



STATE OF NEW YORK  
DEPARTMENT OF HEALTH

Corning Tower The Governor Nelson A. Rockefeller Empire State Plaza Albany, New York 12237

Richard F. Daines, M.D.  
*Commissioner*

Wendy E. Saunders  
*Executive Deputy Commissioner*

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Dear Physician:

The purpose of this letter is to bring your attention to the significant increase in reported cases of congenital syphilis since 2003 and one important contributing cause: cases among foreign born children placed for adoption in New York State. In 2003, twenty cases of congenital syphilis were reported in New York State (excluding New York City, which is a separate health jurisdiction). Of note, four (20 percent) of these cases occurred among children adopted internationally. In 2004, 2006 and 2007, one additional case of congenital syphilis among international adoptees was reported in each year. Medical screening of these seven adoptees identified reactive syphilis serologies. Based on local health department investigation, no medical record documentation of adequate treatment for syphilis of the biologic mother or of the infant in the home country was provided to the adopting parents or placement agency. Given the lack of documentation of prior adequate treatment and the serologic evidence of treponemal antibody, these adoptees, all of whom were greater than twelve months of age, met the federal Centers for Disease Control and Prevention case definition for congenital syphilis. The New York State Department of Health's Bureau of Sexually Transmitted Disease Control (BSTDC) recommended full medical evaluation and treatment in accordance with the Sexually Transmitted Diseases Treatment Guidelines issued by the CDC.

The prevention of congenital syphilis is the number one priority of the BSTDC, as the perinatal consequences of maternal syphilis may be severe, permanent, and potentially fatal. To promote the early identification and treatment of syphilis infection, New York State regulations require serologic screening of pregnant females at the time pregnancy is first diagnosed, and in high risk populations, again during the third trimester. Furthermore, serologic screening of cord blood at delivery is mandated for all live-born infants or stillbirths of at least 20 weeks gestation. This serologic testing is a mainstay of the Bureau's efforts to prevent congenital syphilis as the majority of infected infants are initially asymptomatic.

By law, medical providers and laboratories must report reactive syphilis serologies to the health officers of local health departments. Receipt of a reactive syphilis serology in a pregnant woman results in an immediate, priority investigation by local health department staff to determine the infection status of the individual and, if necessary, to make recommendations for medical management and treatment. Recommendations for the evaluation and treatment of congenital syphilis are based on the identification of syphilis in the (biologic) mother; adequacy of maternal treatment; and, presence of clinical, laboratory, or radiographic evidence of syphilis in the infant. A seroreactive infant who is not treated for congenital syphilis during the perinatal period should receive careful follow-up examinations at 1, 2, 3, 6, and 12 months. Nontreponemal antibody titers should decline by three months of age and should be nonreactive at six months of age if the infant was not infected and the titers were the result of passive transfer of antibody from

the mother. If titers are found to be stable or increasing, the child should be medically evaluated including a long bone radiograph and cerebrospinal fluid analysis for VDRL, cell count and protein, and receive a full ten-day course of penicillin therapy. In contrast, passively transferred treponemal antibody may persist for as long as 1 year. If they are present after 1 year, the infant is considered to be infected and should receive a baseline medical evaluation and treatment for congenital syphilis.

Enclosed with this letter please find BSTDC's addendum to the Centers for Disease Control and Prevention 2006 Sexually Transmitted Diseases Treatment Guidelines (obtain a copy at: [www.cdc.gov/std/treatment/default.htm#tg2006](http://www.cdc.gov/std/treatment/default.htm#tg2006)) as they pertain to the evaluation and management of pregnant women with syphilis and of infants at risk for congenital syphilis. Also enclosed is an article on congenital syphilis in Russia. The article documents study results that found nearly 50% of asymptomatic cases of congenital syphilis did not have a record of any penicillin treatment. Such cases were also less likely to receive clinical or laboratory follow up.

The Bureau of Sexually Transmitted Disease Control's public health mission is to control and prevent sexually transmitted diseases among residents of New York State. Accordingly, the Bureau works with medical providers to assure the best management and treatment outcomes for infected patients in compliance with national and State guidelines. Failure to comply with recommendations for the medical evaluation and treatment of infants meeting the federal case definition for congenital syphilis will be reported by the Bureau of Sexually Transmitted Disease Control to the New York State Office of Professional Medical Conduct for further investigation.

Further consultation regarding this information or assistance with the epidemiologic investigation may be obtained by contacting local Bureau of STD Control personnel located in area offices or the central office of the New York State Department of Health.

Albany Regional Office (Troy)	(518) 402-7411
Western Regional Office (Buffalo)	(716) 855-7074
Rochester Regional Office:	(585) 423-8103 or (800) 757-5803
Syracuse Regional Office	(800) 878-3827
Metro New York - Westchester Area	(914) 654-7160
Metro New York - Long Island Area	(631) 851-3095
Central Office (Albany):	(518) 474-3598

In New York City, questions should be directed to the New York City Office of Mental Health and Hygiene's STD Control Program at (212) 788-4423.

Sincerely,



F. Bruce Coles, D.O.  
Medical Director  
Bureau of STD Control

Enclosures.

# New York State Addendum for Congenital Syphilis Treatment Guidelines

The New York State Bureau of Sexually Transmitted Disease Control has issued an addendum to the Centers for Disease Control and Prevention, [Sexually Transmitted Diseases Treatment Guidelines 2006](#). These modified guidelines, presented below, reflect the Bureau's policy and procedures specifically for the evaluation and management of pregnant women with syphilis, and of infants at risk for congenital syphilis. Clinical providers are encouraged to refer to this addendum for guidance on the evaluation and treatment of syphilis in pregnant women and at-risk infants. The Centers for Disease Control and Prevention, [Sexually Transmitted Diseases Treatment Guidelines 2006](#) are referred to throughout this document.

