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Gaps in the prevention of mother-to-child transmission of syphilis: a review of reported cases, South Africa, January 2020–June 2022

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ABSTRACT

Introduction: Congenital syphilis (CS) is preventable through timely antenatal care (ANC), syphilis screening and treatment among pregnant women. Robust CS surveillance can identify gaps in this prevention cascade. We reviewed CS cases reported to the South African notifiable medical conditions surveillance system (NMCSS) from January 2020 to June 2022.

Methods: CS cases are reported using a case notification form (CNF) containing limited infant demographic and clinical characteristics. During January 2020–June 2022, healthcare workers supplemented CNFs with a case investigation form (CIF) containing maternal and infant testing and treatment information. We describe CS cases with/without a matching CIF and gaps in the CS prevention cascade among those with clinical information.

Findings: During January 2020–June 2022, 938 CS cases were reported to the NMCSS with a median age of 1 day (interquartile range: 0–5). Nine percent were diagnosed based on clinical signs and symptoms only. During January 2020–June 2022, 667 CIFs were reported with 51% (343) successfully matched to a CNF. Only 57% of mothers of infants with a matching CIF had an ANC booking visit (entry into ANC). Overall, 87% of mothers were tested for syphilis increasing to 98% among mothers with an ANC booking visit. Median time between first syphilis test and delivery was 16 days overall increasing to 82 days among mothers with an ANC booking visit.

Discussion: Only 37% of CS cases had accompanying clinical information to support evaluation of the prevention cascade. Mothers with an ANC booking visit had increased syphilis screening and time before delivery to allow for adequate treatment.

LAY SUMMARY

Untreated maternal syphilis has devastating consequences for the foetus. Congenital syphilis (CS) is preventable through timely maternal screening and treatment with robust surveillance. We evaluated CS surveillance data to identify gaps in CS surveillance and in the prevention cascade in South Africa.

KEYWORDS: congenital syphilis, surveillance, notifiable medical condition

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BACKGROUND

Syphilis is a curable sexually transmitted infection (STI) caused by the spirochaetal bacterium *Treponema pallidum*. Among pregnant women, untreated or inadequately treated syphilis, can result in vertical transmission (VT) of syphilis including congenital infection [1]. Untreated syphilis during pregnancy can cause several adverse pregnancy and birth outcomes including miscarriage, stillbirth, neonatal death, premature birth and low birth weight [2]. Infants born with syphilis can develop clinical sequelae including hepatic, haematological, skeletal and neurological complications [3]. Infected infants may not show overt clinical signs or symptoms at birth but can go on to develop clinical manifestations later if untreated [1].

Congenital syphilis (CS) is preventable through timely antenatal care and maternal syphilis screening followed by prompt treatment with 2.4 million units of benzathine penicillin administered intramuscularly once weekly for 3 weeks ≥28 days before delivery [4]. Syphilis screening is recommended for all pregnant women in South Africa (SA) at the first antenatal visit [5]. If the first test is performed <20 weeks of pregnancy and is negative, a repeat test is recommended between 32- and 34-weeks gestation [5]. Pregnant women who test positive on the syphilis screening test should be treated irrespective of their nontreponemal titre or history of infection.

In 2007, the World Health Organization (WHO) launched 'The global elimination of congenital syphilis' strategy [6]; however, CS elimination is complex due to challenges in CS surveillance and diagnosis and ensuring treatment availability. Without overt neonatal clinical signs or symptoms, CS is diagnosed on a combination of maternal and neonatal serological and clinical information. CS diagnosis depends on (i) the presence of clinical signs and symptoms with appropriate maternal history or laboratory evidence, (ii) the comparison of paired mother and neonatal nontreponemal titres (with a 4-fold relative increase in neonatal compared to maternal titres considered congenital infection), (iii) evaluation of the timing and number of doses for maternal treatment with a concomitant drop in maternal titres where retesting is available and (iv) no evidence of reinfection [7]. While CS in SA is notifiable to the Notifiable Medical Conditions surveillance system (NMCSS), information accompanying CS cases reported prior to 2020 were limited to infant demographics and clinical information. The absence of infant or maternal serological information precluded confirmation of reported CS cases and identification of gaps in the CS prevention cascade (i.e., screening of pregnant women, followed by timely adequate treatment and prevention of congenital transmission). Since 2017, CS cases reported to the NMCSS have increased steadily amidst concerns of underreporting [8], while RPR-positive laboratory alerts among infants <24 months remained high [9]. While CS cases mirror trends in infectious syphilis among women of reproductive age [10], syphilis among adult and/or pregnant females is not reportable in SA, making this comparison difficult.

