

A Retrospective Cohort Study on *Treponema pallidum* Infection: Clinical Trends and Treatment Outcomes for Congenital Syphilis in Guangxi, China (2013-2023)

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Background: Syphilis, a prevalent sexually transmitted infection, poses severe risks, especially during pregnancy. This study aimed to elucidate the trends and impacts of syphilis in Guangxi, China, focusing on prevalence, clinical manifestations, and treatment outcomes in pregnant women and newborns. The objectives included understanding the demographic characteristics of affected pregnant women, analysing the clinical manifestations in newborns, and assessing the effectiveness of the treatment protocol.

Methods: Conducted in adherence to ethical guidelines, a retrospective cohort study from January 2013 to December 2023 included 54,048 pregnant women tested for *T. pallidum*. Diagnosis involved a comprehensive approach, utilizing tests like the Tolidine Red Unheated Serum Test (TRUST) and the *Treponema pallidum* Particle Agglutination (TPPA) assay. Infant diagnosis and clinical manifestations were evaluated through a decade-long follow-up. Treatment protocols, including Benzathine penicillin, were implemented. Statistical analyses were conducted using SAS version 9.4.

Results: Among 54,048 pregnant women, 0.10% were syphilis positive, correlating with a rise in hospitalizations. Newborns exhibited varied clinical manifestations, with neonatal pneumonia and jaundice being prevalent. The treatment protocol, especially with Benzathine penicillin, achieved a remarkable 100% cure success rate. The study noted a significant reduction in mother-to-child transmission. Syphilis in mothers and babies was diagnosed at different clinical stages, including primary, secondary, latent, and tertiary.

Conclusion: This study underscores the escalating impact of syphilis on pregnant women and newborns in Guangxi, China. The findings highlight the necessity for robust preventive measures, early diagnosis, and effective treatment strategies. The observed 100% cure success rate with Benzathine penicillin emphasizes the importance of strict treatment protocols in mitigating the adverse effects of congenital syphilis and reducing its transmission.

Keywords: congenital syphilis, mother-to-child transmission, diagnosis, antibiotic treatment

Introduction

Syphilis, a sexually transmitted infection caused by *Treponema pallidum* (*T. pallidum*)¹ remains a significant global health concern, contributing to the intricate landscape of sexually transmitted diseases (STIs).^{2,3} The World Health Organization (WHO) estimates 18 to 36 million cases globally, with an annual incidence of 5.6 to 11.0 million new infections.^{4,5} While predominantly affecting low-income and middle-income countries, a resurgence has been noted in high-income countries over two decades, emphasising an understanding of clinical trends and therapeutic approaches.⁶ Untreated syphilis in pregnant women poses a risk to infants (congenital syphilis-CS), resulting in transmission to >70%

of affected newborns and a 40% incidence of fetal or perinatal death.⁷ The incidence of CS in the United States of America (USA)- Mississippi has a concerning rise by 1000% between 2016–2022.⁸ In China, reported cases increased from 7.2 to 82.7 per 100,000 newborns between 2003–2011. Although this incidence declined to 27.6 per 100,000 newborns in 2016, it still exceeds the targeted goal of 15 cases per 100,000 for the year 2020.⁹ This persistence emphasizes the need for sustained efforts to address and mitigate the rising incidence of CS in China. CS at \$9969 per case highlights the urgency of precise diagnosis to prevent health complications and economic strain on families and communities.¹⁰ National reports on CS cases remain limited. For every 4.6 pregnant women with syphilis, one case of CS emerged.¹¹ It is crucial for all neonates born to mothers with reactive test results to undergo a quantitative non-treponemal test using the neonate's serum and be considered for proper treatment. The limited symptomatology in affected neonates underscores the need for proactive measures, emphasizing the urgency of comprehensive interventions to reduce the incidence of mother-to-child transmission and prevent the devastating consequences of congenital syphilis. Penicillin remains the preferred treatment for syphilis and has been a mainstay in managing this infection.¹² However, its administration poses logistical challenges, especially in cases of neurosyphilis and neonatal syphilis, where intensive intravenous infusions are required. Issues such as production shortages and limited access to specialized healthcare in rural areas further underscore the urgent need for alternative therapeutic avenues. This study seeks to address critical knowledge gaps in the clinical trends of *T. pallidum* infection and congenital syphilis in Guangxi, China, focusing on prevalence, clinical diagnosis, and therapeutic approaches over a decade. Our findings aim to contribute to the evolving understanding of *T. pallidum* infections and offer insights that may shape future therapeutic strategies and public health interventions for this persistent global health challenge.

