Notification and management of congenital syphilis in the Northern Territory 2009 to 2014

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Abstract

Objective: To determine whether cases of congenital syphilis in the Northern Territory between 2009 and 2014 were correctly notified based on probable or confirmed case criteria stipulated by the Communicable Diseases Network Australia (CDNA).

Methods: Pregnant women with positive syphilis serology defined as reactive treponemal test and rapid plasma reagin titre ≥1:8 were identified from the Northern Territory Syphilis Register Information System. Risk classification was performed based on local guidelines, and CDNA criteria for probable/confirmed cases of congenital syphilis were applied to determine whether cases were appropriately notified.

Results: Thirty-four cases of positive maternal syphilis serology in pregnancy were identified from 31 women; all were Indigenous. Twenty-one cases fulfilled criteria for probable congenital syphilis; 1 case was formally notified to the Centre for Disease Control. Twenty cases (95%) fulfilling CDNA criteria for probable congenital syphilis were not notified over the study period.

Conclusions: Application of standard case definitions significantly increases the rate of congenital syphilis cases in the Northern Territory. Improved education regarding CDNA criteria for notification of congenital syphilis is necessary for clinicians and public health staff. Emerging evidence has supported the recent simplification of CDNA criteria for notification of congenital syphilis, effective 1 July 2015. *Commun Dis Intell* 2015;39(3):E323–E328.

Keywords: syphilis, congenital syphilis, notification(s), paediatric, mother-to-child transmission, pregnancy.

Introduction

Mother-to-child transmission (MTCT) of *Treponema pallidum* during pregnancy results in congenital syphilis.[1] Globally, 1.36 million pregnant women are estimated to have active syphilis per annum.[2] The World Health Organization (WHO) regards congenital syphilis as a public health priority, and in 2007 a campaign for its global elimination was launched.[3]

The Syphilis Register Information System (SRIS) is a centralised patient database in the Northern Territory containing all positive syphilis test results and treatment histories. This resource is managed by nursing staff and overseen by a sexual health physician at the Centre for Disease Control (CDC), who are available to provide information to clinicians to help inform treatment decisions.

In the Northern Territory, risk classification and management of syphilis in pregnancy and the neonatal period is directed by the *Guidelines for the Investigation and Treatment of Infants at Risk of Congenital Syphilis in the Northern Territory*.[4] This guideline recommends clinicians notify all low and high risk cases to the CDC. This includes all mothers with rapid plasma reagin (RPR) titres ≥1:8 during pregnancy for whom re-treatment is recommended even if previous adequate syphilotherapy has occurred. Under the *Notifiable Diseases Act* the CDC Northern Territory maintains a database of probable or confirmed congenital syphilis cases as defined by the Communicable Diseases Network Australia (CDNA).[5] These case definitions are also used by clinicians for the purpose of making a formal diagnosis of congenital syphilis. Table 1 shows the correlation of the Northern Territory risk category with CDNA case definitions.

The Northern Territory is a jurisdiction that spans 1.4 million km,[2] with a population of 240,000 people, 30% of whom are Indigenous.[6] Rates of syphilis seropositivity in the Northern Territory are estimated in the order of 1 in 3 Indigenous persons by the age of 40 years based on data derived from a comparable population in the Kimberley region of Western Australia.[7] Until recently, the notification rate of infectious syphilis in the Northern Territory was by far the highest among Australian states and territories;[4] however this has declined substantially from 35.1 per 100,000 in 2008 to 9.1 per 100,000 in 2013.[8] A comparably large reduction in congenital syphilis notifications has also occurred, with 4 cases notified between 2009 and 2013 (3 in 2009 and 1 in 2013).[9]

Table 1: Correlation of the Northern Territory risk category with the Communicable Diseases Network Australia case definitions

NT risk category	Risk category inclusion criteria	CDNA classification
No risk	Mothers who have never had syphilis OR Mothers with adequately treated* syphilis prior to pregnancy AND All rapid plasma reagins in pregnancy <1:8 AND No suspicion of late infection	N/A
Low risk (notify to Communicable Disease Centre)	Mother adequately treated* for syphilis in pregnancy	May meet criteria for probable/confirmed congenital syphilis
High risk (notify to Communicable Disease Centre)	Mother seropositive during pregnancy AND ≥1 of (i) Clinical signs (ii) Inadequate maternal treatment (iii) Child's RPR ≥4 times maternal titre or (iv) Maternal re-infection likely	Probable or confirmed congenital syphilis

* Adequate treatment requires adequate syphilotherapy (appropriate penicillin regime) and adequate serological response (Early disease: 2-titre or 4-fold decline in rapid plasma reagin; Late disease: If no rapid plasma reagin decline then maintenance of a low stable titre <1:8 and not increasing more than 1 titre).

