swiss medical weekly

Original article | Published 01 November 2024 | doi:https://doi.org/10.57187/s.3678
Cite this as: Swiss Med Wkly. 2024;154:3678

Syphilis in pregnant women and congenital syphilis from 2012 to 2021 in Switzerland: a multicentre, retrospective study

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Summary

BACKGROUND AND AIMS OF THE STUDY: Congenital syphilis is a rare complication of syphilis in pregnant women. Vertical transmission may occur at any time during pregnancy. The incidence of congenital syphilis has been increasing worldwide. Congenital syphilis has been a notifiable disease for many years in Switzerland but reporting does not include maternal features associated with syphilis in pregnancy or infant's subsequent development. We described syphilis cases among pregnant women screened over a 10-year period in Switzerland and subsequent cases of congenital syphilis, in order to identify maternal risk profiles and to optimise prevention. Second, we compared the characteristics of pregnant women screened early (1st trimester) vs late in pregnancy (2nd or 3rd trimester). Finally, we assessed the risk factors for premature birth among these women with syphilis.

METHODS: A multicentre retrospective study conducted in Swiss hospitals from 2012 to 2021, including pregnant women who screened positive for syphilis (*Treponema pallidum* haemagglutination assay [TPHA] / *T. pallidum* particle agglutination assay [TPPA] ≥1:80) and newborns exposed to *T. pallidum* in utero and/or congenitally infected and with a positive syphilis serology at birth. Data were collected from medical records.

RESULTS: A total of 147 syphilis-positive pregnant women and 102 infants were included. A history of treated syphilis was known for 44% (65/147) of the mothers corresponding to a serological scar and the remaining 56% (82/147) were newly identified syphilis cases. Syphilis screening was done during the first trimester in 54%, second trimester in 29% and third trimester in 13% of cases. Two babies were diagnosed with congenital syphilis (1.96%). Several potential factors that could contribute to women's risk of syphilis during pregnancy were identified such as a foreign origin (93% of mothers), lack of healthcare insurance (25%), no employment status (37%), drug use (5%), co-infection with other sexually transmitted infections (24%) and a late first antenatal consultation (42%). The number of pregnant women without insurance was higher in women diagnosed in the second or third trimester than in those diagnosed in the first trimester (odds ratio 0.41; 95% CI 0.19–0.89; p = 0.024). Syphilis diagnosed in the second or third trimester was associated with a late first antenatal consultation (odds ratio 77.82; 95% CI 9.81–617.21; p <0.001). A high rate of intrauterine growth retardation and of preterm birth was observed in newborns (18% versus 6% in Switzerland in 2022).

CONCLUSION: Congenital syphilis remains rare in Switzerland. However, we found potential maternal factors associated with a positive syphilis serology during pregnancy, which can help to improve future prevention measures.

The study protocol was registered on ClinicalTrials.gov (ID NCT05975502).

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Introduction

Congenital syphilis is a rare complication of syphilis, an infection caused by the spirochete *Treponema pallidum (T. pallidum)* that can be transmitted vertically at any time during pregnancy from mother to child. The estimated risk of transplacental transmission is up to 80% in untreated mothers [1]. This disease can have serious consequences on the foetus (miscarriage, stillbirth, premature birth, perinatal death, malformations, intrauterine growth retardation, etc) and can also be responsible for life-long health sequelae in the child (neurological and mental deficits, bone deformities, etc) [2]. However, congenital syphilis is easily preventable by prenatal screening and adequate early treatment of maternal syphilis. Therefore, it is universally recommended to screen for syphilis in pregnant women, regardless of their risk-taking behaviours [1].

Since 2007, eradication of congenital syphilis has been one of the World Health Organization's goals, through the reduction of the prevalence of syphilis in pregnant women and the prevention of vertical transmission [1, 3]. Despite this, resurgence of syphilis has been described worldwide since the 2000s [4], in high-income countries such as the United States [5, 6], China [7, 8], Japan [9] and New Zealand [10], but also in middle-income countries such as Brazil [11], resulting in an increase in syphilis among reproductive aged women. This higher incidence can subsequently lead to an increase in congenital syphilis cases.