Methods

The study was conducted per the guidelines of the Declaration of Helsinki and received approval from the Institutional Ethics Committee Reference No. IIT-2024-16, adhering to international ethical standards. All experiments adhered to the biosafety regulations of the hospital. The Ethics Committee determined that, given the retrospective nature of the study, explicit informed consent from patients or their legal guardians was not necessary. Written consent was waived as the research did not use personal information, including names, for research purposes, and data were treated confidentially in line with the principles of the Declaration of Helsinki.

Study Design and Subjects

A retrospective cohort study was conducted at the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning City, Guangxi Zhuang Autonomous Region, China between January 2013 to December 2023. A total 54,048 of pregnant women tested for *T. pallidum* infection (for the test method see diagnosis session). We have conducted preliminary screening for syphilis for each woman at first prenatal check-up. We have followed the guidance from the centre disease control and prevention (CDC) mentioned at the <https://www.cdc.gov/std/treatment-guidelines/congenital-syphilis.htm>. We have considered first infection cases, not past infection history. Furthermore, among them, infected pregnant women registered in China's Information Management System for Prevention of Mother-to-Child Transmission (PMTCT) of syphilis in Guangxi, China. Mothers seropositive for syphilis underwent treatment and regular serological testing. Children born to syphilis-positive mothers were diagnosed with CS and subsequently referred to the pediatric department for further treatment and assessments. Demographic data of confirmed CS children, including gender, age, birth weight, maternal history of miscarriages, number of children, delivery method (normal or caesarean section), and age of mother were retrieved from the hospital's record room.

Mother-to-Child Transmission of Syphilis Diagnosis

Medical staff consistently monitored women diagnosed with syphilis and their fetuses. Symptomatic cases underwent a comprehensive diagnostic approach, combining the TRUST and TPPA. The TRUST test, a non-treponemal diagnostic method, involves examining patient serum for antibodies produced in response to the bacterium *T. pallidum*. The test is centred on the principle that these antibodies react with a mixture of cardiolipin, lecithin, and cholesterol, resulting in visible agglutination. It can be detected after about 6 weeks and has poor auxiliary diagnostic ability for early syphilis. On the other hand, the TPPA test, a specific treponemal diagnostic, confirms syphilis diagnosis by detecting antibodies targeting *T. pallidum* antigens. This test

entails the interaction of patient serum with *T. pallidum* particles, leading to observable particle agglutination under favourable conditions. These meticulous diagnostic methods are crucial tools in the ongoing monitoring and accurate diagnosis of syphilis cases among pregnant women and their fetuses, ensuring timely intervention and effective management. Additionally, A single positive TPPA can only indicate infection or past infection, but cannot determine syphilis activity or recovery period, and cannot be used as monitoring. However, its titer changes are positively correlated with syphilis treatment, but there are many influencing factors. TPPA (-), TRUST (-): Non syphilis, normal population; TPPA (+), TRUST (-): (1) TPPA false positive: middle-aged and elderly people, tumor patients (2) TPPA positive: Syphilis patients have been cured. (3) TRUST false negative: In the early stage of the disease, stage III syphilis, and in the early stages of stage II syphilis, latent syphilis, and neurosyphilis, failure to use diluted sample testing can result in false negative results. TPPA (-), TRUST (+): False positive, when there are recent immune related diseases TRUST (+) +TPPA (+): confirmed syphilis based on the patient's infection history and symptoms.

