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Abstract: AIMS OF THE STUDY We previously reported a re-emergence of syphilis from 2006 to 2009 with detection of congenital syphilis in Switzerland. This study aimed to reassess the incidence of children exposed to maternal syphilis during pregnancy and congenital syphilis in a following 10-year period in the canton of Zurich, the most populous canton in Switzerland with the highest incidences of syphilis. METHODS Children were identified both by reviewing medical records at the four major neonatal and paediatric hospitals providing acute care in the canton of Zurich and by the serological database of the syphilis reference laboratory. Inclusion criteria for children were (a) date of birth in the period 2010-2019, (b) place of birth in the canton of Zurich, (c) evaluation for syphilis due to positive syphilis pregnancy screening and (d) age <1 year at diagnosis. Results were compared with epidemiological data provided by the Federal Office of Public Health (FOPH). RESULTS We identified and evaluated 17 children after potential exposure to maternal syphilis. Residual antibodies of a past infection were found in 11 mothers. Six children were identified as having had real exposure to asymptomatic maternal syphilis. From an epidemiological perspective, the distribution of the cases followed a similar pattern as confirmed syphilis cases in women of childbearing age reported to the FOPH. No cases of congenital syphilis were observed. CONCLUSIONS In contrast to the rise in syphilis infections, this study identified no cases of congenital syphilis in the canton of Zurich, Switzerland, in the period 2010-2019. Syphilis pregnancy screening may have prevented congenital syphilis by diagnosing and allowing adequate treatment of asymptomatic maternal syphilis.

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# Congenital syphilis in Switzerland: a retrospective cohort study, 2010 to 2019

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## Summary

AIMS OF THE STUDY: We previously reported a re-emergence of syphilis from 2006 to 2009 with detection of congenital syphilis in Switzerland. This study aimed to reassess the incidence of children exposed to maternal syphilis during pregnancy and congenital syphilis in a following 10-year period in the canton of Zurich, the most populous canton in Switzerland with the highest incidences of syphilis.

METHODS: Children were identified both by reviewing medical records at the four major neonatal and paediatric hospitals providing acute care in the canton of Zurich and by the serological database of the syphilis reference laboratory. Inclusion criteria for children were (a) date of birth in the period 2010–2019, (b) place of birth in the canton of Zurich, (c) evaluation for syphilis due to positive syphilis pregnancy screening and (d) age <1 year at diagnosis. Results were compared with epidemiological data provided by the Federal Office of Public Health (FOPH).

RESULTS: We identified and evaluated 17 children after potential exposure to maternal syphilis. Residual antibodies of a past infection were found in 11 mothers. Six children were identified as having had *real* exposure to asymptomatic maternal syphilis. From an epidemiological perspective, the distribution of the cases followed a similar pattern as confirmed syphilis cases in women of childbearing age reported to the FOPH. No cases of congenital syphilis were observed.

CONCLUSIONS: In contrast to the rise in syphilis infections, this study identified no cases of congenital syphilis in the canton of Zurich, Switzerland, in the period 2010–2019. Syphilis pregnancy screening may have prevented congenital syphilis by diagnosing and allowing adequate treatment of asymptomatic maternal syphilis.

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## Introduction

Syphilis is caused by the spirochete *Treponema pallidum* and transmitted via sexual exposure or vertical infection during pregnancy [1]. We previously reported a re-emergence of syphilis in Switzerland in the period 2006–2009, along with a substantial increase of syphilis infections in women of childbearing age [2]. The increasing number of infected women in this age group was worrisome as changes in the population incidence have been shown to be followed by similar changes in the incidence of congenital syphilis [3]. Mother-to-child transmission (MTCT) of syphilis can lead to miscarriage, stillbirth, preterm birth, low birthweight and classic disease presentations such as rash, hepatosplenomegaly, bone deformities and neurological involvement [4]. Approximately two-thirds of infants with congenital syphilis are asymptomatic at birth and usually develop symptoms by three to eight weeks in the early congenital form [5, 6]. Almost all exhibit symptoms by three months of age [7]. Less frequently, the late congenital form with dental deformities, neurological sequelae or bone involvement develops after the age of two years and may be diagnosed up to the age of six years [7, 8].

The diagnosis of congenital syphilis is complex. According to the 2020 European guideline on the management of syphilis [9], congenital syphilis is "confirmed" by identifying *T. pallidum* by dark-field microscopy or PCR in the placenta or autopsy material, exudate from suspicious lesions or body fluids (e.g. nasal discharge). Congenital syphilis is "presumed" in children with a positive treponemal serological test for syphilis (e.g. *T. pallidum* particle agglutination test [TPPA], *T. pallidum* haemagglutination test [TPHA], fluorescent treponemal antibody absorption test [FTA-Abs] or treponemal enzyme-linked immunosorbent assay [ELISA]) in combination with one or more of the following: (a) an abnormal physical examination consistent with congenital syphilis; (b) radiological abnormalities of the long bones suggestive of congenital syphilis; (c) a positive non-treponemal serological test (e.g. a Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] test) in the cerebrospinal fluid; (d) a TPPA/TPHA titre in the child's serum at least 4-fold greater than the mother's (both obtained simultaneously at birth); (e) a VDRL/RPR titre in the child's serum at least 4-fold greater

than the mother's (both obtained simultaneously at birth); (f) a 4-fold or greater increase of the titre of VDRL/RPR in the child within three months after birth; (g) a positive anti-treponemal IgM ELISA and/or immunoblot in the child's serum; and/or (h) a mother in whom syphilis was confirmed during pregnancy but who was not adequately treated either before or during pregnancy [9]. Congenital syphilis is also "presumed" in a stillborn neonate or a child >12 months of age with a positive treponemal serological test for syphilis [9].

