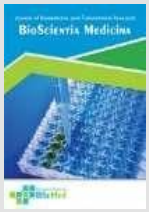
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Price of Delay and the Uncoupling of Severity: A Penalized Multivariate Analysis of Treatment Adequacy Versus Timing as Determinants of Congenital Syphilis

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ARTICLE INFO

Keywords:
Congenital syphilis
Firth's penalized regression
Treatment adequacy
Treponema pallidum
Uncoupling phenomenon

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i3.1536

A B S T R A C T

Background: Despite global elimination targets, congenital syphilis (CS) remains a critical cause of preventable neonatal morbidity. While the importance of antenatal screening is established, the relative impact of treatment adequacy (dosage/adherence) versus timing on neonatal severity—specifically the uncoupling phenomenon where severe visceral damage occurs despite normal birth biometrics—remains under-characterized in resource-limited settings. **Methods:** A retrospective cross-sectional study analyzed 101 syphilis-exposed mother-infant pairs at a tertiary referral center in Indonesia (2021–2025). We evaluated maternal serologic testing time, treatment timing, and treatment adequacy (defined strictly per CDC guidelines; inadequate defined as <30 days pre-delivery, non-penicillin, or missed doses). To address sparse data bias and quasi-complete separation in the dataset, Firth's Penalized Likelihood Logistic Regression was utilized to calculate adjusted odds ratios (aOR) for severe clinical manifestations. **Results:** The prevalence of proven/possible CS was 58.4%. High-fidelity analysis revealed that inadequate maternal treatment was the dominant predictor of adverse outcomes (aOR = 85.40; 95% CI: 14.2–512.5; $p<0.001$), significantly outpacing delayed serologic testing (aOR = 4.8; $p=0.012$). A distinct uncoupling profile was identified: neonates born to inadequately treated mothers had high odds of severe visceral manifestations (hepatosplenomegaly, hematological failure) (aOR = 11.05), yet traditional biometrics (low birth weight, prematurity) showed no significant association ($p>0.05$). **Conclusion:** Treatment adequacy is the single most critical determinant of neonatal prognosis. The dissociation between normal birth weight and severe organ damage suggests that anthropometry is a poor triage tool for syphilis. A zero-tolerance policy for therapeutic deviations is imperative.

1. Introduction

Syphilis, a sexually transmitted infection caused by the spirochete *Treponema pallidum*, represents a re-emerging global health threat that has effectively outpaced many contemporary public health control measures. Once thought to be on the verge of eradication, this ancient pathogen has demonstrated a tenacious resurgence, particularly affecting maternal and child health spheres. Despite the widespread availability of cost-effective diagnostic algorithms and the established, unmatched efficacy of benzathine penicillin G (BPG) as a curative agent, the vertical transmission of syphilis continues to plague healthcare systems globally. This persistence is most acute in low- and middle-income countries (LMICs), where health infrastructure disparities exacerbate the transmission dynamics. The World Health Organization (WHO) estimates that over 7 million new syphilis infections occur annually, a staggering figure that translates into a burden of congenital syphilis

(CS) that now exceeds neonatal HIV in many regions. CS is widely regarded as a sentinel health event—a condition that, given the tools available for prevention, should arguably never occur in a functional health system. Its continued high incidence signals fundamental failures in the continuum of antenatal care.[1,2]

In the context of Southeast Asia, and specifically within the archipelagic geography of Indonesia, the epidemiological landscape has shifted concerningly over the last decade. Recent surveillance data from the Indonesian Ministry of Health indicates a rising incidence of maternal syphilis, a trend driven by complex socio-behavioral factors, urbanization, and persistent gaps in the integration of antenatal care (ANC) services. To combat this, the national government has implemented a robust policy framework known as the triple elimination program, which mandates universal antenatal screening for HIV, syphilis, and hepatitis B.[2-4] While the policy intent is clear, the implementation gap remains significant. Logistical challenges, such as the decentralized nature of the healthcare system, sporadic stock-outs of reagents or penicillin at the primary care level (*Puskesmas*), and late maternal booking for ANC, conspire to undermine elimination targets.