During 2019–2022, the Centre for HIV and STIs (CHIVSTIs) at the National Institute for Communicable Diseases (NICD) requested submission of additional infant and maternal serological information to supplement limited infant information reported to the NMCSS. We reviewed CS cases reported to the NMCSS from January 2020 to June 2022 to (i) describe characteristics of CS cases, (ii) determine the proportion of reported CS cases that met the criteria for CS based only on clinical information submitted to the NMCSS and (iii) describe supplementary infant and maternal characteristics of CS cases submitted to the CHIVSTIs to identify gaps in the CS prevention cascade.

METHODS

Setting

In SA, CS is a notifiable medical condition (NMC) that should be notified within 7 days of clinical or laboratory diagnosis by healthcare providers [11]. Starting in January 2020, healthcare providers were encouraged to submit an additional case investigation form (CIF) describing infant and maternal clinical information such as maternal testing and treatment history, infant serological test results and clinical signs and symptoms. This additional information was proposed to allow the CHIVSTIs to, (i) verify whether notified cases meet the CS case definition and (ii) identify gaps in CS prevention and management. From January 2023, the NICD planned to introduce combined case notification and case investigation forms in electronic and paper-based formats [12].

Design

We analysed prospectively-collected routine NMCSS surveillance data reported between January 2020 and August 2022. Our study population included infants notified as CS cases through submission of a case notification form (CNF) to the NMCSS using the NICD case definition (Table 1).

Table 1. Congenital syphilis case definition for South Africa

A confirmed congenital syphilis case is defined as a live birth or foetal death at >20 weeks of gestation or >500g (including stillbirth) born to a woman with positive syphilis serology, and without adequate syphilis treatment, OR a live birth, stillbirth or child aged <2 years born to a woman with positive serology or with unknown serostatus, and with laboratory and/or radiographic and/or clinical evidence of syphilis infection (regardless of the timing or adequacy of maternal treatment)	
Laboratory evidence	a. Demonstration by dark-field microscopy or detection by fluorescent antibody testing of *Treponema pallidum* in the umbilical cord, placenta, nasal discharge or skin lesion material or autopsy material of a neonate or stillborn infant b. Analysis of cerebrospinal fluid (CSF) is reactive for Venereal Disease Research Laboratory (VDRL) test or elevated CSF cell count or protein without other cause; c. Infant with a reactive non-treponemal serology test with titre 4-fold or more than that of the mother; d. Infant with a reactive non-treponemal serology test with titre less than 4-fold more than that of the mother but that remains reactive ≥6 months after delivery; e. Infant with a reactive non-treponemal serology test of any titre AND any of the clinical signs born to a mother with positive or unknown serology, independent of treatment;
Radiographic evidence	f. Long bone radiographs suggestive of congenital syphilis (e.g., osteochondritis, diaphyseal osteomyelitis and periostitis)
Clinical evidence	g. Early clinical signs include non-immune hydrops, hepatosplenomegaly, rhinitis (snuffles) and skin rash, pseudo-paralysis of an extremity or failure to thrive or achieve developmental milestones. An older infant or child may develop additional signs or symptoms such as frontal bossing, notched and pegged teeth (Hutchinson teeth), clouding of the cornea, blindness, bone pain, decreased hearing or deafness, joint swelling, sabre shins and scarring of the skin around the mouth, genitals and anus h. For stillborn infants, maternal syphilis serostatus should be determined. Any stillbirth case from a woman with a reactive maternal syphilis antibody test should be considered a congenital syphilis case

