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Retrospective Review of Tertiary and Neurosyphilis Cases in Alberta, 1973 to 2017

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Abstract

Objectives: To review the prevalence and characteristics of tertiary and neurosyphilis cases in Alberta, Canada in the post-antibiotic era.

Methods: A retrospective review of all neurosyphilis and tertiary syphilis cases reported in Alberta from 1973 to March 2017 was undertaken and cases classified into early neurosyphilis, late neurosyphilis and cardiovascular syphilis. Variables collected included demographics, sexual partners, HIV status, clinical parameters, symptoms and treatment. Data was analyzed using IBM SPSS Statistics Version 19.0.

Results: 254 cases were identified; 251 were neurosyphilis and 3 were cardiovascular. No cases of gummatous syphilis were reported. Early neurosyphilis accounted for 52.4% (n=133) and 46.1% (n=117) were late neurosyphilis cases; one (0.4%) case with unknown duration. Three outbreaks of infectious syphilis were identified during the study period and a concurrent rise in both early and late neurosyphilis was observed during the outbreak periods. The most common manifestation of symptomatic neurosyphilis was ocular involvement which was more likely in early neurosyphilis. Early neurosyphilis cases were more likely to be younger, Caucasian, born in Canada, HIV positive and reporting same sex partners while late neurosyphilis cases were more likely to be older, born outside of Canada and less likely to report same sex partners.

Conclusions: Our review of tertiary and neurosyphilis cases found that early and late neurosyphilis cases continue to occur in the context of cycling syphilis outbreaks. Cardiovascular syphilis cases were extremely rare. Ongoing identification of new cases of

syphilis and clinical evaluation of cases for complications continues to be important in the context of global resurgence of syphilis.

Keywords: tertiary syphilis, neurosyphilis, Canada

Strengths and Limitations of this study:

- An important strength of our study was the consistent reporting of all cases with positive syphilis serology over the 44 year period by laboratories as well as active follow up of all cases by the provincial STI program.
- Another strength of our study is the retrospective application of current case definitions to all cases by 2 experienced STI clinicians.
- One of the limitations to the retrospective review of data is the possibility of inaccurate classification of cases due to insufficient available information.
- Additional study limitations include changes in data collection practices over time.
- Routine testing for HIV in cases of syphilis was also not conducted in earlier years and as such the number of concurrent HIV infections may have been underestimated.

Manuscript

Background

Syphilis, caused by *Treponema pallidum* subspecies *pallidum*, passes through a series of stages, including primary, secondary, latent and tertiary syphilis if left untreated.[1] Based on data from the pre-antibiotic era, about a third of persons with untreated latent syphilis will develop late neurosyphilis, cardiovascular syphilis or gummatous syphilis.[2] Gummatous syphilis is characterized by the development of indolent granulomatous lesions[3] which typically affect the skin, liver, and bone but can also involve other parts of the body.[4] Syphilitic aortitis is the most common manifestation of cardiovascular syphilis and typically involves the ascending aorta.[4-6]

Neurosyphilis can occur at any stage of syphilis.[1,7] It is classified into early and late forms.[1] Early neurosyphilis affects the cerebrospinal fluid (CSF), cerebral blood vessels, and meninges more often than the brain or spinal cord parenchyma. Typically, manifestations occur within weeks to a few years after primary infection and may occur at the same time as primary or secondary syphilis, or may be asymptomatic. Manifestations may include meningitis with or without cranial nerve involvement, meningovascular disease or stroke. Late neurosyphilis can remain asymptomatic or progress to meningovascular syphilis, tabes dorsalis, or general paresis. Late neurosyphilis is extremely rare in the antibiotic era and usually occurs years to decades after primary infection.1,[8] HIV infection may affect the natural course of disease as atypical presentations and rapid progression of syphilis in HIV positive individuals has been reported.[9-13]

In the pre-antibiotic era, an estimated one third of untreated persons developed tertiary syphilis[14] with about 15% progressing to gummatous disease (1-46 years post-infection), 10% to cardiovascular syphilis (20-30 years after infection), and 4-14% to late neurosyphilis (2-50 years after infection).[1] After the introduction of penicillin in the 1940s, the number of cases of syphilis plummeted in the United States, reaching a nadir in 2000.[1] Nowadays, tertiary syphilis is a rare disease due to easy and effective treatment of infectious and latent syphilis. Antibiotic use for other infections is also likely a factor.

In Canada, syphilis (all stages) has been nationally notifiable since 1924. However national reports only include data on infectious syphilis, since only these cases are of major public health significance.[15] In Alberta, all cases of syphilis, including tertiary and neuro-syphilis have been notifiable to a centralized program under the Public Health Act since 1921. Syphilis rates have fluctuated over the last fifty years with a rise in rates during outbreak periods. Since 2000, rates of infectious syphilis have increased dramatically in Alberta (0.6/100,000 population in 2000 to 12.5/100,000 population in 2017), with the most recent resurgence among men who have sex with men (MSM) and up to 30% of patients co-infected with HIV (personal communication Jennifer Gratrix, Provincial STI Services, Alberta Health Services).[16]

There are few data on the prevalence and characteristics of tertiary and neuro-syphilis cases in the post antibiotic era. We are aware of only one study from the Netherlands which estimated that 10-13% of all syphilis cases from 1999-2010 had neurosyphilis; these data were limited by the fact that the diagnostic criteria used for neurosyphilis was based on hospital discharge

diagnosis rather than clinical examination or laboratory criteria.[17] We sought to determine the prevalence and characteristics of reported cases of tertiary and neurosyphilis in Alberta from 1973 onwards.

Methods

A retrospective review was conducted of all tertiary and neurosyphilis cases in Alberta (current population 4.3 million) from 1973 to March 2017. All cases of syphilis are reportable by laboratories and clinicians to Provincial STI Services under the Alberta Public Health Act. Cases were classified as defined in Table 1.[18]

Table 1: Case Definitions Used for Diagnosis of Neurosyphilis and Tertiary Syphilis (Adapted from[19]:

Syphilis stage	**Definition**
Tertiary syphilis	Reactive treponemal serology together with characteristic late abnormalities of the cardiovascular system, bone, skin or other structures, in the absence of other known causes of these abnormalities and no clinical or laboratory evidence of neurosyphilis
Early Neurosyphilis (< 1 year after infection) *Asymptomatic*	Laboratory confirmation of primary, second or early latent syphilis and i) reactive CSF-VDRL in non-bloody CSF AND/OR ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF

	protein (>45 mg/dL) in the absence of other known causes AND NO signs or symptoms of neurosyphilis
Early Neurosyphilis (< 1 year after infection) *Symptomatic*	Laboratory confirmation of primary, second or early latent syphilis and i) reactive CSF-VDRL in non-bloody CSF AND/OR ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes AND clinical signs or symptoms of neurosyphilis*
Late neurosyphilis (>1 year after infection) *Asymptomatic*	Reactive treponemal serology (not staged as primary, secondary or early latent syphilis) and i) reactive CSF-VDRL in non-bloody CSF AND/OR ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes AND NO clinical signs or symptoms of neurosyphilis
Late neurosyphilis	Reactive treponemal serology (not staged as primary, secondary or early

(>1 year after infection) *Symptomatic*	latent syphilis) and iii) reactive CSF-VDRL in non-bloody CSF AND/OR iv) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes AND clinical signs or symptoms of neurosyphilis*

*if ocular or otic signs or symptoms present with a normal CSF examination, patient was classified as symptomatic neurosyphilis (early or late)

Serological testing for syphilis changed during the study period, with reverse sequence syphilis screening (RSSS) using an enzyme immunoassay being introduced in September 2017; prior to this a quantitative Rapid Plasma Reagin (RPR) was used. Since the criteria for classifying neurosyphilis evolved over time, all neurosyphilis cases during the study period were reviewed by two STI physicians and classified into early asymptomatic, early symptomatic, late asymptomatic, late symptomatic neurosyphilis cases; disagreement between the classifications of cases was resolved by consensus between the two physicians (PS and AES).

Reported rates of other stages of syphilis prior to 2000 were obtained from historical surveillance reports from Alberta STI Services. Population denominators were obtained through government population estimates.[19]

Variables collected for analysis included demographics, sexual partners, HIV status (testing available since 1985[20] and recommended for all syphilis cases once serology available), diagnosis date, clinical parameters, symptoms, and treatment. Variables for cases diagnosed prior to 2004 were captured through chart review, while variables for cases diagnosed after 2004 were extracted from the provincial STI surveillance system. Client reported symptoms were broken into six categories (not mutually exclusive) based on system involvement: ocular (e.g. uveitis, retinal, vision loss), auditory (e.g. hearing loss, tinnitus), stroke, peripheral neuropathy (e.g. impaired gait, numbness), central nervous system (e.g. aphasia, ataxia), and cognitive impairment (e.g. dementia, psychosis).