Low numbers of notifications of congenital syphilis in the Northern Territory in recent years may be the result of low incidence, or cases not being appropriately recognised and/or notified. We conducted an audit of pregnant women with RPR titres ≥1:8 during pregnancy in the Northern Territory between 1 January 2009 and 20 May 2014 in order to capture women posing the highest risk for mother-to-child transmission. The primary objective was to determine whether congenital syphilis cases in the Northern Territory between 2009 and 2014 were correctly notified based on probable or confirmed case criteria stipulated by the CDNA. Additionally, we aimed to characterise the reasons for missed notifications and to determine whether at-risk infants received treatment.

Methods

Selection of participants and extraction of data

Pregnant women with RPR titres ≥1:8 were identified from the Northern Territory SRIS over the study period.[8] Attempts were made to link maternal and newborn patient files in the SRIS and hospital patient databases. Data were obtained from the SRIS and electronically available hospital patient records (including discharge and clinic letters, radiology and pathology results).

Criteria for risk classification, disease notification, and adequate treatment

Risk classification for MTCT of syphilis in pregnancy into no risk, low risk or high risk groups was based on criteria outlined in the *Guidelines for the Investigation and Treatment of Infants at Risk of Congenital Syphilis in the Northern Territory*.[10] Classification was performed by the chief investigator and counter-checked by co-investigators JYS, AI and NR.

Adequate treatment for maternal syphilis was based on local guidelines.[4] For mothers with late syphilis, 3 benzathine penicillin G injections are recommended at 7-day intervals, although up to 14 days between injections was considered acceptable in our cohort based on local and international expert opinion.[11] Serofast status was assigned when an individual's serum showed little or no change in antibody titres (<2-titres or 4-fold drop) despite adequate treatment.

Postnatal treatment for low risk infants comprised 1 dose of intramuscular benzathine penicillin G (37.5 mg/kg). Adequate treatment for high risk infants was defined as benzyl penicillin 50 mg/kg per dose delivered twice daily intravenously for 10 days, which is considered a neuro-penetrating regime.[10] Appropriate follow-up for all low and high risk infants required clinical review and syphilis serology at birth, and 3 and 6 months of age.

Criteria for notification of probable or confirmed congenital syphilis cases were based on CDNA criteria (2010).[5]

Statistical analysis and ethics approval

Descriptive statistical analyses were performed using Microsoft Excel version 14.1.0 (2010). Approval for the study was obtained from the Human Research

Ethics Committee of the Northern Territory Department of Health and Menzies School of Heath Research (HREC-2014-2263).

Results

There were 34 instances of positive maternal syphilis serology (RPR titre ≥1:8) from 31 women over the study period; all were Indigenous. The median maternal age at delivery was 27 years (range 16 to 43 years). The women resided in a wide range of locations; 8 from Katherine, 13 from Central Australia, 2 from East Arnhem, 6 from urban Darwin and 2 from interstate. It was possible to link maternal and neonatal files in the register in 21 instances (62%). For the remaining 13 neonates whose identities were unknown, a date of birth was recorded for seven. Despite an inability to link maternal and neonatal files in a significant proportion of cases, risk classification was possible in all instances using either maternal or neonatal data.

Maternal treatment and risk classification

Risk classification is depicted in the Figure. Overall, 1 woman met criteria for no risk of MTCT, 12 were low risk (35%) and 21 (62%) were high risk. The maternal risk classification recorded in the SRIS was incorrect in 15 (44%) of the 34 pregnancies. Twenty-one of the 34 pregnancies were not adequately treated or did not demonstrate adequate treatment response during pregnancy. Of these, 8 women were not treated (38%), 5 women were not treated in time (24%; 1 case was notified), and 8 women did not meet serological criteria for adequate response (38%).

Congenital syphilis notifications

Of the audited population, there were 21 neonates who met CDNA criteria for probable congenital syphilis over the study period, and none for the confirmed category (Table 2). All 21 cases also met criteria for high-risk classification based on local Northern Territory guidelines, yet only 1 case was formally notified (5%).

Of the 20 cases that were not notified but met CDNA criteria for probable congenital syphilis, 9 cases were incorrectly classified on the SRIS as no risk (n=5) or low risk (n=4), and in 2 cases, risk classification was not recorded. Nine neonates were accurately classified on the SRIS as high risk, yet not notified. One of the 20 cases not notified was delivered interstate.

Neonatal management

Overall, 14 (42%) of the 26 low and high-risk neonates for whom information was available were adequately treated at birth (information was not available in 7 instances).