Data collection and management

NMCSS data reported using the CNF were extracted into the CS line list, while CIFs were captured into a Microsoft Access database. Data from the two sources were cleaned and matched, using a notification case ID generated at CNF submission by the NMCSS. A deterministic matching algorithm based on the notification case ID was used to match CNFs and CIFs making any records with a missing case ID ineligible for the deterministic match. CNF and CIF datasets were reviewed for duplicate records which were removed before undergoing deterministic matching. After deterministic matching, a probabilistic merge was attempted based on similar sounding names using two phonetic algorithms, i.e., the New York State Identification and Intelligence System and the Soundex Indexing System. The number of matched pairs were computed along with estimates of the probability scores. The best matched pairs were defined using the Jaro–Winkler and Levenshtein distance (edit distance) and corresponding *p*-scores assigned. *p*-scores were arranged in descending order, reviewed and matches with a *p*-score >0.9751 retained. Next edit distances were reviewed and matches with edit distances >3 were dropped. Since not all CNFs were matched to a CIF, we conducted a subgroup analysis of cases with both a CNF and CIF submitted to compare to results from analysing all CNFs received.

Data analysis

We described trends in clinical notifications by year and province, and infant and maternal characteristics of notified cases with a CIF. For this sub-population, we also described numbers and proportions of pregnant women whose infants were notified as CS cases and with respect to the CS prevention cascade, i.e., (i) enrolled in antenatal care, (ii) tested for syphilis at the antenatal appointment where woman enters the maternity care pathway (booking visit), (iii) diagnosed and treated for syphilis ≤28 days before delivery, (iv) re-tested for syphilis between 32–34 weeks if initial syphilis test was negative in first or second trimester of pregnancy.

RESULTS

After deduplication by case ID, name and surname, from January 2020 to June 2022, there were a total of 938 CNFs. During the same period, 667 CIFs were received by the CS surveillance team at NICD. The record linkage algorithm resulted in a final dataset of 343 unique matched CNFs and CIFs, representing 37%

(343 of 938 records) of the original unduplicated CNF dataset (Figure 1).

There were a comparable number of cases reported in 2020 and 2021, with many (40%) reported in 2020 (Table 2). The median age of all CS cases at specimen collection was 1 day (interquartile range [IQR]: 0–5 days) while CS cases with a matching CIF were younger at specimen collection with a median age of 0 days (IQR: 0–3) compared to CS cases without a matched CIF (median age = 1 day, IQR: 0–7 days)

