

Mortality Associated With Congenital Syphilis in the United States, 1992–1998

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ABSTRACT. *Objective.* To summarize national trends in the incidence of congenital syphilis (CS) and associated mortality.

Methods. We analyzed CS surveillance data reported to the Centers for Disease Control and Prevention by 50 states and the District of Columbia from 1992–1998.

Results. From 1992–1998, 942 deaths, including 760 stillbirths, were reported among 14 627 cases of CS, yielding a case fatality ratio (stillborns and deaths/all cases) of 6.4%. Untreated, inadequately treated, or undocumented treatment of syphilis during pregnancy accounted for 87.4% of reported cases. Among CS cases, there was an inverse relationship between the number of prenatal care visits (0, 1–4, 5–9, ≥ 10) and risk of fatal outcome. Among deaths, 52% of deliveries occurred by 30 weeks' gestation. Among live born infants with CS, death occurred more often in infants for whom no radiograph or cerebrospinal fluid evaluation was reported. Although both cases and deaths from CS declined from 1992–1998, there was no significant change in the case fatality ratio.

Conclusion. Mortality associated with CS continues to be an important public health problem that will resurge if adult syphilis rates increase. Because a large proportion of deaths occur at low gestational age, earlier diagnosis and treatment of maternal syphilis may substantially reduce the case fatality ratio. *Pediatrics* 2002; 109(5). URL: <http://www.pediatrics.org/cgi/content/full/109/5/e79>; congenital syphilis, mortality, case fatality ratio, prenatal care, early treatment.

ABBREVIATIONS. CS, congenital syphilis; CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; PR, prevalence ratio; CI, confidence interval; PNC, prenatal care.

Congenital syphilis (CS) is a multiorgan infection that may cause neurologic or musculoskeletal disabilities or death in the fetus or newborn. However, when mothers with syphilis are treated early in pregnancy, the disease is almost entirely preventable. From 1992–1998, the rate of CS declined 78.2% in the United States, concurrent with an 80.5% decline in adult infectious syphilis.¹ Nevertheless, CS continues to be an important pediatric

health problem and predictably resurges whenever community outbreaks of infectious syphilis occur.^{2,3}

CS poses significant challenges for the clinician. The disease is difficult to diagnose because infants may be asymptomatic at birth. Symptoms and signs in the infant can be nonspecific for CS; moreover, there is no clinically useful and widely available diagnostic gold standard.⁴ The clinician must rely on the maternal treatment history to determine if treatment is warranted in the asymptomatic infant. Controversies persist in the optimal regimen for treatment of CS^{5,6} as well as for the case definition.^{7,8}

This report summarizes national CS surveillance data from 1992–1998. Our objectives were to assess: 1) the number and ratio of deaths from CS cases over this 7-year period, and 2) the vital status of CS cases in relation to maternal characteristics, results of diagnostic tests on infants, and the specific reason the infant was determined to have a reportable case of CS.

METHODS

CS surveillance data were reported to the Centers for Disease Control and Prevention (CDC) from all 50 states and the District of Columbia. From 1984 to 1991 cases were defined using the Kaufman criteria.⁹ By 1992 most states were using a revised CDC case definition (confirmed, presumptive, stillbirth) to identify CS in infants.¹⁰ To minimize the effects of the change in case definition, the current analysis focuses on the years 1992–1998. Demographic and clinical information was extracted from all case reports and summarized. No postmortem examination results on stillbirths or other deaths were reported through this system.