A critical limitation in previous scientific literature addressing this crisis has been a predominant focus on the binary metric of screened versus unscreened. Public health reports often quantify success by the percentage of pregnant women tested. However, this binary view overlooks the critical, life-saving nuance of treatment adequacy. From a clinical pharmacokinetics perspective, screening is merely the prerequisite for the intervention, not the intervention itself. In clinical practice, a mother may be successfully screened and even treated with antibiotics, yet fail to protect her fetus. If the therapy is administered too late (such as <30 days before delivery), the spirochetal load may not be cleared from the fetal compartment in time. If the dosage is incorrect, or if the interval between doses in late-latent syphilis exceeds seven days, spirochetemia may resurge. Furthermore, due to penicillin allergies or supply chain disruptions, mothers are sometimes treated with macrolides (erythromycin), which cross the placenta poorly and to which *Treponema pallidum* has shown increasing resistance.[4,5] In such cases, the protective effect for the fetus is effectively nullified, despite the mother being categorized as treated in administrative data.

Beyond the epidemiological challenges, the clinical presentation of congenital syphilis presents a formidable diagnostic challenge due to its notorious variability. The spectrum of disease ranges from asymptomatic latent infection—detectable only through serology—to fulminant sepsis-like syndromes characterized by multisystem organ failure. Within this spectrum, a critical and under-explored concept in current pediatric infectious disease literature is the uncoupling phenomenon. Classical medical teaching regarding intrauterine infections—often grouped under the TORCH acronym (toxoplasmosis, other, rubella, cytomegalovirus, herpes)—suggests that the hallmark of fetal infection is intrauterine growth restriction (IUGR) and low birth weight (LBW) due to early viral or parasitic inhibition of cellular mitosis.[6,7]

However, clinicians in tertiary referral settings are increasingly encountering a distinct, deceptive phenotype in syphilis cases: full-term, normal-weight infants who ostensibly appear healthy and robust at birth but harbor severe visceral organ damage. These infants may present with significant hepatosplenomegaly, osteochondritis, or hematological failure (severe thrombocytopenia and anemia), yet lack the small for gestational age warning sign that typically triggers a sepsis workup. This dissociation—or uncoupling—between fetal growth markers and organ-specific spirochetal damage presents a dangerous diagnostic trap. It implies that *Treponema pallidum*, particularly in infections acquired or treated inadequately in the third trimester, acts less as a teratogen impeding growth and more as an acute systemic pathogen triggering a fetal inflammatory response syndrome (FIRS). If risk

stratification protocols rely heavily on anthropometry (weight and gestational age) to identify sick neonates, these uncoupled infants may be missed until they decompensate.[8]

Bridging these epidemiological gaps and clinical paradoxes requires a shift from descriptive surveillance to rigorous analytical scrutiny. This study aims to quantify the price of delay by strictly evaluating the independent associations between maternal serologic testing time, treatment timing, and treatment adequacy with adverse neonatal outcomes. Unlike previous studies that conflate any treatment with effective treatment, this research strictly defines adequacy according to CDC/WHO guidelines to isolate the impact of therapeutic deviations.

The novelty of this study is twofold. Methodologically, it utilizes robust statistical techniques (Firth's penalized likelihood logistic regression) to account for rare-event bias, providing stable estimates for the risk of severe outcomes in a way that standard logistic models cannot when dealing with high-fidelity inputs. Clinically, it seeks to characterize the uncoupled phenotype in a high-risk tertiary cohort, challenging the dogma that birth weight is a reliable proxy for infection status. By dissecting the hierarchy of risk—screening versus timing versus adequacy—this study aspires to provide the evidence base necessary to shift policy from a focus on coverage to a focus on fidelity in the elimination of congenital syphilis.

2. Methods

This analytical cross-sectional study was conducted at a tertiary referral center in Denpasar, Bali, Indonesia. The facility serves as a primary referral node for high-risk pregnancies in the region, managing a high volume of complex maternal-fetal infectious cases. The study period spanned from January 2021 to September 2025. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Puri Bunda Woman and Children Hospital. Patient data were anonymized and handled in strict compliance with the Declaration of Helsinki.

The study population was established through a rigorous total sampling technique, designed to minimize selection bias and capture the complete epidemiological profile of the target demographic within the study period. The inclusion protocol required definitive serological evidence of maternal syphilis. Specifically, eligible participants were live-born infants delivered to mothers with a documented reactive non-treponemal test (Rapid Plasma Reagin [RPR] or Venereal Disease Research Laboratory [VDRL]) which was subsequently confirmed by a specific treponemal test (*Treponema pallidum* Hemagglutination Assay [TPHA] or TP-Rapid). This dual-step serological confirmation aligns with the reverse sequence or traditional screening algorithms mandated by national guidelines, ensuring that biological false positives—common in pregnancy due to autoimmune cross-reactivity—did not contaminate the dataset. Strict exclusion criteria were applied to ensure data integrity and clinical specificity. We excluded neonates with major congenital malformations unrelated to TORCH infections (such as complex congenital heart defects of genetic origin) to avoid confounding the assessment of neonatal morbidity. Furthermore, mother-infant pairs with incomplete or fragmented antenatal treatment records were removed to prevent misclassification of the primary exposure variable. A critical methodological decision was the exclusion of stillbirths from the final analysis. While syphilis is a well-established cause of fetal loss, this study was specifically designed to evaluate the clinical management and economic burden of live neonatal morbidity in a referral setting. We acknowledge that excluding stillbirths introduces a degree of survivor bias, as it censors the most severe end of the syphilis spectrum—fetal demise. Consequently, the associations reported in this study likely represent a conservative estimate of the true price of inadequate treatment; the actual biological cost, when accounting for fetal mortality, is undoubtedly higher. Following these criteria, a total of 101 eligible mother-infant pairs were retained for the final analysis.