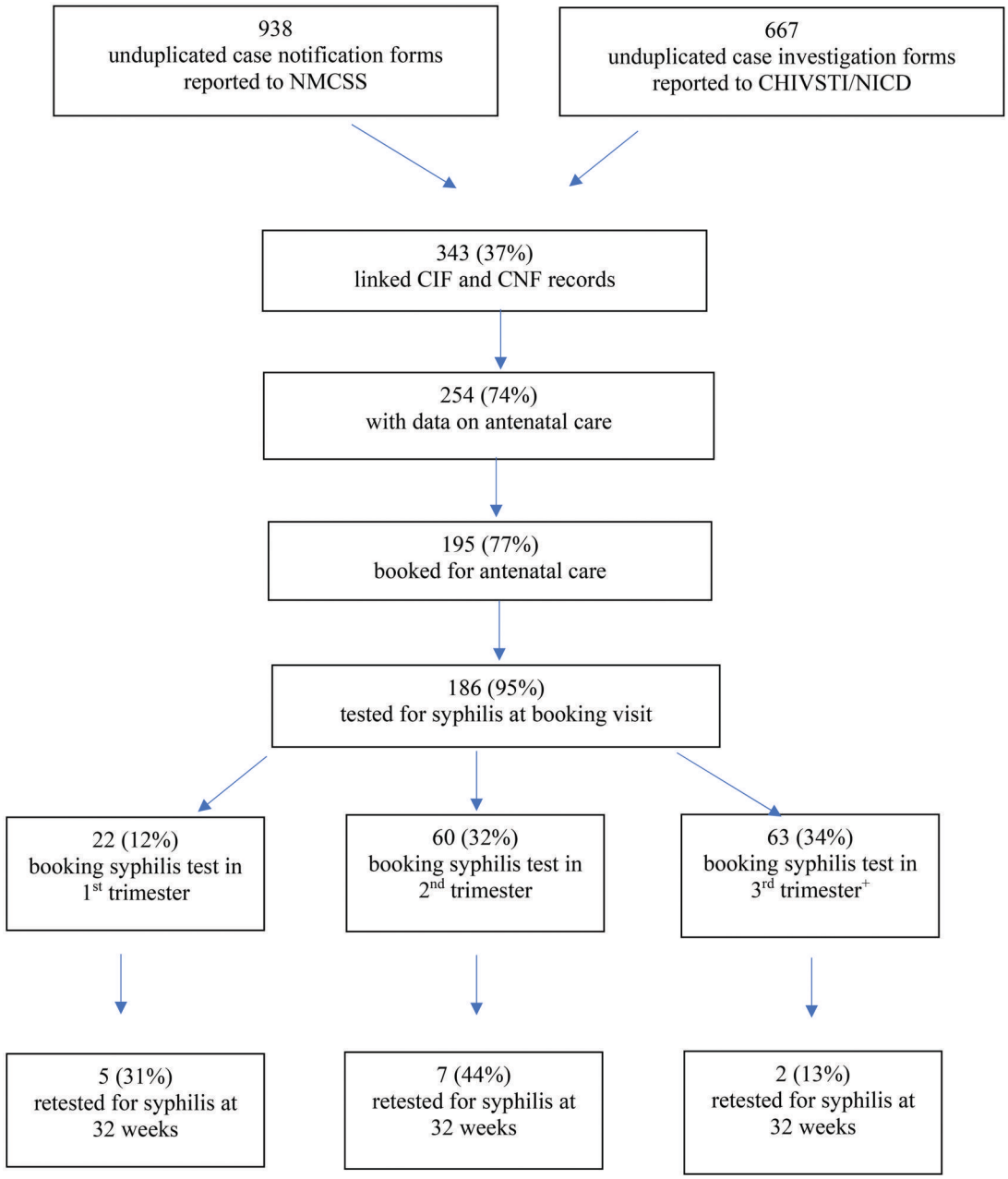

Figure 1. CONSORT diagram. Flow of congenital syphilis case notifications forms reported to the Notifiable Medical Conditions surveillance system (NMCSS) and case investigation forms reported to the Centre for HIV/STIs–January 2020–June 2022. $^{+}$Forty-one (22%) mothers did not have the date of her syphilis test and/or date of delivery to determine during which trimester the booking syphilis test occurred.

Table 2. Demographic and clinical characteristics of congenital syphilis cases reported to the notifiable medical conditions surveillance system by case investigation form (CIF) status, January 2020–June 2022

	Total ($n = 938$)		CIF link ($n = 343$)		No CIF link ($n = 595$)		*p*-value
	N	%	*N*	%	*N*	%	
Year of notification							
2020	379	(40)	194	(57)	185	(31)	<0.01
2021	357	(38)	112	(33)	245	(41)	
2022 (Jan–Jun)	202	(22)	37	(11)	165	(28)	
Median age at notification (days, IQR)	7	(3–20)	6	(2–12)	8	(3–28)	<0.01
Median age at specimen collection (days, IQR)	1	(0–5)	0	(0–3)	1	(0–7)	<0.01
Infant sex							
Male	442	(47)	171	(50)	271	(46)	0.03
Female	480	(51)	162	(47)	318	(53)	
Unknown	16	(2)	10	(3)	6	(1)	
Method of diagnosis							
Clinical signs and symptoms only	88	(9)	29	(8)	59	(10)	0.44
Laboratory-confirmed	679	(72)	260	(76)	419	(70)	
Other	122	(13)	40	(12)	82	(14)	
Rapid test	44	(5)	12	(3)	32	(5)	
X-ray	5	(0.5)	2	(0.6)	3	(0.5)	
Infant treatment documented							
Yes	447	(48)	326	(95)	121	(20)	<0.01
No	491	(52)	17	(5)	474	(80)	
Infant outcome							
Alive	875	(93)	318	(93)	557	(94)	0.23
Died	33	(4)	10	(3)	23	(4)	
Unknown	30	(3)	15	(4)	15	(3)	
Province of residence							
KwaZulu-Natal	239	(53)	129	(57)	110	(49)	<0.01
Gauteng	93	(21)	36	(16)	57	(25)	
Western Cape	80	(18)	51	(22)	29	(13)	
Free State	7	(2)	1	(0.4)	6	(3)	
Other	33	(7)	11	(5)	22	(10)	