## Syphilis During Pregnancy

### New York State Regulations for Screening During Pregnancy

1. **All women must be screened serologically for syphilis at the time pregnancy is first diagnosed.** In communities and populations with high syphilis prevalence or for patients at high risk New York State surveillance data indicates that repeat infection and infection acquired late in pregnancy are not uncommon events; **therefore, women from these settings should be screened repeatedly throughout pregnancy** (perhaps monthly in some instances e.g., high risk women who continue to be sexually active).
2. **New York State law mandates screening at delivery for all infants.** In addition, any woman who delivers a stillborn infant after 20 weeks gestation must be tested for syphilis. No infant should leave the hospital without the serologic status of the infant's mother having been determined at least once during pregnancy.

### Diagnostic Considerations

Seropositive pregnant women should be considered infected unless treatment history is documented clearly in a medical or health department record and sequential serologic antibody titers have appropriately declined. Serofast low antibody titers might not require treatment; however, persistent higher titer antibody tests might indicate reinfection and require treatment.

### Treatment

Penicillin is effective for preventing transmission to fetuses and for treating established infection among fetuses. Evidence is insufficient, however, to determine whether the specific, recommended penicillin regimens are optimal.

#### Recommended Regimens

Treatment during pregnancy should be the **penicillin** regimen appropriate for the woman's stage of syphilis. Some experts recommend additional therapy (e.g., a second dose of benzathine penicillin 2.4 million units IM) one week after the initial dose, particularly for those women in the third trimester of pregnancy and for women who have secondary syphilis during pregnancy.

## **Other Management Considerations**

Women who are treated for syphilis during the second half of pregnancy are at risk for premature labor or fetal distress, or both, if their treatment precipitates the Jarisch-Herxheimer reaction. These women should be advised to seek medical attention following treatment if they notice any decrease in fetal movements or if they have contractions. Stillbirth is a rare complication of treatment; however, since therapy is necessary to prevent further fetal damage, that concern should not delay treatment. All patients with syphilis should be tested for HIV.

### **Follow-Up**

Serologic titers should be checked monthly until adequacy of treatment has been assured. The antibody response should be appropriate for the stage of disease.

### **Management of Sex Partners**

Refer to General Principles, Management of Sex Partners (CDC guidelines, page 24.)

## **Special Considerations**

### **Penicillin Allergy**

There are no proven alternatives to penicillin. A pregnant woman with a history of penicillin allergy should be treated with penicillin, after desensitization, if necessary. Skin testing may be helpful for some patients and in some settings (CDC guidelines, page 33, Management of Patients Who Have a History of Penicillin Allergy). Tetracycline and doxycycline are contraindicated during pregnancy. Erythromycin should not be used because it cannot be relied upon to cure an infected fetus. Data are insufficient to recommend azithromycin or ceftriaxone for treatment of maternal infection and prevention of congenital syphilis.

## **Congenital Syphilis**

### **Evaluation and Treatment of Infants During the First Month of Life**

#### **Who Should Be Evaluated**

Infants should be evaluated for congenital syphilis if they were born to seropositive (nontreponemal test confirmed by treponemal test) women who meet the following criteria:

- Have untreated syphilis; or
- Were treated for syphilis during pregnancy with a non-recommended therapy (including erythromycin, doxycycline, tetracycline or a nonrecommended penicillin regimen); or
- Were treated for syphilis less than 1 month before delivery; or
- Were treated for syphilis during pregnancy with the appropriate penicillin regimen, but nontreponemal antibody titers did not decrease sufficiently after therapy to indicate an adequate response (greater than or equal to fourfold decrease); or
- Do not have a well-documented history of treatment for syphilis; or

- Were treated appropriately before pregnancy but had insufficient serologic follow-up to assure that they had responded appropriately to treatment and are not currently infected (greater than or equal to fourfold decrease for patients treated for early syphilis; stable or declining titers less than or equal to 1:4 for other patients).

**Note:** Serologic tests for the mother and infant can be nonreactive at delivery if the mother was infected late during pregnancy.

### **Evaluation of the Infant**

The clinical and laboratory evaluation of infants born to women described above should include the following:

- A thorough physical examination for evidence of congenital syphilis;
- A quantitative nontreponemal serologic test for syphilis performed on the infant's sera (not on cord blood);
- CSF analysis for VDRL, cell count, and protein;
- Long bone x-rays;
- Other tests as clinically indicated (e.g., chest x-ray, complete blood count, differential and platelet count, liver function tests, cranial ultrasound, ophthalmologic exam, and auditory brainstem response);
- For infants who have no evidence of congenital syphilis on the above evaluation, determination of presence of specific antitreponemal IgM antibody by a testing method recognized by CDC as having either provisional or standard status;
- Pathologic examination of the placenta or amniotic cord using specific fluorescent antitreponemal antibody staining.

## **Treatment**

### **Therapy Decisions**

Infants should be treated for presumed congenital syphilis if they were born to mothers who, at delivery, 1) had untreated syphilis; 2) were treated with a nonrecommended antibiotic regimen; 3) were treated less than one month prior to delivery; or 4) had evidence of relapse or reinfection after treatment (CDC guidelines, page 30-32, Congenital Syphilis). Additional criteria for presumptively treating infants with congenital syphilis are as follows:

- Physical evidence of active disease;
- X-ray evidence of active disease;
- A reactive VDRL-CSF or, for infants born to seroreactive mothers, an abnormal CSF white blood cell count or protein, regardless of CSF results;<sup>†</sup>

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<sup>†</sup> In the immediate newborn period, interpretation of CSF test results may be difficult; normal values vary with gestational age and are higher in preterm infants. Other causes of elevated values also should be considered when an infant is being evaluated for congenital syphilis. Though values as high as 25 white blood cells (WBC) /mm<sup>3</sup> and 150 mg protein/dL occur among normal neonates, some experts recommend that lower values (5 WBC/mm<sup>3</sup> and 40 mg protein/dL) be considered the upper limits of normal. The infant should be treated if test results cannot exclude infection.

- A serum quantitative nontreponemal serologic titer that is at least fourfold greater than the mother's titer;<sup>§</sup>
- Specific antitreponemal IgM antibody detected by a testing method that has been given provisional or standard status by CDC;
- If they meet the previously cited criteria for "Who Should Be Evaluated," but have not been fully evaluated (CDC guidelines, page 30, Congenital Syphilis).

