

Outcome of infants born to pregnant women with syphilis: A nationwide study in Korea

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Research article

Keywords: congenital syphilis, neurosyphilis, outcome

Posted Date: August 20th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-58669/v1>

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Version of Record: A version of this preprint was published on January 22nd, 2021. See the published version at <https://doi.org/10.1186/s12887-021-02502-9>.

Abstract

Background

Although expansion of antenatal syphilis screening programs, congenital syphilis (CS) is still remaining issue. This study aimed to analyze the manifestation and progress of CS including treatment and follow-up based on nationwide study.

Methods

From the Korean National Health Insurance Service database, a total of 548 infants were examined for CS during first year of life from 2013 to 2018. Neurosyphilis and complications were investigated using International Classification of Diseases-10 codes.

Results

The birth rate from mother with syphilis was 2.8 per 10,000 live birth for 5 years, not showing tendency to decrease. One hundred forty-eight infants were proven or highly probable or possible for CS with treatment over 10 days. Sixty-six infants were possible or less likely CS with only 1-day treatment. Jaundice (56%) was most common and hearing impairment (14%), renal disease (8%), mental retardation (8%) followed. Total of 14 cases of neurosyphilis occurred. Patients who have complications such as mental retardation, eye involvement, hearing impairment and renal disease were significantly associated with neurosyphilis (OR 8.49, $P < 0.0001$). Among 250 patients with treatment, 92.8% was treated with 1 medication; Benzathine penicillin G was more used (72.4%) than aqueous crystalline penicillin G. Only 4 patients were retreated due to treatment failure. In addition to the treponemal test, fluorescent treponemal antibody-absorption was the most prescribed tool of diagnosis for follow up.

Conclusion

Sharing a standardized guideline for evaluation and treatment regimens and follow up plan at a national level is needed for maternal neonatal care leading to eradication of CS.

Background

Congenital syphilis (CS), caused by *Treponema pallidum*, is a commonly contracted disease, especially from mother to child during pregnancy or at birth by contact with maternal lesions, that causes substantial global morbidity and mortality.¹ Syphilis has been generally eradicated, however, it still remains in the developing world and is increasing in developed countries.^{2,3} The World Health Organization (WHO) has estimated that nearly one million pregnant women worldwide are infected with syphilis annually.⁴

The number of reported congenital syphilis has increased in Korea after the sentinel surveillance system started in 2001. A total of 94 cases were reported between 2001 and 2010; however, 99 cases were reported from 2011 to 2014.⁵ According to the data from the Korea CDC (Centers for Disease Control and Prevention), the rates of syphilis and congenital syphilis were 1.42 cases per 100,000 people and 0.05 cases per 100,000 live births in 2014.⁶ It has been inferred to be an anthropological change paralleling the rebound increase in congenital syphilis incidence.

Untreated syphilis during pregnancy transmits over 70%, and fetal or perinatal death occurs in 40% of affected infants. Unfortunately, asymptomatic neonates at term may occur in approximately two-thirds of live born cases

with untreated or inappropriately treated mothers. However, there are few national reports about infants with CS. A study in Louisiana and Florida from 2013 to 2014 showed that 20.3% of a total of 3,497 syphilis cases were in pregnant women, and 22% of them were linked to CS, including 5 stillbirths and 5 deaths after birth. Thus, for every 4.6 pregnant women with syphilis, there was 1 case of CS. Therefore, all neonates born to mothers with reactive nontreponemal/treponemal test results should be evaluated with a quantitative nontreponemal test using neonate's serum and be considered for proper treatment according to the scenario.

Treatment should be decided on the basis of identification of syphilis in the mother, adequacy of maternal treatment, presence of clinical, laboratory, or radiologic evidence of syphilis in neonate and comparisons of maternal and neonatal serologic titers. Clinical symptoms are divided into early signs during the first two years of life and late signs developing later over the first two decades of life.⁷ Hearing loss, hydrocephalus, optic nerve atrophy, and mental retardation require follow-up for at least two years.⁸ Significant renal involvements may vary from simple albuminuria to nephritis or nephrotic syndrome.^{7,9} Physicians should be aware of the various clinical features of syphilis to enable early diagnosis. However, there is limited data including the clinical manifestations and long-term outcomes.