Following the global trend, the incidence of syphilis in Switzerland has been increasing over the past two decades, with the most affected age group being individuals between 25 and 44 years old [12]. In Switzerland, notification of *T. pallidum* is mandatory. Coverage of antenatal screening for syphilis is high and the case rate of congenital syphilis is low, with an average incidence of 1.6 cases per year over the last ten years [13]; however there are still reported cases of congenital syphilis, particularly in vulnerable populations [14, 15]. These populations, such as undocumented migrants, remain under the radar in our current health systems. As we know, they are often not covered by health insurance so pregnant women from this population may not undergo the recommended screening. Several studies have identified the role of immigration status, the lack of medical insurance, substance use issues and sexual or domestic violence in cases of congenital syphilis [8, 10, 11, 14, 16–19]. Thus, congenital syphilis seems to be associated with particular maternal characteristics, such as specific sociodemographic and cultural features. This may lead to difficulties in accessing the healthcare system, lack of antenatal care and no adequate timely treatment of syphilis during pregnancy [20].

In this study, we evaluated cases of syphilis among pregnant women identified by screening over a 10-year period in Switzerland and subsequent congenital syphilis, to identify maternal risk profiles and enhance prevention strategies. We also compared characteristics of women diagnosed with syphilis in early pregnancy (1st trimester) versus late pregnancy (2nd and 3rd trimesters), and assessed risk factors for premature birth among women diagnosed with syphilis during their pregnancy.

Methods

Study design and population

A multicentre case series of pregnant women who screened positive for syphilis during their pregnancy and their newborns was conducted in Switzerland in major hospitals (Geneva, Lausanne, Zurich, Bern, Basel, Saint Gallen, Valais, Lugano), including all university hospitals, over a 10-year recruitment period, from 1 January 2012 to 31 December 2021. The study protocol was approved by the Swiss Association of Research Ethics Committees (study number 2022-01296) and registered on ClinicalTrials.gov (ID NCT05975502).

All pregnant women with a positive screen for syphilis (serology using *T. pallidum* haemagglutination assay [TPHA] / *T. pallidum* particle agglutination assay [TPPA] ≥1:80) and all newborns exposed to *T. pallidum* in utero and/or congenitally infected and with a positive syphilis serology at birth, were investigated. Included women had either given their hospital's general research consent or reuse of their health-related personal data was possible by virtue of the Swiss ethics law, article 34.

Patients were excluded if a document in their medical file attested a refusal of consent to reuse of their data. False-positive syphilis test results (low reactive non-treponemal tests or treponemal tests, with negative IgG immunoblot test for *T. pallidum*, on two repeated sera with at least a 1-month interval [21]) were also excluded.

All pregnant women and newborns with a positive TPHA/TPPA were selected using the medical laboratory software of dermatology, gynaecology and paediatric wards of all hospitals.

Data were collected from medical and laboratory patient records, and included sociodemographic characteristics (such as age, country of origin, couple status, presence of the partner, Swiss healthcare insurance, employment status, number of children); pregnancy data (weeks of pregnancy at first antenatal consultation, number of prenatal care visits, substances used during pregnancy, co-infection by other sexually transmitted diseases [HIV, *Chlamydia trachomatis, Neisseria gonorrhoea*, hepatitis B or C virus, *Herpes simplex* virus]); syphilis evaluation (time of diagnosis of syphilis during pregnancy, stage of disease in pregnancy, maternal and infant's subsequent therapy and syphilis serology results (Enzyme-Linked Immuno Sorbent Assay [ELISA], Venereal Disease Research Laboratory test [VDRL] / rapid plasma reagin [RPR], TPHA/TPPA, Immunoglobulins G [IgG] and M [IgM]). Follow-up data was collected for children (weight-bearing, motor and mental development, syphilis serology results) to the age of 6 years whenever available at the date of inclusion and with a follow-up implemented for more recent cases.

Definition of syphilis during pregnancy and congenital syphilis (main outcomes)

Maternal syphilis and congenital syphilis were defined according to the 2020 European guideline on the management of syphilis [22] and the CDC guideline [23]. A syphilis serological scar was defined as a positive treponemal test and a negative non-treponemal test and a history of appropriate treatment for syphilis [22].

Infants of positive mothers who did not meet congenital syphilis criteria were considered to have been "exposed in utero to *T. pallidum* and not infected".

Secondary outcome

The secondary outcome was premature birth, defined as a birth before 37 weeks of gestation.

Statistical analysis

All data were recorded in an online case report form using Research Electronic Data Capture (REDCap) software, and analysed using R software, version 4.0.3.

We used a convenient sample of all pregnant women who screened positive for syphilis during their pregnancy between 1 January 2012 and 31 December 2021 in the reference laboratories in Switzerland following the case definition. With a total of 147 women and 20 premature births, we only reported univariate logistic regression models.

