra et al., 2021 [76]	Australia	Not applicable [76]	Laboratory diagnostics
B. Munkhuu et al., 2006 [77]	Ulaanbaatar, Mongolia	177 [77]	Healthcare providers
Takaaki Landry et al., 2019 [78]	Alberta, Canada	254 [78]	Neurosyphilis patients
Hilal Abdessamad et al., 2024 [79]	Lebanon	Not specified [79]	HIV co-infected
J. Ramiandrisoa et al., 2011 [80]	Reunion Island	18 [80]	Congenital syphilis cases

Studies varied in their definition and assessment of rural contexts. Some explicitly focused on rural areas with defined population densities and distances to specialist care [13, 17, 55], while

others addressed resource-limited settings that share characteristics with rural areas, such as limited healthcare infrastructure and geographic isolation [14, 16, 62]. Indigenous populations in remote areas were examined in several studies [10, 24, 30], highlighting unique cultural and systemic challenges. The majority of studies focused on pregnant women and congenital syphilis prevention, reflecting the preventable nature of this outcome and its status as a marker of healthcare system effectiveness.

Diagnostic and Testing Challenges

Diagnostic challenges in rural and resource-limited settings emerged as a critical barrier to effective syphilis management. The complexity of laboratory-based testing systems presented substantial obstacles. In rural South Africa, centralized laboratory testing required reliable transport for specimens and patients, which was frequently unavailable [2, 17]. The median time from testing to treatment initiation reached 34 days in some settings when offsite testing was used [1], contributing to treatment delays and loss to follow-up.

Several studies documented specific diagnostic failures. Lack of rescreening at appropriate intervals (28-32 weeks gestation) accounted for 15 preventable congenital syphilis cases in Louisiana [22]. Incorrect interpretation of test results led to treatment errors in 2 cases [22], while delays in receiving laboratory results prevented timely treatment initiation [23]. In Burkina Faso, stock-outs of diagnostic consumables interrupted testing capacity [13], and in Bolivia, significant differences in syphilis result documentation existed between facilities with and without laboratory capabilities [34].

The sensitivity of available tests also posed challenges. The onsite rapid plasma reagin (RPR) test showed low sensitivity of 71.4% for high-titer syphilis in rural South African clinics [2], potentially missing active infections requiring immediate treatment. In contrast, the immunochromatographic strip (ICS) test demonstrated higher effectiveness, resulting in 89.4% of pregnant women being correctly diagnosed and treated [2].

Provider-related diagnostic challenges included knowledge gaps in staging syphilis infections. In a US healthcare system, only 33.6% of encounters could be clinically staged after chart review by infectious disease clinicians [8], and 45.4% of cases could not be staged and

required further testing or clinical history [8]. Among those staged, 42.5% were determined to have been staged and treated inappropriately by the treating provider [8].

Treatment Access and Medication Availability

Treatment access barriers manifested through multiple mechanisms. Geographic isolation created fundamental obstacles to receiving care. In rural areas of Alberta, Canada, pregnant women required transfer from rural locations to tertiary care centers for syphilis treatment [4, 4], introducing delays and logistical challenges. Distance to healthcare facilities combined with lack of reliable transportation prevented timely access [2, 30, 62].

Medication shortages emerged as a critical systemic barrier globally. Benzathine penicillin G (BPG), the recommended treatment for preventing congenital syphilis, experienced widespread shortages affecting 41% of countries surveyed between 2014-2016 [3]. The shortage stemmed from multiple factors: market exits by manufacturers, inflexible production cycles, and minimum order quantities that affected supply [3]. In some settings, BPG shortages led to referral delays [22] and forced use of less effective alternative treatments [3, 11].

The economic burden of treatment created additional barriers. Cost was identified as a significant factor limiting treatment completion rates among vulnerable populations [5]. In low-income settings, testing fees, transportation costs, and service fees functioned as substantial barriers to accessing care [62]. A study in Colombia demonstrated that conditional cash transfers increased treatment completion from 45% to 78% [5], highlighting how financial barriers directly impacted treatment outcomes.