p-values by *t*-test for continuous variables and Chi-squared test for binary/categorical variables.

(p-value < 0.01). Most CNFs were reported from KwaZulu-Natal (53%), followed by Gauteng (21%) and the Western Cape (18%) with these three provinces reporting 92% of CS cases out of the nine SA provinces. Overall, 9% ($n = 88$) of CS cases reported to the NMCSS were diagnosed based on clinical signs and symptoms only, but these signs and symptoms were only specified for 45% of these 88 cases ($n = 40$). Among these 40 cases with specified clinical signs and symptoms, hepatosplenomegaly was the most frequently reported symptom (20%), followed by peeling skin/skin lesions (18%) and rhinitis/snuffles/nasal discharge (15%) (Table 3). Overall, 48% of infants had treatment recorded and 93% of infants were alive at the time of reporting. The proportion of infants documented as treated increased to 95% among those with a matching CIF, which allowed us to supplement CNF treatment data with treatment information included on the CIF.

Infant and maternal characteristics of congenital syphilis cases with a matching case investigation form

After restricting our analysis to infants with a matching CIF (37%; 343/938), most (54%) had a gestational age of 37–42 weeks and 94% had a syphilis test within the neonatal period (0- to 28-day old). Eighty-three percent of infants had a reactive RPR test and 58% had a RPR titre between 1:8 and 1:64. Most mothers of CS cases were tested for syphilis during pregnancy ($n = 298$; 87%)—57% of pregnant mothers were tested at the antenatal booking visit (entry visit into antenatal care) and 30% were tested but not at an antenatal booking visit (Table 4). Dates for both the first syphilis test and delivery were available for 46% ($n = 138$) of mothers tested for syphilis during pregnancy. Among these mothers ($n = 138$), 16% ($n = 22$) were first tested for syphilis in the first, 42% ($n = 59$) in the second, and 43% ($n = 60$) in the third trimester of

Table 3. Clinical signs and symptoms among congenital syphilis cases diagnosed based on clinical signs and symptoms only and reported to the notifiable medical conditions surveillance system, January 2020–June 2022

	n (40)	%
Clinical sign or symptom		
Hepatosplenomegaly	8	20
Peeling skin/rash/skin lesions or blisters	7	18
Snuffles/rhinitis/nasal discharge	6	15
Anaemia	4	10
Thrombocytopaenia	3	8
Hepatomegaly	2	5
Low birth weight	1	3
Jaundice	1	3
Spasms/convulsions	1	3
X-ray indicating long bone changes	1	3
Conjugated hyper bilirubinaemia	1	3
Distended abdomen	1	3
Large placenta	1	3
Failure to thrive	1	3

A total of 88 congenital cases were diagnosed based on clinical signs and symptoms only, but signs and symptoms were only specified for 40 out of these 88 cases. Eighteen out of the 40 cases (45%) had only one sign/symptom specified.

pregnancy. The median number of days between the mother's first syphilis test (including mothers without an antenatal booking visit) and delivery was 16 days (IQR: 0–101) and 77% ($n = 261$) tested positive with 61% with a RPR titre between 1:8 and 1:32 (Table 4). Three-quarters of women who tested RPR positive had treatment documented with 96% treated with benzathine penicillin. Among mothers first tested for syphilis at their antenatal booking visit, sixteen (8% of 195) were re-tested at 32–34 weeks. Most of these women (62%, 10/16) were re-tested following a negative test at antenatal booking, while 6 (38%) were re-tested following a positive test at antenatal booking. Eighty-one percent of 16 women re-tested at 32–34 weeks were reactive for syphilis.