Cases were categorized as to why they were classified as having CS based on the algorithm described in the 1991 Congenital Syphilis Case Investigation and Report form (73.126): 1) infants manifesting classic signs of CS or in whom *Treponema pallidum* is identified from lesions, placenta, or umbilical cord; 2) infants whose mothers have a syphilitic lesion at delivery; 3) infants born to mothers with untreated or inadequately treated syphilis at delivery, and 4) infants born to mothers with syphilis during pregnancy whose serologic response to penicillin therapy was not documented or was equivocal, and either a) the infant was not evaluated radiographically and by examination of cerebrospinal fluid (CSF) or b) CSF and radiologic tests were performed and 1 or more was found to be abnormal. In the presence of untreated maternal syphilis, stillbirths were also reportable. Women were considered to be inadequately treated if they received nonpenicillin therapy, or penicillin administered <30 days before delivery.¹¹ The definition of appropriate response for primary or secondary syphilis is a fourfold decline in nontreponemal titers by 3 months and for early latent syphilis is a fourfold decline in nontreponemal titers by 6 months (73.126).

It is important to note that the surveillance case definition operationalized in our case reporting form (73.126) has not yet been revised to be consistent with the 1998 sexually transmitted diseases treatment guidelines. For most of the period described in the article (1992–1998), the pre-1998 treatment guidelines, which

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Received for publication Feb 7, 2000; accepted Dec 28, 2001.

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highlighted the need for evaluation, are consistent with the surveillance case definition. [In the 1998 guidelines, the role for evaluation of the infant is less critical for management and treatment decisions than previous versions.] The 1998 and current guidelines also recommend treatment for presumed CS of all infants born to mothers with syphilis during pregnancy where specific response to therapy was not documented or was equivocal, regardless of the results of the evaluation of the infant.

Data were divided into categories for purposes of analysis. Deaths were divided into stillbirths, deaths that occurred within 28 days of age, and deaths that occurred later than 28 days of age.¹² For all results reported here, total infant deaths were defined as stillbirths plus deaths occurring after birth. Gestational trimesters were designated as follows: first trimester 0–11.9 weeks; second trimester 12.0–26.9 weeks; and third trimester ≥ 27 weeks. Gestational age was divided into 3 groups: <30 weeks, 30.0–36.9 weeks, and ≥ 37 weeks. Mother's age was categorized as ≤ 24 and ≥ 25 years. Birth weight was divided into 3 categories: <1500 g, 1500–2499 g, and ≥ 2500 g. Throughout this report, where not otherwise specified, stillbirths are included in total deaths attributed to CS and thus to calculation of the case fatality ratio.

Prevalence ratios (PRs) and confidence intervals (CIs) were calculated to compare infants by vital status (infants that survived and total deaths) according to maternal characteristics, infant gestational age, and infant birth weight. Additionally, percent of positive results of infant evaluation tests was calculated according to infant vital status. A χ^2 test for linear trend was used to determine if a significant trend existed in the proportion of infants who died (stillbirths plus infants who died after birth) from 1992–1998. Finally, the percentage of CS deaths that could potentially be prevented by treating all pregnant women with syphilis at a given gestational age was calculated. For this calculation, we excluded those cases in which gestational age or birth date was either missing or listed as <20 weeks. We assumed that those cases in which the mother seroconverted during pregnancy could not have been prevented by early diagnosis and treatment; otherwise we assumed that a death would have been prevented if appropriate treatment had been provided to the mother at least 30 days before delivery.

RESULTS

From 1992–1998, 14 627 cases of CS were reported. This number includes all confirmed cases, syphilitic stillbirths, and presumptive cases. Of these, 760 (5.2%) were stillbirths, 182 (1.2%) were infants born alive who later died, and classifications for 9 (0.1%) were missing or unknown. Most infants had a birth weight ≥ 2500 g ($N = 9619$; 65.8%), 3313 (22.6%) had a birth weight of 1500 to 2499 g, 1023 had a birth weight <1500 g (7.0%), and 672 (4.6%) had unknown or missing birth weight. Stillbirths and infant deaths associated with CS steadily declined over this time period, although there was no significant annual trend in the proportion of CS infants who died (stillbirths and deaths after birth) ($\chi^2=0.18$; $P = .66$; Fig 1). Excluding stillbirths, most deaths occurred in the several days immediately after birth with the most infants dying on the day of birth. Of the 170 infants that died and for whom date of death was available, 156 (91.8%) died within 28 days after birth. All deaths occurred within 3 months after birth. The neonatal mortality rate was 11.3 per 1000 live births (156 deaths within 28 days per 13 846 live births).