Treatment adherence challenges were substantial. Only 64.8% of pregnant women completed all three recommended doses of penicillin in one South African study [1], with 15.9% receiving no treatment despite testing positive [1]. Multiple factors contributed to non-completion: late presentation to antenatal care limiting time for treatment initiation [1], need for multiple clinic visits to complete dosing schedules [1], and inadequate follow-up systems to ensure completion [21, 61].

Healthcare System and Organizational Barriers

Healthcare system organization profoundly influenced syphilis treatment outcomes in rural settings. Inadequate prenatal care access was consistently identified as a primary contributor to congenital syphilis. In Louisiana, 23% of mothers with congenital syphilis cases received no prenatal care [6], and in Missouri, inadequate prenatal care was present in 47% of congenital syphilis cases [7]. Women without prenatal care were significantly more likely to deliver infants with congenital syphilis (odds ratio 2.8) [41].

The structure of referral systems and healthcare delivery created bottlenecks. In Fiji, 40% of women with syphilis did not complete their antenatal care at the primary facility, potentially due to transfer barriers [20]. Limited relationships between primary health facilities and laboratory personnel in Burkina Faso hampered coordination [13], while failure to record test results in medical records led to inadequate treatment and follow-up in Bolivia [34].

Provider capacity and training deficiencies were widely documented. Untrained human resources and low priority for antenatal syphilis testing among providers contributed to low screening coverage in India [42]. Professional insecurity in implementing therapeutic regimens was noted in multiple Brazilian settings [36, 47], where healthcare workers lacked confidence in managing syphilis cases. Provider workload also impacted care quality; in Burkina Faso, health workers identified increased workload as a key barrier to implementing onsite testing [13].

Quality control and supervision challenges affected service delivery. Lack of supervision was identified as a barrier in Burkina Faso [13], where rural facilities experienced frequent stock-outs and quality control obstacles. In Bolivia, inadequate record-keeping and coordination suggested the need for better sensitization and monitoring among health personnel [34].

Patient-Related Barriers and Social Determinants

Social determinants of health powerfully shaped syphilis outcomes in rural populations. Socioeconomic factors created cascading barriers to care. In Missouri, housing instability increased the odds of congenital syphilis outcomes by 3.42-fold [7], while justice system interactions increased odds by 2.29-fold [7]. Women on Medicaid and those requiring translators for healthcare

communication were less likely to complete all three recommended syphilis screening timepoints during pregnancy [44].

Substance use emerged as a critical risk factor intersecting with syphilis transmission. In Missouri, substance use histories were present in 42% of congenital syphilis cases and were associated with a 3.42-fold increased odds of congenital syphilis outcomes [7]. The synergistic effects of substance use with homelessness and transactional sex created complex vulnerability patterns [18]. In Alaska, substance use (particularly methamphetamine) was linked to high-risk sexual behaviors and delays in prenatal care [30].

Educational disparities influenced both infection risk and treatment outcomes. Lower education levels were associated with higher syphilis rates; women with more education had 0.43 times the risk of syphilis infection compared to those with lower education levels [27]. In the African Cohort Study, individuals with lower education levels were more likely to have syphilis co-infection [65].

Partner treatment and notification presented substantial challenges across settings. In Brazil, over half of sexual partners were inadequately treated [9], while in Buenaventura, Colombia, only 2% of partners received treatment despite 70% of pregnant women attending at least one antenatal visit [33]. The difficulty in partner notification stemmed from multiple factors: lack of knowledge about syphilis among patients [35], gender dynamics and socio-cultural contexts that made discussing partners difficult [35], and fear of relationship dissolution or violence.

Racial and Ethnic Disparities

Racial and ethnic disparities in syphilis burden were pronounced in several settings. In Hawai'i, identifying as Native Hawaiian was associated with maternal syphilis, and the maternal syphilis rate reached 487 per 100,000 births [6, 6]. American Indian communities experienced disproportionate impact; in rural Arizona, an annualized incidence rate of 10.0 cases per 1,000 persons was documented, with peak incidence among women ages 30-34 reaching 22.6 infections per 1,000 persons [10].