CS is a preventable disease; however, its incidence has not decreased in the last 10 years. It is important to understand the neonatal outcomes of pregnant women with syphilis when deciding on proper treatment. This study aimed to analyze the manifestations and progress of CS including treatment and follow-up.

Methods

The Korean National Health Insurance Service (NHIS) stores healthcare data such as diagnostic codes, diagnostic tests, procedures, and prescription medications of almost all Korean residents, approximately 98% of which are covered by the NHIS and 2% by medical aid, for review and assessment.¹⁰ NHIS records include demographic data of the beneficiaries, such as age, sex, residential area, and income status.¹¹

From the NHIS-NSC (2014 ~ 2018) data, we selected infants under 1 year of age, who underwent nontreponemal and/or treponemal tests, and had been diagnosed with CS (International Classification of Diseases-10 codes: A50.0, A50.1, A50.2, A50.9). Finally, a total of 548 infants were followed up from the date of testing for CS to December 31, 2018. We used birth statistics to estimate the prevalence of congenital syphilis using the number of live births.¹² International Classification of Diseases-10 codes were used to determine the infants with clinical manifestation or complication such as jaundice, hepatosplenomegaly, ascites, renal disease, optic nerve atrophy, hearing impairment, mental retardation, intrauterine growth retardation, and hydrops fetalis. Neurosyphilis was defined as infants diagnosed with International Classification of Diseases-10 codes A52.1, A52.2, A52.3, A50.4. Treatment was provided using benzathine penicillin G or aqueous crystalline Penicillin G.

Statistical analyses

The cohort was stratified by year. One-way ANOVA and t tests were used to compare neonatal characteristics and complications among groups. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). P-values < 0.05 were considered statistically significant.

Ethics statement

In this work, all identifiable variables, including claim-, individual-, and organizational-level identification numbers, were re-generated in random to protect privacy. The study protocol was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (IRB No. 3-2019-0147).

Results

A total of 548 infants were evaluated with a nontreponemal test for the diagnosis of CS between 2014 and 2018. The birth rate from mothers with syphilis was 2.8 per 10,000 live births during the 5-year period, revealing a steady rate. Preterm infants from mothers with syphilis were 0.5 per 10,000 live births, and in-term infants were 3.0 per 10,000 live births. The distribution of prevalence by province is shown in Fig. 1. Seoul and its surrounding area showed lower incidences compared to other areas.

Among 548 infants, CS was considered unlikely in 298 infants. One hundred and forty-eight infants who were proven or highly probable or possible for CS were treated over 10 days. Sixty-six infants with possible or less probable CS were treated for only 1 day with benzamine penicillin. Males accounted for 53.4% of cases.

Jaundice was the most common symptom (56%), followed by hearing impairment (14%), renal disease (8%), and mental retardation (8%). Small for gestational age or intrauterine growth restriction was observed in 6% of cases (Table 1). A total of 14 cases of neurosyphilis occurred in the last 5 years. Among neurosyphilis patients, mental retardation occurred in one case, and hearing impairment occurred in six cases. Hearing impairment was significantly more frequent in patients with neurosyphilis than those without ($P < 0.0001$). Patients who had complications such as mental retardation, eye involvement, hearing impairment, and renal disease significantly associated with neurosyphilis (OR, 8.49; 95% CI, 2.7–26.6; $P < 0.0001$). Infants treated by aqueous penicillin showed a higher risk of complications than benzathine penicillin (OR, 2.42; 95% CI, 1.1–6.2; $P < 0.0001$). Syphilis combined with noted complications tended to increase treatment failure which resulted in prolonged treatment duration (OR, 1.09; 95% CI, 1.03–1.15; $p = 0.0005$; Table 2). Gender, preterm birth, and birth year did not significantly affect the rate of complications.