Treatment data was divided into 3 mutually exclusive categories based on the following minimum treatments: 1) penicillin G 3-4 million units IV q 4 h (18-24 million units/day) for 10 - 14 days, 2) ceftriaxone 2 g IV/IM daily x 10-14 days, 3) Other, which included drugs like chloramphenicol, doxycycline, tetracycline, benzathine penicillin G- long acting, reduced doses of penicillin G or ceftriaxone.

Analysis was stratified by stage of syphilis to compare early and late neurosyphilis by the previously listed variables using Chi-square or Fisher's exact for categorical variables and Mann-Whitney tests for continuous variables. Missing data was categorized as unknown and included in the analysis. As well, each syphilis stage was stratified by asymptomatic and symptomatic for comparison. Associations over time (collection decade) were analyzed using linear association.

Significant changes in rates over time were assessed using a linear trend model. The significance was set at *p*-value of <0.05. Data was analyzed using IBM SPSS Statistics version 19.0 (IBM, Armonk, NY, USA). This study was approved by the University of Alberta Health Research Ethics Board (Approval Number: Pro00075972).

Patient and Public Involvement

Patients were not involved in the design of this research study.

Results

A total of 254 cases were identified during the study period, of which 251 were neurosyphilis and 3 were cardiovascular (CV) cases; one case of CV syphilis was reported in each of the following years: 1976, 1979, and 1984. No cases of gummatous syphilis were reported during this time period. The neurosyphilis cases were evenly divided as early (52.4%; n=133) and late (46.1%; n=117), with one additional case of unknown duration. Three individuals were diagnosed with two distinct episodes of neurosyphilis over the course of the reporting period. All three of these individuals were men who reported same sex partners, all six episodes were diagnosed between 2005 and 2014, and all categorized as early neurosyphilis. Two of these men were co-infected with HIV.

Between 1975 and 2016, 8,874 total cases of syphilis were reported in Alberta. Of these, 4513 (51%) were infectious (i.e. staged as primary, secondary, early latent) and 4361 (49%) were classified as non-infectious (i.e. late latent, tertiary). Over the time period, three outbreaks of

infectious syphilis were identified (Figure 1). The first outbreak (defined as an increase in cases of two standard deviations above the baseline) occurred between 1981 and 1987, the second outbreak commenced in 2000 and declined in 2011, and a third outbreak began in 2015 and continues. Of the infectious syphilis cases, 2.8% (n=128) were staged as early neurosyphilis. When plotting the rate of early neurosyphilis cases against infectious syphilis cases, significant rises were seen during the outbreak periods (outbreak #2, p<0.001; Figure 2). Of the noninfectious syphilis cases staged during this time, 2.6% (115/4316) were staged with late neurosyphilis. When plotting the rate of late neurosyphilis against infectious syphilis during the outbreak periods, a significant rise in late neurosyphilis cases was also noted toward the end of the outbreak periods (outbreak #1, p=0.04, outbreak #2, p=0.02).

Early neurosyphilis cases were significantly younger, more likely to be Caucasian, born in Canada, diagnosed in recent decades (2010's), reported same sex partners, and HIV positive as compared to late neurosyphilis cases (Table 2).

Table 2: Characteristics of Early and Late Neurosyphilis (Alberta, 1973 to March 2017; n=250)

	Early Neurosyphilis				Late Neurosyphilis				Comparison of Early and Late p-Value
	Asymptomatic (n=28)	Symptomatic (n=105)	Total (n=133)	p-Value	Asymptomatic (n=47)	Symptomatic (n=70)	Total (n=117)	p-Value	

Median Age (IQR)	40 (32-46)	47 (39-55)	44 (36-54)	0.02	45 (32-65)	64 (53-75)	58 (45-70)	<0.001	<0.001
Gender									
Female	8 (28.6)	12 (11.4)	20 (15.0)	0.02	6 (12.8)	15 (21.4)	21 (17.9)	0.23	0.54
Male	20 (71.4)	93 (88.6)	113 (85.0)		41 (87.2)	55 (78.6)	96 (82.1)		
Ethnicity									
Indigenous	6 (21.4)	6 (5.7)	12 (9.0)	0.001	6 (12.8)	3 (4.3)	9 (7.7)	0.44	<0.001
Caucasian	10 (35.7)	78 (74.3)	88 (66.2)		14 (29.8)	23 (32.9)	37 (31.6)		
Other	3 (10.7)	4 (3.8)	7 (5.3)		16 (34.0)	27 (38.6)	43 (36.8)		
Unknown	9 (32.1)	17 (16.2)	26 (19.5		11 (23.4)	17 (24.3)	28 (23.9		

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Municipality									
Calgary	9 (32.1)	32 (30.5)	41 (30.8)	0.62	10 (21.3)	22 (31.4)	32 (27.4)	0.46	0.59
Edmonton	15 (53.6)	48 (45.7)	63 (47.4)		28 (59.6)	35 (50.0)	63 (53.8)		
Other	4 (14.3)	25 (23.8)	29 (21.8)		9 (19.1)	13 (18.6)	22 (18.8)		
Country of Birth									
Canada	16 (57.1)	56 (53.3)	72 (54.1)	0.23	23 (48.9)	16 (22.9)	39 (33.3)	0.01	<0.001
Outside of Canada	5 (17.9)	9 (8.6)	14 (10.5)		17 (36.2)	36 (51.4)	53 (45.3)		
Unknow	7 (25.0)	40 (38.1)	47		7 (14.9)	18 (25.7)	25		

n			(35.3)				(21.4)		
Decade of Diagnosis									
1970's	1 (3.6)	1 (1.0)	2 (1.5)	0.001	4 (8.5)	1 (1.4)	5 (4.3)	0.29	<0.001
1980's	6 (21.4)	3 (2.9)	9 (6.8)		13 (27.7)	15 (21.4)	28 (23.9)		
1990's	3 (10.7)	5 (4.8)	8 (6.0)		6 (12.8)	9 (12.7)	15 (12.8)		
2000's	8 (28.6)	28 (26.7)	36 (27.1)		4 (8.5)	20 (28.6)	24 (20.5)		
2010's	10 (35.7)	68 (64.8)	78 (58.6)		20 (42.6)	25 (35.7)	45 (38.5)		
Sexual									

Partners									
heterosexual	12 (42.9)	46 (43.8)	58 (43.6)	1.00	30 (63.8)	38 (54.3)	68 (58.1)	0.002	<0.001
Same Sex	14 (50.0)	52 (49.5)	66 (49.6)		11 (23.4)	5 (7.1)	16 (13.7)		
Unknown	2 (7.1)	7 (6.7)	9 (6.8)		6 (12.8)	27 (38.6)	33 (28.2)		
HIV Status									
Negative	5 (17.9)	68 (64.8)	73 (54.9)	<0.001	19 (40.4)	27 (38.6)	46 (39.3)	0.31	<0.001
Positive	17 (60.7)	30 (28.6)	47 (35.3)		8 (17.0)	6 (8.6)	14 (12.0)		
Unknown	6 (21.4)	7 (6.7)	13 (9.8)		20 (42.6)	37 (52.9)	57 (48.7)		

Treatment									
Penicillin G	22 (78.6)	82 (78.1)	104 (78.2)	0.87	21 (44.7)	63 (90.0)	84 (71.8)	<0.001	0.43
Ceftriaxone	3 (10.7)	14 (13.3)	17 (12.8)		12 (25.5)	5 (7.1)	17 (14.5)		
Other	3 (10.7)	9 (8.6)	12 (9.0)		14 (29.8)	2 (2.9)	16 (13.7)		

Among early neurosyphilis cases, 79.0% (n=105) were symptomatic; symptomatic cases were more likely to be older, male, Caucasian, recently diagnosed (2010's), and HIV negative compared to asymptomatic cases. Among late neurosyphilis cases, 59.8% (n=70) were symptomatic; symptomatic cases were more likely to be older, born outside of Canada, and treated with intravenous penicillin G, and less likely to have a same sex partner as compared to asymptomatic cases.

The majority (78.2%; n=136) of symptomatic cases reported a single manifestation. The most common clinical manifestation of the symptomatic cases (39.4%; n=69) was ocular involvement; early neurosyphilis cases were more likely to have ocular involvement (54.3%;

n=57) than late neurosyphilis cases (n=12; 17.1%; p<0.001). The first case of ocular syphilis was reported in 1990 with the majority (66.7%; n=46) of cases being diagnosed between 2010 and 2017. The second most common (34.3%; n=60) manifestation of symptomatic neurosyphilis was cognitive impairment with significantly more late neurosyphilis cases (55.7%; n=39) reporting these symptoms than early cases (20.0%; n=21; p<0.001). One-quarter of symptomatic cases reported peripheral involvement (26.9%; n=47), seven (4.0%) reported strokes and seven cases with central nervous system manifestations like ataxia, aphasia, and reduced level of consciousness. Eleven (6.3%) cases reported auditory symptoms; all cases were diagnosed with early infection (p=0.003). Thirteen (7.4%) cases reported other symptoms like headache or no specific symptoms.