Continuous variables were described by the mean ± standard deviation, the median and interquartile range (IQR). Categorical variables were described by their counts and relative percentages (including missing or unknown status). We compared continuous variables between the group of women who screened positive for syphilis during late pregnancy (2nd or 3rd trimester) and those who screened positive during early pregnancy (1st trimester) using Mann-Whitney nonparametric tests (and after exclusion of missing or unknown status); categorical variables were compared between both groups using either chi-square test or Fisher's exact test, depending on applicability criteria (and after exclusion of missing or unknown status). We quantified the association between each variable and time of syphilis diagnosis during the pregnancy by performing univariate logistic regression models on complete cases (after exclusion of missing variables). Finally, we explored the variables associated with the likelihood of premature birth by performing univariate logistic regression models.

We reported odds ratios (ORs) along with their corresponding 95% confidence intervals (95% CI). P-values <0.05 were considered statistically significant.

Results

Population characteristics

From 1 December 2012 to 31 December 2021, a total of 147 pregnant women with a positive syphilis serology and 102 children exposed in utero to *T. pallidum* and with a positive syphilis serology at birth were studied (figure 1).

Characteristics of mothers

Characteristics of mothers are reported in table 1.

The median age of pregnant women with a positive syphilis serology was 33 years (IQR 29–37).

They were mainly from outside Switzerland: 34% (47/147) from Latin America (16% from Brazil); 23% (32/147) from Africa; 14% (20/147) from Asia (5% from Mongolia) and 29% (40/147) from Europe (8% from Portugal). Only 7% (10/147) were born in Switzerland.

Mothers were single in 25% of cases (37/147). About one quarter of mothers (25% or 36/147) had no health insurance, and the number of pregnant women without insurance was higher in women diagnosed in the second or third trimester than in those diagnosed in the first trimester (OR 0.41 [95% CI 0.19–0.89], p = 0.024) (available in table S1 in the appendix).

Half of the pregnant women (72/147) had an employment status, the most frequently reported of which was cleaning (38% of cases or 27/72); 37% (55/147) had no employment status and employment status was unknown for 14% (20/147) of women.

The median number of pregnancies per woman was 3, and more than one third (35% or 52/147) of mothers had had 4

Figure 1: Study population.

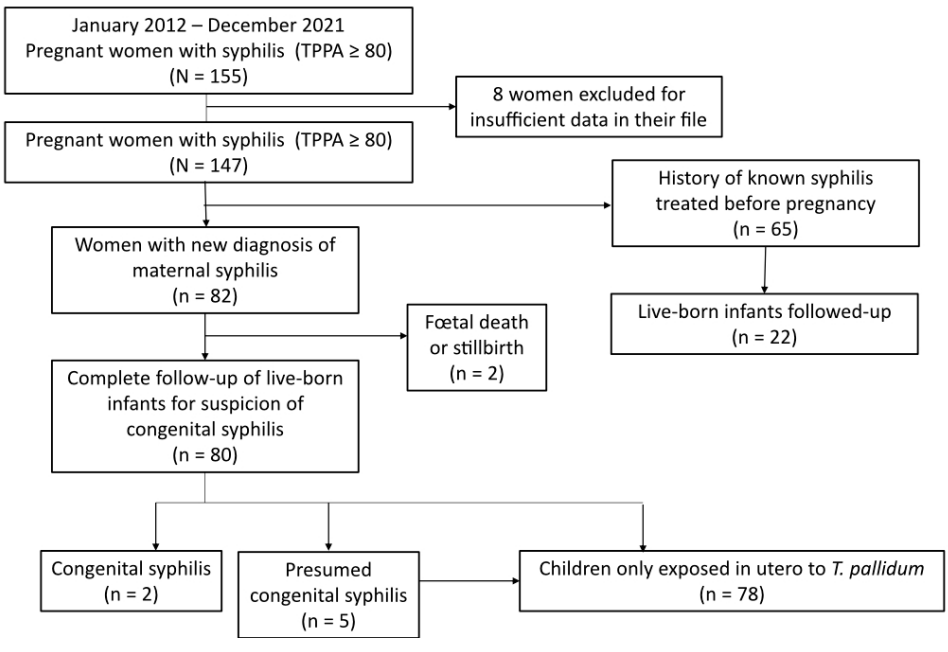

Table 1:
Characteristics of 147 mothers diagnosed with syphilis during pregnancy.