Infant Diagnosis and Clinical Manifestations

Over the course of a decade, from January 2013 to December 2023, a comprehensive follow-up was conducted on a total of 54 suspected infants who underwent tested for CS. The study aimed to assess the incidence of CS among newborns in, the Guangxi Zhuang Autonomous Region. Key parameters, including weight at birth, Apgar score, and International Classification of Diseases-10 (ICD-10) codes, were utilized to identify infants exhibiting clinical manifestations or complications.¹³ Clinical observations encompassed Asphyxia Neonatorum, rash, hepatosplenomegaly, neonatal pneumonia, long bone changes (confirmed by X-rays), jaundice, small for gestational age, abdominal distension, edema, congenital heart disease, neurological manifestations, and other relevant factors includes cholestasis, hepatitis syndrome, coagulation dysfunction, thrombocytopenia, haemangioma, gastrointestinal bleeding, finger deformity, bronchopulmonary dysplasia, temporary hypothyroidism. Specifically, infants diagnosed with ICD-10 codes A52.1, A52.2, A52.3, and A50.4 were confirmed for neurosyphilis, with positive cerebrospinal fluid. This thorough follow-up and assessment of clinical parameters aimed to provide a comprehensive understanding of the incidence and associated clinical manifestations of CS in the studied population over the specified timeframe. Following the clinical observations, a comprehensive analysis of haematological and biochemical parameters was conducted to further understand the health status of the infants. The assessment included key haematological markers such as White Blood Cell count (WBC), Haemoglobin (Hb) levels, and Platelet count (PLT) to understand the overall health and immune response. Additionally, inflammatory markers such as C-reactive protein (CRP), Procalcitonin (PCT), and Interleukin-6 (IL-6) were measured to provide insights into the inflammatory response. These markers play a significant role in indicating the severity of infections or inflammatory conditions.

Treatment

A total of 54 *T. pallidum*-infected women were treated with Benzathine penicillin or aqueous penicillin. Standardized treatment, based on the 2015 version, involved sufficient penicillin treatment with two courses during pregnancy, more than a 2-week interval, and completion in the third trimester. In the 2020 version, standardized treatment required full penicillin treatment completed within one month before delivery¹⁴

Statistical Analyses

The cohort underwent stratification based on the study year. Comparative analyses of neonatal characteristics and complications across diverse groups were conducted utilizing t-tests, Rank Sum Test and chi-square test. Data analysis was performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). Statistical significance was set at a threshold of P values < 0.05 .

Result

Demography of Pregnant Women

A total of 54,048 pregnant women, with a median age of 32 years (IQR:29 years –35 years), participated in the present study conducted from January 2013 to December 2023. Among them, 0.10% (n=54) of pregnant women tested positive for syphilis due to *T. pallidum* infection, confirmed by both TRUST and TPPA tests (Figure 1). Analysis of trends in