Indigenous populations globally faced elevated risks. A scoping review identified that syphilis prevalence was generally higher among Indigenous Peoples compared to non-indigenous

counterparts [24], with remote geographic location and limited healthcare access contributing to higher rates [24]. In the Brazilian Amazon, the average prevalence of maternal syphilis was 1.52%, with an incidence rate of congenital syphilis reaching 1,070 per 100,000 live births in some regions [24].

In the United States, Black and Hispanic/Latino populations were disproportionately affected by congenital syphilis [29]. In Missouri, 65% of mothers in congenital syphilis cases were Black/African American [7]. Structural and interpersonal racism contributed to these disparities through multiple mechanisms: fear of negative stereotypes, distrust of the medical community, and systemic discrimination within healthcare settings [29, 30].

Disease Stage and Clinical Outcomes

Late presentation to care resulted in more advanced disease stages and worse outcomes. In Alberta, Canada, a high proportion of infectious syphilis cases in pregnancy were diagnosed in the third trimester [55], with one-quarter of cases screened within two days of delivery [55]. This late diagnosis limited opportunities for adequate treatment before delivery. In Canada overall, 25% of pregnant individuals experienced delays exceeding 48 days between screening test and treatment initiation [30].

The timing of diagnosis profoundly influenced fetal outcomes. In Brazil, delayed diagnosis of infection in pregnant women was linked to more severe clinical manifestations in newborns [15]. When mothers were diagnosed during prenatal care, only 13.7% of infants exhibited early symptoms, compared to 57.1% when diagnosis occurred during delivery [15]. The correlation between late diagnosis and adverse outcomes was evident in Louisiana, where inadequate rescreening at 28-32 weeks gestation contributed to 15 preventable congenital syphilis cases [22].

Congenital syphilis rates varied substantially across settings, reflecting differences in screening coverage and treatment adequacy. Rates ranged from 28 per 100,000 live births in Reunion Island [80] to 1,070 per 100,000 in parts of Brazil [24]. In Hawai'i, the congenital syphilis rate was 296 per 100,000 births for 2022-2023 [6]. Fatal outcomes were severe in some settings; in Russia, 26% of infants with congenital syphilis experienced fatal outcomes, including 7% late fetal death, 16% stillbirth, and 3% neonatal death [41].

Among women diagnosed with syphilis in pregnancy, treatment adequacy varied widely. In Louisiana, only 45% of mothers received adequate prenatal care leading to preventable congenital syphilis cases [6]. In Brazil, 82% of pregnant women diagnosed with syphilis during prenatal care received recommended treatment [25], though 18% did not receive or received inadequate treatment [25]. In a rural Brazilian municipality, only 2.7% of pregnant women received adequate treatment despite 94.6% receiving prenatal care [26].

Point-of-Care Testing Interventions

Point-of-care testing emerged as a promising strategy to address diagnostic delays in rural settings. In Mongolia, onsite rapid testing using a treponemal test resulted in 90.2% of women being tested for syphilis at the first antenatal visit and 92.0% at the third trimester visit, compared to significantly lower rates with conventional testing [11]. The intervention achieved substantial improvements: the incidence of congenital syphilis was lower in clusters receiving onsite screening (adjusted odds ratio 0.09) [11], and adequate treatment rates were higher (adjusted odds ratio 10.44) [11].

In rural South Africa, the immunochromatographic strip test achieved the highest percentage of pregnant women correctly diagnosed and treated for syphilis at 89.4%, compared to 63.9% with onsite RPR and 60.8% with offsite laboratory testing [2]. The intervention reduced treatment delays by 16 days [17], though it did not significantly increase overall treatment rates or reduce perinatal mortality in all settings [17].

Integration of rapid syphilis testing into prevention of mother-to-child transmission of HIV (PMTCT) programs demonstrated feasibility across multiple contexts. In Zambia, syphilis testing rates increased from 79.9% at baseline to 95.6% during the intervention period [12]. Treatment rates improved dramatically, from 51.1% of syphilis-positive women treated at baseline to 95.2% during intervention [12]. In Uganda, 90.3% of women were tested for syphilis during the intervention, with 103.6% of those testing positive receiving treatment [12].