**NOTE:** Infants with clinically evident congenital syphilis should have an ophthalmologic examination.

### **Recommended Regimens**

**Aqueous crystalline penicillin G**, 100,000-150,000 units/kg/day administered as 50,000 units/kg IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days,

or

**Procaine penicillin G**, 50,000 units/kg IM daily in a single dose for 10 days.

If more than one day of therapy is missed, the entire course should be restarted. When possible, a full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis.

**NOTE:** Due to reports of treatment failure of benzathine penicillin among newborns including cases among initially asymptomatic infants, **the New York State Department of Health does not recommend use of benzathine penicillin G, 50,000 units/kg IM in a single dose for treatment of congenital syphilis.** In some cases, infants with a normal complete evaluation for whom follow-up can be assured can be followed closely without treatment. If the decision is made to treat the baby, the standard 10-day therapy should be given.

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<sup>§</sup> the absence of a fourfold greater titer for an infant *cannot* be used as evidence *against* congenital syphilis.

## **Infants of Women Treated in the Third Trimester**

Although there is uniform agreement that treatment of syphilis in early pregnancy is almost 100% effective in preventing congenital syphilis, the evidence is less certain for treatment in the last trimester. As indicated above (see CDC guidelines, Congenital Syphilis, scenarios page 31-32), if the mother was treated within one month of delivery, treatment of the infant is considered inadequate and the infant must be treated for congenital syphilis.

There are cases reported in the literature and to the Department of Health's surveillance system which suggest that treatment of the mother during the seventh and eighth month of pregnancy may also fail to treat the fetus. While this is an uncommon event, at present it is not possible to predict when treatment failure will occur. Therefore, **if the mother is treated during the seventh or eighth month of pregnancy, both she and her infant must be followed especially closely.** If these infants meet any of the criteria in "Evaluation & Treatment of Infants During the First Month of Life" (CDC guidelines, page 30, Congenital Syphilis), they should be given the standard 10-day therapy. For the baby who does not meet these treatment criteria, the mother should show an expected decrease in serologic titer. If this decrease cannot be documented, these infants should either be followed with repeat serologic testing over a one-year period or empirically treated with the standard 10-day therapy if follow-up cannot be assured.

## **Evaluation and Treatment of Older Infants and Children**

After the newborn period (i.e., aged > 1 month), children diagnosed with syphilis should have a CSF examination to exclude neurosyphilis and records should be reviewed to assess whether the child has congenital or acquired syphilis (CDC guidelines, page 26, Primary and Secondary Syphilis and Latent Syphilis). Any child who is thought to have congenital syphilis or who has neurologic involvement should be treated with aqueous crystalline penicillin G, 200,000-300,000 units/kg/day IV administered as 50,000 units/kg every 4-6 hours for 10 days.

## **Follow-Up**

A seroreactive infant (or an infant whose mother was seroreactive at delivery) who is not treated for congenital syphilis during the perinatal period should receive careful follow-up examinations at 1 month and at 2, 3, 6, and 12 months after therapy. Nontreponemal antibody titers should decline by 3 months of age and should be nonreactive by 6 months of age if the infant was not infected and the titers were the result of passive transfer of antibody from the mother. If these titers are found to be stable or increasing after 6 – 12 months, the child should be re-evaluated, including CSF examination, and fully treated. Passively transferred maternal treponemal antibodies may be present for as long as 1 year. If they are present greater than 1 year, the infant should be re-evaluated and treated for congenital syphilis. Treated infants also should be followed every 2-3 months to assure that nontreponemal antibody titers decline; these infants should have become nonreactive by 6 months of age (response may be slower for infants treated after the neonatal period). Treponemal tests should not be used to evaluate response to treatment because test results can remain positive despite effective therapy if the child was infected. Infants with CSF pleocytosis should undergo CSF examination every 6 months, or until the cell count is normal. If the cell count is still abnormal after 2 years, or if a downward trend is not present at each examination, the child should be re-treated. The VDRL-CSF also should be checked at 6 months; if still reactive, the infant should be re-treated.

Follow-up of children treated for congenital syphilis after the newborn period should be the same as that prescribed for congenital syphilis among neonates.

## Special Considerations

### Penicillin Allergy

Children who require treatment for syphilis after the newborn period ( $\geq 30$  days), but who have a history of penicillin allergy, should be treated with penicillin after desensitization, if necessary. Skin testing may be helpful in some patients and settings (CDC guidelines, page 33, Management of Patients Who Have a History of Penicillin Allergy).

### HIV Infection

Mothers of infants with congenital syphilis should be tested for HIV. Infants born to mothers who have HIV infection should be referred for evaluation and appropriate follow-up.

No data exist to suggest that infants with congenital syphilis whose mothers are co-infected with HIV require different evaluation, therapy, or follow-up for syphilis than is recommended for all infants.

### Penicillin Shortage

During periods when the availability of penicillin is compromised, the following is recommended (see <http://www.cdc.gov/nchstp/dstd/penicillinG.htm>):

1. For infants ( $< 30$  days of age) with clinical evidence of congenital syphilis, check local sources for aqueous crystalline penicillin G (potassium or sodium). If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 U/kg/dose IM a day in a single daily dose for 10 days).
2. For infants at risk of congenital syphilis without any clinical evidence of infection, use procaine penicillin G, 50,000 U/kg/dose IM a day in a single dose for 10 days. As stated previously, **the New York State Department of Health does not recommend use of benzathine penicillin G, 50,000 units/kg IM in a single dose for treatment of congenital syphilis.**

Due to the lack of data, procaine penicillin is not recommended for treating infants  $\geq 30$  days old.