Only 17 of the 33 low and high-risk neonates underwent the required serological testing for

Figure: Audited risk classification for mother-to-child-transmission of syphilis

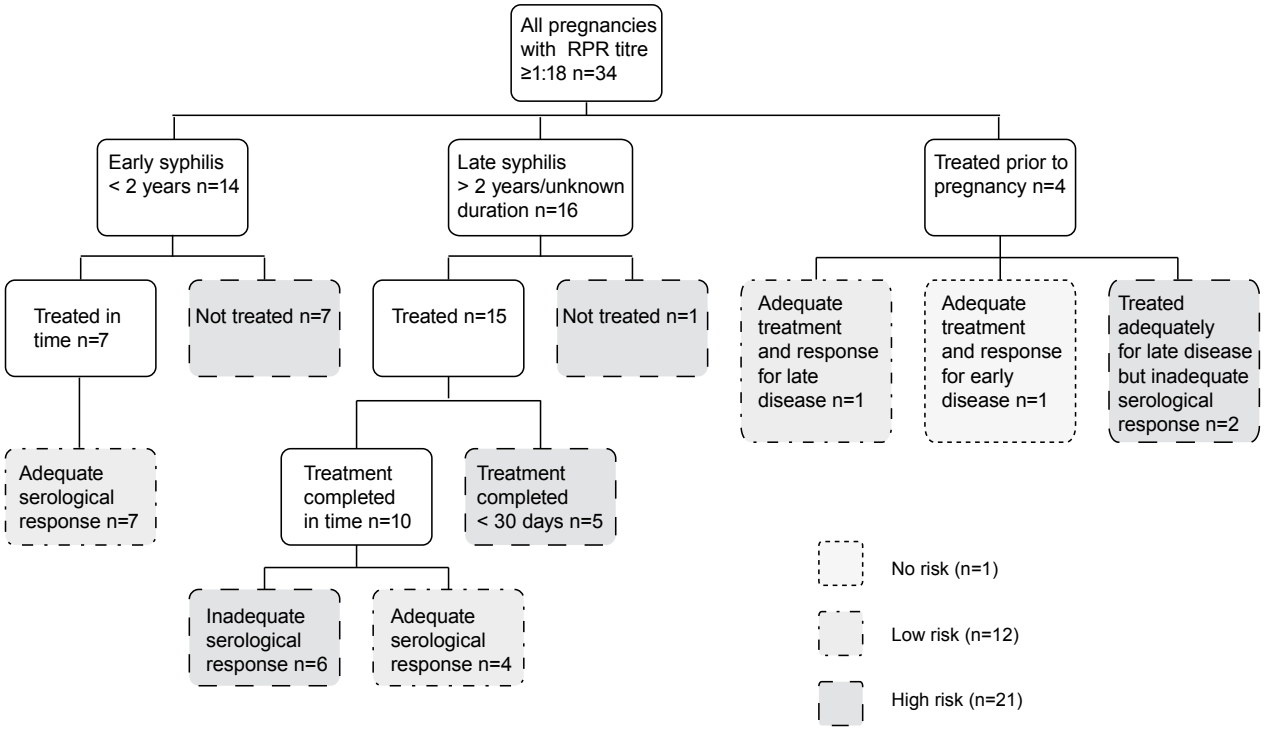

Table 2: Reasons probable congenital syphilis cases were not notified based on Communicable Diseases Network Australia case definitions

Cases at risk of mother-to-child-transmission of syphilis (n=34)	Total	Notifications
Cases not requiring notification	13	–
Cases requiring notification	21	1
Indications for notification		
Maternal factors– early disease		
Not treated	7	–
Maternal factors– late disease		
Not treated	1	–
Treatment completed <30 days	5	1
Inadequate serological response (no 2-titre/4-fold drop)	8	–

syphilis at birth (52%). Eight of the 33 infants (24%) had follow-up serology performed (ranging from 11 days post-delivery to 11 months of age). In 7 instances, follow-up serology was negative, while in 1 case serology was positive, but less than 4-fold higher than the maternal results.

There were no neonates who were notified based on signs detected on physical examination or radiography alone. One pregnant woman with early syphilis who was adequately treated, suffered a foetal death in utero at 19 weeks. Ureaplasma was detected on placental culture. This foetus did not meet CDNA case criteria for probable congenital syphilis.

Discussion

Our study found that the overwhelming majority of audited cases (20/21, 95%) that met the criteria for probable congenital syphilis according to CDNA criteria, were not notified during the study period. As there were only 4 cases of congenital syphilis notified in the Northern Territory during this period overall, notifying the additional 20 cases identified during this audit would produce a 6-fold increase in the congenital syphilis rate. However, this may still be an underestimate, as only women with titres ≥1:8 were included in this audit. The other 3 notified cases during the study period, who were not included in our cohort, occurred in women who had RPR titres < 1:8 in pregnancy, who were classified as high risk due to inadequate previous treatment for late syphilis.