			n	%
Maternal country of origin (n = 147)	Latin America		47	34%
	Africa		32	23%
	Asia		20	14%
	Europe		40	29%
		Switzerland	10	7%
	Oceania		1	0.7%
	Unknown		7	5%
Marital status (n = 147)	Married or common-law union		108	74%
	Single or separated / divorced or widowed		37	25%
	Unknown		2	1%
Swiss healthcare insurance (n = 147)	Yes		106	72%
	No		36	25%
	Unknown		5	3%
Employment status (n = 147)	Yes		72	49%
	No		55	37%
	Unknown		20	14%
Number of pregnancies (including the current pregnancy) (n = 147)	One		25	17%
	Two		41	28%
	Three		26	18%
	Four or more		52	35%
	Unknown		3	2%
Parity (including the current birth) (n = 147)	Zero		3	2%
	One		59	40%
	Two		36	25%
	Three		30	20%
	Four or more		17	12%
	Unknown		2	1%
Previous syphilis diagnosis (n = 147)	Yes		65	44%
	No		60	41%
	Unknown		22	15%
Type of syphilis diagnosed (n = 147)	Primary syphilis		1	0.7%
	Secondary syphilis		1	0.7%
	Early latent syphilis		4	3%
	Late latent syphilis		9	6%
	Syphilis of undetermined duration		63	43%
	Serological scar		69	47%
	Unknown		0	0%
Timing of screening in pregnancy (n = 147)	First trimester		79	54%
	Second trimester		42	29%
	Third trimester		19	13%
	Unknown		7	5%
Syphilis treated in pregnancy (n = 147)	Yes		80	54%
	No (97% were serological scars / 3% were syphilis of undetermined duration)		67	46%
Syphilis treatment (n = 80)	Benzathine penicillin, 1 injection		6	8%
	Benzathine penicillin, 3 injections		72	90%
	Ceftriaxone		1	1%
	Other drugs (Penicillin G)		1	1%
Co-infection with other sexually transmitted infections in pregnancy (n = 147)	No		112	76%
	Yes		35	24%
		HIV	6	4%
		Chlamydia trachomatis	6	4%
		Neisseria gonorrhoeae	0	0%
		Hepatitis B virus	25	17%
		Hepatitis C virus	3	2%
		HSV	1	0.7%
	Unknown		0	0%
Reported use of substances during pregnancy (n = 147)	No		113	77%
	Yes		28	19%
		Alcohol	4	3%
		Tobacco	23	16%
		Intravenous drugs	2	1%

		Smoked drugs	5	3%
	Unknown		6	4%
Premature birth (n = 147)	No		82	55.8%
	Yes		20	13.6%
	Unknown		45	30.6%
			Median (IQR)	
Maternal age			33 (29–37)	
Weeks of pregnancy at first antenatal consultation			10 (8–14.5)	
Number of prenatal care visits			8 (5–11)	
Gestational age at delivery			39 (37.25–40)	

or more pregnancies. Median parity was 2, with 12% (17/147) of mothers having had 4 or more children.

Median weeks of amenorrhoea at first antenatal consultation was 10 (IQR 8–14.5) and the median number of prenatal care visits was 8 (IQR 5–11).

A history of treated syphilis prior to the pregnancy was known in 44% (65/147) of the pregnant women (corresponding to a serological scar), with new syphilis identified in the remaining 56% (82/147). Among these newly diagnosed syphilis cases, 77% (63/82) were syphilis of undetermined duration, 11% (9/82) were late latent syphilis and 5% (4/82) were early latent syphilis. Only one primary and one secondary syphilis were diagnosed.

Syphilis screening was done in the first trimester in 54% (79/147) of pregnancies, in the second trimester in 29% (42/147) and in the third trimester in 13% (19/147).

Substance use was reported by 19% (28/147) of women, of whom 5% (7/147) declared drug use (smoked or intravenous drugs), 3% (4/147) alcohol and 16% (23/147) tobacco.

24% (35/147) of mothers with syphilis presented with a concomitant sexually transmitted infection: 4% (6/147) were living with HIV, 4% (6/147) had *Chlamydia trachomatis*, 1% (25/147) had hepatitis B (mostly healed), 2% (3/147) had hepatitis C and 0.7% (1/147) had herpes simplex virus.