Congenital syphilis can be prevented by early detection of maternal infection and treatment >4 weeks before delivery [10]. In Switzerland, universal syphilis pregnancy screening in the first trimester has been recommended since 2015, with repeated screening in the third trimester and close monitoring until delivery for women who are at increased individual risk [11].

In a retrospective study for the period 2000–2009 at Triemli Hospital Zurich, an urban hospital with approximately the seventh largest maternity unit in Switzerland (2175 live births in 2019), we observed one case of symptomatic congenital syphilis in 2009 [2]. The disease was caused by re-infection following adequate treatment after maternal syphilis diagnosis at a third trimester screening [2]. The epidemiological data suggested even more cases due to the rise of syphilis in Switzerland at that time. The overall syphilis incidence further increased between 2011 and 2019 from 6.4 to 8.4 cases per 100,000 persons, with the highest number of 17.2 cases per 100,000 in the major region of Zurich in 2019 [12, 13].

On a worldwide scale, congenital syphilis significantly increased from 2010 to 2019 in high-income countries such as USA and UK [5, 14, 15]. The increased number of congenital syphilis infections reflects the worldwide syphilis epidemic and growing trend of syphilis infections in women of childbearing age [16, 17].

We therefore aimed to reassess the incidence of congenital syphilis in a follow-up 10-year period (2010–2019) in the canton of Zurich, the most populous canton in Switzerland with the highest incidences of syphilis [13]. Further, we evaluated the numbers of confirmed syphilis cases among women of childbearing age and the clinical management and outcome of children exposed to maternal syphilis during pregnancy in this region.

## Materials and methods

### Ethics statement

The study was approved by the ethics committee of the Canton of Zurich (BASEC no. 2022-01556). A general consent policy was introduced at the participating hospitals between 2014 and 2021 [18]. Thus, further use of health-related personal data for this retrospective cohort study without general consent pursuant to the Swiss Federal Human Research Act (HRA, RS 810.30) [18] was allowed based on the following reasons: (a) there was a risk of discrimination against patients with syphilis upon re-contact, (b) it would have been impossible or disproportionately difficult to locate patients from this 10-year period and (c) the importance of this retrospective cohort study was considered high.

### Patients

The study was conducted at the four major neonatal and paediatric hospitals providing acute care in the canton of Zurich: University Children's Hospital Zurich, Neonatology University Hospital Zurich, Triemli Hospital Zurich and Cantonal Hospital Winterthur. The canton of Zurich had a population of 1.54 million on 31 December 2019, making it the most populous canton in Switzerland (overall population in Switzerland: 8.58 million) [19]. Inclusion criteria for children were (a) date of birth between 1 January 2010 and 31 December 2019, (b) place of birth in the canton of Zurich, Switzerland, (c) evaluation for syphilis due to potential exposure to maternal syphilis during pregnancy (e.g. a positive syphilis screening test) and (d) age <1 year at diagnosis. Older children with investigations for syphilis for reasons other than exposure to maternal syphilis during pregnancy were not included [3]. Congenital syphilis was defined according to the 2020 European guideline on the management of syphilis by fulfilling criteria for "confirmed" or "presumptive" congenital syphilis [9].

Children were identified using two complementary strategies. First, electronic medical records were systematically reviewed at each of the four hospitals for evaluation of syphilis during the study period using exactly the same algorithm, which was in line with the RECORD statement [20]. The clinical information system was screened by computer scientists applying the search terms "syphilis", "lues" and "Treponema pallidum". Next, the search results were reviewed by the infectious diseases specialists at the local site and they excluded (a) children of age ≥1 at the time of investigation for syphilis, (b) children born outside the study period and the canton of Zurich, (c) children with investigations for syphilis for reasons other than exposure to maternal syphilis during pregnancy, such as immunosuppression, immunodeficiency or serological investigation for Lyme disease (to exclude cross-reactivity between syphilis and Lyme screening assays) and (d) children who had the search term "lues" contained in another word (e.g. "blue spells").

Second, the serological database of the syphilis reference laboratory at the Department of Dermatology, University Hospital Zurich was reviewed for serological testing among children aged <1 year and born during the study period in the canton of Zurich. The syphilis reference laboratory performed all confirmatory tests in children for the four hospitals during the study period if the syphilis pregnancy screening (TPPA) was positive (≥1:80) at the local laboratory.

Uncoded data from participating hospitals and the syphilis reference laboratory was passed to the project leader (PMMS) via HIN-secured email transfer. Patients identified at the hospitals were matched with the patients included in the serological database of the syphilis reference laboratory. After merging the data, each mother-infant pair was assigned a number. The coded data were transferred to a password-protected Microsoft Excel spreadsheet, ensuring controlled access, user rights and change tracking. The key code will be destroyed after publication, and the data will be stored for 10 years.