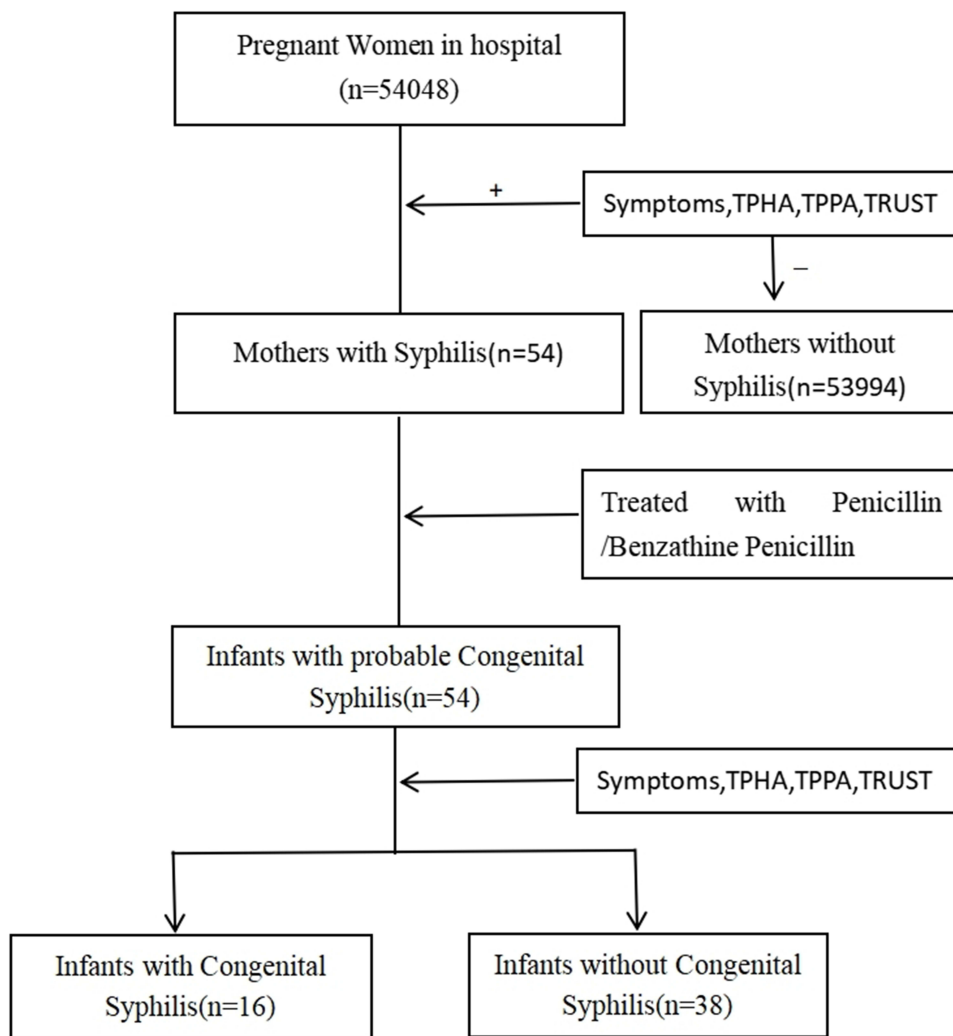


Figure 1 Incidence of Syphilis among Pregnant Women in Nanning, Guangxi Zhuang Autonomous Region (2013–2023).

hospitalization among pregnant women revealed a notable increase (Table S1), particularly in 2019 at 0.17% (n=10/5658), and a further rise in 2022 to 0.24% (n=10/4065), representing a 41.18% increase over the decade (Figure 2). The age distribution of pregnant women diagnosed with syphilis indicated age groups <25 years, 25–30, 30–35, 35–40, and ≥40 years. Among them, 70.37% (n=38/54) had a history of miscarriage, and 25.93% (n=14/54) experienced premature births. In terms of delivery methods, 66.67% (n=36/54) underwent caesarean sections, while 33.33% (n=18/54) opted for natural childbirth (Table 1).

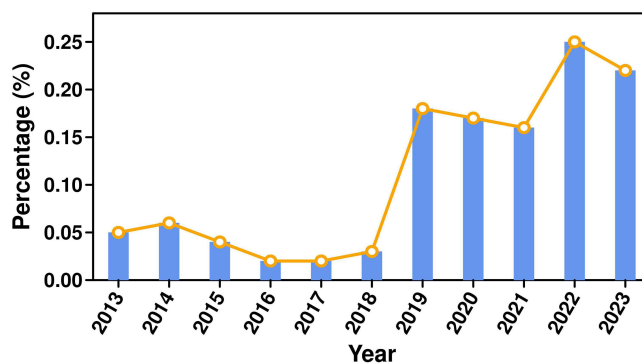


Figure 2 Incidence of Congenital Syphilis in Nanning, Guangxi Zhuang Autonomous Region (2013–2023).