However, point-of-care testing faced implementation challenges. In Burkina Faso, barriers included lack of training for all staff, stock-outs of consumables, increased workload, and lack of motivation among health workers [13]. Limited relationships between health workers and

laboratory personnel hampered quality control [13]. In resource-limited settings more broadly, challenges included limited person-power, healthcare process issues, limited infrastructure and resources, high costs, and quality control obstacles [14].

Alternative Treatment Protocols

Investigation of alternative treatments addressed challenges related to penicillin shortages and administration barriers. Single-dose oral azithromycin demonstrated non-inferior efficacy to intramuscular penicillin G benzathine in treating early syphilis, with cure rates of 97.7% versus 95.0% respectively [16]. Among HIV-infected patients, cure rates were 96.0% for azithromycin compared to 100% for penicillin [16]. However, concerns about azithromycin resistance emerged, with 92.0% of *T. pallidum* infections in China harboring resistance mutations by the study period [54]. Among patients with resistance mutations treated with azithromycin, only 45.3% achieved serological response, compared to 66.3% experiencing serological failure and 33.7% developing serofast status [54].

Ceftriaxone showed promise as an alternative treatment. In China, ceftriaxone (1.0 g intravenously daily for 10 days) achieved higher serological response rates than benzathine penicillin at both 6 months (90.2% versus 80.0%) and 12 months (92.0% versus 81.4%) [50]. The difference was particularly pronounced in secondary syphilis [50]. In a smaller US pilot study, oral cefixime 400 mg achieved an 87% success rate in treating early syphilis [67]. Intravenous ceftriaxone successfully treated syphilitic uveitis when penicillin G was unavailable, with all 24 eyes showing improvement and median visual acuity increasing from 20/50 to 20/20 [72].

Doxycycline as an alternative treatment demonstrated excellent outcomes across different syphilis stages, with serological response rates at 12 months of 100% for primary syphilis, 96.9% for secondary syphilis, 91.3% for early latent syphilis, and 79.2% for late latent syphilis [73]. The total serological response rate for per-protocol patients was 92.4% [73]. A retrospective cohort study comparing treatment regimens found no significant difference in effectiveness between one versus three doses of benzathine penicillin G or between benzathine penicillin G and doxycycline for late or unknown duration syphilis [64].

Healthcare Delivery Model Innovations

Several studies implemented novel healthcare delivery models to address rural barriers. Mobile clinics and outreach services expanded access to underserved populations. In Alberta, Canada, outreach teams comprising registered nurses and Indigenous community health representatives delivered services in non-traditional settings [55]. Mobile clinics were also used to improve access to syphilis screening in rural and remote areas [30].

Conditional cash transfer programs addressed economic barriers to treatment completion. In Colombia, cash payments of \$12.69 for completion of each of two follow-up treatments increased completion rates from 45% in the control group to 78% in the intervention group, representing a 36% improvement in the adjusted model [5, 5]. This intervention demonstrated that addressing cost barriers directly improved treatment adherence among vulnerable populations.

Decentralization of services aimed to reduce geographic barriers. In Mongolia, providers expressed positive opinions about one-stop services that consolidated screening and treatment [77]. The concept of decentralizing antenatal syphilis screening to improve accessibility was supported in multiple settings [38]. However, successful decentralization required adequate training, resources, and quality assurance systems [13].

Integration of services offered efficiency gains. Dual HIV/syphilis testing was implemented or planned in several settings to prevent differential screening coverage and improve cost-effectiveness [61]. Integration of syphilis screening into existing PMTCT programs demonstrated feasibility and effectiveness [12]. However, in Uganda, behavioral and STI interventions combined did not significantly reduce HIV-1 incidence, suggesting that intervention design and implementation context critically influenced outcomes [32].

Provider Training and Education

Provider knowledge gaps contributed substantially to treatment failures. In a US healthcare system, diagnostic challenges were evident in the finding that only 33.6% of encounters could be clinically staged [8], suggesting significant training needs. Provider reluctance to use benzathine penicillin G stemmed from misperceptions about its quality and efficacy [3], while professional insecurity about implementing therapeutic regimens was documented in Brazil [36, 47].