### Epidemiological data

Epidemiological data for syphilis in the canton of Zurich was provided by the Federal Office of Public Health (FOPH). Since 2006, syphilis cases in Switzerland have to be reported to the FOPH by treating clinicians and/or laboratories. From 2006 to 2017, the reporting of detailed clinical and laboratory evaluation allowed classification by the FOPH into "possible", "probable" or "confirmed" cases, with only "confirmed" cases reported. Since 2018, the FOPH receives a more general clinical and laboratory assessment, classifying cases in a binary manner as "confirmed" or "unconfirmed", with only the former cases reported [13]. Out of this database of reported cases, total numbers of confirmed syphilis cases in Switzerland, in the canton of Zurich, and among women of childbearing age (20–44 years) in the canton of Zurich from 2010 to 2019 were extracted for this study. Further, the number of cases with congenital syphilis in residents of the canton of Zurich reported mandatorily to the FOPH [13], was compared with the number of children identified in this study.

### Clinical data

Clinical characteristics, management and outcome of children evaluated for congenital syphilis were analysed by review of the patient's medical records.

### Serological data

Detailed information on serological tests for syphilis and its interpretation, particularly in the context of MTCT, are described in international guidelines [21, 22]. The TPPA (Fujirebio, Tokyo, Japan) was used as a screening test. Confirmatory tests included the FTA-Abs (Biomérieux SA, Marcy-l'Etoile, France) until 2016 and afterwards the IgG ELISA (Euroimmun AG, Lübeck, Germany). As an activity marker, the VDRL (Dade Behring, Düdingen, Germany) was performed until 2014 and the RPR (Biomérieux SA, Marcy-l'Etoile, France) afterwards. In addition, an IgM ELISA (Euroimmun AG, Lübeck, Germany) was used. All tests were performed according to manufacturers' instructions.

### Statistical analyses

The Spearman rank correlation was used to evaluate relationships between variables. Data were analysed using the R software environment, version 4.2.2 [23].

## Results

A total of 17 children were identified and evaluated for potential exposure to maternal syphilis during pregnancy (figure 1). Clinical characteristics and serological test results of the children and their mothers are shown in table 1. The mothers of all these children had a positive TPPA result at any time during pregnancy, which was confirmed at the syphilis reference laboratory.

Eleven (65%) of the 17 children were born to mothers who had a positive TPPA result due to residual antibodies of a past (non-active) infection (table 1). A history of syphilis was only known in four of these mothers, all of whom received adequate antimicrobial treatment before pregnancy. In the other seven mothers, a previous infection was not known and was identified by pregnancy screening. In three mothers, the screening occurred only shortly before or at birth. Their children were consequently treated until negative results were obtained. A child of a mother with residual antibodies of a past infection had negative VDRL and IgM ELISA at birth but showed a positive IgM ELISA result at a 4-month follow-up. This mother was treated during pregnancy with three doses of penicillin G benzathine intramuscularly after receiving the positive screening result at 18 weeks of gestation, although there was no indication of an active infection and increased individual risk for sexually transmitted infections. The mother's VDRL and IgM ELISA remained negative during pregnancy, at delivery and two months after delivery. Physical examination was normal and there was no evidence of re-infection in this mother. The TPPA titre of the child was less than 4-fold the maternal titre at delivery (maternal titre, 1:5,120; neonatal titre, 1:5,120) and significantly declined until four months of age (1:320). The physical examination of the child was completely normal at birth, at a 4-month follow-up, at a 2-year clinical visit due to investigations for haemoglobinopathy (diagnosis of compound heterozygote states for haemoglobin C) and later during preventive medical examinations by the paediatrician. The single reactivity of the IgM ELISA at the 4-month follow-up was considered to be a false-positive result. No further follow-up serology was performed.

Finally, six (35%) of the 17 children were identified as having *real* exposure to maternal syphilis during pregnancy (figure 1). All except one of their mothers were asymptomatic and identified as having early latent or late latent syphilis detected by universal screening for syphilis in the first trimester (table 1). Only one mother had a skin lesion on the mons pubis recurring in the last two years, which was observed at a routine pregnancy examination. All mothers were adequately treated for latent syphilis with three doses of penicillin G benzathine intramuscularly >4 weeks before delivery and serological evidence of favourable response was documented at or after delivery. Physical examination was normal in all six children. They all had a TPPA titre and VDRL/RPR titre less than 4-fold the corresponding maternal titre at delivery, and/or a negative IgM ELISA result at birth. A clinical and serological follow-up was unsuspicious, but not performed in one of the six children because the maternal VDRL titre following adequate treatment decreased already more than 4-fold before birth and the clinical and serological evaluation at birth was unsuspicious. No cases of congenital syphilis, defined according to the 2020 European guideline on the management of syphilis [9], were observed during the study period. Thus, the incidence of congenital syphilis (numerator) among all (live) births in the given centres within the study period (denominator) was 0% (95% confidence interval: 0.0–0.0).