3. For premature infants at risk of congenital syphilis but who have no other clinical evidence of infection and who might not tolerate IM injections because of decreased muscle mass, IV ceftriaxone may be considered **only if careful clinical and serologic follow-up can be assured.**

If aqueous or procaine penicillin G is not available, IV ampicillin (200 mg/kg a day in 4 divided doses for 10-14 days) or, alternatively, ceftriaxone may be considered with careful clinical and serologic follow-up. Ceftriaxone must be used with caution in

jaundiced infants and dosed according to age and weight. For infants < 30 days old, use 75 mg/kg IV/IM a day in a single daily dose for 10-14 days. For older infants, this dose should be 100 mg/kg a day in a single daily dose. Studies that strongly support ampicillin or ceftriaxone for the treatment of congenital syphilis have not been done. As a result, their use requires management in consultation with an expert in the treatment of infants with congenital syphilis.

## Congenital Syphilis in Russia

### The Value of Counting Epidemiologic Cases and Clinical Cases

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**Background:** Congenital syphilis (CS) reports in Russia increased 26-fold from 1991 to 1999. Case reports included only infants who were clinical cases, had persistent serologic changes, or confirmed syphilitic stillbirth. Although not reported, policies stipulate that infants of inadequately treated or untreated mothers receive preventive penicillin treatment.

**Goal:** We examined whether risk factors and consequences for epidemiologic cases of CS (infants of inadequately treated mothers) resembled those of clinical cases and differed from those of noncases (infants of adequately treated mothers).

**Study Design:** A retrospective record review from Maternity Houses in 5 sites identified 715 syphilis-infected women who gave birth.

**Results:** Among women with maternal syphilis, 11% (n = 81) of infants were clinical cases, 56% (n = 402) were epidemiologic cases, and 33% (n = 232) were noncases of CS. Compared with noncases, maternal risk factors for epidemiologic cases included nonresidence ( $P < 0.01$ ), late syphilis ( $P < 0.01$ ), unemployment ( $P < 0.01$ ), no prenatal care ( $P < 0.01$ ), and syphilis testing at  $\geq 28$  weeks ( $P < 0.01$ ). Each of these was also significant for being a clinical case. Associated consequences of CS for the epidemiologic cases included increases in stillbirth ( $P < 0.01$ ), preterm birth ( $P < 0.01$ ), low birth weight ( $P < 0.01$ ), transfer to a pediatric hospital ( $P < 0.01$ ), and abandonment ( $P < 0.05$ ). Each of these except stillbirth was significantly elevated among clinical cases. Nearly half of the epidemiologic cases had no record of any penicillin treatment for the infant. Epidemiologic cases were signifi-

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cantly more likely than noncases to have no clinical or laboratory follow up.

**Conclusion:** In Russia, maternal risk factors and perinatal consequences for epidemiologic cases of CS resembled those of clinical cases. Expanding national reporting to include epidemiologic cases would strengthen CS prevention and monitoring.

THE RECENT EPIDEMIC OF syphilis in Russia has received widespread attention, both nationally and internationally. Reports have addressed the public health impact of the epidemic, risk factors, costs, its potential to exacerbate the HIV epidemic, and the threat of the syphilis epidemic's spread to neighboring countries, including Norway, Bulgaria, England, Wales, Finland, and Estonia.<sup>1-10</sup> Despite wide availability of laboratory facilities and treatment since the collapse of the Soviet Union in the early 1990s, syphilis rates among women aged 18 and above increased from 8.04 per 100,000 in 1991 to 209 per 100,000 in 1999.<sup>11</sup> A natural, but avoidable, consequence of the epidemic in women was that parallel increases were observed in congenital syphilis (CS). From 1991 to 1999, the number of reported cases of CS in the Russian Federation rose sharply from 29 to 743. Congenital syphilis rates during this period increased from 0.09 in 10,000 live births to 0.85 in 10,000 live births.<sup>11</sup>

The perinatal consequences of maternal syphilis can be severe, permanent, and even fatal. If not adequately treated, 75% or more of pregnant women with early syphilis will suffer adverse pregnancy and infant outcomes, including stillbirth, infant death, or various anatomic abnormalities or system disorders involving the skin and central nervous system.<sup>12,13</sup> However, CS should be almost entirely preventable in the Russian Federation because of widespread availability of serologic testing and inexpensive penicillin treatment.<sup>12,14</sup> Timely prenatal care is the mainstay of CS prevention, because early diagnosis of maternal syphilis facilitates completion of adequate therapy before delivery.<sup>12,15</sup>

The CS case definition recommended by the Ministry of Health of the Russian Federation for reporting purposes is a clinical one and is similar to that used in the United States until the late 1980s; it includes only infants who are symptomatic, have persistent serologic abnormalities, or are confirmed syphilitic stillbirths. Al-

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though not reported, asymptomatic infants of inadequately treated or untreated mothers should receive treatment according to Russian national policy. A case definition based on clinical and serologic indicators, like is currently in place in Russia, is prone to underestimation because large numbers of syphilis-infected infants are asymptomatic at birth and those who eventually manifest symptoms might never come to medical attention.<sup>16</sup> Because the potential to miss asymptomatic cases is high and the consequences of missing cases could be irreversible and devastating, both the World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC) include live-born and stillborn infants of mothers who received no or inadequate treatment for syphilis during pregnancy in their CS case definitions<sup>17,18</sup>; for the purposes of this report, infants born to untreated or inadequately treated mothers are referred to as "epidemiologic cases."

Previously, we used data from the Study of Congenital Syphilis in the Russian Federation to describe the magnitude, determinants, and consequences of CS in Russia.<sup>19</sup> Here, we examined whether maternal risk factors, perinatal consequences, and clinical care of epidemiologic cases of CS in the Russian Federation resembled those of clinical cases and differed significantly from those of noncases.

### Methods

Tikhonova et al. have described methods for this multisite study,<sup>19</sup> which included collaborators from the Ministry of Health of the Russian Federation, regional health authorities, academic institutions, and national nongovernmental organizations. The study was approved by the Ethics Board representing the Ministry of Health in the Russian Federation and by the CDC Internal Review Board. A retrospective design was used based on medical record review.