Although the first HIV co-infected case was reported in 1986, over one-half (57.4%; n=35) of HIV co-infected cases were reported between 2010 and 2017. The majority (62.2%; n= 46) of cases with an unknown HIV status occurred between the 1970's and 1980's, prior to the clinical availability of diagnostic serology. As well cases that had HIV test results were significantly younger (47 years; IQR: 37-55) than cases without HIV test results (64 years; IQR: 44-70; p<0.001).

Thirty-six (14.2%) of all the cases were diagnosed without a lumbar puncture result. Nearly all of these clinical cases (97.2%; n=35) were symptomatic. The remaining asymptomatic case was diagnosed based on an inadequate fall in RPR titres over time. There was no significant difference by HIV status for those who had and did not have a lumbar puncture (p=0.62).

Clinical parameters by HIV status are outlined in Figure 3. Of the 2 HIV-positive and 6 HIV-negative cases with negative clinical parameters, all were symptomatic cases.

The majority (74.4%; n=189) of all cases were treated with intravenous penicillin G. Asymptomatic late neurosyphilis cases were less likely to be treated with penicillin G (44.7%; n=21) as compared to late neurosyphilis (90.0%; n=63; p<0.001). There was a rise in the use of ceftriaxone in late neurosyphilis treatment from no use in the 1970's to 1990's, to 12.5% (n=3) in 2000's and 31.1% (n=14) in the 2010's. Other drug combinations for neurosyphilis was highest in the 1970's (85.7%; n=6) and dropped to a low of 4.3% (n=1) in the 1990's.

Discussion

A review of the trends in reported cases of infectious syphilis from 1975 to 2016 in Alberta shows a cycling in the number of cases over time. During this time period, the first major outbreak of infectious syphilis occurred between 1981 and1987, with the majority of cases between 1983 and 1985.[21] A quiescent period of approximately two decades followed with a resurgence in infectious cases in 2000 followed by a decline in 2011 and then another rise in 2015. These observations are consistent with a study of long term trends in reported primary and secondary syphilis cases in the United States which showed recurrent peaks and troughs in approximately 10-year cycles.[22] This pattern of periodic resurgence of syphilis has variously been attributed to either failure to sustain control efforts, changing risk behaviours (such as crack cocaine use), and waxing and waning partial host immunity to infection at the population level.[23,24] Interestingly, our province observed a 20-year gap between the outbreak in the mid

1980s and the mid 2000s. The reasons for this prolonged gap are unclear but are likely multi-factorial including a well-established and sustained prevention and control program for STIs in the province, emergence of HIV and the mass education that occurred during this time period. Our observed rising rates of infectious syphilis since the mid-2000s are consistent with many jurisdictions across Canada and the United States.[15,25] The rise in late latent syphilis in 2007 has been attributed to the introduction of RSSS.[26]

Some studies have reported a rise in cases of neurosyphilis related to outbreaks of infectious syphilis. One possible explanation for this is that the overall rise in rates of infectious syphilis could potentially increase the pool of persons progressing to neurosyphilis and tertiary syphilis. For example, a study conducted in British Columbia, one of Alberta's neighboring provinces, reported that in the context of rising rates of infectious syphilis, the neurosyphilis rate was 0.03 per 100,000 in 1992 and increased 27-fold to 0.8 per 100,000 in 2012.[27] Investigators from Guangdong province in China similarly reported an incidence rate increase in neurosyphilis cases from 0.21 cases per 100,000 persons in 2009 to 0.31 cases per 100,000 persons in 2014 and in tertiary cases from 0.28 cases per 100,000 persons in 2009 to 0.36 cases per 100,000 persons in 2014.[28] Neither of these studies, however, distinguished between early and late neurosyphilis cases. In our review, we observed a significant rise in early neurosyphilis during the outbreak periods and a significant decline after the outbreak periods, e.g. only one case was observed in 2012 after the second outbreak. We had expected to see a sustained increase in late neurosyphilis cases based on the hypothesis that the number of untreated infected persons with syphilis would increase over time but there was no significant increase during the

overall observation period. Interestingly, a rise in late neurosyphilis cases was observed towards the end of the outbreak periods, perhaps due to heightened awareness and increased testing due to public health announcements during the outbreak periods.

Early neurosyphilis cases were more likely to be younger, Caucasian, born in Canada, HIV positive and reporting same sex partners. These observations parallel the observed rise in infectious syphilis during the third outbreak and may also be related to selection bias since lumbar punctures were more likely to be performed in HIV positive persons in the early years, especially those with low CD_4 counts (<350) and/or RPR $\geq$ 1:32 dilutions as recommended in the Canadian STI Guidelines.[29]

The most common manifestation (40%) of symptomatic neurosyphilis was ocular involvement with cases of early neurosyphilis more likely than cases of late neurosyphilis to have ocular involvement (54% vs 17%, p<0.001). Two-thirds of ocular cases were reported between 2010 and 2017, with 46.4% reported among MSM, similar to other studies.[30] Late neurosyphilis cases were more likely to be older, born outside of Canada and less likely to report same sex partners, paralleling the demographics of late latent cases of syphilis in our province (data not shown).

Our study identified very few (n=3) cardiovascular cases of tertiary syphilis with all cases identified at the time of a diagnosis of aortic aneurysm. This likely represents an underestimate in the actual number of cases of CV syphilis as we suspect that most patients with aortic aneurysm or initial cardiovascular involvement do not have syphilis testing performed. In

Alberta, the provincial STI program facilitates the assessment of all late stage syphilis cases by a physician who then conducts a neurological and cardiovascular examination. A chest radiograph, recommended in the past in some jurisdictions to look for linear calcification of the ascending aorta, a radiological sign of syphilitic aortitis is not routinely done. Chest radiographs for the evaluation of CV syphilis in asymptomatic patients with LLS is of such low yield, that it is not routinely recommended.[31] Neither clinical examination nor chest radiograph is likely to be sensitive enough to identify cases of CV syphilis and given the presumed rarity of this condition and that the treatment is the same as for LLS, further evaluations (e.g. echocardiograms) are not warranted.

No cases of gummatous syphilis were reported during our study period. Although syphilitic gummas were reported in up to 15% cases in the pre-antibiotic era, it is possible that the widespread use of antibiotics for other conditions, which may indirectly treat or partially treat syphilis, has affected the occurrence.

One of the strengths of our study is that there was consistent reporting of all cases with positive syphilis serology over time by laboratories and active follow up by the provincial STI program with health care providers. We were able to apply current case definitions retrospectively to all cases; however, one of the limitations to retrospective review of data is the possibility of inaccurate classification of cases. Our review by two experienced medical consultants resulted in only one case where insufficient information was available to classify the case with reasonable accuracy. Additional study limitations include changes in data

collection practices over time. The information about gender of sex partners may have been inaccurate in earlier years due to stigma associated with same sex partners. Routine testing for HIV in cases of syphilis was also not conducted in earlier years and as such the number of concurrent HIV infections may be underestimated.

In summary, our review of tertiary and neurosyphilis cases in Alberta over a 44-year period found that early and late neurosyphilis cases continue to occur in the context of cycling of infectious syphilis outbreaks. Ocular disease was the most common manifestation of neurosyphilis in our study. On the other hand, cardiovascular syphilis was extremely rare and no cases of gumma were identified. Ongoing identification of syphilis cases with prompt treatment and follow up continues to be important in the context of resurgence of infectious syphilis worldwide.

Author contributions: TL reviewed hard copy records of all cases and conducted data entry into an Excel file; PS and AS reviewed and re-classified all cases; JG conducted data analysis; JG and AS drafted initial versions of the manuscript; all authors helped develop the study design and reviewed drafts of the manuscript.

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Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada, 1975-2016)

Figure 2. Rates of Early and Late Neurosyphilis during 2 Different Outbreak Periods with Linear Trend Line (Alberta, 1975-2016)

Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases (Alberta, 1975-March 2017)

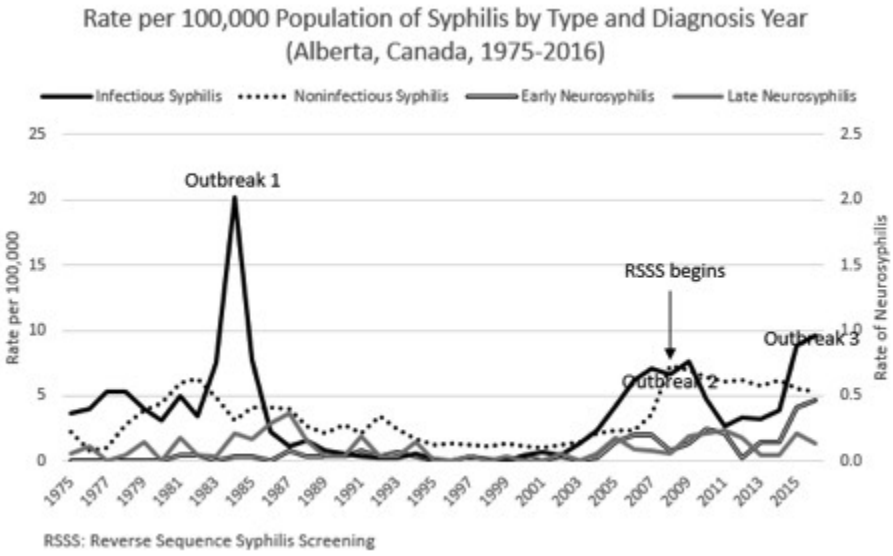

Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada, 1975-2016)

