Original article

Was infectious syphilis being misclassified in remote Australian outbreaks? Evidence that informed modification of the national case definition

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Abstract

Objective: To assess the ability of the national case definition to identify infectious syphilis during an outbreak affecting predominantly Aboriginal and Torres Strait Islander people in a remote Australian region.

Methods: A retrospective case series study of all non-congenital syphilis cases in the region notified between 1 January 2009 and 31 December 2012 was performed. The national infectious syphilis case definition was compared with an expanded case definition derived from experienced clinician assessment and the definition proposed in the *Interim Guidelines for the Public Health Management of Syphilis Outbreaks in Remote Populations in Australia* from the Communicable Diseases Network Australia (CDNA).

Results: Two hundred and forty syphilis cases were notified, of which 44 (18.3%) were symptomatic. The national case definition classified 106 (44.2%) cases as infectious, compared with 182 (75.8%) using the clinician-derived expanded case definition and 165 (68.8%) by the interim guidelines case definition. Seven confirmed and 6 probable cases were diagnosed as a result of contact tracing of probable infectious cases identified using the expanded case definition.

Conclusions and implications: The national case definition for infectious syphilis applied in this remote Australian outbreak underestimated infectious cases when compared with experienced clinicians' evaluation by up to 76 cases (42%) and was inadequate to monitor the magnitude of a syphilis outbreak in such a setting. This may compromise surveillance and resource allocation decisions, and could reduce the capacity to interrupt transmission and contain an outbreak. A revised national case definition, informed by this analysis, was released by CDNA in July 2015. *Commun Dis Intell* 2015;39(4):E571–E577.

Keywords: infectious syphilis; case definition; Aboriginal health

Introduction

Syphilis is a sexually transmissible infection (STI) of public health importance due to the significant perinatal morbidity and mortality caused when it is acquired in pregnancy,[1] the increased potential for HIV transmission,[2] the immediate impacts on the individual—symptoms, shame, stigma—and the risk of transmission to others. The natural history of syphilis is complex. Primary, secondary and tertiary stages of the infection have clinical manifestations and patients with the first 2 stages are infectious. There are also asymptomatic stages (early latent and late latent syphilis) detectable only by serology. The classification of an asymptomatic person with positive serology as early (infectious) or late (non-infectious) latent disease depends on the interpretation of previous serology, clinical and treatment history and, arguably, epidemiological context. A person with late latent syphilis remains at risk of progression to tertiary disease, but is not considered infectious.

The classification of the stage of infection has clinical, public health and surveillance implications.[3] Treatment decisions are based on the stage of infection. To prevent tertiary syphilis, an infectious case requires 1 dose of 1.8 gm intromuscular (IM) benzathine penicillin, whereas late latent disease requires 3 weekly doses.[4] From a public health perspective, the priority is to identify all potentially infectious cases so they and their sexual contacts can be treated and to stop transmission. National surveillance monitors syphilis epidemiology to help inform policy and prevention strategies and to facilitate disease control. For surveillance, data collected must be reliable and consistent.

Syphilis is a legally notifiable condition in every state and territory in Australia and nationally. The Communicable Diseases Network Australia (CDNA) periodically reviews the national case definition for infectious syphilis. Prior to July 2015, this definition included symptomatic primary and secondary cases and asymptomatic cases for

which there was definitive evidence of serological conversion within the previous 2 years (early latent syphilis) (Table 1).[5] Only cases with unequivocal proof of recent infection were counted as infectious (i.e. the definition was highly specific). Asymptomatic cases for which there was no syphilis serology documented within the preceding 2 years were classified as 'syphilis of more than 2 years duration or unspecified duration' (late latent/unknown duration) even in the presence of compelling clinical or epidemiological evidence suggesting recent infection. The reliance on dated serological testing techniques in combination with relatively non-specific clinical information to confirm cases results in imperfect public health case definitions compared with most other notifiable diseases. Furthermore, while it is known that intrinsic assay variability requires rapid plasma reagin (RPR) titres to be tested in parallel with previous specimens from the same laboratory, in most Australian settings laboratories are unable to perform this, as they no longer retain specimens.