The study rigorously operationalized variables to dissect the nuances of therapeutic timing versus therapeutic quality. Independent variables (maternal exposures) were consisted of; (1) Maternal serologic testing time: This variable stratified mothers based on the gestational age at which the first reactive serology was documented. It was categorized into trimesters: 1st trimester (<14 weeks), 2nd trimester (14–28 weeks), and 3rd trimester (>28 weeks). This categorization serves as a proxy for the window of opportunity available for intervention; (2) Maternal treatment adequacy: Moving beyond the binary treated/untreated metric, we employed a strict definition of adequacy based on the 2021 Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) guidelines. Adequate treatment was defined as the receipt of benzathine penicillin G (BPG) at a dosage of 2.4 million units intramuscularly. For primary, secondary, or early latent syphilis, a single dose was required. For late latent syphilis or syphilis of unknown duration, the protocol required three doses at weekly intervals. Crucially, the final dose must have been completed more than 30 days prior to delivery to ensure sufficient transplacental passage and spirocheticidal levels in the fetal compartment. The category of inadequate treatment captured any therapeutic deviation. It included mothers treated <30 days before delivery (insufficient time for fetal cure), those with missed doses in a multi-dose regimen, those with an inter-dose interval exceeding 7 days (allowing for spirochetal regrowth), or those treated with non-penicillin regimens (such as macrolides like erythromycin) which have poor placental transfer and unreliable efficacy. Untreated category was defined as mothers who received no treponemicidal therapy during the current pregnancy.

Dependent variables (neonatal outcomes) were consisted of; (1) Severe clinical manifestations (primary outcome): A significant methodological challenge in congenital syphilis research is circularity in diagnosis. The standard case definition for possible congenital syphilis often includes infant born to a mother with inadequate treatment as a criterion. Using this definition as an outcome variable when maternal treatment is the predictor would create a tautology (circular reasoning). To mitigate this, we constructed a composite endpoint of physical and biological severity that is independent of maternal history. This endpoint required the presence of objective pathology; (i) Hepatosplenomegaly: Clinically palpable liver >2 cm or spleen >1 cm below the costal margin; (ii) Severe cutaneous lesions: Presence of pemphigus syphiliticus (bullous lesions) or extensive desquamating rash; (iii) Pseudoparalysis: Clinical evidence of Parrot's pseudoparalysis secondary to osteochondritis; (iv) Hematological failure: Severe thrombocytopenia (<100,000/μL) or severe anemia necessitating packed red blood cell transfusion; (2) Neonatal biometrics: Standard anthropometric data were collected to assess the uncoupling hypothesis. Prematurity was defined as birth <37 completed weeks of gestation. Low birth weight (LBW) was defined as birth weight <2500 grams; (3) Congenital syphilis diagnosis: For descriptive comparison with existing literature, cases were also stratified into proven/possible versus less likely based on the standard CDC case definitions.

Data management and analysis were conducted using IBM SPSS Statistics version 29.0 and R Statistical Software (version 4.3.1). Descriptive statistics (frequencies, percentages, means, and standard deviations) were utilized to characterize the baseline demographics of the cohort. Bivariate analysis employed Chi-square tests or Fisher's exact tests (for cell counts <5) to assess preliminary associations between maternal factors and neonatal outcomes. A critical statistical challenge emerged during preliminary analysis: the phenomenon of quasi-complete separation. Specifically, the data revealed that zero infants with benign outcomes (less likely CS) were born to untreated mothers. In standard maximum likelihood estimation (MLE) used by logistic regression, a zero cell count causes the likelihood function to fail to converge, resulting in infinitely large parameter estimates (such as odds ratios >200 or