The number of cases of children exposed to maternal syphilis during pregnancy in this study was set in relation to confirmed syphilis cases from 2010 to 2019 in Zurich provided by the FOPH. In contrast to the overall increase of syphilis in Zurich (179 cases in 2010 to 375 cases in 2019), there was no correlation with cases of syphilis in women of childbearing age (figure 2). The number of cases in women of childbearing age over the study period rather

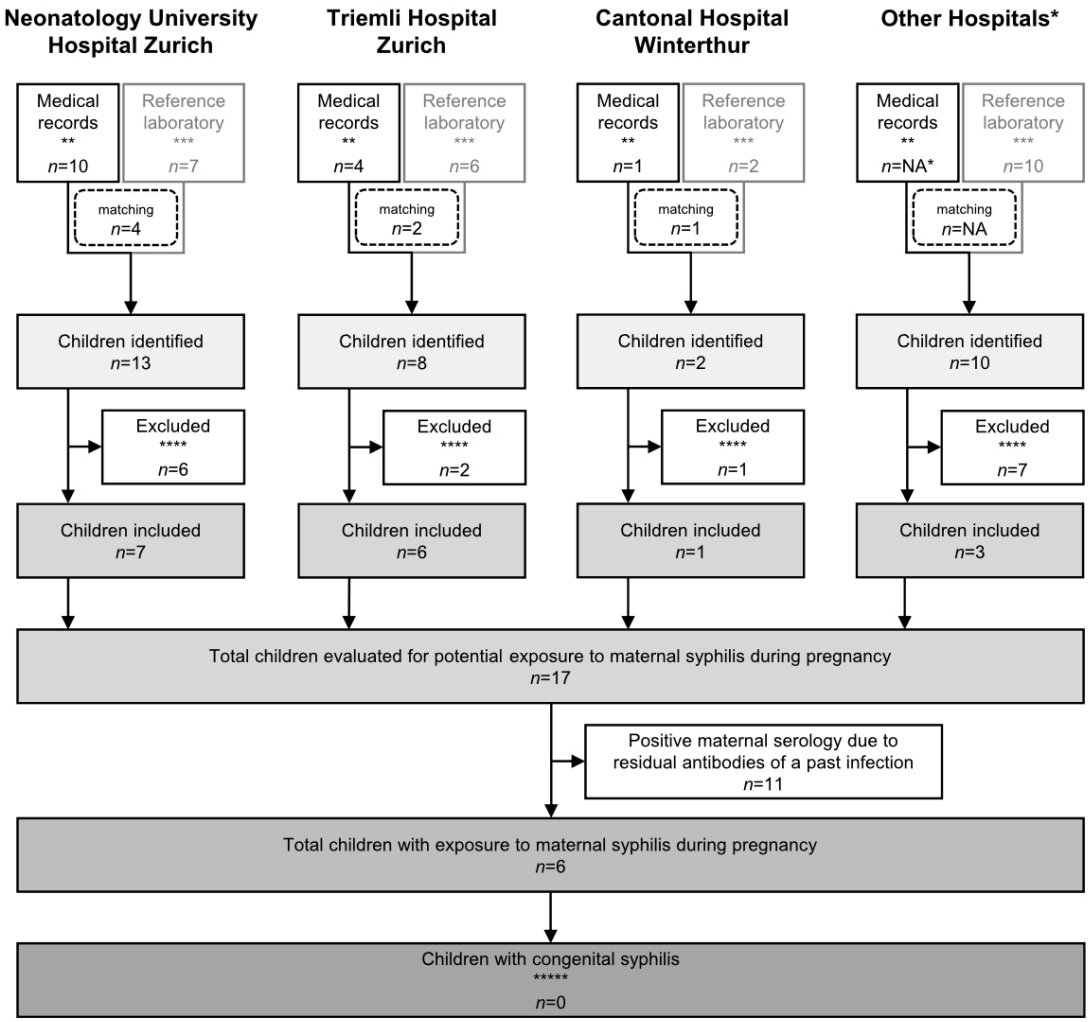
suggests a double-peaked distribution (2012 and 2017), which may be followed by a similar pattern in cases of children exposed to maternal syphilis during pregnancy in this study (2012–2013 and 2017–2018). However, numbers of cases were too small to show a statistically significant correlation. The FOPH syphilis database corroborated the findings of this study: no case of congenital syphilis was reported among residents of the canton of Zurich during the study period.

## Discussion

In contrast to the overall rise in syphilis case numbers, this study identified no cases of congenital syphilis in the canton of Zurich, Switzerland, from 2010 to 2019. The number of confirmed syphilis cases among women of childbearing age also did not follow the broader pattern of an increase of syphilis in the region. All except one of the six active syphilis cases in pregnant women identified in this study were asymptomatic and only detected through syphilis pregnancy screening. This allowed adequate maternal treatment in the early weeks of pregnancy in these cases (all before 20 weeks of gestation), and thus, prevention of congenital syphilis in all six exposed children [22]. Adequate maternal treatment and follow-up have been shown to prevent disease and sequelae in the child [24].