Treatment and follow-up did not comply with the Northern Territory and national guidelines in the majority of cases. Firstly, nearly two-thirds of women were not adequately treated for syphilis in pregnancy. Secondly, only half of the neonates received the recommended prophylactic treatment at birth. Lastly, few neonates received appropriate follow-up.

Late and/or inconsistent attendance at antenatal care may have contributed to the failure to adequately treat prior to delivery. Indigenous women, particularly those living in remote locations, are less likely to present for antenatal care in the first trimester.[12] However, while this may account for some missed (n=8) and late maternal treatment (n=5) it cannot account for either the failure to correctly treat neonates at birth or the failure to notify the cases. Furthermore, as most untreated cases were also not classified correctly on the SRIS, it seems unlikely that failure to present for antenatal care accounts for a large proportion of inadequately managed cases.

The diagnosis of syphilis reinfection in a previously treated person is open to a level of subjectivity. The intrinsic variability of RPR results between batches, operators and laboratories is an issue that merits attention. It is not uncommon to see different serological values for the same woman recorded on the same day at different laboratories. These 'outlier' results create a problem for clinicians and syphilis register staff responsible for interpreting results, especially if they support CDNA case criteria warranting notification. Six of the 8 untreated cases described in this paper were deemed by treating clinicians not to require treatment on the basis of 'outlier' laboratory results. However, as the CDNA criteria for adequate previous treatment are stringent we applied the same level of rigidity to the criteria for the diagnosis of new syphilis cases, and all women with a 2-titre increase in RPR were defined as cases.

Eight cases in our study that were not notified met CDNA criteria for notification due to inadequate maternal serological response to treatment. Interestingly, a recent retrospective review[13] of 166 pregnant women with syphilis (>18 weeks) who received adequate syphiliotherapy, found failure to achieve a 4-titre serological drop was more

a reflection of treatment timing than treatment failure ($P<0.001$). Inadequate serological response was significantly correlated with late syphilis or syphilis of unknown duration and older maternal age. The findings of this landmark study and recommendations of the early draft of this paper provided to the working group responsible for the revision of national case definitions for congenital syphilis, have contributed to the release of the new national case definitions on 1 July 2015. In this new case definition, inadequate maternal serological response has been removed as constituting laboratory evidence for probable congenital syphilis. This not only simplifies the Australian national case definitions, but also brings them more in line with those currently used in the United States of America.[14] The 8 cases described above would no longer meet criteria for probable congenital syphilis based on the new CDNA case definitions.

Clinical practice did appear to diverge from local management guidelines in a significant proportion of our cases, and CDNA criteria for notification are not currently being stringently applied. This is alarming, given congenital syphilis represents a significant public health threat in the Northern Territory, and notification of cases is vital in order to ensure an appropriate public health response. Transmission is easily prevented in a cost-effective manner when appropriately identified and treated.[15] Improved education about management of congenital syphilis and CDNA criteria for notification of probable or confirmed cases is needed, both for clinicians involved in patient care and relevant public health and CDC staff involved in local Northern Territory and national surveillance. This is likely to be true for other Australian states with similar epidemiology of infectious syphilis.

A further issue that merits review is the utility of re-treating all women with RPR titres ≥1:8 in pregnancy including those who have received adequate syphilotherapy prior to pregnancy. Whilst this approach helps ensure that all neonates with potential untreated congenital syphilis receive prophylactic treatment, the incremental benefit of re-treating serofast patients is likely to be minimal, with one study suggesting only 25% demonstrate serological response with re-treatment.[7] This calls into question the cost-effectiveness of this strategy.

This study has a number of limitations, including the fact that information was obtained from electronic records only, and a more extensive chart review was not performed owing to difficulties in accessing records from remote centres. Outcomes of post-natal follow-up were also not assessed in this audit, and so it is unknown whether adverse outcomes occurred for cases that met criteria for probable congenital syphilis but were not notified. However, the Northern Territory CDC is currently conducting another audit on the outcomes of cases of congenital syphilis, which will shed some light on this aspect. The likely cause of foetal death in utero at 19 weeks in the mother with early stage, adequately treated syphilis was ureaplasma chorioamnionits, and not syphilis, although an autopsy was not performed. In light of the findings of this audit, we have liaised with the Royal Darwin Hospital Paediatric unit to ensure that clinical follow-up for missed cases occurs, where possible.

There is a need for prospective longitudinal studies examining long-term outcomes for neonates at risk of MTCT of syphilis, detailing their initial management, follow-up and clinical course. This would allow an improved understanding of clearly at risk neonates, and facilitate improved risk categorisation and management.

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