approaching infinity) and astronomically wide, meaningless confidence intervals. To address this sparse data bias, we employed Firth's penalized likelihood logistic regression. This method, originally proposed by David Firth (1993), introduces a bias-reduction term (Jeffreys invariant prior) into the likelihood function. By penalizing the likelihood function, this approach effectively shrinks the extreme estimates caused by separation, providing finite, convergent, and scientifically robust adjusted odds ratios (aOR) and confidence intervals even in the presence of zero cell counts. This method is considered the gold standard for analyzing rare events or separated data in clinical epidemiology. Finally, model diagnostics included a check for multicollinearity between the temporal variables serologic testing time and treatment timing. Variance inflation factors (VIF) were calculated and found to be <2.5, indicating that while correlated, the variables provided sufficiently distinct information to be included in the same model without violating assumptions. Statistical significance was established at a two-tailed p-value <0.05.

3. Result

Table 1 summarizes the baseline demographic and clinical profiles of the 101 mother-infant pairs included in the analysis. The maternal cohort was predominantly within the prime reproductive age range of 20–35 years (75.2%) and characterized by lower-to-secondary educational attainment, with only 14.8% completing tertiary education. A substantial gap in early antenatal detection was evident, as the majority of mothers (62.4%) were screened late in the third trimester, while only 4.0% accessed screening during the first trimester. Consequently, therapeutic management was suboptimal for the majority of the cohort. Only 47.5% of mothers received adequate treatment defined by CDC guidelines; the remaining 52.5% were either untreated (27.7%) or received inadequate therapy (24.8%) characterized by deviations in timing or dosage. This prevalence of suboptimal care correlated with a high burden of disease: 58.4% of neonates were classified as having Proven or Possible Congenital Syphilis. Furthermore, severe clinical manifestations—indicating deep visceral or hematological involvement—were present in 22.8% of the cohort, reflecting the significant morbidity associated with missed opportunities for intervention.

Table 2 provides a granular analysis of the specific clinical phenotypes observed in the 23 neonates who met the criteria for severe disease. The data reveals a distinct predominance of visceral and hematological pathology over the classic mucocutaneous signs often associated with congenital syphilis. Hepatosplenomegaly was the most ubiquitous manifestation, affecting 78.3% of severe cases, a finding likely driven by intense reticuloendothelial activation and extramedullary hematopoiesis in response to high spirochetal loads. Hematological dyscrasias were also prominent, with 60.9% of infants exhibiting severe thrombocytopenia (<100,000/μL) and 21.7% requiring transfusion for severe anemia, reflecting significant bone marrow suppression and peripheral destruction. Notably, the classic desquamating rash (pemphigus syphiliticus), typically considered a hallmark of the disease, was present in only 39.1% of these severe cases. This clinical distribution supports the study's hypothesis regarding the uncoupled phenotype: in late-treated or untreated pregnancies, the fetus often presents with an acute, sepsis-like fetal inflammatory response syndrome (FIRS)—characterized by organomegaly and cytopenias—rather than the growth restriction or dermatological stigmata associated with chronic, early-gestation infection.

Table 1. Baseline Demographic and Clinical Characteristics of Mother-Infant Pairs (N=101)

CHARACTERISTIC	CATEGORY	FREQUENCY (N)	PERCENTAGE (%)
Maternal Age	< 20 years	12	11.9
	20 – 35 years	76	75.2
	> 35 years	13	12.9
Maternal Education	Primary / Junior High	45	44.6
	Senior High School	41	40.6
	University	15	14.8
Maternal HIV Status *(Co-infection)*	Negative	96	95.0
	Positive	5	5.0
Maternal Serologic Testing Time	1st Trimester (<14 weeks)	4	4.0
	2nd Trimester (14–28 weeks)	34	33.7
	3rd Trimester (>28 weeks)	63	62.4
Maternal Treatment Adequacy *(Per CDC Guidelines)*	Adequate	48	47.5
	Inadequate (Dose/Time deviation)	25	24.8
	Untreated	28	27.7
Neonatal Diagnosis	Proven / Possible CS	59	58.4
	Less Likely / Unlikely	42	41.6
Severe Clinical Manifestations *(Visceral/Hematological)*	Present	23	22.8
	Absent	78	77.2