The most effective way to prevent congenital syphilis is to stop community transmission of syphilis. In line with the worldwide syphilis epidemic [16], cases of syphilis also significantly increased in Switzerland with the highest incidence ever reported in 2019 (8.4 cases per 100,000 population) [13]. However, there were large regional differences. The highest incidences were found in the region of

**Figure 1:** Study flow. Identification and inclusion of children with exposure to maternal syphilis during pregnancy and congenital syphilis in the canton of Zurich, Switzerland, from 2010 to 2019. * The University Children's Hospital Zurich has no maternity unit so that children evaluated for syphilis at this centre are born at other hospitals, e.g. regional maternity hospitals (majority of cases). ** Search criteria for reviewing electronic medical records: (a) date of birth between 1 January 2010 and 31 December 2019, (b) place of birth in the canton of Zurich, (c) age <1 year and (d) search terms "syphilis", "lues" and "Treponema pallidum". *** Search criteria for reference laboratory: (a) date of birth between 1 January 2010 and 31 December 2019, (b) place of birth in the canton of Zurich and (c) age <1 year. The number of children identified by both electronic medical records review and reference laboratory is indicated with a dashed box (denoted as "matching"). **** Exclusion criteria: investigations of syphilis for reasons other than exposure to maternal syphilis during pregnancy (e.g. immunosuppression, immunodeficiency or serological investigation for Lyme disease). ***** Study results were matched with the syphilis database of the Swiss Federal Office of Public Health (FOPH).



Zurich (17.2 cases per 100,000 population) and Geneva (9.4 cases per 100,000 population), where the largest urban centres are located in Switzerland [13]. Around one-third of all syphilis cases in Switzerland originated from the canton of Zurich. Urban areas provide not only easier access to medical care and diagnostics, but also to paid sex and multiple sexual partners, particularly for members of sexual minorities [13]. In contrast to previous observations from the USA [3] and Switzerland (2000–2009) [2], syphilis cases in women of childbearing age from 2010 to 2019 did

**Table 1:**
Clinical characteristics and serological test results of children with potential exposure to maternal syphilis during pregnancy (lower half) and their mothers (upper half) in the canton of Zurich, Switzerland, 2010–2019.
Abbreviations: +, positive; –, negative; d, day(s); ELISA, enzyme-linked immunosorbent assay; FTA-Abs, fluorescent treponemal antibody absorption test; GA, gestational age; Ig, immunoglobulin; i.m., intramuscular; i.v., intravenous; m, month(s); NA, not available; RPR, rapid plasma reagin test; TPPA, *T. pallidum* particle agglutination test; VDRL, Venereal Disease Research Laboratory test; w, week(s); y, year(s). Positive test results, diagnosis of active syphilis and/or treatment is indicated in bold. Early syphilis (primary, secondary or early latent) and late syphilis (late latent or tertiary) are defined within 12 months and >12 months after initial infection, respectively [22]. Late latent syphilis is presumed if the timing of an infection is unknown. Penicillin stands for penicillin G benzathine.
[1] History of syphilis before pregnancy (adequately treated). [2] Mother with recurrent skin lesion (mons pubis) since 2 years. Additional serology of the mother 60 months after treatment showed TPPA + (1,280), VDRL + (2), IgM ELISA – (0.25). No follow-up serology was performed in this child with real exposure to maternal syphilis because maternal VDRL titre decreased already more than 4-fold following adequate treatment and before birth, and the child was completely asymptomatic. TPPA was less than 4-fold the mother's and IgM ELISA was negative. [3] Treatment for group B streptococcal sepsis. [4] Child was completely asymptomatic at a 4-month follow-up, a 2-year clinical visit due to investigations for haemoglobinopathy (diagnosis of compound heterozygote states for haemoglobin C) and later during preventive medical examinations by the paediatrician.