Table 1
Clinical characteristics of infants evaluated for congenital syphilis

	2014	2015	2016	2017	2018	Total
	N = 77	N = 56	N = 45	N = 32	N = 40	N = 250
Prevalence /10000 births	3.86	2.78	2.42	1.96	2.78	2.80
Male, n (%)	39 (50)	32 (57)	23(51)	16 (49)	24 (61)	134 (54)
Preterm, n (%)	3 (4)	1 (2)	0 (0)	0 (0)	1 (3)	5 (1)
Jaundice, n (%)	48 (62)	31 (58)	23 (51)	14 (45)	24 (59)	140 (56)
Hepatosplenomegaly, n (%)	2 (3)	1 (2)	0 (0)	0 (0)	1 (3)	4 (1)
Ascites, n (%)	2 (3)	1 (2)	1 (2)	0 (0)	1 (3)	5 (2)
Renal disease, n (%)	7 (9)	5 (9)	5 (11)	2 (6)	2 (5)	21 (8)
Optic nerve atrophy, n (%)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (0)
Hearing impairment, n (%)	12 (16)	8 (14)	7 (16)	6 (19)	1 (3)	34 (14)
Mental retardation, n (%)	8 (10)	7 (13)	4 (9)	0 (0)	0 (0)	19 (8)
IUGR or SGA, n (%)	4 (5)	3 (5)	3 (7)	3 (9)	2 (5)	15 (6)
Hydrops fetalis, n (%)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1(0)
IUGR, Intrauterine growth restriction; SGA, small for gestational age						

Table 2

Comparisons of characteristics between infants with and without long-term complications of congenital syphilis

Year	MR + Eye + Hearing + Renal (N = 51)	None (N = 199)	P-value	MR + Eye + Hearing (N = 33)	None (N = 217)	P-value
2014	16 (21%)	60 (79%)	0.4626	11 (14%)	65 (86%)	0.4429
2015	15 (22%)	53 (78%)		10 (15%)	58 (85%)	
2016	9 (21%)	34 (79%)		6 (14%)	37 (86%)	
2017	8 (25%)	24 (75%)		5 (16%)	27 (84%)	
2018	3 (3%)	32 (91%)		1 (3%)	34 (97%)	
Male	21 (41%)	108 (53%)	0.1248	13 (39%)	116 (52%)	0.1605
Preterm	0 (0)	7 (3)	0.6155	6 (18)	1 (0.5)	0.6986
Neurosyphilis	7 (14)	7 (3)	< 0.0001	7 (21)	7 (3)	< 0.0001
Aqueous penicillin	7 (14)	57 (28)	0.0394	3 (10)	61 (30)	0.0282
Benzathine penicillin	39 (76)	131 (63)		26 (90)	144 (70)	
Duration of Tx ≥ 10	48 (6)	165 (17)	0.1691	30 (9)	183 (15)	0.1691
MR, mental retardation; Tx, treatment						

Among 250 patients who underwent treatment, 92.8% were treated with one medication (aqueous crystalline penicillin G or benzathine penicillin G). Benzathine penicillin G was used more frequently (72.4%) than aqueous crystalline penicillin G. Eighteen patients received both benzathine penicillin G and aqueous crystalline penicillin G (Table 3). Only four patients were re-treated due to treatment failure: one each at two weeks, one month, three months, and six months. Two received aqueous crystalline penicillin G and the other two received both aqueous crystalline penicillin G and benzathine penicillin G with an average treatment duration of 15.5 days. There were no gender disparities and all were full term. The re-treatment group showed one infant with renal involvement and one infant with hearing impairment. Treatment duration for the 1st treatment was 1 day in one infant and 10 and 16 days each.

Table 3
Drugs and duration of treatment

Initial Treatment N = 250	Treatment with one drug, n(%)	232 (93%)
	Aqueous crystalline penicillin G, n(%)	80 (32%)
	Benzathine penicillin G, n(%)	182 (73%)
	Duration of treatment 1 day, n(%)	66 (26%)
	2–9 days, n(%)	36 (14%)
	≥10 days, n(%)	148 (59%)
Re-treatment N = 4	Treatment with one drug, n(%)	2 (50%)
	Aqueous crystalline penicillin G, n(%)	2 (50%)
	Benzathine penicillin G, n(%)	4 (100%)
	Duration of treatment, median(range)	15.5 (3–26)

The numbers of treponemal tests in addition to the nontreponemal test for follow-up and detail methods of treponemal tests only in 2018 are described in Table 4. In addition to the nontreponemal test, fluorescent treponemal antibody-absorption (FTA-ABS) was the most prescribed tool of diagnosis for follow-up and treponemal pallidum particle agglutination (TPPA) was the next most used tool for follow up.