Maternal Characteristics and Risk of Infant Death

Some maternal characteristics were related to infant death. Prevalence of total deaths was higher among infants born to single (never married) women (PR = 1.6; CI = 1.3, 2.0) compared with those born to married women and among infants born to women

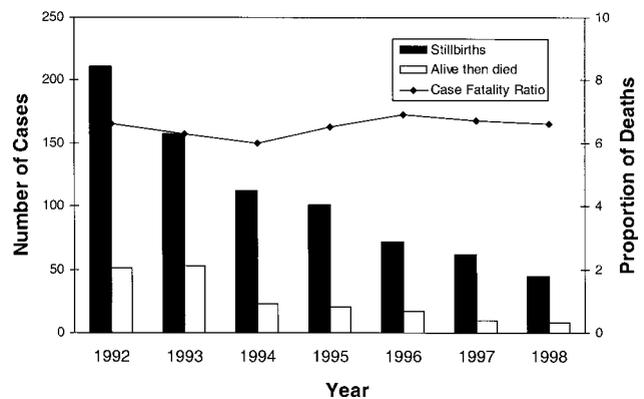


Fig 1. Number of stillbirths and deaths among infants reported to have CS and the proportion of infants that died (total of stillbirths and deaths after birth), United States, 1992–1998.

≤ 24 years (PR = 1.4; CI = 1.3, 1.6) compared with those born to women ≥ 25 years (Table 1). Women with no prenatal care (PNC) were more likely to deliver stillborn infants or infants that died (PR = 2.3; CI = 2.0, 2.6) when compared with women who had at least 1 PNC visit. The median number of PNC visits was 6. The number of PNC visits was inversely related to the prevalence of total deaths; a woman who had no PNC was almost 8 times more likely to deliver a stillborn or an infant who died as compared with a woman who had ≥ 10 visits (PR = 7.7; CI = 4.8, 12.3), while a woman who had 5 to 9 visits was almost 3 times more likely to deliver a stillborn or an infant who died (PR = 2.9; CI = 1.7, 4.8). The timing of the first PNC visit was generally predictive of the vital status of the infant but the relationship was not as strong as the number of PNC visits. Compared with women who had their first PNC visits during the first trimester, the prevalence of total deaths was almost 3 times as high in women who did not have any PNC visits (PR = 2.8; CI = 2.1, 3.7) and slightly higher in women who did not have their first PNC visit until the second trimester (PR = 1.4; CI = 1.0, 1.9) or third trimester (PR = 1.3; CI = 0.9, 1.9). Few of the mothers who lost their infants (3.8%; 36/942) had appropriate treatment at least 30 days before delivery.

Infant Characteristics Associated With Death

Gestational age and birth weight were strongly associated with birth outcome. Fifty-two percent of deaths occurred among infants <30 weeks' gestation; infants born at <30 weeks' gestation were almost 44 times more likely to be stillborn or die after birth than infants born after at least 37 weeks' gestation (PR = 43.6; CI = 35.6, 53.4) and infants 30 to 36 weeks' gestation were almost 9 times more likely to be stillborn or die after birth (PR = 8.5; CI = 6.8, 10.6). In 84 of the cases, mothers had acquired syphilis during pregnancy, having been found to be seronegative sometime before delivery. In Fig 2, we evaluated the percentage of CS deaths that might have been prevented by treating all pregnant women with syphilis at a given gestational age. We assumed that the 84 cases in which mothers had acquired syphilis during pregnancy (ie, they were seronegative earlier