#### *Study Population and Setting*

The study population included women with a positive test for syphilis during pregnancy who delivered at 20 weeks gestation or later from 2 metropolitan (Moscow and St. Petersburg) and 3 nonmetropolitan areas (Novgorod, Moscow Oblast, and Ryazan). Participants were identified using delivery and laboratory logs of women giving birth in maternity houses between January 1996 and October 1999. The needed sample was collected from 3 of the sites in 1 calendar year (1999); for the 2 less-populated nonmetropolitan areas (Novgorod and Ryazan), data collection spanned 1996 to 1999. Little between-site variation in results was observed. We presumptively enrolled 1071 women with positive nontreponemal (usually, Wassermann tests) or treponemal tests (known as immunofluorescence reaction, which is comparable to the fluorescent treponemal antibody absorption test [FTA-ABS]) or both, subsequently restricting our sample to women with evidence of active syphilis infection (see subsequently in this article). The majority of women received only nontreponemal testing without confirmation by treponemal testing. Almost all pregnant women in the Russian Federation deliver in maternity houses; those with prenatal care undergo multiple syphilis tests, which are performed in central laboratories; women without prenatal care are routinely tested at delivery.

Trained abstractors collected standardized data from records in maternity houses, dermatovenerology dispensaries, women's consultation (antenatal) clinics, and pediatric hospitals. A total of 850 women had evidence of active syphilis infection during the current pregnancy, including: 1) those with first known syphilis infection during the current pregnancy (n = 613, 72%); and 2)

women with previous syphilis who were either not treated (n = 103, 12%), had laboratory evidence (a qualitative 2-unit increase in nontreponemal test, n = 98, 12%), or had clinical and laboratory (a positive 1-unit increase in nontreponemal test) evidence of lack of resolution of infection (n = 36, 4%). Our analysis was restricted to the 715 of these 850 women who had active syphilis during pregnancy and who gave birth; the remaining 135 women had either spontaneous (n = 36) or induced abortions (n = 97) after 20 weeks gestation or unknown birth outcome.

#### *Case Definition, Maternal and Infant Characteristics*

We identified 3 groups of infants: 1) noncases, defined as asymptomatic infants born to adequately treated mothers; 2) clinical cases, defined as infants who were clinically diagnosed by dermatovenerologists based on serologic and clinical findings (including lymphadenopathy, leukoderma, alopecia, characteristic mucocutaneous lesions, pneumonia, or hepatosplenomegaly) with either a definite (n = 63) or presumptive (n = 18) diagnosis recorded in the medical records; by Russian standards, a diagnosis of "syphilitic stillbirth" requires that spirochetes be visualized, most typically, on placental examination; and 3) epidemiologic cases, defined as infants with no diagnosis recorded in the medical record who met the WHO case definition primarily because of birth to an untreated or inadequately treated mother and who should have received penicillin treatment. (Russian standards specify that clinical cases should receive "specific treatment" and epidemiologic cases should receive "prophylactic treatment"; both the specific and prophylactic regimens use injectable penicillin G; the specific regimens require penicillin of longer duration and are often given as inpatient treatment.) Treatment is necessary for these epidemiologic cases as a result of the unavailability of a commercial test to determine whether an asymptomatic infant is infected. In the Russian context, "epidemiologic case" is preferable to the term "presumptive case" to describe these infants. Adequate treatment during pregnancy was defined as completion of treatment with either short- or long-acting penicillin G at least 30 days before delivery; all other women were classified as having received inadequate treatment. Women considered to have received inadequate treatment included those with no treatment, completion of treatment less than 30 days before delivery, or nonpenicillin antibiotic treatment. Epidemiologic cases also included a small number of infants with no diagnosis of CS in the medical record but with clinical and/or serologic indicators of CS that are consistent with the WHO case definition (an infant with a reactive serologic test and evidence of CS on physical examination). We compared each group of cases (clinical cases and epidemiologic cases) with the noncases who were not clinical or epidemiologic cases.

Maternal risk factors or risk markers for clinical cases and epidemiologic cases included age <19 at delivery, late stage of syphilis, being unmarried, being unemployed, receiving no prenatal care, first syphilis testing at >28 weeks gestation, and being a nonresident of the town in which they delivered. Late stage of syphilis was defined by the stage listed on the medical record for the maternal diagnosis and included any form of latent syphilis (early and late), as well as syphilis of unknown duration; in contrast, early syphilis was defined by a written diagnosis of primary or secondary syphilis. Nonresidents were those who are residing in a city or region that differs from their official place of permanent residency; they could face obstacles to receiving prenatal care because their identification documents list as their permanent residence a city or region other than their current one. Possible perinatal consequences or outcomes for both clinical and epidemiologic cases included stillbirth, neonatal death, premature

TABLE 1. Distribution of Selected Characteristics of Study Population Among Pregnant Women With Active Syphilis Who Gave Birth (N = 715) in the Russian Federation

	Percentage (no.)
Maternal age at diagnosis	
<19	22.0 (157)
>19	78.0 (558)
Nonresident	
Yes	21.0 (150)
No	79.0 (565)
Stage of syphilis	
Late	76.8 (549)
Early	23.2 (166)
Unmarried	
Yes	18.0 (128)
No	82.0 (584)
Employed or student	
Yes	26.6 (188)
No	73.4 (518)
No prenatal care	
Yes	39.2 (280)
No	60.8 (434)
Syphilis testing at $\geq 28$ weeks of gestation	
Yes	50.5 (326)
No	49.5 (320)

birth, low birth weight, symptoms of CS, treatment for CS, clinical and laboratory follow up, transfer to a pediatric hospital, and abandonment. Descriptive analyses of data from the 2 nonmetropolitan areas from 1996 to 1999 (during which time laboratory testing policies were consistent) allowed us to evaluate trends for clinical and epidemiologic cases.

#### Data Analysis

All data were entered at each site using EpiInfo, version 6.0 software<sup>20</sup> and then converted to SAS for analyses (SAS Institute, Cary, NC). Mantel-Haentzel chi-squares were used to perform bivariate analysis of the associations between each maternal risk factor and CS for both the epidemiologic and clinical cases. A similar approach was used to identify significant perinatal consequences for the epidemiologic and clinical cases. Two logistic

models were developed to identify independent maternal risk factors for the epidemiologic and clinical cases.