| **Serological testing** | | | | **First serology (initial)** | | | | **Diagnosis and treatment** | | **Follow-up serology (latest)** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mother (no.)** | **Age (y)** | **Indication for serology** | **GA at diagnosis (w)** | **TPPA (<1:80) (screening)** | **FTA-Abs (+/-) / IgG ELISA (<0.9) (confirmation)** | **VDRL / RPR (<1:2) (activity)** | **IgM ELISA (<0.9) (active infection)** | **Diagnosis** | **Treatment during pregnancy** | **Course of serology (months after treatment)** | **TPPA (<1:80) (screening)** | **FTA-Abs (+/–) / IgG ELISA (<0.9) (confirmation)** | **VDRL / RPR (<1:2) (activity)** | **IgM ELISA (<0.9) (active infection)** |
| 1 | 35 | Prenatal care[1] | NA (<12) | **+ (320)** | **+** | – | – | Residual antibodies[1] | – | NA | | | | |
| 2 | 33 | At birth[1] | | **+ (80)** | **+** | – | NA | Residual antibodies[1] | – | NA | | | | |
| 3 | 24 | Prenatal care[1] | 19 | **+** | **+** | – | – | Residual antibodies[1] | – | NA | | | | |
| 4 | 41 | Prenatal care[1] | 20 | **+ (2,560)** | NA | **+ (8)** | NA | Residual antibodies[1] | – | At birth | NA | **+** | **+ (2)** | – |
| 5 | 33 | Prenatal care | 18 | **+ (2,560)** | **+** | – | – (0.08) | Residual antibodies | **Penicillin i.m. (3×)** | At birth | **+ (5,120)** | **+** | – | – (0.09) |
| 6 | 30 | Prenatal care | 9 | **+ (2,560)** | **+** | – | – (0.75) | Residual antibodies | **Penicillin i.m. (3×)** | 8 | **+ (2,560)** | NA | – | NA |
| 7 | 27 | Prenatal care | 9 | **+ (80)** | **+** | – | – (0.19) | Residual antibodies | **Penicillin i.m. (3×)** | 7 | – | NA | – | NA |
| 8 | 40 | Prenatal care | 15 | **+ (80)** | **+** | – | NA | Residual antibodies | – | NA | | | | |
| 9 | 35 | At birth | | **+** | **+** | – | – | Residual antibodies | – | NA | | | | |
| 10 | 30 | At birth | | **+ (640)** | **+** | – | – | Residual antibodies | **Penicillin i.m. (1×)** | NA | | | | |
| 11 | 31 | Prenatal care | 37 | **+** | **+** | – | – | Residual antibodies | **Ceftriaxone i.m. (1×)** | At birth | – | **+** | – | – |
| 12 | 25 | Prenatal care | 14 | **+ (5,120)** | NA | **+ (8)** | **+ (>3.5)** | **Early latent syphilis** | **Penicillin i.m. (3×)** | At birth | **+ (640)** | NA | **+ (4)** | **+ (1.76)** |
| 13 | 26 | Prenatal care | 8 | **+ (20,480)** | **+ (3.5)** | **+ (32)** | – (0.59) | **Early latent syphilis** | **Penicillin i.m. (3×)** | 6 | **+ (2,560)** | NA | **+ (2)** | – (0.37) |
| 14 | 25 | **Skin lesion[2]** | 8 | **+ (2,560)** | **+** | **+ (8)** | – (0.76) | **Late latent syphilis** | **Penicillin i.m. (3×)** | 6 | **+ (10,240)** | NA | – | – (0.72) |
| 15 | 37 | Prenatal care | 15 | **+ (1,280)** | **+ (3.5)** | **+ (8)** | NA | **Late latent syphilis** | **Penicillin i.m. (3×)** | 12 | **+ (1,280)** | NA | **+ (2)** | NA |
| 16 | 35 | Prenatal care | 10 | **+ (5,120)** | NA | **+ (16)** | – (0.4) | **Late latent syphilis** | **Penicillin i.m. (3×)** | 5 | **+ (5,120)** | NA | **+ (8)** | NA |
| 17 | 32 | Prenatal care | 6 | **+ (20,480)** | **+** | NA | NA | **Late latent syphilis** | **Penicillin i.m. (3×)** | At birth | **+ (2,560)** | **+** | **+ (2)** | – (0.55) |
| **Child (no.)** | **GA at diagnosis (w)** | **Sex** | **Birth weight (g)** | **GA at birth (w)** | **TPPA (<1:80) (screening)** | **FTA-Abs (+/-) / IgG ELISA (<0.9) (confirmation)** | **VDRL / RPR (<1:2) (activity)** | **IgM ELISA (<0.9) (active infection)** | **Diagnosis** | **Treatment** | **Course of serology (age in months)** | **TPPA (<1:80) (screening)** | **FTA-Abs (+/-) / IgG ELISA (<0.9) (confirmation)** | **VDRL / RPR (<1:2) (activity)** | **IgM ELISA (<0.9) (active infection)** |
| 1 | NA (<12) | M | 3070 | 41 | **+ (320)** | **+** | – | – | Transplacental antibodies | **Amoxicillin i.v. (10 d)[3]** | 3 | **+ (80)** | **+** | – | – (0.01) |
| 2 | At birth | M | 2720 | 41 | NA | | | | | | | | | | |
| 3 | 19 | F | 3850 | 40 | NA | | | | | | | | | | |
| 4 | 20 | M | 3750 | 39 | **+ (2,560)** | **+ (>3.5)** | – | – (0.04) | Transplacental antibodies | – | NA | | | | |
| 5 | 18 | F | 3510 | 40 | **+ (5,120)** | NA | – | – (0.08) | Transplacental antibodies | – | 4 | **+ (320)** | NA | NA | **+ (2.77)[4]** |
| 6 | 9 | M | 4350 | 38 | **+ (2,560)** | **+** | **+ (2)** | – (0.02) | Transplacental antibodies | – | 3 | **+ (160)** | NA | – | – (0.53) |
| 7 | 9 | M | 4060 | 39 | NA | | | | | | | | | | |
| 8 | 15 | F | 2520 | 38 | NA | | | | | | | | | | |
| 9 | At birth | M | 2550 | 38 | **+ (80)** | **+** | – | – (0.01) | Transplacental antibodies | **Penicillin i.m. (1×)** | 6 | – | NA | – | – (0.22) |
| 10 | At birth | M | 3600 | 40 | **+ (640)** | **+** | – | – | Transplacental antibodies | **Penicillin i.m. (1×)** | 3 | NA | NA | NA | – |
| 11 | 37 | M | 3860 | 40 | – | **+** | – | – (0.02) | Transplacental antibodies | **Penicillin i.m./i.v. (4 d)** | NA | | | | |
| 12 | 14 | F | 2970 | 38 | **+ (1,280)** | NA | **+ (2)** | – (0.01) | Transplacental antibodies | – | 3 | **+ (320)** | NA | – | – (0.30) |
| 13 | 8 | F | 2880 | 38 | **+ (10,240)** | **+ (>3.5)** | – | – (0.03) | Transplacental antibodies | – | 3 | **+ (320)** | **+ (>3.5)** | **+ (2)** | – (0.33) |
| 14 | 8 | M | 3730 | 38 | **+ (2,560)** | NA | NA | – (0.11) | Transplacental antibodies | – | NA[2] | | | | |
| 15 | 15 | F | 4370 | 40 | **+ (1,280)** | NA | – | NA | Transplacental antibodies | – | 2 | **+ (80)** | **+ (2.53)** | – | – (0.06) |
| 16 | 17 | F | 3520 | 40 | **+ (2,560)** | NA | **+ (2)** | – (0.1) | Transplacental antibodies | – | 8 | **– (<80)** | NA | – | – (0.33) |
| 17 | 6 | M | 3580 | 40 | **+ (2,560)** | **+** | **+** | – (0.11) | Transplacental antibodies | **Penicillin i.m. (1×)** | 6 | – | NA | – | – (0.12) |