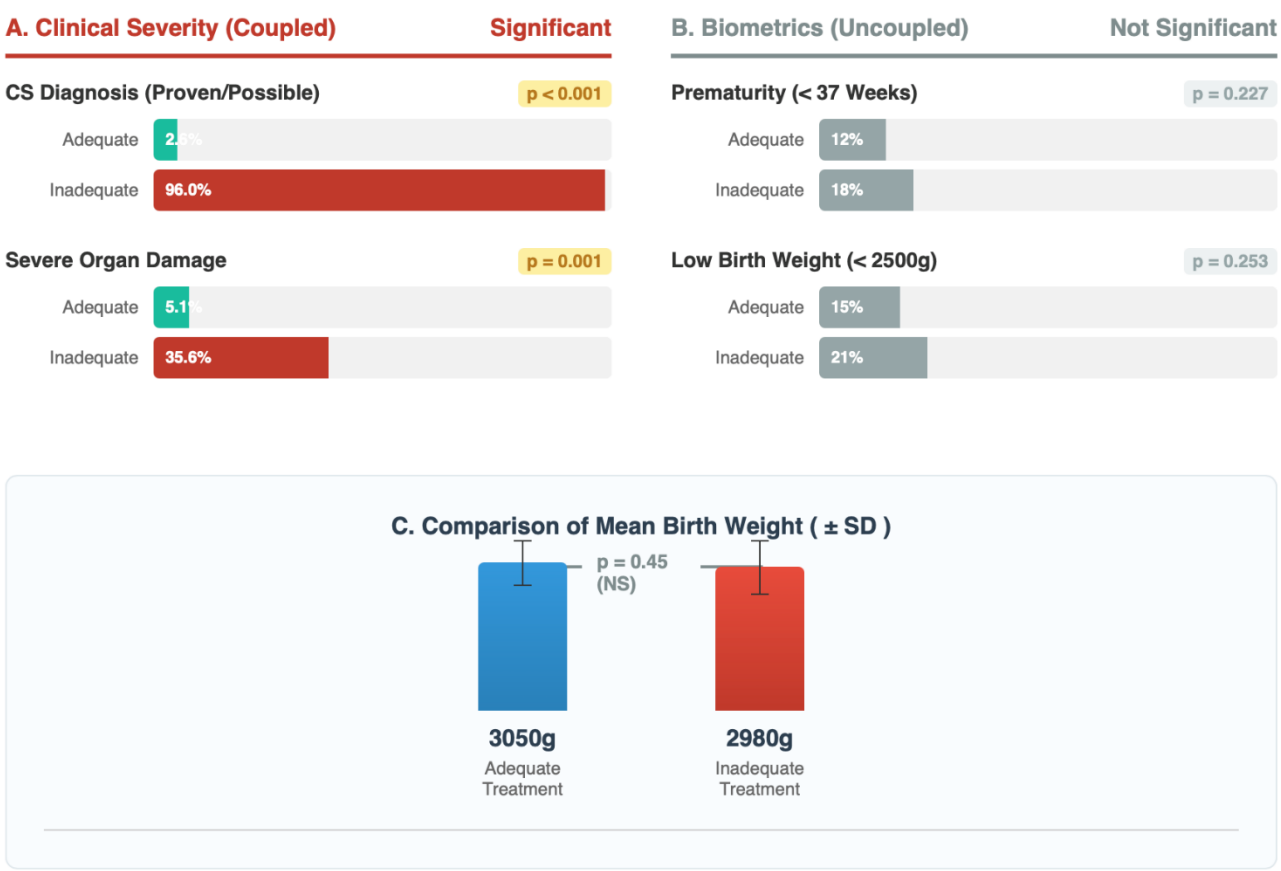
Note: Data are presented as frequency (n) and percentage (%). **CS:** Congenital Syphilis. **CDC:** Centers for Disease Control and Prevention. Severe manifestations defined as hepatosplenomegaly, severe rash, pseudoparalysis, or hematological failure.

Table 2. Spectrum of Severe Clinical Manifestations (n=23)

CLINICAL SIGN	FREQUENCY (N)	PERCENTAGE (%)	*PATHOPHYSIOLOGICAL CORRELATE*
Hepatosplenomegaly	18	78.3%	*Reticuloendothelial activation / Extramedullary hematopoiesis*
Thrombocytopenia (<100,000/μL)	14	60.9%	*Splenic sequestration / Peripheral immune destruction*
Elevated Direct Bilirubin	11	47.8%	*Syphilitic hepatitis / Cholestatic inflammation*
Desquamating Rash (Pemphigus Syphiliticus)	9	39.1%	*High spirochetal burden in dermis / Epidermal necrolysis*
Osteochondritis / Pseudoparalysis	6	26.1%	*Periosteal inflammation / Metaphyseal destruction*
Severe Anemia (Requiring Transfusion)	5	21.7%	*Hemolysis / Bone marrow suppression*

Note: Patients may exhibit multiple overlapping signs; therefore, percentages do not sum to 100%. Data represents the subset of infants (n=23) classified as having severe clinical manifestations among the "Proven/Possible CS" group.