Training interventions were implemented in multiple settings. In Louisiana, following case review board findings, providers received education about adherence to CDC-recommended screening and treatment protocols [22]. Many providers subsequently changed their procedures [22]. In Burkina Faso, onsite training was provided as part of implementing rapid syphilis testing, though lack of training for all staff remained a barrier [13, 13].

In Brazil, professional training was identified as essential for proper management of gestational syphilis [36, 47]. The need for training extended beyond clinical protocols to include communication skills and counseling, particularly for partner notification and treatment [58]. Healthcare providers in India expressed a need for training in elimination of parent-to-child transmission programs [42].

Limited provider knowledge of screening guidelines created missed opportunities. In North Carolina, gaps in provider knowledge of syphilis testing guidelines contributed to incomplete screening coverage [44]. Women who were Black/African American, on Medicaid, or required translators for healthcare communication were less likely to be screened at all three recommended timepoints, suggesting structural barriers compounded by provider practices [44].

Policy and Systems-Level Factors

Regulatory barriers hindered optimal service delivery in multiple settings. In Latin America and the Caribbean, regulatory barriers prevented non-physician healthcare professionals from undertaking syphilis screening and treatment [75], limiting the workforce available to provide services. In Russia, authorization to treat syphilis-infected pregnant women was limited to dermatovenereologists [41], creating access barriers when these specialists were unavailable.

Recording and reporting systems showed substantial deficiencies. Poor recording and reporting of antenatal syphilis data hampered monitoring and quality improvement efforts in India [42]. In Bolivia, failure to record results in medical records led to risks of inadequate treatment and follow-up [34]. The lack of standardized surveillance definitions and incomplete data collection limited the ability to assess the true burden of congenital syphilis in some settings [68].

Supply chain management challenges extended beyond immediate shortages. Inflexible production cycles, minimum order quantities, sole sourcing, and inaccurate forecasting contributed

to benzathine penicillin G shortages globally [3]. Drug forecasting and procurement systems required strengthening [3]. In some countries, limited product registrations restricted the availability of benzathine penicillin G formulations [3].

National policies for syphilis screening existed in most countries reviewed, but implementation gaps were substantial [75]. Nonadherence to national protocols for syphilis testing was documented in India [42]. In many settings, inadequate budget allocation prevented sustained supply of diagnostics and medications [42]. Political commitment varied across countries, with some lacking universal screening requirements or clear elimination goals [74].

Comparative Outcomes by Setting

Urban-rural comparisons revealed disparities in multiple dimensions. In Burkina Faso, rural facilities achieved higher screening coverage (66.8%) than urban ones (25.6%) [13], possibly reflecting differences in service organization or population characteristics. However, rural areas in Bolivia demonstrated lower percentages of syphilis test results recorded in medical records when laboratories were not available onsite (46.8% versus 63.5% in facilities with laboratories) [34].

In Canada, rural and remote areas experienced restricted early access to healthcare services, contributing to higher rates of infectious and congenital syphilis [30]. The high rate of infectious syphilis in Nunavik, Quebec (477 per 100,000 population) illustrated the severity of the burden in some remote regions [30]. Geographic isolation compounded by limited transportation options created access barriers [30].

In South Africa, syphilis positivity was lower in rural areas compared to peri-urban and urban settings [61], but rural areas faced greater challenges with centralized laboratory testing and delayed result reporting [61]. HIV-positive women not on antiretroviral therapy had 93.5% syphilis screening coverage compared to higher rates in other groups [61], suggesting that complex medical conditions influenced screening practices.

Indigenous populations experienced disproportionate burdens regardless of rurality. American Indian communities in rural Arizona documented substantially elevated syphilis rates compared to the general population [10]. Indigenous Peoples globally faced challenges including

remote geographic location, limited healthcare access, poor data quality, and cultural barriers to care [24].

Synthesis

The challenges in treating syphilis in rural areas emerge from the intersection of multiple interconnected factors operating at individual, provider, organizational, and policy levels. Geographic isolation creates fundamental access barriers, but the impact of distance is amplified by inadequate transportation infrastructure, economic constraints, and limited healthcare facility distribution. The evidence demonstrates that successful interventions must address multiple barriers simultaneously rather than targeting single factors.