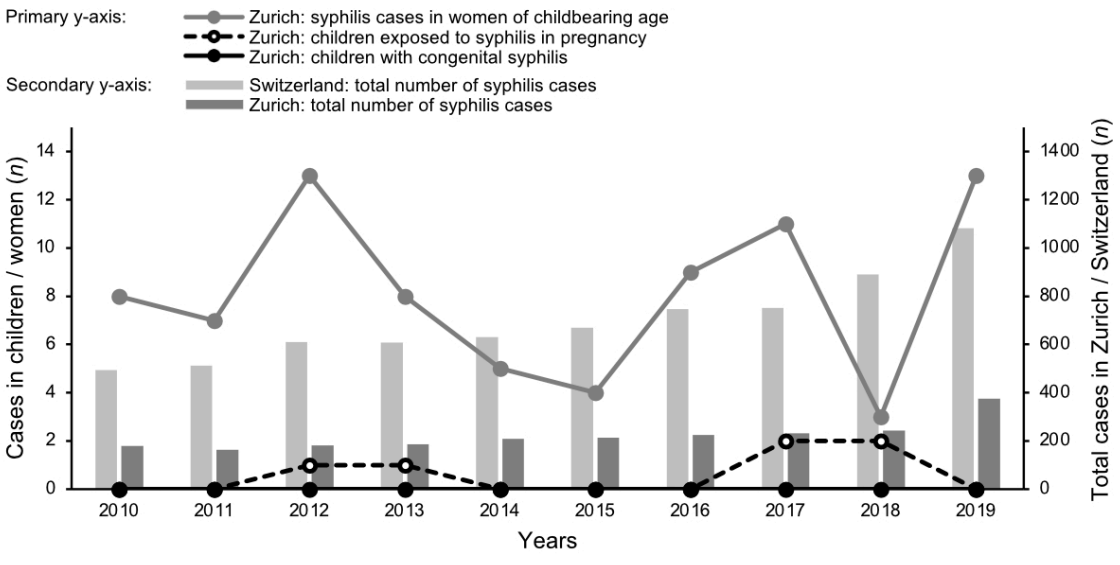
not correlate with the rise in syphilis cases in the canton of Zurich. The rise in syphilis infections in Switzerland was attributable largely to increased testing, as well as improved diagnostics and more accurate disease classification, especially in men. No clear trend was observed for the number of syphilis cases among men and women infected through heterosexual contact [12, 13]. The community of men who have sex with men (MSM) was mainly affected by syphilis, although it accounted only for an estimated proportion of 3% of the sexually active male population in Switzerland [25]. More MSM lived in the region of Zurich than in other regions of Switzerland [25], and thus, the proportion of MSM with a syphilis diagnosis was particularly high in this region [13].

Although congenital syphilis can be prevented by both universal screening in pregnancy and treatment of positive mothers >4 weeks before delivery [21, 22], the incidence of congenital syphilis is steadily increasing even in high-income countries such as the USA [15, 17]. In Switzerland, universal syphilis pregnancy screening in the first trimester, officially recommended only since 2015, seems to be effective considering that no cases of congenital syphilis have been observed in the canton of Zurich from 2010 to 2019. The results appear comparable between the study periods 2000–2009 [2] and 2010–2019, as the number of live births even significantly increased in Zurich during the 10 years (e.g. from 1654 in 2009 [2] to 2175 in 2019 at Triemli Hospital Zurich). Overall, only five cases of congenital syphilis in Switzerland were reported to the FOPH between 2011 and 2020 [13]. The mandate for reporting syphilis cases in Switzerland does not include negative screening results [13]. Thus, the overall number of screenings and prevalence is unknown. Prior to the introduction of universal syphilis pregnancy screening in 2015, there were significant differences between regions for screening of infections during pregnancy, with lower rates of reported testing in the region of Zurich (69%) compared with other regions (range 77–88%) [26]. However, feedback from cantonal medical authorities to the FOPH currently indicates an overall high level of compliance in screening (FOPH personal communication 2023).