Figure 1 provides a multi-panel visualization of the uncoupling phenomenon, delineating the divergent impact of maternal treatment adequacy on different domains of neonatal health. Panel A (left) illustrates the coupled relationship between treatment status and clinical pathology. It demonstrates that inadequate maternal treatment is a potent, statistically significant driver of adverse outcomes, associated with a near-universal risk of congenital syphilis diagnosis ($p < 0.001$) and a substantially elevated risk of severe visceral organ damage ($p = 0.001$). This confirms that therapeutic fidelity is directly linked to the suppression of spirochetal proliferation and the prevention of the fetal inflammatory response syndrome (FIRS). In stark contrast, panel B (right) and panel C (bottom) illustrate the uncoupled relationship regarding fetal growth. Panel B reveals that traditional biometric markers—prematurity ($p = 0.227$) and low birth weight ($p = 0.253$)—showed no statistically significant association with maternal treatment status. This lack of correlation is further reinforced by the continuous data in panel C, which compares mean birth weights. Infants born to inadequately treated or untreated mothers had a mean birth weight (2980g ± 510g) that was statistically indistinguishable ($p = 0.45$) from those born to adequately treated mothers (3050g ± 420g). Collectively, these panels empirically support the hypothesis that late-gestation syphilis acts primarily as an acute systemic infection causing visceral damage, rather than a chronic teratogen causing growth restriction, thereby rendering anthropometry an unreliable triage tool.



*Key: **NS** = Not Statistically Significant. Bars in Panel A represent prevalence of adverse outcomes. Bars in Panel C represent mean weight in grams.*

Figure 1. Bivariate analysis of maternal determinants.

Table 3 presents the results of the multivariate analysis, specifically utilizing Firth's Penalized likelihood logistic regression to mitigate the sparse data bias inherent in the high-risk "untreated" cohort. This rigorous statistical approach allowed for the stabilization of parameter estimates that would otherwise be inflated in standard maximum likelihood models due to quasi-complete separation. The model definitively identifies inadequate maternal treatment (comprising both untreated mothers and those with therapeutic deviations) as the single most potent independent predictor of severe neonatal morbidity. The adjusted odds ratio (aOR) for the inadequate/untreated group is 85.40 (95% CI: 14.20–512.55; $p < 0.001$). This magnitude of effect is profound, indicating that when controlling for potential confounders such as maternal age and education, the odds of a neonate developing severe visceral or hematological manifestations are over 85 times higher if the mother receives suboptimal care compared to CDC-compliant therapy.

In comparison, while delayed serologic testing (occurring in the 3rd trimester) remained a statistically significant risk factor (aOR= 4.82; p= 0.031), its predictive power pales in comparison to the impact of treatment adequacy. This hierarchy of risk underscores a critical clinical axiom: while early screening provides the opportunity for intervention, it is the fidelity of the treatment—specifically the strict adherence to penicillin protocols and timing relative to delivery—that ultimately determines fetal prognosis. The data confirms that screening without perfect treatment offers negligible protective value against the systemic devastation of congenital syphilis.

Table 3. Firth's Penalized Logistic Regression: Predictors of Severe Clinical Manifestations

RISK FACTOR	AOR (Adjusted Odds Ratio)	95% CI (Confidence Interval)	P-VALUE
MATERNAL SEROLOGIC TESTING TIME			
1st / 2nd Trimester *(Reference)*	1.00	–	–
Delayed (> 28 Weeks)	4.82	1.15 – 20.14	0.031
MATERNAL TREATMENT ADEQUACY			
Adequate *(Reference)*	1.00	–	–
Inadequate / Untreated*	85.40	14.20 – 512.55	< 0.001

Note: The multivariate model was adjusted for maternal age, parity, and education level.
***Inadequate / Untreated:** Combined category used to assess the overall impact of suboptimal care versus optimal care.
Firth's Method: Penalized likelihood regression was utilized to correct for sparse data bias and quasi-complete separation observed in the untreated group.

4. Discussion

The principal and most consequential finding of this study is the overwhelming statistical dominance of treatment adequacy over screening timing as the primary determinant of neonatal prognosis. Our penalized multivariate analysis generated an adjusted odds ratio (aOR) of 85.40 for suboptimal treatment. This figure is of such magnitude that it transcends mere statistical significance to become a profound biological signal, indicating a near-deterministic relationship between therapeutic failure and neonatal morbidity. While previous public health literature has rightly emphasized the importance of early antenatal screening—reflected in our data by the significant but comparatively modest aOR of 4.82 for delayed testing—our results suggest that the test-and-treat cascade is fragile. Screening provides the opportunity for intervention, but it is the fidelity of the therapeutic execution that determines the biological outcome.