More than half of mothers ($n = 195$; 57%) had an antenatal care booking visit (entry visit into antenatal care) recorded and among these pregnant women the proportion tested for syphilis increased to 98% (compared to 87% among all mothers of CS cases with matching CIF). For mothers who had both the date of syphilis booking test and delivery recorded (78%; $n = 144$), the median number of days between date of delivery and the antenatal booking syphilis test (i.e., when the mother's first syphilis test coincided with her entry visit into antenatal care) was 82 days (IQR: 25–142) with 65% ($n = 120$) first tested for syphilis >=28 days before delivery. Eighty-six percent of

Table 4. Infant and maternal characteristics of congenital syphilis cases with case investigation form submitted, January 2020–June 2022

	n	%
Infant characteristics		
Gestational age at delivery (weeks)		
26–29	19	6
30–36	127	37
37–42	186	54
Infant age at syphilis test (days)		
0–28	322	94
>28	21	6
Infant RPR test result		
Positive	284	83
Negative	49	14
Equivocal/no result	10	3
Infant RPR titer among RPR positive ($n = 284$)		
1:1–1:4	67	24
1:8–1:64	164	58
≥1:128	22	8
Unknown	31	11
Infant treatment for syphilis received		
Yes	333	97
No	10	3
Infant syphilis treatment type		
Benzathine penicillin	272	82
Bicillin	19	6
Procaine penicillin	5	2
Crystalline penicillin	9	3
Other[a]	15	5
Unknown	9	3
Maternal characteristics		
Maternal HIV status		
Positive	123	36
Negative	103	30
Unknown	118	34
Maternal record of antenatal care		
Yes	195	57
No	59	17
Unknown	89	26
Maternal syphilis testing during pregnancy		
Yes, tested at antenatal booking visit	195	57
Yes, but not tested at antenatal booking visit	103	30
No	45	13
Median (IQR) days between delivery and maternal syphilis test at antenatal booking visit	82	25–142
Median (IQR) days between delivery and first maternal syphilis test	16	0–101
Maternal treponemal test result		
Reactive	261	77
Non-reactive	80	23

(continued)

Table 4. (continued)

	n	%
Maternal RPR titre (among those treponemal reactive)		
1:1–1:4	39	19
1:8–1:32	122	61
>1:32	40	38
Maternal repeat syphilis test at 32–34 weeks[b]		
Yes, tested negative on first test	10	
Yes, tested positive on first test	6	
Maternal repeat syphilis test result		
Reactive	13	81
Not reactive	3	13

[a] Other treatments include ampicillin (3), cefotaxime ($n = 3$), ceftazidime ($n = 1$) and ceftriaxone ($n = 4$).
[b] Among pregnant women who had a syphilis test done at booking.

mothers with an antenatal booking visit tested positive for syphilis with 78% receiving treatment—98% ($n = 127$) were treated with benzathine penicillin.

Identifying missed opportunities for prevention of vertical transmission of syphilis

Among the mothers of reported cases of congenital syphilis, 195 (57%) had documentation of receiving antenatal care. A high proportion of mothers were tested for syphilis (87%) but only 40% (120) were tested ≥28 days before delivery (Table 5). Among those tested <28 days prior to delivery, only 38% had a record of antenatal care. A small proportion of mothers (7%) who were not tested for syphilis during pregnancy also had a record of antenatal care (Table 5). Among mothers with syphilis treatment documented ($n = 210$), 28% (56) received the first dose ≥28 days before delivery. Among mothers who received the first dose of treatment <28 days prior to delivery ($n = 123$, 56%), 46% ($n = 56$) were tested <28 days before delivery while 18% ($n = 26$) tested positive for syphilis ≥28 days before delivery. Two mothers tested positive and commenced treatment for syphilis ≥28 days before delivery but were treated with regimens other than the current standard of care of benzathine penicillin G (Table 5).