Table 4

Numbers and methods of treponemal tests additionally performed with nontreponemal tests for follow-up in 2018

		At birth	1st follow-up	2nd follow-up	3rd follow-up
		N = 60	N = 11	N = 5	N = 1
Number of tests	1	38 (63)	5 (45)	3 (60)	0
	2	15 (25)	4 (36)	1 (20)	1 (100)
	3	7 (12)	1 (9)	1 (20)	0
	4	0	1 (9)	0	0
Test method	TPPA	20 (33)	8 (73)	3 (60)	0
	EIA	20 (33)	5 (45)	4 (80)	1 (100)
	FTA-ABS	48 (80)	6 (55)	1 (20)	1 (100)
	PCR	1 (2)	0	3	0

TPPA, treponema pallidum particle agglutination; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorbed test; PCR, polymerase chain reaction

Discussion

Despite the expansion of antenatal syphilis screening programs over the past few decades, syphilis continues to be a major public health concern worldwide. This is the first nationwide study on the manifestation and treatment of CS in Korea. As transplacental transmission can occur at any time during pregnancy and at any stage of maternal

disease,¹³ the WHO launched a global initiative to eliminate mother-to-child transmission of syphilis in 2007, by performing antenatal screenings during the first and third trimester for every pregnant woman. Currently in Korea, pregnant women are routinely tested for syphilis at the beginning of pregnancy, and those who are at high risk of syphilis are advised to take an additional test during the third trimester.

Syphilis in Korean adults decreased to 0.2% in 2000 compared to 2.5% in 1977. However, in recent years CS has re-emerged, both in developing and higher income countries including the USA and Canada.^{14,15} The number of CS cases declined between 2008–2012, followed by another sharp increase from 2012–2014, representing an increase in rate from 8.4 to 11.6 cases per 100,000 live births.¹⁶ From our data in the last 5 years, the number of syphilis patients tended to decrease but considering the decreasing annual birth total, the prevalence of CS fluctuated around 1.4–3.8% for the past five years, which can be related to the increasing prevalence of international marriage.⁵

Seoul and its surrounding area showed a lower incidence of syphilis compared to other areas. Disease prevalence tended to increase as with further distance from the capital and surrounding area. It can be related to the diversity of the antenatal care system and patient's compliance to antenatal care. Increasing incidence of CS in immigrant mothers were reported due to the failure of prenatal care.⁵ Gestational syphilis was shown with a higher proportion of more vulnerable women with low schooling, and women of color.^{17,18} In this study, no socioeconomic data were included, and only trends by region could be seen.

Intrauterine infection may result in spontaneous abortion, hydrops fetalis, preterm birth, and low birth weight. Clinical manifestations in infected infants within the first 1–2 months of age include hepatosplenomegaly, lymphadenopathy, rash, mucocutaneous lesions, copious nasal secretions, pneumonia, hemolytic anemia, thrombocytopenia, and skeletal involvement.¹⁹ Due to the limited maternal information in the current study, syphilis-related stillbirths/abortions were not included. Only one case of hydrops fetalis is noted and the prevalence of preterm births was 0.495 per 10000 births, compared to 2.976 per 10000 births for term birth. There were no cases of mortality after birth. For the last 5 years, male patients showed a non-significantly higher prevalence (53%), which agrees with temporal studies conducted in the United Kingdom and Brazil.^{20,21}

The surveillance of neurosyphilis, an uncommon but severe consequence of syphilis, is complex.^{22,23} Among 14 patients (2.5%) with neurosyphilis, mental retardation occurred in one case, and hearing impairment occurred in 6 cases (43%). We emphasized the importance of screening for syphilis in the central nervous system even if symptoms are lacking for a diagnosis of syphilis, because the central nervous system is crucial for neurodevelopmental outcomes. Early diagnosis and treatment are important to prevent late manifestations of the infection.

While the prognosis is considered to be very good for infants treated during the first two months of life, if left untreated, progressive disease may result in death or disability in children.²⁴ In our study, no death was noted; however, over 20% suffered from complications such as mental retardation, eye and renal involvement, and hearing impairment. The presence of complications led to a prolonged duration of treatment. Complication rates were similar throughout the 5 years except in 2018, considering the timepoint of data collection. Patients who received aqueous penicillin G had more complications and neurosyphilis compared to those who received Benzathine penicillin G. Gender and preterm infants were not significantly associated with complication risk. Besides high-

quality antenatal screening and care, early detection of neurosyphilis and appropriate treatment indications with Benzathine penicillin G can improve prognosis.