Table 1 Demographic Characteristics of Pregnant Women with Syphilis in Nanning, Guangxi Zhuang Autonomous Region (2013–2023)

	Total (n=54,048)	Pregnant Women with Syphilis (n=54)	Pregnant Women without Syphilis (n=53,994)	P value
Age				<0.001
<25y	2353 (4.35%)	9 (16.67%)	2344 (4.34%)	
25y-30y	15,145 (28.02%)	8 (14.81%)	15,137 (28.03%)	
30y-35y	21,502 (39.78%)	13 (24.07%)	21,489 (39.80%)	
35y-40y	11,824 (21.88%)	16 (29.63%)	11,808 (21.87%)	
≥40y	3224 (5.97%)	8 (14.81%)	3216 (5.96%)	
Miscarriage	23,814 (44.06%)	38 (70.37%)	23,776 (44.03%)	<0.001
Delivery method				0.001
Natural childbirth	30,512 (56.45%)	18 (33.33%)	30,494 (56.48%)	
Caesarean section	23,536 (43.55%)	36 (66.67%)	23,500 (43.52%)	

Clinical Characteristics and CS Diagnosis

A total of 54 newborns diagnosed with probable syphilis were observed in the pediatric department. Among them, 44.44% (n=24/54) were female, while 55.56% (n=30/54) were male, with an average birth weight of 3kg. However, 20.37% (n=11/54) were underweight, with an average weight of 1.850 kg. Apgar scores at 1 minute, 5 minutes, and 10 minutes indicated asphyxia neonatorum in 7.4% (n=4) cases. Clinical manifestations included rash (4%, n=2/54), hepatosplenomegaly (4%, n=2/54), neonatal pneumonia (24%, n=13/54), long bone changes confirmed by X-rays (20%, n=11/54), pathological jaundice (57%, n=31/54), small for gestational age (17%, n=9/54), abdominal distension (7%, n=4/54), congenital heart disease (4%, n=2/54), and neurological manifestations (2%, n=1/54). No edema was observed, while other manifestations, including cholestasis, hepatitis syndrome, coagulation dysfunction, thrombocytopenia, and haemangioma, were reported in few cases (Table-2). Haematological marker detection revealed that only one infant had a high white blood cell count, 3 infants had thrombocytopenia, and CRP > 6 was observed in 2 out of 54 cases, while haemoglobin and IL-6 were normal in all cases (Table S2). The combination of TRUST and TPPA test results, compared with mother results (Table S3), revealed 16 out of 54 cases of congenital syphilis (Table S1). The prevalence of syphilis-positive mothers and congenital syphilis cases spiked in the year 2020, accounting for about 62% (n=5/8) (Figure 3A).

Table 2 Characteristics of Infants with Probable Congenital Syphilis in Nanning, Guangxi Zhuang Autonomous Region (2013–2023)

Characteristics	Infants with probable Congenital Syphilis (n=54)	Infants with Congenital Syphilis (n=16)	Infants without Congenital Syphilis (n=38)	P value
Gender (M/F)	30/24	8/8	22/16	0.594
Gestational age	38w+5d (36w+6d~39w+5d)	38w+5d (38w~39w+6d)	38w+5d (36w+3d~39w+5d)	0.323
Birth weight				0.333
<1500g	2 (3.77%)	0 (0.00%)	2 (5.26%)	
1500g~2500g	10 (18.52%)	3 (18.75%)	7 (18.42%)	
2500g~4000g	41 (77.36%)	13 (86.67%)	28 (73.68%)	
>4000g	1 (1.89%)	0 (0.00%)	1 (2.63%)	
Pregnant mother's history of miscarriage	38 (70.37%)	10 (62.50%)	28 (73.68%)	0.620
Delivery method				0.673
Natural childbirth	18 (33.33%)	6 (37.50%)	12 (31.58%)	
Caesarean section	36 (66.67%)	10 (62.50%)	26 (68.42%)	

(Continued)

Table 2 (Continued).