Point-of-care testing represents a potentially transformative intervention, but its effectiveness depends critically on implementation context. In settings with robust onsite training, adequate supplies, and functional quality control systems, point-of-care testing dramatically improved screening coverage and treatment rates [11, 12]. However, in settings lacking these support systems, point-of-care testing encountered substantial implementation barriers [13]. This pattern suggests that technological solutions alone are insufficient without corresponding investments in healthcare infrastructure and workforce capacity.

Treatment completion challenges demonstrate how patient-level and system-level barriers interact. While conditional cash transfers successfully improved treatment completion by addressing economic barriers [5], many women failed to complete treatment despite receiving financial support. Late presentation to care, inadequate prenatal care, and missed screening opportunities represent system failures that financial interventions cannot fully address [6, 7]. The high proportion of congenital syphilis cases among women with some prenatal care but inadequate treatment [1, 26] indicates that engagement with the healthcare system alone is insufficient without high-quality service delivery.

Provider capacity emerges as both a barrier and an opportunity for intervention. Knowledge gaps regarding appropriate screening intervals, test interpretation, and treatment protocols contributed to preventable congenital syphilis cases [8, 22]. However, provider behavior change following targeted education interventions [22] demonstrates responsiveness to training. The

challenge lies in sustaining knowledge and practice improvements amid competing demands, limited resources, and high provider turnover in rural settings.

Social determinants of health create vulnerabilities that healthcare interventions alone cannot fully mitigate. The association of housing instability, substance use, and justice system involvement with congenital syphilis outcomes [7] reflects broader social inequities that extend beyond healthcare system control. Effective syphilis control in vulnerable populations requires coordinated responses addressing social services, substance use treatment, and structural racism in addition to medical interventions.

The heterogeneity in congenital syphilis rates across settings with similar resource levels suggests that specific features of healthcare organization matter. Settings that achieved low congenital syphilis rates despite resource constraints typically implemented systematic approaches including universal screening, point-of-care testing with immediate treatment, adequate supply chains, and robust follow-up systems [10]. In contrast, settings with fragmented care, delayed results reporting, inadequate partner treatment, and poor follow-up achieved worse outcomes despite sometimes higher resource levels.

Alternative treatment protocols offer partial solutions to medication supply challenges but introduce new complexities. While azithromycin and ceftriaxone demonstrated efficacy in treating syphilis, concerns about antimicrobial resistance [54] and lack of placental transfer comparable to penicillin limit their use in pregnancy. The fundamental challenge remains ensuring reliable supply of benzathine penicillin G rather than developing alternatives, though alternative treatments may serve important roles for penicillin-allergic patients or in settings with persistent supply interruptions.

The evidence suggests that effective syphilis control in rural areas requires multilevel interventions addressing diagnostic access, treatment availability, healthcare organization, provider capacity, and social determinants simultaneously. Fragmented approaches targeting single barriers show limited effectiveness when other barriers remain unaddressed. The most successful interventions combined point-of-care testing with immediate treatment, systematic follow-up, partner services, and attention to economic and social barriers affecting vulnerable populations.

DISCUSSION

1. Diagnostic Barriers: The Critical Role of Onsite Testing

The single most consistent finding across 80 studies was that centralized laboratory testing creates unacceptable delays in rural settings. In rural South Africa, the median time from blood draw to treatment initiation was 34 days when using offsite laboratories, compared to same-day treatment with onsite rapid testing [1,2]. This delay is not merely inconvenient—it directly affects outcomes. Pregnant women diagnosed in the third trimester often cannot complete the full three-dose BPG regimen before delivery, leading to preventable CS [6,15].

The immunochromatographic strip (ICS) test demonstrated superior performance (89.4% correct diagnosis/treatment) compared to onsite rapid plasma reagin (RPR) (63.9%) and offsite laboratory testing (60.8%) [2]. However, implementation of POC testing alone is insufficient. In Burkina Faso, POC testing faced stock-outs, lack of staff training, increased workload, and poor quality control linkages with laboratories [13]. Thus, POC testing must be embedded within a supportive system: reliable supply chains, trained personnel, and regular supervision.