46% (67/147) of mothers were not treated for syphilis during their pregnancy; among the untreated mothers, 97% (65/67) had a serological scar and 3% (2/67) had syphilis of undetermined duration. Among the 54% (80/147) of mothers treated during pregnancy, 83% (66/80) were correctly treated (1 injection of benzathine penicillin G for early syphilis <1 year or 3 injections for late syphilis >1 year, as recommended by the European guideline [22]) to prevent vertical transmission. Among incorrectly treated syphilis cases, 5 of 6 early syphilis cases were treated with 3 injections of (overtreated), 5 late syphilis cases were treated with 1 injection of BPG, another late syphilis was treated with 1 injection of ceftriaxone and 1 with 1 injection of penicillin G which resulted in a congenital syphilis.

Syphilis diagnosed in the second or third trimester was associated with a late first antenatal consultation (defined as a first consultation occurring after more than 13 weeks of pregnancy; p <0.001) (table 2).

Characteristics of children

Among the 102 babies born to syphilis-seropositive women, only 2 (2%) were diagnosed with confirmed congenital syphilis, while the others were considered exposed but not infected by syphilis. Five cases were initially presumed to be congenital syphilis but the diagnosis was ultimately retracted.

There were 49% girls. Median birthweight was 3.1 kg (IQR 2.6–3.5), with 18% of infants weighing <2.5 kg and median height was 49 cm (IQR 47–51)].

Median gestational age at delivery was 39 weeks of amenorrhoea (IQR 37.25–40). Preterm delivery rate (<37 weeks of gestation) was 18%. Ten children (9.8%) were born very preterm (<32 weeks of gestation). Prematurity was observed in newborns exposed to mothers with syphilis of undetermined duration (70%), mothers with a serological scar (25%) and with late latent syphilis (5%).

Intrauterine growth retardation was observed in 9.8% (10/102) of the children.

The two cases of congenital syphilis are described in table 3. The first case of congenital syphilis occurred in a mother from Brazil who was diagnosed with syphilis of undetermined duration in the first trimester, and treated during her pregnancy but with an inappropriate treatment of 3 injections of aqueous penicillin G; the outcome was a recurrence as it was benzathine penicillin that was required. This case presented with cutaneous signs, periostitis of long bones, fever, anaemia, thrombocytopenia and intrauterine growth retardation. The second case was diagnosed in a mother who immigrated from Angola during her pregnancy, and with a positive primary syphilis screen in the third trimester. This case presented with cutaneous signs, pancreatic steatosis, osteitis, thrombocytopenia, elevated liver enzymes and bilirubin. Both cases had a positive syphilis serology at birth (with an 8-fold increase in rapid plasma reagin within 3 months after birth for the first child); the second case also had inflammatory cerebrospinal fluid with a positive non-treponemal test.

Intravenous aqueous penicillin G (150,000 U/kg) was administered in 31% (32/102) of the exposed infants for 1 or 2 days for 30 children corresponding to the time to obtain the syphilis laboratory results. The duration of this antibiotherapy was, respectively, 12 and 10 days for the two confirmed congenital syphilis cases (table 3).

We compared the maternal characteristics between premature (n = 20) and at-term births (n = 82) and we did not find any statistically significant differences (all p-values >0.05 [table 4]).

Discussion

Over a 10-year period, we reported 82 mothers newly diagnosed with syphilis during pregnancy, and only 2 confirmed cases of congenital syphilis. Fortunately, high cov-

erage of antenatal screening has kept congenital syphilis rates low in Switzerland in recent years [24].

Our study identified several potential factors that could contribute to women's risk of syphilis during pregnancy

Table 2:
Comparison of women who screened positive for syphilis during early vs late pregnancy (n = 140; 7 missing data points).