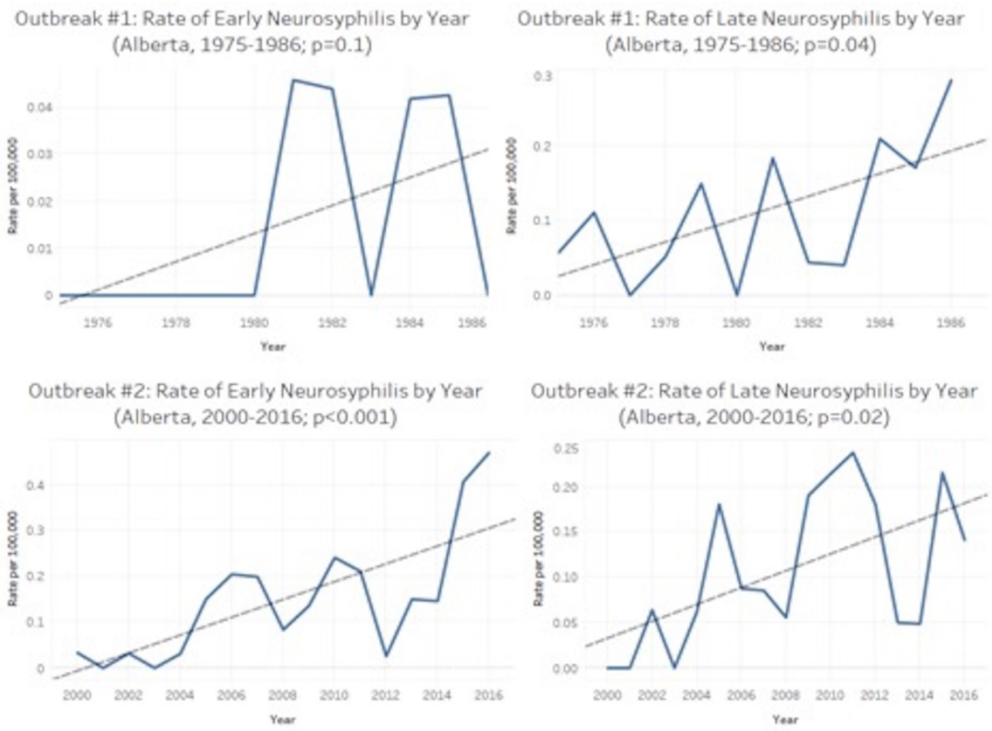

Figure 2. Rates of Early and Late Neurosyphilis during 2 Different Outbreak Periods with Linear Trend Line (Alberta, 1975-2016)

122x90mm (300 x 300 DPI)

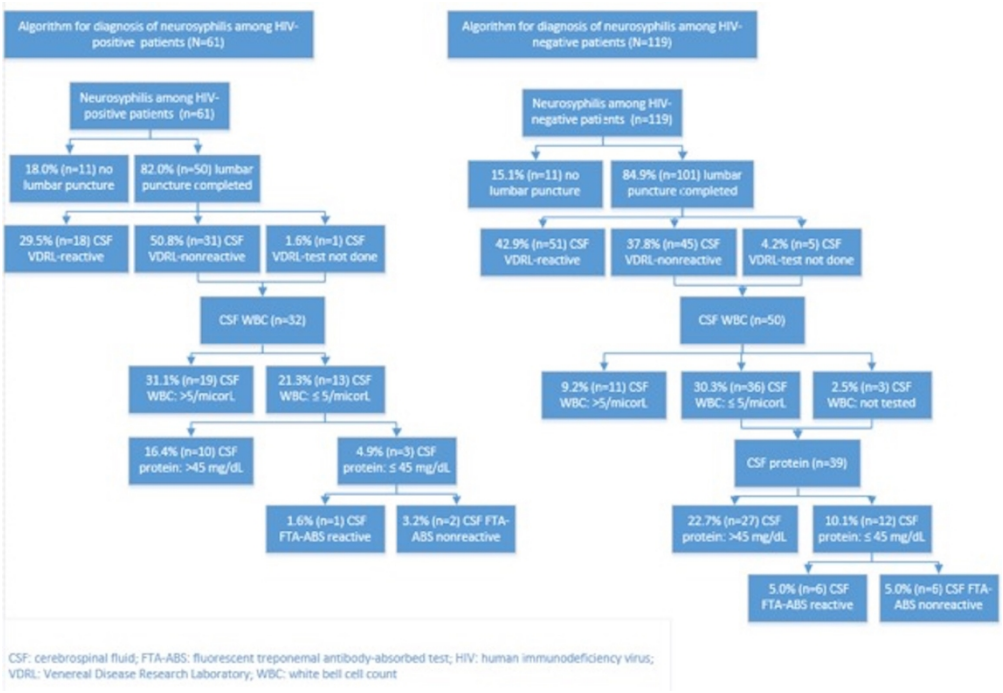

Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases (Alberta, 1975-March 2017)

130x90mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	

		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 2 8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Retrospective Review of Tertiary and Neurosyphilis Cases in Alberta, 1973 to 2017

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Retrospective Review of Tertiary and Neurosyphilis Cases in Alberta, 1973 to 2017

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Abstract

Objectives: To review the notification rate and characteristics of tertiary and neurosyphilis cases in Alberta, Canada in the post-antibiotic era.

Methods: A retrospective review of all neurosyphilis and tertiary syphilis cases reported in Alberta from 1973 to March 2017 was undertaken and cases classified into early neurosyphilis, late neurosyphilis and cardiovascular syphilis. Variables collected included demographics, sexual partners, HIV status, clinical parameters, symptoms and treatment and distributions were compared between early versus late neurosyphilis and asymptomatic versus symptomatic cases (stratified by early versus late stage). Data was analyzed using IBM SPSS Statistics Version 19.0.

Results: 254 cases were identified; 251 were neurosyphilis and 3 were cardiovascular. No cases of gummatous syphilis were reported. Early neurosyphilis accounted for 52.4% (n=133) and 46.1% (n=117) were late neurosyphilis cases; one (0.4%) case with unknown duration. Three outbreaks of infectious syphilis were identified during the study period and a concurrent rise in both early and late neurosyphilis was observed during the outbreak periods. The most common manifestation of symptomatic neurosyphilis was ocular involvement which was more likely in early neurosyphilis. Relative to late neurosyphilis cases, early neurosyphilis cases were more likely to be younger, Caucasian, born in Canada, HIV positive and reporting same sex partners while late neurosyphilis cases were more likely to be older, born outside of Canada and less likely to report same sex partners.

Conclusions: Our review of tertiary and neurosyphilis cases found that early and late neurosyphilis cases continue to occur in the context of cycling syphilis outbreaks.

Cardiovascular syphilis cases were extremely rare. Ongoing identification of new cases of syphilis and clinical evaluation of cases for complications continues to be important in the context of global resurgence of syphilis.

Keywords: tertiary syphilis, neurosyphilis, Canada

Strengths and Limitations of this study:

- An important strength of our study was the consistent reporting of all cases with positive syphilis serology over the 44 year period by laboratories as well as active follow up of all cases by the provincial STI program.
- Another strength of our study is the retrospective application of current case definitions to all cases by 2 experienced STI clinicians.
- One of the limitations to the retrospective review of data is the possibility of inaccurate classification of cases due to insufficient available information.
- Additional study limitations include changes in testing policies and practices, as well as changes in social norms over time.
- Routine testing for HIV in cases of syphilis was also not conducted in earlier years and as such the number of concurrent HIV infections may have been underestimated.

Manuscript

Background

Syphilis, caused by *Treponema pallidum* subspecies *pallidum*, passes through a series of stages, including primary, secondary, latent, and tertiary syphilis if left untreated.[1] Based on data from the pre-antibiotic era, about a third of persons with untreated latent syphilis will develop late neurosyphilis, cardiovascular syphilis or gummatous syphilis.[2] Gummatous syphilis is characterized by the development of indolent granulomatous lesions[3] which typically affect the skin, liver, and bone but can also involve other parts of the body.[4] Syphilitic aortitis is the most common manifestation of cardiovascular syphilis and typically involves the ascending aorta.[4-6]

Neurosyphilis can occur at any stage of syphilis.[1,7] It is classified into early and late forms.[1] Early neurosyphilis affects the cerebrospinal fluid (CSF), cerebral blood vessels, and meninges more often than the brain or spinal cord parenchyma. Typically, manifestations occur within weeks to a few years after primary infection and may occur at the same time as primary or secondary syphilis, or may be asymptomatic. Manifestations may include meningitis with or without cranial nerve involvement, meningovascular disease or stroke. Late neurosyphilis can remain asymptomatic or progress to meningovascular syphilis, tabes dorsalis, or general paresis. Late neurosyphilis is extremely rare in the antibiotic era and usually occurs years to decades after primary infection.[1,8] HIV infection may affect the natural course of disease as atypical presentations and rapid progression of syphilis in HIV positive individuals has been reported.[9-13]

In the pre-antibiotic era, an estimated one third of untreated persons developed tertiary syphilis with about 15% progressing to gummatous disease (1-46 years post-infection), 10% to cardiovascular syphilis (20-30 years after infection), and 4-14% to late neurosyphilis (2-50 years after infection).[1] After the introduction of penicillin in the 1940s, the number of cases of syphilis plummeted in the United States, reaching a nadir in 2000.[1] Nowadays, tertiary syphilis is a rare disease due to easy and effective treatment of infectious and latent syphilis. Antibiotic use for other infections is also likely a factor.