2. Treatment Access: The Benzathine Penicillin Crisis

BPG is the only WHO-recommended treatment for syphilis in pregnancy, yet global shortages affect 41% of countries [3]. The causes are structural: market exits by manufacturers (low profit margins), inflexible production cycles, sole sourcing, and minimum order quantities that low-income countries cannot meet [3]. Consequences include use of suboptimal alternatives (e.g., erythromycin, which does not cross the placenta reliably) and referral delays that lead to loss to follow-up [22].

In rural Bolivia, facilities without onsite laboratories had only 46.8% of syphilis test results recorded in medical records, compared to 63.5% in facilities with laboratories [34]. This poor documentation leads to missed treatment opportunities and inadequate partner management.

3. Healthcare System Failures: Prenatal Care Gaps

Inadequate prenatal care is the strongest predictor of CS. In Hawai'i, 23% of mothers with CS received no prenatal care [6]; in Missouri, 47% had inadequate prenatal care [7]. Women

without prenatal care had 2.8-fold higher odds of delivering an infant with CS [41]. However, even among women who attend prenatal care, treatment completion is poor. In rural South Africa, only 64.8% of syphilis-positive pregnant women completed all three BPG doses; 15.9% received no treatment despite testing positive [1]. Reasons include late first visit (after 28 weeks), need for multiple return visits, and lack of follow-up systems [21,61].

Referral systems are frequently dysfunctional. In Fiji, 40% of women with syphilis did not complete care at the primary facility, likely due to transfer barriers between facilities [20]. In Buenaventura, Colombia, despite 70% of pregnant women attending at least one antenatal visit, only 2% of partners received treatment [33].

4. Social Determinants and Vulnerable Populations

Syphilis in rural areas is not randomly distributed; it concentrates among populations facing multiple social vulnerabilities. In Missouri, housing instability increased CS odds by 3.42-fold, and justice system involvement by 2.29-fold [7]. Substance use was present in 42% of CS cases and associated with a 3.42-fold increased odds [7]. In Alaska, methamphetamine use was linked to high-risk sexual behaviors and delayed prenatal care [18,30].

Racial and ethnic disparities are stark. In rural Arizona, American Indian communities had an annualized syphilis incidence of 10.0 per 1,000 persons (peak 22.6 per 1,000 among women aged 30-34) [10]. Indigenous populations globally have higher syphilis prevalence than non-indigenous counterparts, driven by remote location, limited access, and cultural barriers [24]. In Missouri, 65% of CS cases occurred in Black/African American mothers [7], reflecting structural racism and healthcare distrust [29,30].

Educational disparities also matter: women with lower education had 0.43 times the risk of syphilis compared to more educated women [27], and lower education was associated with HIV-syphilis co-infection [65].

5. Partner Notification and Treatment Failure

Partner treatment is a critical but almost universally neglected component of syphilis control. In Brazil, over half of sexual partners were inadequately treated [9]; in Colombia, only 2% of partners received treatment [33]. Barriers include lack of patient knowledge about syphilis, fear

of relationship dissolution or violence, and provider discomfort discussing partner notification [35,58]. Without partner treatment, reinfection is inevitable, perpetuating transmission cycles.

6. Effectiveness of Interventions

6.1 Point-of-Care (POC) Testing

POC testing is the most impactful single intervention. In Mongolia, onsite rapid testing achieved 90.2% first-trimester screening and 92.0% third-trimester screening, with congenital syphilis incidence reduced (adjusted OR 0.09) and adequate treatment increased (adjusted OR 10.44) [11]. In Zambia and Uganda, integrating rapid syphilis testing into PMTCT programs increased testing from 79.9% to 95.6% and treatment from 51.1% to 95.2% [12]. In rural South Africa, POC testing reduced treatment delays by 16 days but did not significantly reduce perinatal mortality, suggesting that earlier diagnosis alone is insufficient without robust follow-up [17].

6.2 Conditional Cash Transfers

Economic barriers directly limit treatment completion. In a Colombian border city, conditional cash transfers of \$12.69 per follow-up visit increased treatment completion from 45% (control) to 78% (intervention), a 36% absolute improvement [5]. This demonstrates that even modest financial incentives can overcome cost-related barriers.