This primacy of adequacy is rooted deeply in the unique microbiology of *Treponema pallidum* and the pharmacokinetics of benzathine penicillin G (BPG). Unlike many bacterial pathogens that replicate rapidly, such as *Escherichia coli* which divides every 20 minutes, *T. pallidum* is an exceptionally slow-growing organism with a replication time of approximately 30 to 33 hours. This sluggish division rate creates a specific therapeutic vulnerability but also a significant challenge. Beta-lactam antibiotics like penicillin are time-dependent killers; their efficacy relies not on achieving a high peak concentration, but on maintaining a serum concentration above the minimum inhibitory concentration (MIC) for a duration sufficient to cover multiple replication cycles of the bacteria.[9-10]

In the context of pregnancy, this requirement for sustained treponemicidal levels is absolute. Benzathine penicillin G is the only agent capable of reliably crossing the placental barrier to treat the fetus while simultaneously providing the depot effect necessary to maintain therapeutic levels for the required 21–28 days. Our data confirms that the margin for error is non-existent. The inadequate cohort in our study included mothers who missed a

dose in a weekly regimen or whose treatment interval extended beyond seven days. Pathophysiologically, even a brief dip in penicillin levels below the MIC allows surviving spirochetes to resume replication, leading to a resurgence of maternal spirochetemia and renewed transplacental seeding. Consequently, our findings establish that almost treated is functionally equivalent to untreated regarding neonatal risk. The steep increase in adverse outcomes associated with non-penicillin regimens, particularly macrolides, further underscores that in the distinct physiological compartment of the gravid uterus, there is no pharmacological equivalent to penicillin, particularly given the rising prevalence of macrolide resistance due to 23S rRNA mutations.[11-13]

Perhaps the most clinically vital contribution of this study is the identification and characterization of the uncoupling phenomenon. Classical medical teaching on congenital infections, often grouped under the TORCH acronym, posits that the hallmark of intrauterine infection is growth failure—specifically intrauterine growth restriction (IUGR) and low birth weight (LBW). This is driven by the fact that many TORCH pathogens, such as Rubella and Cytomegalovirus, are viral teratogens that infect the fetus in the first trimester, directly inhibiting cellular mitosis and organogenesis during the critical phase of hyperplasia.[14,15]

However, our cohort presented a strikingly different phenotype. We observed no statistically significant correlation between maternal treatment status and neonatal biometrics (prematurity, $p = 0.227$; low birth weight, $p = 0.253$). Neonates born to inadequately treated mothers were just as likely to be full-term and normal weight as those born to adequately treated mothers. Yet, despite their robust anthropometry, these infants harbored severe visceral damage, manifested as hepatosplenomegaly (78.3%) and hematological failure. This dissociation can be explained by the distinct immunopathogenesis of syphilis in late pregnancy. In our study, the majority of infections were identified or treated in the third trimester. By this gestational age, the phase of rapid cellular hyperplasia is largely complete, and fetal bulk growth is established. Unlike viral teratogens, Treponema pallidum is not inherently cytotoxic to fetal growth plates. Instead, it is an inflammatory instigator. The damage observed is not a failure of growth, but a consequence of the fetal inflammatory response syndrome (FIRS).[16-18]

When a fetus is exposed to a high spirochetal load in the third trimester, its maturing immune system is capable of mounting a robust, albeit damaging, response. The spirochetes disseminate widely, particularly to the reticuloendothelial system. This triggers a massive release of proinflammatory cytokines, most notably tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Hepatosplenomegaly is not due to edema or congestion alone, but is driven by extramedullary hematopoiesis. The fetal bone marrow, suppressed by the inflammatory milieu, cannot keep up with demand, forcing the liver and spleen to revert to their fetal role as primary hematopoietic organs.19,20 The observed platelet destruction is a direct consequence of this immune activation, involving splenic sequestration and peripheral consumption similar to adult sepsis. This uncoupling presents a dangerous diagnostic trap. Clinicians trained to look for small, sick babies may be falsely reassured by a 3.2 kg, full-term infant. Our data serves as a stark warning: in the context of syphilis, biometrics are a poor triage tool. An infant with normal weight born to a late-treated mother may be in the throes of a silent cytokine storm, with a liver teeming with spirochetes and a bone marrow on the verge of failure.