In Canada, syphilis (all stages) has been nationally notifiable since 1924. However national reports only include data on infectious syphilis, since only these cases are of major public health significance.[14] In Alberta, all cases of syphilis, including tertiary and neuro-syphilis have been notifiable to a centralized program under the Public Health Act since 1921. Syphilis notification rates have fluctuated over the last fifty years with a rise in notification rates during outbreak periods. Since 2000, notification rates of infectious syphilis have increased dramatically in Alberta (0.6/100,000 population in 2000 to 12.5/100,000 population in 2017), with the most recent resurgence among men who have sex with men (MSM) and up to 30% of patients co-infected with HIV (personal communication Jennifer Gratrix, Provincial STI Services, Alberta Health Services).[15]

There are few data on the prevalence and characteristics of tertiary and neuro-syphilis cases in the post antibiotic era. We are aware of only one study from the Netherlands which estimated that 10-13% of all syphilis cases from 1999-2010 had neurosyphilis; these data were limited by

the fact that the diagnostic criteria used for neurosyphilis was based on hospital discharge diagnosis rather than clinical examination or laboratory criteria.[16] We sought to determine the notification rate and characteristics of reported cases of tertiary and neurosyphilis in Alberta from 1973 onwards.

Methods

A retrospective review was conducted of all tertiary and neurosyphilis cases in Alberta (current population 4.3 million) from 1973 (when syphilis data was first available by staging) to March 2017 (most recent cases staged at time of data collection). All cases of syphilis are reportable by laboratories and clinicians to Provincial STI Services under the Alberta Public Health Act. A paper chart was created for each syphilis case containing laboratory results, medical correspondence, syphilis-relevant history, clinical findings, and staging. Cases diagnosed since 2000 were also entered into a provincial surveillance database. Cases were classified as defined in Table 1.[17]

Table 1: Case Definitions Used for Diagnosis of Neurosyphilis and Tertiary Syphilis (Adapted from[17]:

Syphilis stage	Definition
Tertiary syphilis	Reactive treponemal serology together with characteristic late abnormalities of the cardiovascular system, bone, skin or other structures, in the absence of other known causes of these abnormalities and no clinical or laboratory evidence of neurosyphilis

Early Neurosyphilis (< 1 year after infection) *Asymptomatic*	Laboratory confirmation of primary, second or early latent syphilis and i) reactive CSF-VDRL in non-bloody CSF AND/OR ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes AND NO signs or symptoms of neurosyphilis
Early Neurosyphilis (< 1 year after infection) *Symptomatic*	Laboratory confirmation of primary, second or early latent syphilis and i) reactive CSF-VDRL in non-bloody CSF AND/OR ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes AND clinical signs or symptoms of neurosyphilis*
Late neurosyphilis (>1 year after infection) *Asymptomatic*	Reactive treponemal serology (not staged as primary, secondary or early latent syphilis) and i) reactive CSF-VDRL in non-bloody CSF AND/OR ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes

	AND NO clinical signs or symptoms of neurosyphilis
Late neurosyphilis (>1 year after infection) *Symptomatic*	Reactive treponemal serology (not staged as primary, secondary or early latent syphilis) and iii) reactive CSF-VDRL in non-bloody CSF AND/OR iv) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes AND clinical signs or symptoms of neurosyphilis*

*if ocular or otic signs or symptoms present with a normal CSF examination, patient was classified as symptomatic neurosyphilis (early or late)

Serological testing for syphilis changed during the study period, with reverse sequence syphilis screening (RSSS) using an enzyme immunoassay being introduced in September 2007; prior to this a quantitative Rapid Plasma Reagin (RPR) was used. Since the criteria for classifying neurosyphilis evolved over time, all neurosyphilis cases during the study period were reviewed by two STI physicians and classified into early asymptomatic, early symptomatic, late asymptomatic, late symptomatic neurosyphilis cases; disagreement between the classifications of cases was resolved by consensus between the two physicians (PS and AES).

Reported notification rates of other stages of syphilis prior to 2000 were obtained from historical surveillance reports from Alberta STI Services beginning in 1975. Population denominators were obtained through government population estimates.[18] An outbreak was defined as an increase in infectious syphilis cases of two standard deviations above the baseline for the given time period.

Variables collected for analysis included demographics, sexual partners, HIV status (testing available since 1985[19] and recommended for all syphilis cases once serology available), diagnosis date, clinical parameters, symptoms, and treatment. Variables for cases diagnosed prior to 2004 were captured through chart review, while variables for cases diagnosed after 2004 were extracted from the provincial STI surveillance system. Client reported symptoms were broken into five categories (not mutually exclusive) based on system involvement: ocular (e.g. uveitis, retinal, vision loss), auditory (e.g. hearing loss, tinnitus), ataxia, cognitive impairment (e.g. dementia, psychosis), and other (aphasia, stroke, reduced level of consciousness, headache, and unspecified neurological symptoms).

Treatment data was divided into 3 mutually exclusive categories based on the following minimum treatments: 1) penicillin G 3-4 million units IV q 4 h (18-24 million units/day) for 10 - 14 days, 2) ceftriaxone 2 g IV/IM daily x 10-14 days, 3) Other, which included drugs like chloramphenicol, doxycycline, tetracycline, benzathine penicillin G- long acting, reduced doses of penicillin G or ceftriaxone.

Analysis was stratified by stage of syphilis to compare early and late neurosyphilis by the previously listed variables using Chi-square or Fisher's exact for categorical variables and Mann-Whitney tests for continuous variables. Missing data was categorized as unknown and included in the analysis. As well, each syphilis stage was stratified by asymptomatic and symptomatic for comparison. The significance was set at a two-sided *p*-value of <0.05. A sensitivity analysis was conducted to determine if associations between early and late neurosyphilis were directionally consistent over time by analyzing associations with gender, ethnicity, country of birth, and sexual partners by decades. Data was analyzed using IBM SPSS Statistics version 19.0 (IBM, Armonk, NY, USA). This study was approved by the University of Alberta Health Research Ethics Board (Approval Number: Pro00075972).

Patient and Public Involvement

Patients were not involved in the design of this research study.

Results

A total of 254 cases were identified during the study period, of which 251 were neurosyphilis and 3 were cardiovascular (CV) cases; one case of CV syphilis was reported in each of the following years: 1976, 1979, and 1984. No cases of gummatous syphilis were reported during this time period. The neurosyphilis cases were evenly divided as early (52.4%; n=133) and late (46.1%; n=117), with one additional case of unknown duration. Three individuals were diagnosed with two distinct episodes of neurosyphilis over the course of the reporting period.

All three of these individuals were men who reported same sex partners, all six episodes were diagnosed between 2005 and 2014, and all categorized as early neurosyphilis. Two of these men were co-infected with HIV.

Between 1975 and 2016, 8,874 total cases of syphilis were reported in Alberta. Of these, 4,513 (51%) were infectious (i.e. staged as primary, secondary, early latent) and 4,361 (49%) were classified as non-infectious (i.e. late latent, tertiary). Over the time period, three outbreaks of infectious syphilis were identified (Figure 1). The first outbreak occurred between 1981 and 1987, the second outbreak commenced in 2000 and declined in 2011, and a third outbreak began in 2015 and continues. Of the infectious syphilis cases, 2.8% (n=128) were staged as early neurosyphilis. When plotting the notification rate of early neurosyphilis cases, increases in the rate were found at corresponding times to infectious syphilis outbreaks #2 and #3 (Figure 2). Of the noninfectious syphilis cases staged during this time, 2.6% (115/4316) were staged with late neurosyphilis. Similarly, for late neurosyphilis, peaks in notification rates were found shortly after outbreak #1 and outbreak #2 (Figure 2).

Early neurosyphilis cases were significantly younger, more likely to be Caucasian, born in Canada, diagnosed in recent decades (2010's), reported same sex partners, and HIV positive as compared to late neurosyphilis cases (Table 2).