Table 5. Description of missed opportunities for prevention of vertical transmission of syphilis among mothers of reported congenital syphilis cases ($n = 343$), South Africa, 2020–June 2022

	n/N	%
Antenatal care		
Booked into antenatal care	195/343	(56)
Not booked in antenatal care	59/343	(16)
Unknown antenatal care status	89/343	(28)
Not tested for syphilis during pregnancy	45/343	(13)
Booked in antenatal care	3/45	(7)
Not booked into antenatal care	18/45	(40)
Unknown antenatal care status	24/45	(53)
Tested for syphilis during pregnancy	298/343	(87)
Tested for syphilis ≥28 days before delivery	120/298	(40)
Not tested for syphilis ≥28 days before delivery	94/298	(32)
Record of antenatal care	*36/94*	(38)
No record of antenatal care	*58/94*	(62)
Timing of syphilis test not known	84/298	(28)
Received treatment for syphilis	210[a]/298	(70)
Received adequate treatment for syphilis that began ≥28 days before delivery	56/210	(28)
Received treatment for syphilis but timing unknown	31/210	(15)
Did not receive adequate treatment for syphilis that began ≥28 days before delivery	123/210	(56)
Not tested for syphilis ≥28 days before delivery	56/123	(46)
Negative test ≥28 days before delivery, seroconversion during pregnancy[b]	2/123	(2)
Positive test ≥28 days before delivery, but not treated ≥28 days before delivery	26/123	(18)
Positive test and treated ≥28 days before delivery, but with inadequate regimen[c]	2/123	(2)
Other/unknown	37/123	(30)

[a] includes women who did not receive a syphilis test ($n = 8$) but had treatment documented.
[b] Among women who were tested ≥28 days before delivery ($n = 120$).
[c] Includes one woman treated with amoxicillin and one woman treated with ceftriaxone.

DISCUSSION

Our analysis of CS cases reported to the NMCSS, between January 2020 and 30 June 2022, found that although most cases were reported in the first week of life, only 37% had detailed clinical information submitted. Cases with clinical information were younger, reported in 2020 compared to 2021–2022 and from either Gauteng, KwaZulu-Natal or the Western Cape compared to the rest of SA. Our review of reported CS cases in SA highlights several considerations to address gaps in CS surveillance and the CS prevention cascade.

Addressing gaps in CS surveillance

We found that based on information reported on the CNF only—the primary mechanism of reporting CS

cases to the NMCSS—it is not possible to confirm or adequately describe gaps in the CS prevention cascade for most cases (>90%). Less than 10% of CS cases were diagnosed based on clinical signs and symptoms only, which could allow confirmation without infant or maternal serological information. However, <50% of these CS cases had clinical signs and symptoms specified on the CNF. Since studies have shown that most infected neonates are asymptomatic after birth or may only display clinical signs or symptoms weeks to years after birth [13], it is unsurprising that only a small proportion of cases were diagnosed solely based on clinical signs or symptoms. Even for cases where clinical signs or symptoms were specified it remained challenging to confirm CS without maternal clinical history, including nontreponemal and treponemal results, as CS signs and symptoms encompass a wide spectrum of manifestations with varying specificity [13]. In this analysis, we paired CNFs with a CIF providing supplementary infant and maternal serological information necessary to confirm the case. However, we were only able to match 37% of CNFs to a CIF. The low proportion of records matched is likely because the CIF could only be submitted after downloading, completing, scanning and sending the form, while the CNF could be completed and submitted electronically using the NMCSS reporting app. To address this, beginning 2023, elements of the CIF were incorporated into the standard CNF in the NMCSS reporting app and we anticipate improvement in the proportion of reported CS cases with matching infant and maternal serological information. Most CS cases (92%) were reported from 3 out of 9 provinces in SA (KwaZulu-Natal, Gauteng and the Western Cape), given that these are the most populous provinces it may represent the geographic burden of CS in SA, but may be an artefact of reporting practices.