#### Results

Characteristics of the 715 women with active syphilis during pregnancy who gave birth were fairly diverse, including a range of ages, both married and nonmarried women, and women who were both employed and unemployed (Table 1): 78% were aged 20 years and over, more than 20% were nonresidents of the city or town in which they delivered, 82% were married, and 73% were not employed outside the home. We found that 39% of syphilis-infected pregnant women received no prenatal care, and more than 50% had their first test for syphilis at 28 weeks gestation or later.

Among those infants born to syphilis-infected mothers, 11% (81) were clinical cases, 56% (402) were epidemiologic cases, and 33% (232) were noncases (Table 2). Compared with women whose infants were noncases, those whose infants were clinical cases were significantly more likely to be nonresidents (28% vs. 11%,  $P < 0.01$ ), to have late-stage syphilis (73% vs. 61%,  $P < 0.05$ ), to be unmarried (37% vs. 15%,  $P < 0.001$ ), to be unemployed (80% vs. 66%,  $P < 0.02$ ), to obtain no prenatal care (65% vs. 16%,  $P < 0.01$ ), and to be first tested for syphilis at  $\geq 28$  weeks of gestation (73% vs. 23%,  $P < 0.01$ ). Women whose infants were epidemiologic cases had increased risks for almost all of these same characteristics: nonresident status (25% vs. 11%,  $P < 0.01$ ), late stage of syphilis (87% vs. 61%,  $P < 0.01$ ), unemployed (76% vs. 66%,  $P < 0.01$ ), obtaining no prenatal care for this particular pregnancy (48% vs. 16%,  $P < 0.01$ ), and first syphilis testing at  $\geq 28$  weeks (63% vs. 23%,  $P < 0.01$ ). Logistic modeling identified that after adjustment for age at diagnosis, being a nonresident, being unemployed, and stage of syphilis, risk factors for being a clinical case of CS included having no prenatal care (adjusted odds ratio [OR], 5.2, 95% confidence interval [CI], 2.4–11.1), first serologic test for syphilis at  $\geq 28$  weeks gestation (OR, 5.6; 95% CI, 2.8–11.3), and being unmarried (OR, 3.1; 95% CI, 1.4–7.1). Similarly, independent risk factors for being an epidemiologic case included having no prenatal care (OR, 3.1; 95% CI, 1.8–5.4), first serologic test for syphilis at  $\geq 28$  weeks gestation (OR, 3.8; 95% CI, 2.5–5.9), and having late-stage syphilis (OR, 4.0; 95% CI, 2.6–6.4), after adjustment for maternal age, being a nonresident, being unemployed, and being unmarried.

TABLE 2. Comparison of Clinically Diagnosed and Epidemiologic Case Definitions Among Pregnant Women With Active Syphilis Who Gave Birth (N = 715): Maternal Characteristics, Russian Federation

	Cases of Congenital Syphilis				Noncases (neither clinical nor epidemiologic cases) (N = 232) Percent (no.)
	Clinically Diagnosed Cases (N = 81) Percent (no.)	P Value for Comparison With Noncases Percent (no.)	Epidemiologic Cases (N = 402) Percent (no.)	P Value for Comparison With Noncases Percent (no.)	
Maternal age at diagnosis of syphilis					
<19 y	24.7 (20)	NS	22.1 (89)	NS	20.7 (48)
Nonresident	28.4 (23)	<0.01	25.4 (102)	<0.01	10.8 (25)
Late-stage syphilis	72.8 (59)	<0.05	86.8 (349)	<0.01	60.8 (141)
Unmarried	37.0 (30)	<0.01	16.0 (64)	NS	14.8 (34)
Employed or student	20.0 (16)	<0.02	23.9 (95)	<0.01	33.8 (77)
No prenatal care	65.4 (53)	<0.01	47.5 (191)	<0.01	15.6 (36)
Inadequate treatment	60.5 (49)	<0.01	94.8 (381)	<0.01	0.0 (0)
Syphilis testing $\geq 28$ weeks of gestation	73.2 (52)	<0.01	62.8 (224)	<0.01	22.9 (50)

\*Total sample decreased as a result of missing data.  
NS = not significant.

TABLE 3. Comparison of Clinically Diagnosed and Epidemiologic Case Definitions Among Pregnant Women With Active Syphilis Who Gave Birth (N = 715): Pregnancy Outcomes and Infant Characteristics, Russian Federation

	Cases of Congenital Syphilis				Noncases (neither clinical nor epidemiologic cases) (N = 232) Percent (no.)
	Clinically Diagnosed Cases (N = 81) Percent (no.)	P Value for Comparison With Noncases Percent (no.)	Epidemiologic Cases (N = 402) Percent (no.)	P Value for Comparison With Noncases Percent (no.)	
<b>Pregnancy outcomes</b>					
Stillbirth	2.5 (2)		15.2 (61)		3.5 (8)
Neonatal death	7.4 (6)	<0.01	1.7 (7)	<0.001	0.9 (2)
Live birth	90.1 (73)		83.1 (334)		95.7 (222)
Preterm	40.7 (33)	<0.001	27.6 (111)	<0.001	9.5 (22)
Low birth weight	48.2 (39)	<0.001	18.3 (65)	<0.001	7.5 (17)
<b>Presence of symptoms suggestive of congenital syphilis among infants*</b>	55.7 (44)	<0.001	26.4 (90)	NS	15.2 (34)
Baby received any treatment**	96.2 (76)	<0.001	66.6 (227)	<0.05	55.4 (124)
Baby received penicillin treatment**	76.0 (60)	<0.001	52.8 (180)	NS	50.0 (112)
Clinical follow up after discharge*	50.6 (40)	NS	23.2 (79)	<0.001	53.1 (119)
Lab follow up after discharge*	63.3 (50)	NS	41.4 (141)	<0.001	56.7 (127)
Baby transferred to pediatric hospital*	91.1 (72)	<0.001	76.9 (259)	<0.001	57.1 (128)
Baby abandoned*	30.8 (24)	<0.001	12.8 (42)	<0.05	5.8 (13)

\*Total sample restricted to 644 births (79 clinical cases, 341 epidemiologic cases, 224 noncases), because stillbirths (n = 71) were excluded.