Sensitivity analysis found similar directionally associations for gender, country of birth, and ethnicity for early neurosyphilis. Throughout the decades, cases reporting same sex partners had the highest proportion of cases, except during the 2000's. Consistent directional associations were found for gender and sexual partners. During the 2000's, missing values for

ethnicity and country of birth were the lowest, causing the other ethnicity and non-Canadian born to their highest proportions during the 5 decades.

Table 2: Characteristics of Early and Late Neurosyphilis (Alberta, 1973 to March 2017; n=250)

	Early Neurosyphilis				Late Neurosyphilis				Comparison of Early and Late p-Value
	Asymptomatic (n=28)	Symptomatic (n=105)	Total (n=133)	p-Value	Asymptomatic (n=47)	Symptomatic (n=70)	Total (n=117)	p-Value	
Median Age (IQR)	40 (32-46)	47 (39-55)	44 (36-54)	0.02	45 (32-65)	64 (53-75)	58 (45-70)	<0.001	<0.001
Gender									
Female	8 (28.6)	12 (11.4)	20 (15.0)	0.02	6 (12.8)	15 (21.4)	21 (17.9)	0.23	0.54
Male	20 (71.4)	93 (88.6)	113 (85.0)		41 (87.2)	55 (78.6)	96 (82.1)		
Ethnicity									

Indigenous	6 (21.4)	6 (5.7)	12 (9.0)	0.001	6 (12.8)	3 (4.3)	9 (7.7)	0.44	<0.001
Caucasian	10 (35.7)	78 (74.3)	88 (66.2)		14 (29.8)	23 (32.9)	37 (31.6)		
Other	3 (10.7)	4 (3.8)	7 (5.3)		16 (34.0)	27 (38.6)	43 (36.8)		
Unknown	9 (32.1)	17 (16.2)	26 (19.5)		11 (23.4)	17 (24.3)	28 (23.9)		
Municipality									
Calgary	9 (32.1)	32 (30.5)	41 (30.8)	0.62	10 (21.3)	22 (31.4)	32 (27.4)	0.46	0.59
Edmonton	15 (53.6)	48 (45.7)	63 (47.4)		28 (59.6)	35 (50.0)	63 (53.8)		

Other	4 (14.3)	25 (23.8)	29 (21.8)		9 (19.1)	13 (18.6)	22 (18.8)		
Country of Birth									
Canada	16 (57.1)	56 (53.3)	72 (54.1)	0.23	23 (48.9)	16 (22.9)	39 (33.3)	0.01	<0.001
Outside of Canada	5 (17.9)	9 (8.6)	14 (10.5)		17 (36.2)	36 (51.4)	53 (45.3)		
Unknown	7 (25.0)	40 (38.1)	47 (35.3)		7 (14.9)	18 (25.7)	25 (21.4)		
Decade of Diagnosis									
1970's	1 (3.6)	1 (1.0)	2 (1.5)	0.001	4 (8.5)	1 (1.4)	5 (4.3)	0.29	<0.001

1980's	6 (21.4)	3 (2.9)	9 (6.8)		13 (27.7)	15 (21.4)	28 (23.9)		
1990's	3 (10.7)	5 (4.8)	8 (6.0)		6 (12.8)	9 (12.7)	15 (12.8)		
2000's	8 (28.6)	28 (26.7)	36 (27.1)		4 (8.5)	20 (28.6)	24 (20.5)		
2010's	10 (35.7)	68 (64.8)	78 (58.6)		20 (42.6)	25 (35.7)	45 (38.5)		
Sexual Partners									
heteros exual	12 (42.9)	46 (43.8)	58 (43.6)	1.00	30 (63.8)	38 (54.3)	68 (58.1)	0.002	<0.001
Same Sex	14 (50.0)	52 (49.5)	66 (49.6)		11 (23.4)	5 (7.1)	16 (13.7)		

Unknown	2 (7.1)	7 (6.7)	9 (6.8)		6 (12.8)	27 (38.6)	33 (28.2)		
HIV Status									
Negative	5 (17.9)	68 (64.8)	73 (54.9)	<0.001	19 (40.4)	27 (38.6)	46 (39.3)	0.31	<0.001
Positive	17 (60.7)	30 (28.6)	47 (35.3)		8 (17.0)	6 (8.6)	14 (12.0)		
Unknown	6 (21.4)	7 (6.7)	13 (9.8)		20 (42.6)	37 (52.9)	57 (48.7)		
Treatment									
Penicillin G	22 (78.6)	82 (78.1)	104 (78.2)	0.87	21 (44.7)	63 (90.0)	84 (71.8)	<0.001	0.43

Ceftriaxone	3 (10.7)	14 (13.3)	17 (12.8)		12 (25.5)	5 (7.1)	17 (14.5)		
Other	3 (10.7)	9 (8.6)	12 (9.0)		14 (29.8)	2 (2.9)	16 (13.7)		

Among early neurosyphilis cases, 79.0% (n=105) were symptomatic; symptomatic cases were more likely to be older, male, Caucasian, recently diagnosed (2010's), and HIV negative compared to asymptomatic cases. Among late neurosyphilis cases, 59.8% (n=70) were symptomatic; symptomatic cases were more likely to be older, born outside of Canada, and treated with intravenous penicillin G, and less likely to have a same sex partner as compared to asymptomatic cases.

The majority (79.9%; n=139) of symptomatic cases reported a single manifestation. The most common clinical manifestation of the symptomatic cases (41.1%; n=72) was ocular involvement; early neurosyphilis cases were more likely to have ocular involvement than late neurosyphilis cases (Table 3). The first case of ocular syphilis was reported in 1990 with the majority (68.1%; n=49) of cases being diagnosed between 2010 and 2017. The second most common (33.7%; n=59) manifestation of symptomatic neurosyphilis was cognitive impairment with significantly more late neurosyphilis cases reporting these symptoms than early cases. Twelve (6.9 %) cases reported auditory symptoms and 10.9% (n=19) reported ataxia. Nearly

one-third (29.7%; n=52) of cases reported other symptoms including aphasia, stroke, reduced level of consciousness, headache, and unspecified neurological symptoms..

Table 3: Manifestations of Early and Late Symptomatic Neurosyphilis (Alberta, 1973 to March 2017; n=175)

Manifestation	Early Neurosyphilis (n=105)	Late Neurosyphilis (n=70)	P-Value
Ocular	59 (56.2)	13 (18.6)	<0.001
Cognitive Impairment	20 (19.0)	39 (55.7)	<0.001
Ataxia	9 (8.6)	10 (14.3)	0.23
Auditory	10 (9.5)	2 (2.9)	0.13
Other*	30 (28.6)	22 (31.4)	0.69

- *Aphasia, reduced level of consciousness, headache, unspecified neurological symptoms

Although the first HIV co-infected case was reported in 1986, over one-half (57.4%; n=35) of HIV co-infected cases were reported between 2010 and 2017. The majority (62.2%; n= 46) of cases with an unknown HIV status occurred between the 1970's and 1980's, prior to the clinical availability of diagnostic serology. Cases that had HIV test results were significantly younger (47 years; IQR: 37-55) than cases without HIV test results (64 years; IQR: 44-70; p<0.001).

Thirty-six (14.2%) of all the cases were diagnosed without a lumbar puncture result. Nearly all of these clinical cases (97.2%; n=35) were symptomatic. The remaining asymptomatic case was diagnosed based on an inadequate fall in RPR titres over time. There was no significant difference by HIV status for those who had and did not have a lumbar puncture (p=0.62).

Clinical parameters by HIV status are outlined in Figure 3. Of the 2 HIV-positive and 6 HIV-negative cases with negative clinical parameters, all were symptomatic cases.

The majority (74.4%; n=189) of all cases were treated with intravenous penicillin G. Asymptomatic late neurosyphilis cases were less likely to be treated with penicillin G (44.7%; n=21) as compared to symptomatic late neurosyphilis (90.0%; n=63; p<0.001). There was a rise in the use of ceftriaxone in late neurosyphilis treatment from no use in the 1970's to 1990's, to 12.5% (n=3) in 2000's and 31.1% (n=14) in the 2010's. Other drug combinations for neurosyphilis was highest in the 1970's (85.7%; n=6) and dropped to a low of 4.3% (n=1) in the 1990's.