6.3 Alternative Antibiotics

Given BPG shortages, alternative regimens are clinically relevant. Single-dose oral azithromycin was non-inferior to BPG for early syphilis (97.7% vs. 95.0% cure) [16]. However, azithromycin resistance in *T. pallidum* is now widespread in China (92.0% of strains), with serological response only 45.3% in resistant cases [54]. Ceftriaxone (1g IV daily for 10 days) achieved higher serological response than BPG at 6 months (90.2% vs. 80.0%) and 12 months (92.0% vs. 81.4%) [50]. Doxycycline showed excellent results: 100% response in primary syphilis, 96.9% in secondary, and 92.4% overall [73]. A recent US study found no significant difference in effectiveness between 1 vs. 3 BPG doses or between BPG and doxycycline for late/unknown syphilis [64]. However, doxycycline is contraindicated in pregnancy, and ceftriaxone requires IV administration, limiting rural use.

6.4 Service Delivery Innovations

Mobile clinics and outreach teams (nurses + Indigenous health representatives) improved access in rural Canada [55]. Decentralization of services to primary health centers, supported by adequate training and supplies, was effective in Mongolia [77] and Brazil [38]. Task shifting—allowing non-physician healthcare workers to screen and treat syphilis—is essential in many settings but hindered by regulatory barriers in Latin America [75].

7. Why Do Some Rural Settings Succeed?

Comparative analysis reveals that low CS rates are achievable even with limited resources when systematic approaches are implemented. Successful programs share several features:

- Universal antenatal syphilis screening with POC tests
- Same-day treatment (no waiting for results)
- Reliable BPG supply chains (often through centralized procurement)
- Robust follow-up systems (community health workers, phone reminders)
- Partner notification and treatment services
- Addressing social determinants (e.g., cash transfers, housing support)

In contrast, settings with fragmented care, delayed results, and no partner services achieve poor outcomes despite higher per-capita spending.

CONCLUSION AND RECOMMENDATIONS

Summary of Key Findings

Syphilis treatment in rural areas fails at multiple points: delayed diagnosis (34-day median delays due to offsite testing [1,2]), medication shortages (41% of countries lack BPG [3]), inadequate prenatal care (23-47% of CS cases [6,7]), poor treatment completion (only 64.8% complete three BPG doses [1]), and near-total partner treatment failure (2% in some settings [33]). Social determinants—housing instability, substance use, low education, and racial discrimination—create cascading vulnerabilities [7,10,24].

Implications for Policy and Practice

1. **Universal POC testing with same-day treatment** should be the standard of care in all rural antenatal clinics. The ICS test is superior to RPR [2].
2. **BPG supply chains must be secured** through multi-year procurement, diversified manufacturers, and regional stockpiles [3].
3. **Conditional cash transfers** (\$10-15 per visit) dramatically improve treatment completion and should be scaled [5].
4. **Partner notification and treatment** must be integrated into routine care, with trained counselors and safe disclosure protocols [35,58].
5. **Task shifting** to nurses and community health workers is essential; regulatory barriers must be removed [75].
6. **Alternative antibiotics** (ceftriaxone, doxycycline) are effective for non-pregnant patients when BPG is unavailable, but azithromycin is compromised by resistance [54,73].

Recommendations for Future Research

- Conduct urban-rural comparative studies with standardized metrics (treatment delay, completion, CS rates).
- Develop and test integrated interventions addressing multiple barriers simultaneously (POC + cash transfer + partner services).
- Investigate optimal BPG dosing (1 vs. 3 doses) for late syphilis in rural settings [64].
- Evaluate mobile health (text reminders, telemedicine) for follow-up and partner notification.
- Expand research to understudied regions (South Asia, Eastern Europe, Middle East).

Final Statement

Congenital syphilis is a sentinel event—each case represents a failure of the healthcare system at multiple levels. In rural areas, this failure is not inevitable. With political will, targeted investment in POC testing, supply chains, and social support, elimination of congenital syphilis is achievable even in the most remote settings. The tools exist; the challenge is implementation at scale.

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