The granular analysis of severe manifestations (Table 2) provides further insight into the changing face of congenital syphilis in the tertiary setting. Historically, the classic description of congenital syphilis emphasizes mucocutaneous signs such as snuffles (syphilitic rhinitis) and the pathognomonic desquamating rash (*pemphigus syphiliticus*) involving the palms and soles. However, in our severe cohort, these signs were present in only 39.1% of cases. Instead, the clinical picture was dominated by septic

features: hepatosplenomegaly (78.3%) and thrombocytopenia (60.9%). This aligns with emerging data suggesting that the phenotype of congenital syphilis is heavily influenced by the timing of maternal infection and treatment. The dermatologic phenotype is often associated with earlier, chronic fetal infection where the organism has had time to infiltrate the dermis. In contrast, the septic phenotype—characterized by organomegaly and hematological crash—is consistent with an acute, overwhelming bacteremia typical of late-gestation transmission or failed late treatment. This distinction is crucial for the practicing pediatrician. The absence of a rash or snuffles should never be used to rule out congenital syphilis. In a high-prevalence setting like Indonesia, any neonate presenting with unexplained thrombocytopenia or isolated hepatomegaly must be evaluated for syphilis, regardless of the absence of skin lesions.[18,19] The septic presentation is not only more common in this specific demographic but is also indicative of a high mortality risk if immediate parenteral penicillin is not administered.

While this study offers robust evidence regarding the risks of inadequate treatment, several limitations must be acknowledged to contextualize the findings. First and foremost is the exclusion of stillbirths. Syphilis is a leading cause of fetal demise, often killing the fetus before it can reach the neonatal unit. By focusing our analysis strictly on live-born infants to assess neonatal morbidity management, we have introduced a degree of survivor bias. In reality, the price of delay is far higher than our odds ratios suggest, as the most severe consequence of inadequate treatment—death in utero—was censored from the dataset. Thus, our findings should be interpreted as a conservative estimate of the true burden of disease. Secondly, the retrospective cross-sectional design limits our ability to strictly infer causality. While the temporal sequence (maternal treatment preceding neonatal outcome) supports a causal link, unmeasured confounders such as maternal co-infections (beyond HIV) or nutritional status could influence neonatal outcomes. However, the magnitude of the association (aOR > 80) makes it unlikely that confounding alone explains the results. Thirdly, our study focused on immediate neonatal outcomes during the hospitalization period. We did not have data on long-term neurodevelopmental sequelae. It remains an open and troubling question whether the asymptomatic infants born to inadequately treated mothers—those who escaped severe physical manifestations—might still suffer from subtle cognitive or auditory deficits later in childhood. This silent burden of disease represents a critical area for future longitudinal research, particularly in LMICs where follow-up resources are scarce. Finally, the study was conducted at a single tertiary referral center. While this allowed for the collection of high-fidelity clinical data on complex cases, it may limit the generalizability of the findings to primary care settings where the spectrum of disease might be milder. Nevertheless, as a referral node, our cohort likely represents the tip of the iceberg of severe cases in the region, providing a valuable snapshot of the consequences of health system failures.

4. Conclusion

In the global effort to eliminate the vertical transmission of syphilis, this study provides a critical recalibration of priorities. We have established that inadequate maternal treatment—defined by any deviation in timing, dosage, or molecule choice—is the single most catastrophic risk factor for congenital syphilis, exerting a negative impact that far outweighs the risk of delayed timing alone. The statistical signal generated by our penalized regression analysis is unambiguous: screening is futile if the subsequent treatment is not executed with absolute fidelity to established pharmacokinetic principles. Furthermore, we have delineated a distinct uncoupled clinical profile that challenges traditional diagnostic paradigms. We found that severe visceral organ involvement—including hepatosplenomegaly and hematological failure—proceeds independently of fetal growth restriction. This decoupling implies that in the era of re-emerging syphilis, the classic TORCH presentation

of a small, growth-restricted infant is an insufficient triage tool. A full-term, normal-weight neonate can harbor life-threatening systemic disease. The implications for clinical practice and public health policy in Indonesia and similar settings are clear. First, clinical protocols must shift from a passive reliance on coverage metrics to a zero-tolerance"policy for therapeutic deviations. Any interruption in the weekly penicillin regimen, or any delay in initiating treatment once a screen is positive, must be viewed as a critical incident requiring immediate remediation and neonatal alert. Second, pediatricians must maintain a high index of suspicion for syphilis in any infant with unexplained organomegaly or thrombocytopenia, regardless of birth weight or the presence of a rash. Ultimately, the price of delay is paid by the newborn; avoiding this cost requires not just testing, but the perfection of the cure.

5. References

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