			Early pregnancy (1st trimester) (n = 79)	Late pregnancy (2nd or 3rd trimester) (n = 61)	p-value
Maternal age (mean ± SD, median: interquartile range) (n = 140)			32.8 ± 6.0, 34: 29–37	32.6 ± 6.5, 33: 28–37	0.287*
Maternal country of origin (n = 140)					0.233**
	Latin America		28 (35.4%)	18 (29.5%)	
	Africa		17 (21.5%)	13 (21.3%)	
	Asia		7 (8.9%)	13 (21.3%)	
	Europe		23 (29.1%)	15 (24.6%)	
	Oceania		0 (0%)	1 (1.6%)	
	Unknown		4 (5.1%)	1 (1.6%)	
Marital status (n = 140)					0.632***
	Married or common-law union		56 (70.9%)	46 (75.4%)	
	Single or separated / divorced or widowed		22 (27.8%)	15 (24.6%)	
	Unknown		1 (1.3%)	0 (0%)	
Swiss healthcare insurance (n = 140)					0.022***
	Yes		14 (17.7%)	22 (36.1%)	
	No		61 (77.2%)	39 (63.9%)	
	Unknown		4 (5.1%)	0 (0%)	
First antenatal visit (n = 140)					
	<13 weeks		49 (62%)	17 (27.9%)	<0.001*
	≥13 weeks		1 (1.3%)	27 (44.3%)	
	Unknown		29 (36.7%)	17 (27.9%)	
Employment status (n = 140)					0.083***
	Yes		44 (55.7%)	26 (42.6%)	
	No		25 (31.6%)	28 (45.9%)	
	Unknown		10 (12.7%)	7 (11.5%)	
Number of pregnancies (including the current pregnancy) (n = 140)					0.448***
	One		17 (21.5%)	7 (11.5%)	
	Two		20 (25.3%)	19 (31.2%)	
	Three		13 (16.5%)	12 (19.7%)	
	Four or more		29 (36.7%)	23 (37.7%)	
	Unknown		0 (0%)	0 (0%)	
Parity (including current birth) (n = 140)					0.391***
	≤2 children		54 (68.3%)	38 (62.3%)	
	≥3 children		24 (30.4%)	23 (37.7%)	
	Unknown		1 (1.3%)	0 (0%)	
Co-infection with other sexually transmitted infections in pregnancy (n = 140)					0.879***
	No		60 (76.0%)	47 (77.0%)	
	Yes		19 (24.0%)	14 (23.0%)	
		HIV	3 (3.8%)	1 (1.6%)	
		Chlamydia trachomatis	2 (2.5%)	4 (6.6%)	
		Neisseria gonorrhoeae	0 (0%)	0 (0%)	
		Hepatitis B virus	14 (17.7%)	11 (18.0%)	
		Hepatitis C virus	0 (0%)	3 (4.9%)	
		HSV	1 (1.3%)	0 (0%)	
	Unknown		0 (0%)	0 (0%)	
Reported use of substances during pregnancy (n = 140)					0.668***
	No		62 (80.5%)	46 (79.3%)	
	Yes		15 (19.5%)	12 (20.7%)	
		Alcohol	2	2	
		Tobacco	13	9	
		Intravenous drugs	1	1	
		Smoked drugs	3	2	
	Unknown		–	–	
Premature birth (n = 140)					0.180***
	No		50 (63.3%)	28 (45.9%)	
	Yes		9 (11.4%)	10 (16.4%)	
	Unknown		20 (25.3%)	23 (37.7%)	

* Mann-Whitney nonparametric test; ** Fisher's exact test; *** Chi-square test; all tests excluded missing data.

such as the lack of medical insurance, the use of drugs, concomitant other sexually transmitted infections and lack of early prenatal care. We also noted that among women with syphilis during pregnancy there was a high number of pregnancies and children per woman, higher than the Swiss national average, which was calculated as 1.52 children per woman in 2021 [25]. Most of the syphilis-positive pregnant women in our study were not from Switzerland, but mainly from Latin America, where the prevalence of syphilis is much higher than in Switzerland and no antenatal testing exists. A lot of them have an immigrant background, linked to the high immigration rate in Switzerland [26], with difficulties accessing health facilities and often a low rate of healthcare insurance [19]. Our two cases of congenital syphilis mirror findings from the Netherlands where reported cases of congenital syphilis are due to delayed or non screening of pregnant women and late or inadequate treatment [27].

Table 3:
Characteristics of the two congenital syphilis cases.

	1	**2**
Sex	M	M
Origin	Brazil	Angola
Birth weight (kg)	2.1	2.9
Gestational age (weeks)	37	38
Pregnancy stage at diagnosis	1st trimester	3rd trimester
Maternal treatment during pregnancy	Penicillin G, 3 injections	Benzathine penicillin G, 1 injection
Type of maternal syphilis	Undetermined duration	Primary syphilis
Congenital syphilis diagnosis: serologic tests and other investigations	Symptoms, 8-fold increase in rapid plasma reagin within 3 months after birth	Symptoms, cerebrospinal fluid positive
Congenital syphilis diagnosis: Clinical features	Cutaneous signs, fever, anaemia, thrombocytopenia, intrauterine growth retardation	Cutaneous signs, thrombocytopenia, elevated liver enzymes and bilirubin, pancreatic steatosis
Long bone X-ray	Periostitis of long bones	Osteitis
Cerebrospinal fluid	White blood cells 20/mm^3	White blood cells 15/mm^3, proteins 1.02 g/l, non-treponemal tests positive
Treatment	Penicillin G IV 50,000 IU/kg, 12 days	Penicillin G IV 50,000 IU/kg, 10 days
Outcome	Normal psychomotor development; severe growth retardation	Normal psychomotor development

Table 4:
Risk factors for premature birth among pregnant women infected by syphilis (complete case analysis, univariate logistic regression models).