TABLE 1. From 1992–1998, Characteristics of Mothers of Infants With CS Who Were Born Alive Compared to Infants Who Died ≤ 28 Days, > 28 Days, or Were Stillborn

	Number <i>n</i> = 14 627	Stillborn <i>n</i> = 760	Died < 28 Days <i>n</i> = 156	Died ≥ 28 Days <i>n</i> = 14	Total Died* <i>n</i> = 942	Alive <i>n</i> = 13 676	PR (CI) for Total Mortality
Marital status							
Married	1622 (11)	57 (8)	14 (9)	0 (0)	72 (8)	1548 (11)	1.0
Single	10 281 (70)	591 (78)	116 (74)	13 (93)	731 (78)	9547 (70)	1.6 (1.3, 2.0)
Other/unknown	2724 (19)	112 (15)	26 (17)	1 (7)	139 (15)	2581 (19)	1.2 (0.9, 1.5)
Mother's age							
≥ 25 y	8542 (58)	371 (49)	88 (56)	7 (50)	471 (50)	8068 (59)	1.0
≤ 24 y	5735 (39)	375 (49)	66 (42)	6 (43)	454 (48)	5277 (39)	1.4 (1.3, 1.6)
Unknown	350 (2)	14 (2)	2 (1)	1 (7)	17 (2)	331 (2)	0.9 (0.6, 1.4)
PNC							
Yes	7852 (54)	270 (36)	53 (34)	5 (36)	337 (36)	7510 (55)	1.0
No	5385 (37)	425 (56)	85 (55)	8 (57)	521 (55)	4863 (36)	2.3 (2.0, 2.6)
Unknown	1390 (10)	65 (9)	18 (12)	1 (7)	84 (9)	1303 (10)	1.4 (1.1, 1.8)
PNC visits†							
≥ 10	1430 (11)	12 (2)	4 (3)	0 (0)	18 (2)	1412 (11)	1.0
5–9	1997 (15)	58 (8)	10 (7)	1 (8)	72 (8)	1924 (16)	2.9 (1.7, 4.8)
1–4	2294 (17)	127 (18)	23 (17)	3 (23)	155 (18)	2137 (17)	5.4 (3.3, 8.7)
0 or no PNC	5385 (41)	425 (61)	85 (62)	8 (62)	521 (61)	4863 (39)	7.7 (4.8, 12.3)
Unknown number of visits	2131 (16)	73 (11)	16 (12)	1 (8)	92 (11)	2037 (16)	3.4 (2.1, 5.7)
First PNC visit††							
First trimester	1580 (12)	48 (7)	4 (3)	1 (8)	55 (6)	1525 (12)	1.0
Second trimester	2695 (20)	106 (15)	20 (14)	1 (8)	130 (15)	2563 (21)	1.4 (1.0, 1.9)
Third trimester	1568 (12)	55 (8)	14 (10)	2 (15)	72 (8)	1494 (12)	1.3 (0.9, 1.9)
Never	5385 (41)	425 (61)	85 (62)	8 (62)	521 (61)	4863 (39)	2.8 (2.1, 3.7)
Unknown first visit	2009 (15)	61 (9)	15 (11)	1 (8)	80 (9)	1928 (16)	1.1 (0.8, 1.6)
Gestational age							
≥ 37 wk	9494 (65)	75 (10)	20 (13)	3 (21)	103 (11)	9385 (69)	1.0
30–36.9 wk	3252 (22)	257 (34)	34 (22)	6 (43)	300 (32)	2951 (22)	8.5 (6.8, 10.6)
< 30 wk	1034 (7)	387 (51)	95 (61)	5 (36)	489 (52)	544 (4)	43.6 (35.6, 53.4)
Unknown	847 (6)	41 (5)	7 (5)	0 (0)	50 (5)	796 (6)	5.4 (3.9, 7.6)
Birth weight							
≥ 2500 g	9619 (66)	97 (13)	18 (12)	2 (14)	124 (13)	9490 (69)	1.0
1500–2499 g	3313 (23)	206 (27)	34 (22)	3 (21)	244 (26)	3068 (22)	5.7 (4.6, 7.0)
< 1500 g	1023 (7)	332 (44)	91 (58)	7 (50)	432 (46)	590 (4)	32.6 (27.0, 39.4)
Unknown	672 (5)	125 (16)	13 (8)	2 (14)	142 (15)	528 (4)	16.4 (13.1, 20.6)

* Includes 12 live born infants who died for whom date of death was not reported.