Characteristics	Infants with probable Congenital Syphilis (n=54)	Infants with Congenital Syphilis (n=16)	Infants without Congenital Syphilis (n=38)	P value
Clinical symptoms				
Asphyxia neonatorum	4 (7.41%)	0 (0.00%)	4 (10.53%)	0.436
Rash	2 (3.70%)	0 (0.00%)	2 (5.26%)	1.000
Hepatosplenomegaly	2 (3.70%)	1 (6.25%)	1 (2.63%)	0.509
Neonatal pneumonia	13 (24.07%)	2 (12.50%)	11 (28.95%)	0.346
Pathological jaundice	31 (57.41%)	10 (62.50%)	21 (55.26%)	0.623
Small for gestational age	9 (16.67%)	2 (12.50%)	7 (18.42%)	0.894
Abdominal distension	4 (7.41%)	2 (12.50%)	2 (5.26%)	0.720
Congenital heart disease	2 (3.70%)	0 (0.00%)	2 (5.26%)	1.000
Long bone changes (By X-rays)	11 (20.37%)	6 (37.50%)	5 (13.16%)	0.097

Treatment Outcome

Out of the 54 Infants, a total of 61% (n=33) received treatment with Benzathine penicillin, 11% (n=6) received a combination of Benzathine penicillin and penicillin, 9% (n=5) received only penicillin, while 19% (n=10) did not receive any treatment (Figure 3B). We are proud to report a 100% cure success rate due to our strict treatment protocol, with no mortality occurring due to CS. All infants became healthy after treatment. Additionally, optimal treatment and follow-up have significantly reduced mother-to-child transmission of syphilis over the last decade. In the present study, 38 infants out of 54 were born without syphilis (Figure 3A).

Discussion

The study's findings present a comprehensive overview of the demographic characteristics, clinical manifestations, and treatment outcomes in cases of congenital syphilis (CS) over a decade in a general hospital in Guangxi Zhuang Autonomous Region, China over the decades. The demographic profile of pregnant women participating in the study revealed a median age of 32 years, with a minimal percentage (0.10%) testing positive for syphilis. This finding is comparable to the national data while very low compared with neighboring Asian countries.^{11,15} As the published report CDC USA showed a random increase of syphilis cases.¹⁶ According to Cohen MS and his co-worker, China was declared a syphilis-free country until the really 1980s, but after the economic reform was introduced, cases now reported in some areas.¹⁷ In China, the government implemented a special program specifically aimed at Preventing PMTCT of HIV, syphilis, and hepatitis B.¹⁸ The government allocated a special fund of \$140 million was earmarked annually for the comprehensive prevention of the PMTCT program, which includes syphilis prevention as one of its crucial components. These financial commitments signify a robust foundation and a high level of dedication to syphilis control within the country, demonstrating a proactive approach to address and mitigate the impact of syphilis on public health. The observed

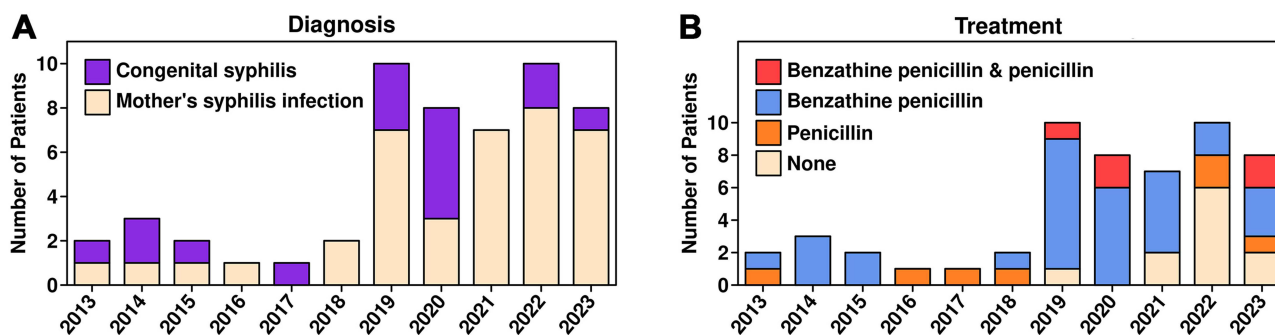


Figure 3 (A) Prevalence of Syphilis-Positive Mothers and Congenital Syphilis Cases Over the Years in Nanning, Guangxi Zhuang Autonomous Region (2013–2023). (B) Treatment Patterns and Outcomes in Mothers with Syphilis and Their Infants.