†For infants born with clinical and/or serologic signs, recommended therapy is a 20–28-day “specific” penicillin regimen, whereas recommended therapy for infants born to inadequately treated or untreated mothers is a “prophylactic 10–14-day penicillin regimen. According to Russian standards, alternative therapies for congenital syphilis include doxycycline, cephtriaxone, ampicillin, and erythromycin. NS = not significant.

Despite the known increased risk of stillbirth among syphilis-infected pregnant women, clinical cases of CS were less likely than the noncases to be stillborn (Table 3). Infants who were epidemiologic cases were significantly more likely than noncases to be stillborns (15% vs. 4%,  $P < 0.01$ ). Perinatal characteristics that were significantly elevated for the clinical cases, compared with the noncases, included prematurity (41% vs. 10%,  $P < 0.01$ ), low birth weight (48% vs. 8%,  $P < 0.01$ ), symptoms suggestive of CS (56% vs. 15%,  $P < 0.01$ ), any treatment for syphilis (96% vs. 55%,  $P < 0.001$ ), penicillin treatment (76% vs. 50%,  $P < 0.001$ ), transfer to a pediatric hospital (91% vs. 57%,  $P < 0.01$ ), and maternal abandonment at birth (31% vs. 6%,  $P < 0.001$ ). Similarly, epidemiologic cases were significantly more likely than noncases to be premature (28% vs. 10%,  $P < 0.01$ ), have low birth weight (18% vs. 8%,  $P < 0.01$ ), be transferred to a pediatric hospital (77% vs. 57%,  $P < 0.01$ ), and to be abandoned at birth (13% vs. 6%,  $P < 0.05$ ). Only 53% of the epidemiologic cases had a record of penicillin treatment of the infant. Those infants who were epidemiologic cases were significantly less likely than noncases to have any record of clinical or laboratory follow up after birth. Infants who were clinical cases of CS were no more likely than those who were noncases to have laboratory or clinical follow up after discharge.

Our observation of high rates of nontreatment in the epidemiologic cases led us to perform further analyses restricted to the subgroup of epidemiologic cases and noncases. Specifically, for infants born alive, we compared maternal and infant characteristics according to whether the infant had received any treatment for congenital syphilis (Table 4). Among mothers of infants who were epidemiologic cases, those infants who were treated were significantly more likely than those who were not treated to have mothers who received no prenatal care and who had their first prenatal test for syphilis at 28 weeks or greater. Epidemiologic cases (infants) who received no treatment were significantly more likely than those who received treatment to have a mother who received no treatment for maternal syphilis (86% vs. 75%,  $P < 0.01$ ) and to have no record of laboratory follow up (81% vs. 48%,  $P < 0.001$ ).

Finally, we compared trends for epidemiologic and clinical cases for the 2 regions with data spanning a 4-year period (Fig. 1). Whereas clinical cases remained relatively stable from 1996 through 1999, noteworthy increases occurred in epidemiologic cases during this time period.

## Discussion

We found that epidemiologic cases of CS were very similar to clinical cases with regard to maternal risk factors. Compared with the noncases, mothers of epidemiologic cases and of clinical cases were significantly more likely to be nonresidents, have late stage of syphilis, to be unmarried, unemployed, to have no prenatal care, and to undergo first syphilis testing at  $\geq 28$  weeks of gestation. Furthermore, well-known consequences of CS, namely, prematurity and low birth weight, as well as transfer to a pediatric hospital and abandonment, were significantly more frequent among the epidemiologic cases and among clinical cases than among noncases. Stillbirths were rarely classified as clinical cases of CS.

Among live-born infants, almost all clinical cases received penicillin treatment; however, nearly half of the infants who were epidemiologic cases had no record of any penicillin treatment (prophylactic or specific). The risk of developing CS for untreated infants who were epidemiologic cases is especially high because 9 of 10 of them were born to syphilis-infected mothers who had received no penicillin treatment whatsoever during pregnancy. Of note, 17% of untreated epidemiologic cases were premature. Although the etiology of prematurity among high-risk pregnant women varies, CS is one well-documented cause.<sup>13</sup> A preterm infant who is an epidemiologic case is at especially high risk of being infected with CS. Although our data do not explain the increased risk of abandonment observed among treated compared with untreated epidemiologic cases, it is possible that treatment raised concerns for the mothers and/or pediatricians about whether the baby was at risk for developing CS in the future.

The striking maternal and perinatal similarities between epi-

TABLE 4. Comparison of Treated and Nontreated Epidemiologic Cases and Noncases

	Epidemiologic Cases			Noncases		
	Infant Treated* Percent (no.) (N = 227)	Infant Not Treated Percent (no.) (N = 114)	P Value	Infant Treated* Percent (no.) (N = 124)	Infant Not Treated Percent (no.) (N = 100)	P Value
<b>Maternal characteristics</b>						
No prenatal care	47.1 (107)	25.4 (29)	<0.001	21.8 (27)	7.0 (7)	<0.01
Nonresident	20.7 (47)	14.0 (16)	NS	12.9 (16)	8.0 (8)	NS
Late test for syphilis at >28 weeks of gestation	63.1 (123)	49.5 (54)	<0.05	24.4 (28)	19.0 (18)	NS
No maternal treatment†	74.9 (170)	86.0 (98)	<0.01	0.0 (0)	0.0 (0)	NS
<b>Infant characteristics</b>						
Low birth weight	14.6 (33)	17.0 (19)	NS	11.3 (14)	1.0 (1)	<0.05
Preterm birth	15.9 (36)	16.7 (19)	NS	12.1 (15)	1.0 (1)	<0.05
No clinical follow up	75.3 (171)	79.8 (91)	NS	47.6 (59)	46.0 (46)	NS
No laboratory follow up	47.6 (108)	80.7 (92)	<0.001	34.7 (43)	54.0 (54)	<0.05
Abandonment	15.5 (34)	7.5 (8)	<0.05	7.3 (9)	4.0 (4)	NS

\*Treated infants were those received any treatment for congenital syphilis; although treatment was primarily penicillin, some additional antibiotics were used such as cephtriaxone and erythromycin.