† Total does not add to 14 627 because for 1390 cases it was unknown whether they had PNC.

Data were reported to CDC from 50 states and the District of Columbia on CS case report forms. PR compares the total infants who died (including stillbirths) with those who survived. Percentages are presented in parentheses and are rounded to the nearest whole number. Nine cases did not have a vital status recorded.

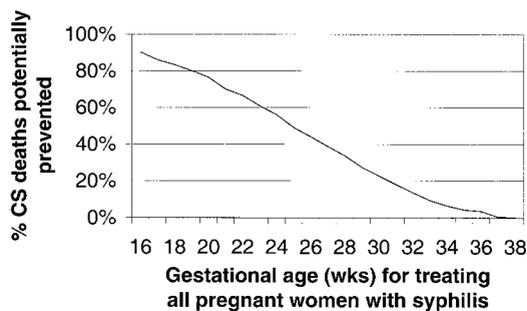


Fig 2. Percentage of CS deaths potentially prevented by treating all pregnant women with syphilis at a given gestational age.

in pregnancy) could not have been prevented but that all other deaths could have been prevented if the mother had received adequate treatment while pregnant. As this graph shows, to potentially reduce mortality by 70%, all pregnant women with syphilis must be treated by 21 weeks of gestation.

Infants weighing 1500 to 2499 g at birth were almost 6 times more likely (PR = 5.7; CI = 4.6, 7.0) and infants weighing < 1500 g at birth were almost 33 times more likely to be stillborn or die after birth than infants weighing ≥ 2500 g at birth (PR = 32.6;

CI = 27.0, 39.4). For the 3793 infants < 2500 g at birth, 125 died within 28 days for a neonatal mortality rate of 33.0 per 1000 live births; for the 9510 infants who were ≥ 2500 g, 18 died within 28 days, for a neonatal mortality rate of 1.9 per 1000 live births.

Infant Evaluation and Tests

The proportion of live born infants reported to have received diagnostic tests and physical examinations, and the proportion of those with data who tested positive are presented in Table 2. Infants who lived were more likely to have laboratory test results reported than were infants who died; those who died at < 28 days had the lowest proportion with results reported. Even when these data were stratified by age and infants who died earlier than 2 days after birth were excluded from the analysis, a greater percentage of infants who survived received radiographs and CSF tests than those who died. However, those who died had a greater proportion of positive test results.

Reason Infant Classified as a CS Case

Most infants were designated as CS cases because their mother had untreated or inadequately treated

TABLE 2. From 1992 to 1998, the Proportion of Live Born Infants With Data on Physical Examinations and Test Results, and the Proportion of Those With Data Who Tested Positive (*Shown in Italics*), Categorized by Vital Status of the Infant at the Time the Case Reported Was Completed