Discussion

A review of the trends in reported cases of infectious syphilis from 1975 to March, 2017 in Alberta shows a cycling in the number of cases over time. During this time period, the first major outbreak of infectious syphilis occurred between 1981 and1987, with the majority of cases between 1983 and 1985.[20] A quiescent period of approximately two decades followed with a resurgence in infectious cases in 2000 followed by a decline in 2011 and then another rise in 2015. These observations are consistent with a study of long term trends in reported primary and secondary syphilis cases in the United States which showed recurrent peaks and troughs in approximately 10-year cycles.[21] This pattern of periodic resurgence of syphilis has variously been attributed to either failure to sustain control efforts, changing risk behaviours (such as crack cocaine use), and waxing and waning partial host immunity to infection at the

population level.[22,23] Interestingly, our province observed a 20-year gap between the outbreak in the mid 1980s and the mid 2000s. The reasons for this prolonged gap are unclear but are likely multi-factorial including a well-established and sustained prevention and control program for STIs in the province, emergence of HIV and the mass education that occurred during this time period. This theory is supported by declining notification rates of gonorrhea and chlamydia until 1998 and then subsequent rises to current rates.[24] Our observed rising notification rates of infectious syphilis since the mid-2000s are consistent with many jurisdictions across Canada and the United States.[14,25] The rise in late latent syphilis in 2007 has been attributed to the introduction of RSSS.[26]

Some studies have reported a rise in cases of neurosyphilis related to outbreaks of infectious syphilis. One possible explanation for this is that the overall rise in notification rates of infectious syphilis could potentially increase the pool of persons progressing to neurosyphilis and tertiary syphilis. For example, a study conducted in British Columbia, one of Alberta's neighboring provinces, reported that in the context of rising rates of infectious syphilis, the neurosyphilis rate was 0.03 per 100,000 in 1992 and increased 27-fold to 0.8 per 100,000 in 2012.[27] Investigators from Guangdong province in China similarly reported an incidence rate increase in neurosyphilis cases from 0.21 cases per 100,000 persons in 2009 to 0.31 cases per 100,000 persons in 2014 and in tertiary cases from 0.28 cases per 100,000 persons in 2009 to 0.36 cases per 100,000 persons in 2014.[28] Neither of these studies, however, distinguished between early and late neurosyphilis cases. In our review, we observed a significant rise in early neurosyphilis during the outbreak periods and a significant decline after the outbreak periods,

e.g. only one case was observed in 2012 after the second outbreak. We had expected to see a sustained increase in late neurosyphilis cases based on the hypothesis that the number of untreated infected persons with syphilis would increase over time but there was no significant increase during the overall observation period. Interestingly, a rise in late neurosyphilis cases was observed towards the end of the outbreak periods, perhaps due to heightened awareness and increased testing due to public health announcements during the outbreak periods and also because late (tertiary) neurosyphilis can occur as soon as two years post-infection.[1] Although individuals diagnosed with late symptomatic neurosyphilis are not infectious and therefore not of concern from a public health perspective, these individuals would benefit from screening and appropriate treatment for syphilis to prevent complications of tertiary syphilis.[1]

Early neurosyphilis cases were more likely to be younger, Caucasian, born in Canada, HIV positive and reporting same sex partners. These observations parallel the observed rise in infectious syphilis during the third outbreak and may also be related to selection bias since lumbar punctures were more likely to be performed in HIV positive persons in the early years, especially those with low CD_4 counts (<350) and/or RPR $\geq$ 1:32 dilutions as recommended in the Canadian STI Guidelines.[29] In addition, most clinicians providing care to HIV positive individuals in Alberta would have offered regular syphilis screening in HIV positive individuals, as endorsed for several years in the U.S. Department of Health and Human Services guidelines.[30]

The most common manifestation (40%) of symptomatic neurosyphilis was ocular involvement with cases of early neurosyphilis more likely than cases of late neurosyphilis to have ocular

involvement (54% vs 17%, p<0.001). Two-thirds of ocular cases were reported between 2010 and 2017, with 46.4% reported among MSM, similar to other studies.[31] Late neurosyphilis cases were more likely to be older, born outside of Canada and less likely to report same sex partners, paralleling the demographics of late latent cases of syphilis in our province (data not shown).

Our study identified very few (n=3) cardiovascular cases of tertiary syphilis with all cases identified at the time of a diagnosis of aortic aneurysm. This likely represents an underestimate in the actual number of cases of CV syphilis as we suspect that most patients with aortic aneurysm or initial cardiovascular involvement do not have syphilis testing performed. In Alberta, the provincial STI program facilitates the assessment of all late stage syphilis cases by a physician who then conducts a neurological and cardiovascular examination. A chest radiograph, recommended in the past in some jurisdictions to look for linear calcification of the ascending aorta, a radiological sign of syphilitic aortitis is not routinely done. Chest radiographs for the evaluation of CV syphilis in asymptomatic patients with LLS is of such low yield, that it is not routinely recommended.[32] Neither clinical examination nor chest radiograph is likely to be sensitive enough to identify cases of CV syphilis and given the presumed rarity of this condition and that the treatment is the same as for LLS, further evaluations (e.g. echocardiograms) are not warranted.

No cases of gummatous syphilis were reported during our study period. Although syphilitic gummas were reported in up to 15% cases in the pre-antibiotic era, it is possible that the

widespread use of antibiotics for other conditions, which may indirectly treat or partially treat syphilis, has affected the occurrence.

One of the strengths of our study is that there was consistent reporting of all cases with positive syphilis serology over time by laboratories and active follow up by the provincial STI program with health care providers. We were able to apply current case definitions retrospectively to all cases; however, one of the limitations to retrospective review of data is the possibility of inaccurate classification of cases. Our review by two experienced medical consultants resulted in only one case where insufficient information was available to classify the case with reasonable accuracy. Additional study limitations include changes in and quality of data collection practices over time, with improved data quality over time. The information about gender of sex partners may have been inaccurate in earlier years due to stigma associated with same sex partners. Routine testing for HIV in cases of syphilis was also not conducted in earlier years and as such the number of concurrent HIV infections may be underestimated.

In summary, our review of tertiary and neurosyphilis cases in Alberta over a 44-year period found that early and late neurosyphilis cases continue to occur in the context of cycling of infectious syphilis outbreaks. Ocular disease was the most common manifestation of neurosyphilis in our study. On the other hand, cardiovascular syphilis was extremely rare and no cases of gumma were identified. Ongoing identification of syphilis cases with prompt

treatment and follow up continues to be important in the context of resurgence of infectious syphilis worldwide.

Author contributions: TL reviewed hard copy records of all cases and conducted data entry into an Excel file; PS and AS reviewed and re-classified all cases; JG conducted data analysis; JG and AS drafted initial versions of the manuscript; TL, PS, RC, JG, LB, RR, BR and AES helped develop the study design and reviewed drafts of the manuscript.

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Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada, 1975-2016)

Figure 2. Rates of Early and Late Neurosyphilis during 2 Different Outbreak Periods with Linear Trend Line (Alberta, 1975-2016)

Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases (Alberta, 1975-March 2017)

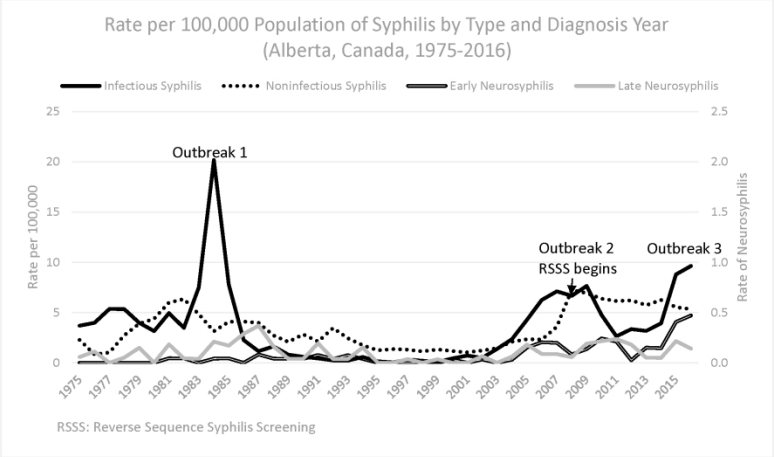

Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada, 1975-2016)

215x279mm (300 x 300 DPI)

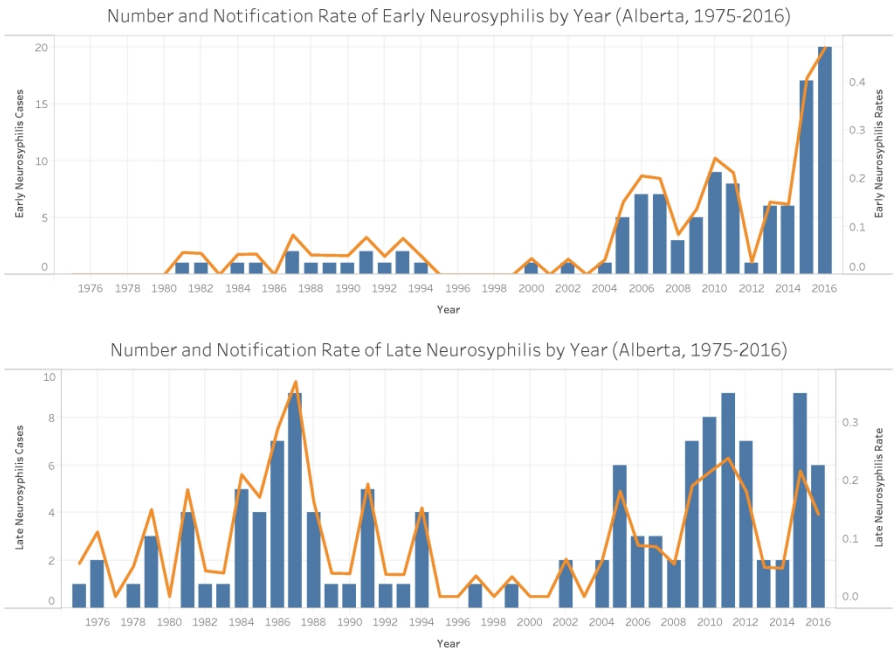

Figure 2. Rates of Early and Late Neurosyphilis during 2 Different Outbreak Periods with Linear Trend Line (Alberta, 1975-2016)