The occurrence of congenital syphilis in high-income countries with a high rate of syphilis pregnancy screening has also been reported as a result of late maternal infection after screening was performed [27] and re-infection following adequate treatment of maternal syphilis [2]. According to international guidelines [21, 22], repeated screening in the third trimester and close monitoring until delivery for women who are at increased individual risk is also recommended in Switzerland [11]. Testing of fathers and potential sexual partners of pregnant women is additionally requested [21, 22]. Any woman who had no syphilis pregnancy screening before delivery should be screened immediately at or after birth [21, 22]. Even in the context of negative screening(s) during pregnancy, paediatricians need to be aware of the diverse manifestations of congenital syphilis and consider the disease in the differential diagnosis, also beyond the neonatal period [27, 28].

The complex diagnosis and management of maternal syphilis is reflected in this study by the diversity of the management of seropositive mothers and their children. The Centers for Disease Control and Prevention (CDC) describes four different congenital syphilis scenarios ("confirmed proven or highly probable", "possible", "less likely" and "unlikely") for the recommended evaluation and treatment of children born to women who had reactive nontreponemal and treponemal serological tests during pregnancy (VDRL/RPR-positive and TPPA/FTA-Abs/IgG ELISA-positive) and have a reactive nontreponemal test at delivery (VDRL/RPR-positive) [22]. Even though two-thirds of mothers with a positive TPPA result in this study had a negative VDRL/RPR during pregnancy (i.e. residual

**Figure 2:** Confirmed syphilis cases from 2010 to 2019 in Zurich, Switzerland, together with children exposed to maternal syphilis during pregnancy. Total numbers of children exposed to maternal syphilis during pregnancy (black dashed line) or infected during pregnancy (black line), as well as confirmed syphilis cases among women of childbearing age (20–44 years) (grey line) in the canton of Zurich are illustrated (primary y-axis). Epidemiological data for syphilis were provided by the Swiss Federal Office of Public Health (FOPH) as total numbers in Switzerland (light grey bar), in the canton of Zurich (dark grey bar) (both secondary y-axes) and among women of childbearing age (grey line) in the canton of Zurich (primary y-axis). FOPH reporting characteristics changed in 2018 as previously described in detail [13].



antibodies of a past infection), some were treated and/or the children serologically followed, which would not have been necessary according to the recommendations [22]. One of these children was the one who later demonstrated a positive IgM ELISA result at a 4-month follow-up. Although incubating congenital syphilis can be seronegative at the time of birth and later show seroconversion of non-treponemal tests and IgM ELISA [21, 22], the following constellation argued against an asymptomatic congenital syphilis in this case: a negative maternal VDRL and IgM ELISA during pregnancy, at delivery and two months after delivery; and an infant TPPA titre that was equal to the maternal titre at delivery and decreased 4-fold by the 4-month follow-up [9]. On the other hand, even if the specificity of current IgM ELISAs is very good, false-positive results may occur with any of the serological tests for syphilis [21] and false-positive IgM ELISA results have been described with negative control sera [29].

This multicentre study during a follow-up 10-year period (2010–2019) in the most populous canton with the highest incidences of syphilis provides another estimate about the epidemiology of congenital syphilis in Switzerland and the implementation of prenatal care and syphilis control programmes. The search criteria and the two complementary strategies, including the database of the syphilis reference laboratory, which performed all confirmatory tests in children for the four hospitals, allowed reliable identification of children exposed to maternal syphilis during pregnancy and/or with congenital syphilis. In this way, children with congenital syphilis could be identified including those who were exposed to late maternal infection or re-infection and/or presented with symptoms and signs of congenital syphilis beyond the neonatal period. However, the study has some limitations. First, the study is confined to the canton of Zurich. There may be geographical variations in population characteristics (members of sexual minorities) and epidemiology of congenital syphilis (five cases reported to the FOPH from 2011 to 2020). Second, most syphilis pregnancy screenings were performed in private practices and seronegative mothers also gave birth at regional maternity hospitals, so we were not able to calculate seroprevalences [2, 26]. Third, seropositive mothers may have been managed at regional maternity hospitals without confirmation of serology at the syphilis reference laboratory. Thus, the number of children exposed to maternal syphilis during pregnancy in this study may be a rough estimate of cases. Nevertheless, it is most likely that symptomatic mothers and especially children with abnormal serologies or even signs and symptoms of congenital syphilis would have been referred to one of the four major and specialised hospitals providing acute care in the canton of Zurich included in this study. The comparison of the number of cases with congenital syphilis in residents of the canton of Zurich reported mandatorily to the FOPH with the number of children identified in this study confirmed the results of this study.

## Conclusion

Contrary to the prediction based on our previous study for the period from 2000 to 2009, the rise in syphilis infections did not lead to an increase in confirmed syphilis cases among women of childbearing age in the canton of Zurich, Switzerland, from 2010 to 2019. The rise in syphilis in Switzerland was attributable to the increasing detection of syphilis in men, as a result of increased testing and improved diagnostics. The study data showed that active syphilis cases in asymptomatic pregnant women were identified and as a result there were no cases of congenital syphilis, supporting continuation of the current prenatal care and syphilis control programmes in Switzerland. The findings should guide societies of the clinical disciplines involved and public health professionals in targeting further preventive campaigns, developing clear recommendations for screening and further diagnosis and treatment of maternal syphilis and exposed children and planning prospective surveillance programmes. To this end, a national multicentre epidemiological study about congenital syphilis in Switzerland started this year and will set the results of this study in a national context.

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**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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