	Alive <i>n</i> = 13 676	Died <28 Days <i>n</i> = 156	Died ≥28 Days <i>n</i> = 14
Classic signs			
Physical examination, %	12 981 (94.9)	101 (64.7)	11 (78.6)
<i>Classic signs present, %</i>	<i>654 (5.0)</i>	<i>38 (37.6)</i>	<i>3 (27.3)</i>
Radiographs			
Results reported, %	6403 (46.8)	21 (13.5)	5 (35.7)
<i>Findings consistent with CS, %</i>	<i>528 (8.2)</i>	<i>12 (57.1)</i>	<i>1 (20.0)</i>
CSF VDRL			
Results reported, %	8464 (61.9)	19 (12.2)	8 (57.1)
<i>Reactive Venereal Disease Research Laboratory, %</i>	<i>887 (10.5)</i>	<i>9 (47.4)</i>	<i>3 (37.5)</i>
CSF cell count/protein			
Results reported, %	5514 (40.3)	11 (7.1)	6 (42.9)
<i>Increased cell count or protein, %</i>	<i>3658 (66.3)</i>	<i>9 (81.8)</i>	<i>6 (100.0)</i>
Radiograph or CSF VDRL			
Results reported, %	9646 (70.5)	33 (21.1)	10 (71.4)
<i>Findings consistent with CS or reactive</i>	<i>1237 (12.8)</i>	<i>19 (57.6)</i>	<i>3 (30.0)</i>
Immunoglobulin M			
Results reported, %	926 (6.8)	4 (2.6)	0 (0)
<i>Positive tests, %</i>	<i>362 (39.1)</i>	<i>2 (25.0)</i>	<i>0 (0)</i>
Darkfield			
Results reported, %	64 (0.5)	2 (1.3)	0 (0)
<i>Positive tests, %</i>	<i>19 (29.7)</i>	<i>2 (100)</i>	<i>0 (0)</i>

Nine cases did not have a vital status recorded. Data were reported to CDC from 50 states and the District of Columbia on CS case report forms. Classic signs of CS include, for instance, condyloma lata, snuffles, and syphilitic skin rash (Form 73.126). It is recommended in the case reporting form (73.126) that CSF cell count and protein in a term or preterm infant be interpreted by the clinician.

or undocumented treatment of syphilis during pregnancy (87.4%); 96.2% of deaths (including stillbirths) occurred among these infants. In 6.6% of cases, the mother was treated adequately but did not have a fourfold decline in titer and the infant was inadequately evaluated for CS. In 3.9% of cases, the mother did not have a fourfold decline in titer and the infant's evaluation revealed laboratory or clinical signs of CS. The remaining cases (2.1%) were reported for other reasons.

DISCUSSION

Between 1992 and 1998, despite the lowest rates of adult syphilis ever reported in the United States, almost 1000 CS fetal and infant deaths were reported. Although the prevalence of CS consistently declined over this period, the case fatality ratio remained fairly stable. Lack of PNC was associated with overall risk of mortality (infant deaths and stillbirths). Clearly, maternal syphilis is an important cause of intrauterine demise. However, the contribution of CS to neonatal mortality is not readily apparent. Among CS infants born alive, neonatal mortality for those 2500 g or greater was 1.9 per 1000 live births and for those <2500 g was 33.0 per 1000 live births. Compared with national rates, the neonatal mortality rate for CS infants was somewhat higher for infants ≥2500 g and somewhat lower for infants <2500 g (eg, in 1996, the national rate for infants ≥2500 g was 1.0 per 1000 and for infants <2500 g the national rate was 50.9 per 1000.¹³) However, in 1996, 7.4% of all US births were <2500 g, but among live born infants with CS 27.4% were in this category. Therefore, it appears that the main contribution to mortality among live born infants with CS is attributable to the

association with low birth weight and prematurity. Maternal syphilis is associated with some of the same risk factors as preterm delivery (eg, lack of PNC and drug use).