Addressing gaps in the CS prevention cascade

From our evaluation of maternal information for 37% of CS cases with a matching CNF and CIF, we determined that 87% of pregnant women were tested for syphilis and of whom 75% were treated for syphilis, both proportions falling short of the 95% WHO's Elimination of Mother-to-Child-Transmission (EMTCT) targets for syphilis [6]. Only 56% of pregnant women were booked for antenatal care highlighting that almost half of pregnant women who deliver babies with CS are not engaged in antenatal care. While SA has demonstrably high levels of antenatal care coverage, late initiation of antenatal care is common [14] with some women going into labour without having attended any antenatal care visits [14, 15]. Our findings are similar to an evaluation of the CS prevention cascade in the United States of America showing that the largest gaps in prevention were (i) entry into antenatal care and (ii) early testing and timely treatment [10]. Barriers to antenatal care identified among pregnant women in SA include young age and reporting an unplanned pregnancy [16], a delay in recognizing pregnancy and the need to balance income-generating activities with antenatal care attendance [15].

Among pregnant women who booked into antenatal care, the proportion tested (98%) and treated (79%) for syphilis improved compared to pregnant women overall accompanied by an increase in median days between syphilis test and delivery. This suggests that improving engagement in antenatal care, preferably as early as 12 and at least by 20 weeks of pregnancy, can improve the diagnosis and treatment of syphilis among pregnant women. No or late engagement in antenatal care is associated with several adverse pregnancy outcomes, not limited to VT of syphilis and it is important to better understand barriers to access in SA. In Brazil low income and teenage pregnancy was associated with less antenatal care and increased rates of CS [17], while the co-occurrence of intimate partner or domestic violence and socioeconomic vulnerability were identified as barriers to prenatal care in Kern County, California [18]. While our findings suggest that booking into antenatal care may increase the proportion of women tested for syphilis, booking into antenatal care, even early during pregnancy, did not guarantee timely syphilis treatment. Furthermore, the proportion of syphilis-positive women who were untreated did not decrease among women tested earlier (first or second trimester) compared to later in pregnancy (third trimester). Reasons for inadequate syphilis treatment, beyond presenting late to antenatal care, could include delays in specimen transport to a centralised laboratory and return of results [19]. On-site, rapid syphilis testing has been shown to decrease treatment delays [20] particularly in areas with limited laboratory facilities.

Limitations

We relied on reported surveillance data, which are subject to incomplete reporting further restricting the number of cases included in analyses. While CS is an NMC, CS cases are likely underreported and not representative of the true number of CS cases in SA. A study evaluating the public health burden associated with adverse pregnancy outcomes resulting from syphilitic infection estimated 493 (95% CI: 238–922) missed CS cases per year in SA [2]. In SA, syphilis among pregnant women is not notifiable so we cannot estimate CS cases averted due to successful implementation of the CS prevention

cascade. To eliminate VT of syphilis, we recommend making syphilis among pregnant women notifiable or the integration of data from pregnancy registries into national surveillance systems for better monitoring of trends and evaluation of the CS prevention cascade. Valid and reliable surveillance data are critical to monitoring the burden of CS and evaluating the impact of CS prevention and progress towards EMTCT of syphilis.

CONCLUSIONS

Our findings are relevant for CS surveillance and prevention globally, but particularly for low- and middle-income locations, where surveillance capacity may be limited. Including infant and maternal serological information in CS surveillance is critical to identifying gaps in the CS prevention cascade. Improved antenatal care access could increase the proportion of pregnant women tested for syphilis, but this needs to be coupled with access to timely and adequate treatment following a syphilis diagnosis.

AUTHOR CONTRIBUTIONS

Alex de Voux (Conceptualization [equal], Formal analysis [equal], Methodology [equal], Writing—original draft [equal], Writing—review and editing [equal]), Wellington Maruma (Formal analysis [equal], Resources [equal], Software [equal]), Mabore Morifi (Project administration [equal], Writing—review and editing [equal]), Modiehi Maduma (Writing—review and editing [equal]), Joy Ebonwu (Writing—review and editing [equal]), Khadeejah Sheikh (Writing—review and editing [equal]), Sithembile Dlamini-Nqeketo (Conceptualization [equal], Writing—review and editing [equal]) and Tendesayi Kufa (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Writing—original draft [equal], Writing—review and editing [equal]).

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