The recommended treatment for definite or probable CS is intravenous penicillin G for a total duration of 10 days. If more than one day of therapy is missed, the entire course should be restarted. In infants with possible syphilis, single intramuscular dose of Benzathine penicillin is an alternative treatment choice in select circumstances, but only if follow-up is assured.²⁵ According to our data, Benzathine penicillin G is prescribed more frequently than aqueous crystalline penicillin G, with a variable treatment duration. Four patients underwent re-treatment with various manifestations, treatment regimens, and durations, which may be due to the rare prevalence of disease and site differences. This reflects the lack of standard guidelines for evaluation and therapeutic measures of CS.

Once CS is diagnosed, serial laboratory follow-up is required to assess whether to continue treatment.²⁶ In this study, the number of tests during serial follow-up varied from 1 to 4. Method of test are also variable. Reverse sequence testing is emerging as a high throughput and cost effective method for syphilis screening.²⁷ however it is still limited in clinics. Different algorithms of follow-up tests between sites are reflected in our data. The management seems to deviate from the different algorithms of diagnosis and clinical judgement. Considering the scarce prevalence, it is important to share a standardized algorithm for the evaluation and treatment of CS at the national level to improve outcomes.

In Korea, CS cases have been reported occasionally in specific case reports. There are no published data with yearly long-term follow-up. Differences in numbers reported in the CDC(10–33 infants with proven CS) and NHIS databases indicates the clinical complexity of diagnosis and limitations of self-reporting at the proper time. A strength of this study was that it used nationwide accumulative data with updates on recent rates of CS, including long-term complications.

A limitation of this study was that it depended on infant claim data; therefore, maternal information including adequate treatment, spontaneous abortion, and stillbirths are not included. Data analysis after 2018 can add some additional trends and outcomes of CS. The data did not have records collected from laboratories, notably on the severity of conditions and health behavior of beneficiaries. Since the information was obtained from the diagnosis code entered by each hospital, there could be data omission or limited detailed information about the diseases of each subjects. There is a discrepancy between diagnoses entered in the database and the actual diseases that the patients had. Furthermore, as the claims data were generated to reimburse healthcare services eligible for coverage, non-covered healthcare services were not assessed. The information about the residence of beneficiaries may not be reliable because HIRA data is collected based on the location of providers. A beneficiary may have received healthcare services in a different area from where they actually reside.

Conclusions

In conclusion, although antenatal syphilis screening programs have expanded, CS still remains an issue in Korea. Due to the rarity of CS, sharing standardized guidelines for evaluation and treatment regimens and follow-up plans at a national level are required for improving quality of maternal neonatal care which leads to eradication of CS.

Abbreviations

CS: Congenital syphilis; WHO: World Health Organization; NHIS: The Korean National Health Insurance Service; IRB: Institutional Review Board; FTA-ABS: Fluorescent treponemal antibody-absorption; TPPA: Treponemal pallidum particle agglutination; CDC: Centers for Disease Control and Prevention

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (IRB No. 3-2019-0147) and informed consent was waived.

Consent for publication: Not applicable

Availability of data and materials: There are ethical restrictions on sharing a identified data set unless permitted by the Korean National Health Insurance Service. Data availability was subjected to the Act on Bioethics and Safety [Law No. 1518, article 18 (Provision of Personal Information)]. Contact for sharing the data or access the data can be possible only through the data committee of Korean National Health Insurance Service (<http://nhiss.or.kr>) and after permitted by the Korean National Health Insurance Service.

Competing interest: All authors have declared that they have no conflict of interest related to this study

Funding: This study was supported by a faculty research grants of Yonsei University College of Medicine (6-2016-0125). Fund supported the data collection and analysis costs and other direct costs of research.

Authors' contributions: Conceptualization: Lee SM; Methodology: Lee SM, Lim JH; Software: Lee SM, Lim JH; Validation: Yoon SJ, Shin JE, Han JH, Eun HS, Park MS, Park KI; Investigation: Lim JH; Writing original draft: Lim JH, Lee SM; Writing-reviewing & editing: Lee SM. All authors have read and approved the manuscript.