	Odds ratio	**95% confidence interval**	**p-value**
Period of diagnosis (n = 97)			0.734
Early pregnancy (ref)	1.00	–	
Late pregnancy	1.275	0.314–5.173	
Maternal age (n = 98)	1.057	0.972–1.150	0.193
Maternal country of origin (n = 95)			0.8175
Europe	1.00	–	–
Latin America	0.89	0.25–3.20	0.854
Africa	0.95	0.22–4.16	0.946
Asia	1.52	0.33–6.96	0.590
Marital status (n = 100)			0.148
Married or common-law union	1.00	–	
Single or separated / divorced or widowed	2.140	0.762–6.010	
Swiss healthcare insurance (n = 97)			0.781
Yes	1.00	–	
No	0.850	0.270–2.675	
Employment status (n = 86)			0.752
Yes	0.848	0.305–2.356	
No	1.00		
Number of pregnancies (including the current pregnancy) (n = 101)			0.707
One	1.00	–	–
Two	0.739	0.203–2.695	0.647
Three	0.354	0.062–2.017	0.242
Four or more	0.680	0.187–2.466	0.557
Parity (including the current birth) (n = 100)			0.830
≤2 children	1.00	–	
≥3 children	0.890	0.307–2.581	
Co-infection with other sexually transmitted infections in pregnancy (n = 102)			0.110
No	1.00	–	
Yes	2.405	0.820–7.054	
Reported use of substances during pregnancy (n = 96)			0.802
No	1.00	–	
Yes	0.840	0.215–3.278	

All these socioeconomic factors may contribute to barriers hampering timely and adequate prenatal screening and care, leading to missed diagnosis and treatment of syphilis in pregnancy. Ensuring that all pregnant women, even the most socially underserved women, have access to prenatal care and healthcare services (for example for free in cases of illegal immigration) is crucial. When risk factors and features indicating an elevated maternal risk profile are identified, focused preventive measures during pregnancy should be implemented. In our cohort, only half of the women were screened for syphilis during the first trimester. To maintain congenital syphilis at a low incidence, screening of syphilis during the first trimester of pregnancy should be mandatory. As congenital syphilis has also been described as a result of late maternal infection after screening was performed or re-infection following treatment of maternal syphilis [24, 28], syphilis serology should also be repeated during pregnancy. When maternal risk factors are identified (living in a community with high syphilis morbidity or at risk of syphilis acquisition during pregnancy [drug use, sexually transmitted infections during pregnancy, multiple partners, a new partner, partner with sexually transmitted infections]), closer monitoring with repeated serologies should be done at least at the beginning of the third trimester (28 weeks of amenorrhoea) and again at delivery, as recommended by the European guideline [22] and the CDC [23]. A study in Florida and Louisiana has shown that a universal repeated third trimester screen effectively prevented most congenital syphilis cases [29]. Adequate surveillance and reporting systems are also necessary to monitor the prevalence of syphilis and congenital syphilis cases as underreporting or incomplete data can hinder the assessment of the problem and the development of effective interventions. A proactive sentinel network could be developed with tools that could send electronic alerts to the various specialists involved (biologist, gynaecologist, paediatrician, infectious diseases specialist, dermatologist) when a syphilis serology comes back positive, in order to track, treat and follow these pregnant women. Moreover, ensuring that the partners of pregnant women with syphilis are notified and treated is essential to prevent reinfection and transmission to the unborn child. This can be challenging, especially when individuals are not willing to disclose their infection or when partners are difficult to reach in vulnerable or illegal populations.

We observed in our cohort a low birthweight with 18% (95% CI 10.8–26.4%) of infants weighing <2.5 kg, a higher rate than in the general population (6% in Switzerland in 2022 [30]). A high rate of intrauterine growth retardation and of prematurity (18%; 95% CI 11.6–27.6%) was also seen, which is higher than in the general population (6% of children were born preterm in Switzerland in 2022 [30]). This may be related to syphilis but also to other confounding factors such as tobacco or drug use, alcohol, multiple pregnancies, other sexually transmitted infections, a late maternal age, late or no health care during pregnancy or environmental factors such as domestic violence, lack of social support, etc. These risk factors are also more common in economically disadvantaged populations.