There is no gold standard for the diagnosis of asymptomatic infectious syphilis. Case definitions from America, New Zealand and Europe include consideration of clinical history and/or an epidemiological link with an infectious case.[6–8]

Despite a general decline in syphilis notifications in the Australian Aboriginal and Torres Strait Islander population over recent decades,[9] sporadic outbreaks have continued to occur in remote settings.[10] From late 2010, the number of cases of syphilis notified from a single health district in remote North Queensland increased dramatically, predominantly affecting young Aboriginal and Torres Strait Islander people (Queensland Health, Statewide Syphilis Surveillance System, unpublished data). During the outbreak investigation a considerable number of cases had evidence suggesting recent syphilis acquisition but could not be classified as 'infectious' using the national case definition, being asymptomatic and without recent prior syphilis serology. If the national case definition alone were relied on to determine the magnitude of the outbreak and need for contact tracing, understanding of the extent of public health response required and interruption of disease transmission would have been jeopardised. In recognition of this, an additional classification category 'probable infectious syphilis' was proposed in the CDNA *Interim Guidelines for the Public Health Management of Syphilis Outbreaks in Remote Populations in Australia* (Interim Guidelines), released in February 2014 (Table 1). This new category includes consideration of additional epidemiological and case history information.[11]

This study assessed the extent to which potentially infectious syphilis cases may have been misclassified as non-infectious during the first years of this outbreak by comparing the number of cases classified as infectious using the national case definition with 1. an expert clinician-derived expanded case definition that takes into account clinical and epidemiological factors, and 2. the Interim Guidelines case definition.[11]

Methods

Demographic, clinical and laboratory characteristics of all non-congenital cases of syphilis diagnosed in a north Queensland district from 1 January 2009 to 31 December 2012 were extracted from the Queensland Health state-wide syphilis surveillance system database. Data assessed were age, gender, Indigenous status, clinical history, epidemiological link with a confirmed case, reported gender of sexual partner(s), previous serology and RPR titre. Data had been collected in the course of routine enhanced surveillance. All cases met criteria for notification with either positive syphilis serology and/or a positive nucleic acid amplification test.

The cases were independently assessed by 2 clinicians (PF and NR) experienced in syphilis diagnosis. The clinicians classified each case as either infectious, probable infectious or non-infectious taking all factors into account. Where a discrepancy existed between the clinicians, available data were clarified and they reviewed their original classification. The extent to which the clinicians' classifications were concordant was analysed using Cohen's kappa coefficient. The first author then reviewed the cases classified as 'probable infectious' by the clinicians, and thus derived the expanded case definition outlined in Table 1.

A review was conducted of the case classifications (infectious, probable infectious or non-infectious syphilis) resulting from the application of the national case definition for infectious syphilis; the clinician-derived expanded case definition, and the Interim Guidelines case definition.

The absence of a gold standard for the diagnosis of infectious cases prevents identification of 'true positives', precluding statistical analysis of the positive or negative predictive value of the case definitions. A comparative analysis of the proportion of cases identified as infectious by the 3 case definitions was conducted. The number of additional contacts and positive contacts identified using the expanded case definition was assessed.

The research project, performed on de-identified notifiable condition data for clinical audit and quality improvement, was exempt from ethical review.

Table 1: Case definitions for infectious syphilis comparing the national case definition; expanded case definition derived from experienced clinician assessment and Interim Guidelines case definition

Case definition	National- less than 2 years duration	Expanded case definition	Interim guidelines
Confirmed infectious cases (primary, secondary or early latent syphilis)	1. Laboratory definitive evidence* **OR** 2. Laboratory suggestive evidence AND clinical evidence†		
Probable infectious cases	Not Applicable	Does not meet the criteria for infectious syphilis (primary, secondary or of less than 2 years duration) **AND** A. RPR 1:128 or higher **OR** B. RPR 1:8 or higher **AND** the case satisfies one of the following: 1. Aboriginal and/or Torres Strait Islander and age less than 30 years at the time of testing **OR** 2. A contact of a case of infectious syphilis‡ **OR** C. Aboriginal and/or Torres Strait Islander and age less than 20 years, in a community with an infectious syphilis outbreak and suggestive clinical history or epidemiological link with outbreak	Does not meet the criteria for infectious syphilis (primary, secondary or of less than 2 years duration) **AND** RPR 1:32 or higher **AND** the case satisfies one of the following: 1. Aboriginal and/or Torres Strait Islander and age less than 30 years at the time of testing **OR** 2. A man of any age who has sex with men **OR** 3. A contact of a case of infectious syphilis

* Laboratory definitive evidence is defined by either seroconversion in the past two years (reactive specific test confirmed by either reactive non-specific or a different specific treponemal test) or a 4-fold or greater rise in rapid plasma reagin (RPR), with confirmation of positive results by a reactive specific treponemal test.