Acknowledgments: The authors thank MID (Medical Illustration & Design) for helping to design Figure 1.

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Figures

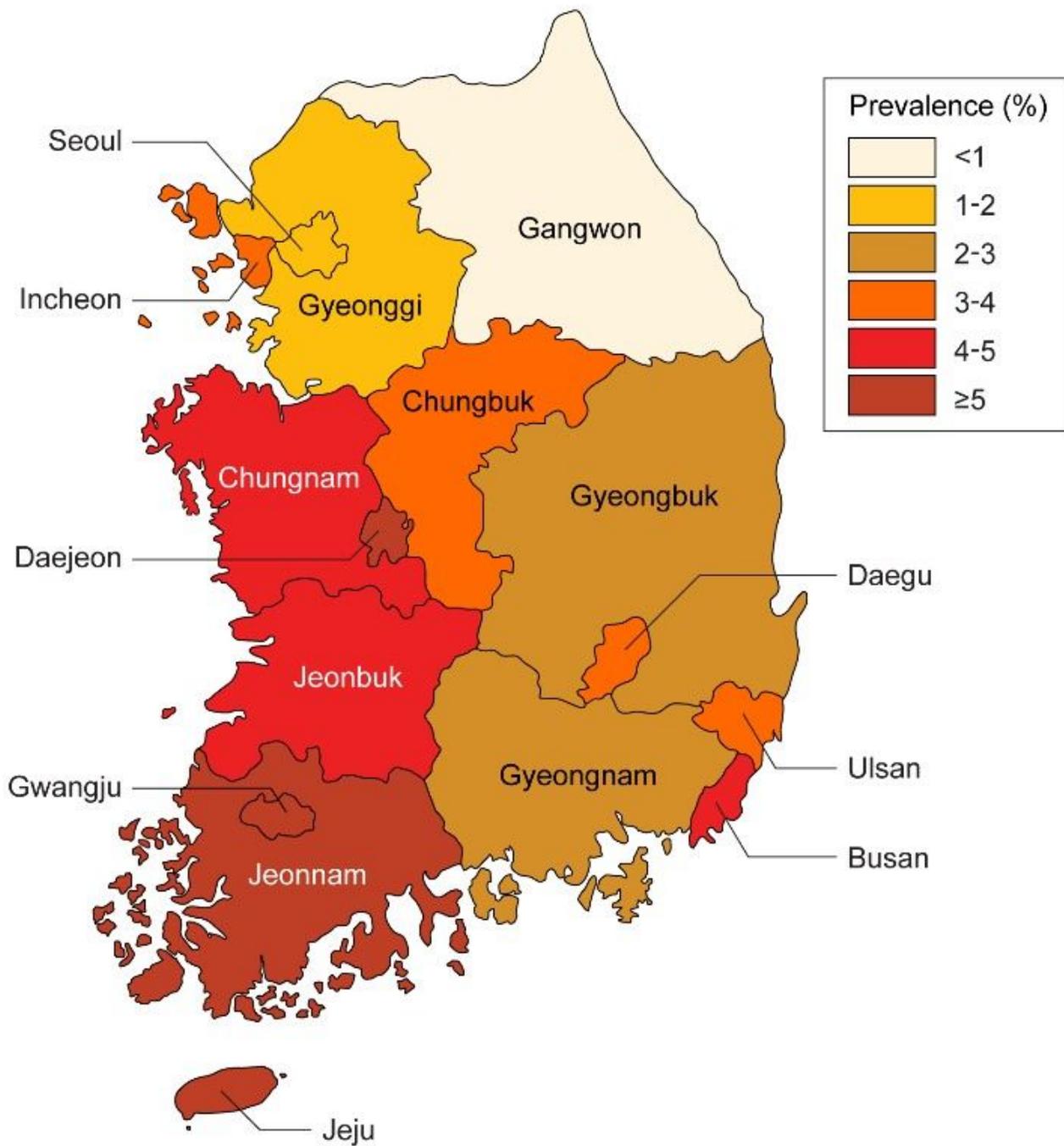


Figure 1

Prevalence of infants born to mothers with syphilis by region (/10000 births)