Despite a reported high rate of screening, our findings highlighted some inadequacies in the management of syphilis-positive pregnant women [31]. Of those who received treatment, 18% (14/80) were not treated as recommended by the European guideline. Among them, 5 of 6 cases of early syphilis were treated with three injections instead of the recommended one. This possibly reflects a precautionary approach to treatment, whereas insufficient dosages are of greater concern. One of the congenital syphilis cases was due to an inadequate treatment and illustrates well that a lack of knowledge in the treatment of pregnant women with syphilis can have serious consequences. Regular errors in penicillin formulations and dosages are still observed in many countries. In addition, a regular shortage of benzathine penicillin has been reported in many European countries [32] which sometimes leads to the use of alternative treatments that do not cross the foetoplacental barrier.

While our study highlights characteristics of a vulnerable population that could benefit from a targeted preventive intervention, there are several limitations. First, syphilis cases in pregnant women in this study only partially represent cases reported in Switzerland (62%, 147/236) during the 10-year period as some pregnancy screening was performed in private practices. However positive syphilis serologies are most of the time referred to university hospitals to be handled, so it is likely that cases not reported in this study correspond to syphilis serological scars. Second, follow-up data in children was limited, leading to potential missed congenital syphilis revealed after the neonatal period. Third, we did not obtain data from a few women who could have been at high risk of syphilis (8 women or 5.8%) due to the retrospective collection of data. Lastly, again owing to retrospective collection of data from medical files, some information is missing such as women's educational level, which was poorly documented (unknown in 71% of cases), male partner syphilis status, which was not obtained from the mother's file. The rate of reinfection during pregnancy was also not evaluated. Therefore, some risk factors may have been overlooked.

Conclusion

Women who had a positive syphilis screening test in pregnancy presented several health determinants, such as late antenatal consultation and preterm delivery, especially in vulnerable population groups, which deserve more targeted prevention. Such determinants should be identified to improve surveillance and healthcare. Moreover, we highlight the importance of better treatment knowledge for infrequent diseases.

Open science

Data will be shared on an open data repository on Yareta / University of Geneva.

Acknowledgments

With contributions of the Clinical Research Center, Geneva University Hospitals and Faculty of Medicine, Geneva (data manager Laurent Brodier and statistical advice Angèle Gayet-Ageron).

We would like to thank all the biologists who participated in the identification of the cases, and especially Alexis Dumoulin from the Laboratory of Bacteriology in Valais.

Financial disclosure
This work was supported by the Swiss National Science Foundation (An interdisciplinary project: searching for an integrated model to explain never-ending infectious diseases) (grant number CR-SII5-186394).

Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix: supplementary table

Table S1:
Association (univariate analyses) between women who screened positive for syphilis during early vs late pregnancy and maternal characteristics (complete case analyses, unknown status excluded).

		Odds ratio	95% CI	p-value
Maternal age, in years		0.99	0.94–1.05	0.808
Maternal country of origin	Europe (= ref)			0.248
	Africa	1.17	0.44–3.10	0.748
	Asia	2.85	0.92–8.78	0.068
	Latin America	0.99	0.41–2.38	0.974
	Oceania	–	–	–
Marital status	Married or common-law union (= ref)			0.632
	Single or separated / divorced or widowed	0.83	0.39–1.78	
Swiss healthcare insurance	Yes (= ref)			0.024
	No	0.41	0.19–0.89	
First antenatal visit	<13 weeks (= ref)			<0.001
	≥13 weeks	77.82	9.81–617.21	
Employment status	Yes (= ref)			0.084
	No	0.53	0.26–1.09	
Number of pregnancies (including the current pregnancy)	One (= ref)			0.4605
	Two	2.31	0.78–6.80	0.130
	Three	2.24	0.69–7.29	0.180
	Four or more	1.93	0.68–5.43	0.215
Parity (including the current birth)	≤2 children (= ref)			0.392
	≥3 children	1.36	0.67–2.76	
Co-infection with other sexually transmitted infections in pregnancy	No (= ref)			0.879
	Yes	0.94	0.43–2.07	
Reported use of substances during pregnancy	No (= ref)			0.862
	Yes	1.08	0.46–2.52	
Premature birth	No (= ref)			0.185
	Yes	1.98	0.72–5.46	