Lack of or late PNC is a recognized risk factor for the occurrence of CS, but we also investigated it as a risk factor for fatal outcome of CS. Among CS cases, a mother who had no PNC was almost 8 times more likely to deliver an infant who was stillborn or who died than a woman who had 10 or more PNC visits. At least 1 PNC visit was reported for slightly more than half of the mothers of cases. Of these women, approximately half had 6 or fewer visits and the most common number of visits was only 1. In contrast, current recommendations are visits every 4 weeks for the first 28 weeks, every 2 to 3 weeks until 36 weeks' gestation and weekly thereafter.¹⁴ Eighty percent of all women in the United States in 1994 received PNC in the first trimester¹⁵ as compared with 12% of the women with infants diagnosed with CS during 1992–1998. Moreover, only 1.4% of mothers in 1994¹⁵ received no PNC compared with 37% of mothers of infants with CS during the period of this analysis. That the number of PNC visits is strongly related to the outcome of the infant is not unique to CS. Early and frequent PNC allows the health care provider to encourage healthy behaviors and inform women about proper nutrition, dangers of smoking, alcohol, drugs, environmental hazards, and unsafe sexual practices¹⁵ as well as to screen for syphilis and other infectious diseases. Inadequate treatment for pregnant mothers with syphilis during the PNC period thus appears to be a major factor contributing to infant mortality and cases of CS.

The fact that 52% of CS deaths occurred before 30

weeks' gestation indicates that efforts to significantly reduce mortality associated with the disease will require treatment substantially earlier than 30 weeks, at least by the mid-second trimester. That so few deaths occurred when the mother received appropriate treatment early is consistent with the assumed effectiveness of this recommendation. By the third trimester, infants have survived the most vulnerable period, providing the most likely explanation for the lack of association between starting PNC in the third trimester and mortality. It should also be noted that the strong inverse relationship between high number of PNC visits and infant mortality exists primarily because those women who had more visits had a viable fetus well into the third trimester.

The vast majority of infants were classified as having CS because their mothers were untreated or inadequately treated or because treatment history was unknown. This is because many women had no PNC and many received no treatment for syphilis. Others may have initiated PNC too late in pregnancy to permit effective in utero treatment. Some women may not have returned for treatment, or there may have been a delay from testing to treatment,³ so that the women were not treated >30 days before delivery, which is necessary for effective in utero treatment. In addition, some may not have had a repeat test early in the third trimester as is recommended for high-risk populations.¹⁶ Finally, medical information, such as documentation of maternal treatment may not have been readily available, resulting in a classification of the birth as a CS case.

There are limitations in the findings presented. First, the report of CS may not always be based on consistent application of the case definition across geographic areas. Second, case ascertainment may be incomplete because some CS case report forms may have been filled out before complications from CS occurred. Third, reporting of maternal treatment history and infant laboratory data were sometimes incomplete. Fourth, questions regarding important risk information (eg, drug use, health insurance, and if the pregnancy is wanted) are not included in the case report form, although the importance of these variables in influencing the occurrence of CS has been suggested by other studies.^{3,17}

The present data, based on 7 years of surveillance reports, show that prevalence of CS has declined, corresponding to the decline in syphilis,¹ though the case fatality ratio has remained fairly stable. Mortality associated with CS continues to be an important public health problem that will resurge if adult syphilis rates increase. Proximately, the continued occurrence of CS is attributable predominantly to lack of adequate screening and treatment for pregnant mothers during the prenatal period. Particularly in areas where syphilis morbidity is high, strong efforts must be made to influence persons at high risk for CS to initiate PNC in the first trimester because, as shown in this report, the second trimester is often too late to prevent stillbirths and deaths. Ultimately, the

continued occurrence of this disease is attributable to the ongoing acquisition of syphilis in a population of women at high risk for many other social problems such as poverty, substance abuse, violence, lack of health insurance and lack of access to or use of contraception, resulting in unwanted and/or unplanned pregnancies. Only by approaching the problem of CS from the standpoint of the health care providers and the standpoint of the broader social context in which these women are living can the elimination of syphilis and CS be achieved.

ACKNOWLEDGMENTS

Appreciation is extended to Sharon Clanton for her skillful management of the CS database; to Akbar Zaidi for his expert statistical advice; and to Lyn Finelli, Madeline Sutton, and Susan Wang for their useful comments on an earlier version of the manuscript.

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