†Total sample decreased as a result of missing data.

NS = not significant.

miologic and clinical cases of CS in selected regions of the Russian Federation implies that the epidemiologic cases could include a large number of syphilis-infected infants who were asymptomatic at birth. The natural history of CS in the prepenicillin era is well known and confirms the fact that many asymptomatic infants could eventually develop symptoms of CS.<sup>12-14,16,21,22</sup> These reports suggest that untreated women with early-stage syphilis are more likely than those with late-stage syphilis to deliver an infant with congenital syphilis. It is possible that our findings, which indicated the reverse, could be related to the increased likelihood that women with early-stage syphilis received adequate treatment (data not shown). Although Russian policy recommends that infants at risk of CS should receive penicillin treatment, we found that nearly half of such epidemiologic cases had no record of penicillin therapy. An added small percentage of at-risk infants did receive treatment with other antibiotics such as ceftriaxone or erythromycin. Furthermore, the majority of epidemiologic cases had no record of clinical or laboratory follow up after hospital discharge. Although some of those without recorded

follow up could have received care from private providers, national expert opinion suggests that a substantial number might never have received any follow up. It appears that obstacles to the receipt of prenatal care by syphilis-infected pregnant women could persist as obstacles to obtaining follow-up care for their infants. Recognition of the uncertainty of preventive treatment and adequate follow up of infants at risk for CS led other countries such as the United States to expand the CS case definition to include infants born to untreated or inadequately treated mothers.<sup>14,23</sup> This change improves case management because assigning a presumptive diagnosis of congenital syphilis helps to assure that a decision about an infant's need for penicillin treatment is made before discharge from the hospital.

Selection of an optimal case definition invariably involves tradeoffs between sensitivity and specificity. According to Teutsch and Hennekens, a highly specific case definition such as that used in the Russian Federation for CS is appropriate when it is important to minimize false-positives because of societal prejudice associated with the disease.<sup>24,25</sup> Data from our study, which were previously not available, suggest that a consequence of using a highly specific case definition could be that a number of at-risk infants born to syphilis-infected mothers (epidemiologic cases) had no record of treatment. It might be possible to improve physician awareness of the need both for treatment and follow up of infants at risk of CS in the Russian Federation by adding a separate category of "epidemiologic cases" of CS to official case reports. The increased risk of abandonment that was observed among treated epidemiologic cases suggests that strengthening patient and physician education programs would be a necessary component of implementing an expanded reporting system.

We considered limitations that could have biased our findings. Because Wasserman tests have limited specificity (and sensitivity),<sup>26,27</sup> because their performance could not be retrospectively validated, and because confirmatory testing was not routine, we could have enrolled some women with false-positive results. However, the frequent occurrence of stillbirth and other perinatal complications suggests that few false-positives were included. If some participants had false-positive results, we would have underestimated the occurrence of clinical and epidemiologic CS. Our use of

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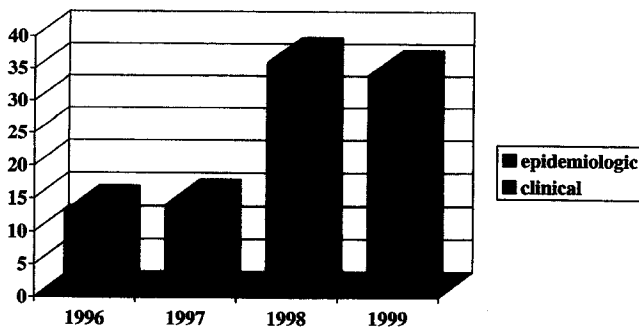


Fig. 1. TO COME.

the epidemiologic case definition, although highly sensitive, does misclassify some uninfected infants as epidemiologic cases; however, the epidemiologic definition correctly identifies all infants needing treatment. The generalizability of our results regarding similarities between epidemiologic and clinical cases of CS appears high, because our findings were similar across 5 sites.

The occurrence of large numbers of clinical and epidemiologic cases of CS in the Russian Federation is an alarming public health event, signaling a breakdown in the disease control activities and in prenatal care services that are essential for protecting the health of mothers and babies. Evidence is unclear and expert opinion is contradictory regarding whether high-risk pregnant women in the Russian Federation have adequate access to prenatal care. During Soviet times, reporting of clinical cases of CS might have sufficed, because it was highly likely that almost all syphilis-infected women and their contacts would have been identified and treated.<sup>28</sup> However, in the new environment in Russia, when not all cases are identified and treated; when anonymous, private, and self-treatment are common; when known risk behaviors such as drug use and commercial sex work are on the rise; when the presence of marginalized populations in urban centers is ever-expanding; and when the HIV epidemic is increasing at a staggering rate,<sup>29-34</sup> the use of a "clinical" case definition alone could have limited relevance for local, regional, and national health authorities. A more accurate measure of "infants at risk for CS would include separate reports of epidemiologic cases born to untreated or inadequately treated syphilis-infected mothers, in addition to clinical cases. After the CS case definition was modified in the United States to combine both clinical and epidemiologic cases in 1988, a 6-fold increase in CS rates occurred during the ensuing 4 years.<sup>14</sup> The proposed separate reporting of epidemiologic and clinical cases in the Russian Federation, however, should not affect case counts for clinical CS. Such expanded monitoring would strengthen CS prevention by providing a more valid measure of the magnitude of the CS problem at the local, regional, and national levels; trends in preventive factors such as prenatal care and treatment; trends in risk factors such as nonresidence and drug use; as well as trends in consequences. These data are essential for strengthening linkages between disease control and reproductive health services, linkages that will become even more critical as the HIV epidemic in Russia escalates.

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