† Laboratory suggestive evidence includes *Treponema pallidum* identification by microscopy (darkfield, fluorescent antibody or equivalent) or nucleic acid testing, or a combination of reactive specific and non-specific serological tests. Clinical evidence is defined as 'presence of a primary chancre (or ulcer) or clinical signs of secondary syphilis'.

‡ Defined as: contact with a case of confirmed primary, secondary or early latent syphilis in the 12 months before, or 3 months after diagnosis.

Results

Demographics

Two hundred and forty cases of non-congenital syphilis were notified in the district during 2009–2012. Case demographics are shown in Table 2. None were co-infected with HIV. The median age of the 44 symptomatic cases was 21 years, range 12–46 years. Thirty-six (81.8%) of these were aged less than 30 years.

Infectious syphilis

Table 3 displays the classification of syphilis cases by year, comparing the number of cases classified as infectious by the 3 case definitions.

With regard to infectious status, there was 97.8% agreement, kappa coefficient k=0.953 (CI 0.91–0.99) between the clinician assessors. For four of the 240 cases (2.2% of the infectious cases as classified by the expanded case definition) the clinicians were unable to reach consensus. All 4 cases were Indigenous, aged 18–21 years and with RPR titres of 1:2, 1:4, 1:8 and non-reactive, respectively. None were known contacts of infectious syphilis cases. These were classified as non-infectious.

The national case definition classified 106 (44.2%) of the 240 cases as infectious, compared with 182 (75.8%) by the expanded case definition (Table 3), i.e. 76 additional probable infectious cases were identified. These cases named 141 contacts, of whom 111 were successfully followed

Table 2: Demographic characteristics of all non-congenital syphilis cases compared with infectious syphilis cases defined by national case definition in a north Queensland district, 2009 to 2012

	All cases of syphilis	Per cent of all cases	Cases of infectious syphilis	Per cent of infectious cases
Number of cases	240		106	
Females	135	56.3	61	57.5
Males	105	43.7	45	42.5
Indigenous status:				
Aboriginal and/or Torres Strait Islander	232	96.7	104	98.1
Non-Indigenous	8	3.3	2	1.9
Median age	21		20	
Aged less than 30 years	174	72.5	92	86.8
Age range (years)	12–84		12–59	
Transmission (self-report):				
Heterosexual	210	87.5	103	97.2
Homosexual	1	0.4	1	0.9
Not stated	29	12.1	2	1.9
Primary or secondary (symptomatic) infection	44	18.3	44	41.5

Table 3: Non-congenital syphilis notifications in a district of north Queensland, 2009 to 2012, and number of cases of infectious and non-infectious syphilis classified by the national case definition, expanded case definition and Interim Guidelines case definition

Year	Total notifications of syphilis	Classification by national case definition		Classification by expanded case definition		Classification by Interim Guidelines case definition	
		Infectious	Non-infectious*	Infectious and probable infectious	Non-infectious	Infectious and probable infectious	Non-infectious
2009	22	1	21	2	20	2	20
2010	21	15	6	16	5	16	5
2011	99	44	55	85	14	74	25
2012	98	46	52	79	19	73	25
Total	240	106	134	182	58	165	75

* Case definition includes cases of unknown duration.

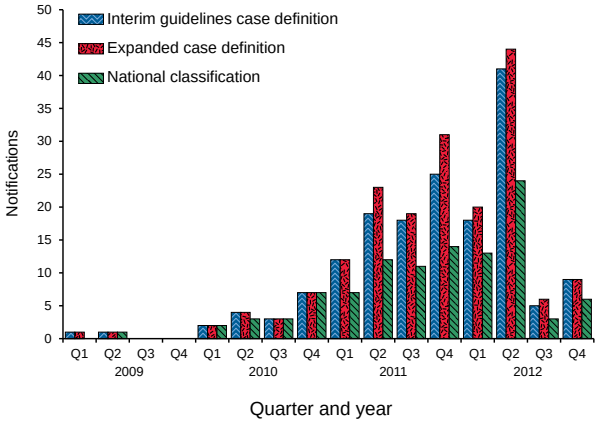
up. Seven of the confirmed and six of the probable cases of infectious syphilis included in our analysis had been identified as a consequence of contact tracing of the probable infectious cases. Demographics of the additional 76 probable infectious cases were similar to, though slightly younger than the infectious cases identified by national criteria. All 76 cases were Indigenous, 49 (64.5%) female, median age 18 years, range 12–37 years; 73 (96.1%) were aged less than 30 years. Twenty had an epidemiological link with a confirmed case of infectious syphilis.