rise in hospitalization trends among pregnant women, but syphilis spike particularly in 2019 and 2022, highlights the need for continued vigilance and preventive measures. The best our knowledge similar data not found from other part of the China. Sexually Transmitted Infections Surveillance, 2022 program of USA reported a similar report, revealed the syphilis cases spike in 2019 and 2022.¹⁹ We have reported prevalence of syphilis in different five age groups and the association with adverse outcomes, such as a history of miscarriage and premature births, underscores the potential impact on maternal and neonatal health. The study reported from the California USA, suggested similar results that maternal syphilis infection in pregnancy is associated with specific adverse pregnancy outcomes.²⁰ We have observed the clinical characteristics and CS diagnosis in newborns emphasize the multifaceted nature of the disease. The notable proportion of underweight infants and the spectrum of clinical manifestations, including asphyxia neonatorum, rash, neonatal pneumonia, and other complications, reflect the severity of CS which is similar to the previous studies.²¹ The observed spike in CS cases in 2020 aligns with global concerns about the persistence and resurgence of syphilis, emphasizing the need for targeted interventions.²² The treatment outcomes reported in the study, with 81% of infants receiving Benzathine penicillin, showcase a commendable 100% cure success rate. The strict adherence to treatment protocols and the absence of mortality due to CS highlight the efficacy of the chosen therapeutic approach. The published study reported that the risk of treating pregnant women with benzathine penicillin to prevent congenital syphilis appears very low and does not outweigh its benefits.²³ The significant reduction in mother-to-child transmission over the past decade underscores the success of optimal treatment and follow-up measures.²⁴ Comparing these results with national and global trends, the study contributes valuable insights. The rising incidence of CS in Guangxi echoes global challenges posed by syphilis, with the World Health Organization estimating millions of cases annually.²⁵ The demographic and clinical characteristics observed in this study align with patterns seen in other regions, emphasizing the universality of the impact of syphilis on maternal and neonatal health.²⁶ The study's success in achieving a 100% cure rate is noteworthy in contrast to the challenges faced globally, such as access to healthcare and treatment shortages.²⁷ The findings underscore the importance of tailored, effective treatment strategies in mitigating the impact of CS. However, the study's focus on a specific region necessitates caution in generalizing the results to represent the entire diversity of syphilis cases globally. The study's findings carry implications for public health interventions, emphasizing the need for targeted efforts in antenatal care, especially in populations with a higher risk of syphilis. The success in achieving a 100% cure rate prompts a closer examination of the treatment protocols employed in Guangxi, which could potentially serve as a model for other regions grappling with congenital syphilis. Future research avenues may include an in-depth exploration of the socio-economic factors contributing to syphilis incidence, a closer examination of the specific components of the treatment protocol, and an assessment of the long-term health outcomes of infants born to mothers with syphilis.

Conclusion

In conclusion, the Guangxi study provides a valuable contribution to the understanding of congenital syphilis, offering insights into demographics, clinical features, and treatment outcomes. The success in achieving a 100% cure rate and preventing CS-related mortality underscores the importance of stringent treatment protocols. While the study aligns with national and global trends in syphilis incidence, its positive outcomes highlight the potential for targeted interventions to mitigate the impact of congenital syphilis.

Data Sharing Statement

The data and materials used in this study are available upon request. Researchers interested in accessing the dataset or related materials for academic and non-commercial purposes can contact the corresponding author for further information.

Ethics Approval

Present study approved form The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning City, Guangxi Zhuang Autonomous Region, China.

Consent for Publication

Due to the retrospective nature of this study, the Institutional Ethics Committee determined that explicit written consent from patients or their legal guardians was not required. The study adhered to the guidelines of the Declaration of Helsinki and international ethical standards.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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