Applying the Interim Guidelines criteria classified 59 cases as probable infectious syphilis, in addition to those confirmed as infectious cases using the national definition. All of the cases identified using this case definition had also been classified as probable infectious syphilis by the expanded case definition. The Figure compares the epidemic curve of infectious syphilis over time in the district utilising the three classification methods.

Discussion

This large outbreak has provided a valuable opportunity to examine the implications of infectious syphilis case definitions for public health surveillance and response in a real world situation. This study demonstrated that the national case

Figure: Epidemic curve of infectious syphilis in a north Queensland district, 2009 to 2012, by national definition, expanded case definition and Interim Guidelines case definition



definition for infectious syphilis underestimated infectious cases by up to 42% when compared with an expert clinician-derived expanded case definition. Application of the expanded case definition and the resultant increased number of contacts traced in this setting resulted in the identification of a further 13 probable or confirmed infectious cases. This highlights that adherence to the narrow national case definition could have implications for outbreak control if these additional cases were not assessed and treated. Applying the Interim Guidelines case definition identified 59 of the 76 cases of probable infectious syphilis that were considered probably infectious by the clinicians and did not result in any clinician classified non-infectious cases being identified as probably infectious.

Use of the probable infectious syphilis category would not have resulted in earlier identification of this outbreak; the divergence in the number of cases identified as infectious by use of the expanded case definition became apparent in the 1st quarter of 2011, after the outbreak was established. There may still be implications for the timeliness of an outbreak response. Missed identification opportunities and delays in STI outbreak response in this remote setting have significant consequences given the sexual and reproductive health vulnerability of this population, evidenced by the excess burden of chlamydia and gonorrhoea,[9] and the on-going risk of HIV/AIDS in remote Australia.

The national case definition for infectious syphilis requires clinical symptoms and/or baseline laboratory evidence to confirm a recent infection. If a person is asymptomatic and has not had syphilis serology performed in the previous 2 years, as is the case for many young Aboriginal and Torres Strait Islander people, they cannot be classified as infectious, even in the context of an established outbreak, a high RPR titre, or a clear epidemiological link to an infectious case. In our study, 55 probable infectious cases had never been tested previously for syphilis, and 21 probable infectious cases had previous serology performed more than 2 years ago. Under the national case definition, a change in the amount of syphilis testing performed could affect the number of cases classified as infectious, purely because of a change in the number of people with a baseline serology result.

There are anecdotal reports that the specificity of the national case definition for infectious syphilis in Australia has led to dissonance among public health professionals who classify cases, resulting in an inconsistent approach within and across jurisdictions. This could have an impact on the consistency of national data, as in the American context.[3] One American study found that approximately half of notified early latent cases did not meet the national case definition, and different jurisdictions had developed their own case definitions. They were applying these case definitions to the nationally reported notifications, resulting in inconsistent data that could not be aggregated.[3] Additionally, loosely defined criteria resulted in inconsistent misclassification within the jurisdiction. To our knowledge, no such study has been performed in Australia.

Establishing a 'probable infectious syphilis' category is one mechanism to clarify management of affected individuals, optimise outbreak control and at the same time preserve national data consistency. Other surveillance programs have definitions that include consideration of clinical and/or epidemiological information. The American case definition for 'probable early latent syphilis' includes asymptomatic cases with evidence of recent serological conversion, but also allows for cases with laboratory evidence of syphilis and 1. a clinical history of primary or secondary syphilis symptoms in the previous 12 months, 2. an epidemiological link to a partner with infectious syphilis within the previous 12 months, or 3. a history of sexual debut within the last 12 months.[6] However, the reliance on recall of symptoms and clinician interpretation of such findings has been criticised as difficult to standardise.[12] The European Centre for Disease Prevention and Control classification of 'probable early latent syphilis' is defined as a person with clinical criteria and an epidemiological link.[8] The New Zealand case definition for early latent syphilis includes a clear history of primary or secondary syphilis symptoms within the previous 2 years or sexual contact with a confirmed case of infectious syphilis within the previous 2 years.[7]

The Interim Guidelines 'probable infectious syphilis' case definition relies on a RPR of ≥ 1:32 and allows consideration of an epidemiological link. The inclusion of cases due to ethnicity, age or sexual orientation may warrant further refinement, as these criteria bias case classification towards groups currently experiencing higher rates of syphilis and potentially amplify this rate differential because the ability to detect infectious cases in other populations would not be similarly enhanced.

RPR titre has been proposed for use in early latent syphilis case definitions, based on pre-treatment titre or rapid decrease in response to treatment, suggestive of early disease.[12] Although high RPR titres are strongly associated with recent infection,[13] there is no specific level of RPR titre that can reliably distinguish between early latent and late latent syphilis in asymptomatic people. One study found considerable overlap in RPR titre distributions between stages of disease,[12] making the choice of a threshold titre for disease staging problematic. However, the authors concluded that in asymptomatic patients, RPR titre could provide a more objective and reliable record of syphilis trends compared with a system based on inconsistently applied definitions. We assessed the number of probable infectious cases that would be identified using the Interim Guidelines case definition, but with an RPR titre cut-off of 1:8, instead of 1:32. This resulted in an additional 12 probable infectious cases (in total, 92% of the probable infectious cases by the expanded case definition), however it also captured 2 cases as 'probable infectious' that were assessed to be non-infectious by the clinicians.

The strength of the agreement between the clinicians in this study was very good. The clinician assessors made their classifications independently of each other based on data provided by the statewide surveillance system.

Limitations

There is no gold standard for the diagnosis of asymptomatic infectious syphilis, which precludes accurate assessment of the validity of the proposed probable infectious syphilis case definition. In lieu of this we employed an expert clinician derived expanded case definition that took account of the clinical, laboratory and epidemiological information of all of the cases as a 'proxy gold standard'.

This study is based on a retrospective analysis of cases, however enhanced surveillance at the time of notification resulted in comprehensive clinical information being obtained. The 2 clinician assessors independently agreed on all but 4 cases. One of the clinicians (PF) was the author of the Interim Guidelines and the other (NR) was a member of the reference group for the project. It is possible that this could bias the concordance of the clinician consensus with the Interim Guidelines definition. However, the number of clinicians with experience in this area is limited, and most of those with relevant expertise would most likely have been consulted during the guideline development.

In Australia, there are 2 groups among whom the majority of syphilis cases are diagnosed; men who have sex with men (MSM) and predominantly heterosexual transmission in young, regional and remote-living Indigenous people.[9] The criterion in the Interim Guidelines case definition relating to MSM is largely redundant in the remote Australian setting. It is likely that similar issues as identified here relating to the adequacy of case definitions operate in the context of MSM, however it is unclear to what extent these findings would be applicable in consideration of case definitions for MSM. This may increase the challenge in developing appropriate case definitions. As observed in Peterman's study,[3] criteria that cases met to qualify as early latent syphilis varied by site, and these variations may be more extreme when considering the vastly different life circumstances of the 2 population groups mainly affected by syphilis in Australia.

Conclusion

The national case definition for infectious syphilis identified only cases with definite evidence of recent infection, and did not capture many cases with strong clinical or epidemiological evidence suggesting recent infection. This study does not claim to resolve the conundrum of a perfect infectious syphilis case definition, but demonstrates that in the context of an outbreak in a remote Indigenous setting, a considerable number of likely infectious cases are not captured. This can result in an inability to adequately monitor and contain outbreaks and an underestimate of their size, with implications for resourcing an adequate public health response. There are also implications for the reliability of national surveillance data. This study assessed the utility of an additional 'probable infectious syphilis' classification, which performed well in this setting. The national case definition for infectious syphilis should be revised to improve monitoring of this serious public health issue.

At the time this article was undergoing peer review, CDNA released a revised infectious syphilis case definition, in part informed by this study, incorporating a 'probable infectious' category.[14] Applying the new CDNA case definition to this dataset identified 67 of the 76 probable infectious cases as classified by the expanded case definition.

The authors believe the revised definition will better reflect the true extent of an outbreak in remote Indigenous settings, and commend this revision.

Acknowledgements

The authors thank all those who contributed, especially Therese Howard, Public Health Nurse, North Queensland Syphilis Surveillance Centre.

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