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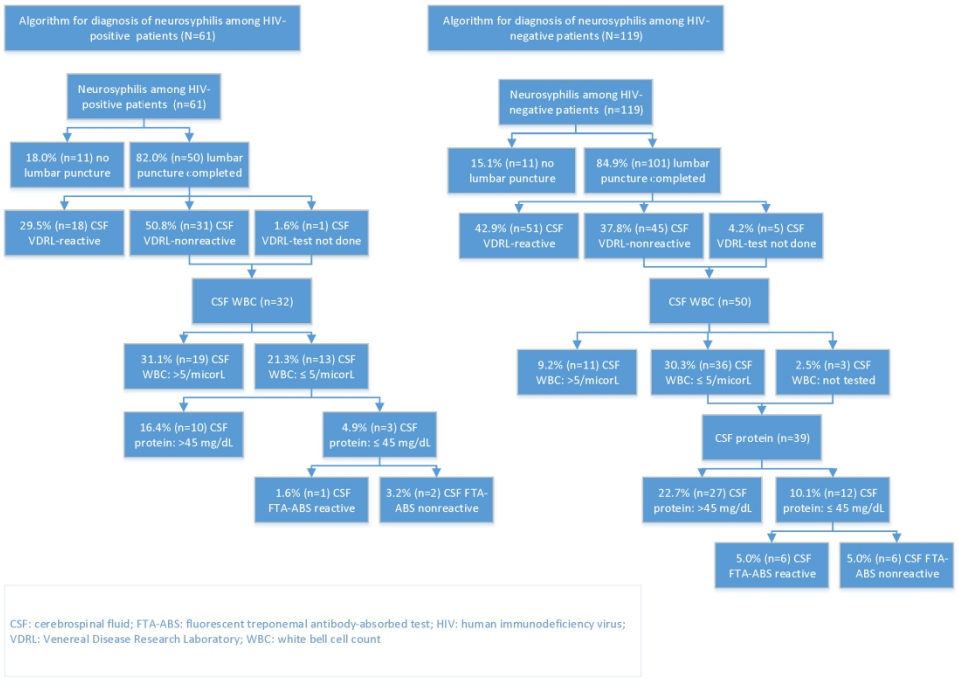

Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases (Alberta, 1975-March 2017)

279x215mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	

		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 2 8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Retrospective Review of Tertiary and Neurosyphilis Cases in Alberta, 1973 to 2017

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Retrospective Review of Tertiary and Neurosyphilis Cases in Alberta, 1973 to 2017

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Abstract

Objectives: To review the notification rate and characteristics of tertiary and neurosyphilis cases in Alberta, Canada in the post-antibiotic era.

Methods: A retrospective review of all neurosyphilis and tertiary syphilis cases reported in Alberta from 1973 to March 2017 was undertaken and cases classified into early neurosyphilis, late neurosyphilis and cardiovascular syphilis. Variables collected included demographics, sexual partners, HIV status, clinical parameters, symptoms and treatment and distributions were compared between early versus late neurosyphilis and asymptomatic versus symptomatic cases (stratified by early versus late stage). Data was analyzed using IBM SPSS Statistics Version 19.0.

Results: 254 cases were identified; 251 were neurosyphilis and 3 were cardiovascular. No cases of gummatous syphilis were reported. Early neurosyphilis accounted for 52.4% (n=133) and 46.1% (n=117) were late neurosyphilis cases; one (0.4%) case with unknown duration. Three outbreaks of infectious syphilis were identified during the study period and a concurrent rise in both early and late neurosyphilis was observed during the outbreak periods. The most common manifestation of symptomatic neurosyphilis was ocular involvement which was more likely in early neurosyphilis. Relative to late neurosyphilis cases, early neurosyphilis cases were more likely to be younger, Caucasian, born in Canada, HIV positive and reporting same sex partners..

Conclusions: Our review of tertiary and neurosyphilis cases found that early and late neurosyphilis cases continue to occur in the context of cycling syphilis outbreaks. Cardiovascular syphilis cases were extremely rare. Ongoing identification of new cases of

syphilis and clinical evaluation of cases for complications continues to be important in the context of global resurgence of syphilis.

Keywords: tertiary syphilis, neurosyphilis, Canada

Strengths and Limitations of this study:

- An important strength of our study was the consistent reporting of all cases with positive syphilis serology over the 44 year period by laboratories as well as active follow up of all cases by the provincial STI program.
- Another strength of our study is the retrospective application of current case definitions to all cases by 2 experienced STI clinicians.
- One of the limitations to the retrospective review of data is the possibility of inaccurate classification of cases due to insufficient available information.
- Additional study limitations include changes in testing policies and practices, as well as changes in social norms over time.
- Routine testing for HIV in cases of syphilis was also not conducted in earlier years and as such the number of concurrent HIV infections may have been underestimated.

Manuscript

Background

Syphilis, caused by *Treponema pallidum* subspecies *pallidum*, passes through a series of stages, including primary, secondary, latent, and tertiary syphilis if left untreated.[1] Based on data from the pre-antibiotic era, about a third of persons with untreated latent syphilis will develop late neurosyphilis, cardiovascular syphilis or gummatous syphilis.[2] Gummatous syphilis is characterized by the development of indolent granulomatous lesions[3] which typically affect the skin, liver, and bone but can also involve other parts of the body.[4] Syphilitic aortitis is the most common manifestation of cardiovascular syphilis and typically involves the ascending aorta.[4-6]

Neurosyphilis can occur at any stage of syphilis.[1,7] It is classified into early and late forms.[1] Early neurosyphilis affects the cerebrospinal fluid (CSF), cerebral blood vessels, and meninges more often than the brain or spinal cord parenchyma. Typically, manifestations occur within weeks to a few years after primary infection and may occur at the same time as primary or secondary syphilis, or may be asymptomatic. Manifestations may include meningitis with or without cranial nerve involvement, meningovascular disease or stroke. Late neurosyphilis can remain asymptomatic or progress to meningovascular syphilis, tabes dorsalis, or general paresis. Late neurosyphilis is extremely rare in the antibiotic era and usually occurs years to decades after primary infection.[1,8] HIV infection may affect the natural course of disease as atypical presentations and rapid progression of syphilis in HIV positive individuals has been reported.[9-13]

In the pre-antibiotic era, an estimated one third of untreated persons developed tertiary syphilis with about 15% progressing to gummatous disease (1-46 years post-infection), 10% to cardiovascular syphilis (20-30 years after infection), and 4-14% to late neurosyphilis (2-50 years after infection).[1] After the introduction of penicillin in the 1940s, the number of cases of syphilis plummeted in the United States, reaching a nadir in 2000.[1] Nowadays, tertiary syphilis is a rare disease due to easy and effective treatment of infectious and latent syphilis. Antibiotic use for other infections is also likely a factor.

In Canada, syphilis (all stages) has been nationally notifiable since 1924. However national reports only include data on infectious syphilis, since only these cases are of major public health significance.[14] In Alberta, all cases of syphilis, including tertiary and neuro-syphilis have been notifiable to a centralized program under the Public Health Act since 1921. Syphilis notification rates have fluctuated over the last fifty years with a rise in notification rates during outbreak periods. Since 2000, notification rates of infectious syphilis have increased dramatically in Alberta (0.6/100,000 population in 2000 to 12.5/100,000 population in 2017), with the most recent resurgence among men who have sex with men (MSM) and up to 30% of patients co-infected with HIV (personal communication Jennifer Gratrix, Provincial STI Services, Alberta Health Services).[15]

There are few data on the prevalence and characteristics of tertiary and neuro-syphilis cases in the post antibiotic era. We are aware of only one study from the Netherlands which estimated that 10-13% of all syphilis cases from 1999-2010 had neurosyphilis; these data were limited by

the fact that the diagnostic criteria used for neurosyphilis was based on hospital discharge diagnosis rather than clinical examination or laboratory criteria.[16] We sought to determine the notification rate and characteristics of reported cases of tertiary and neurosyphilis in Alberta from 1973 onwards.

Methods

A retrospective review was conducted of all tertiary and neurosyphilis cases in Alberta (current population 4.3 million) from 1973 (when syphilis data was first available by staging) to March 2017 (most recent cases staged at time of data collection). All cases of syphilis are reportable by laboratories and clinicians to Provincial STI Services under the Alberta Public Health Act. A paper chart was created for each syphilis case containing laboratory results, medical correspondence, syphilis-relevant history, clinical findings, and staging. Cases diagnosed since 2000 were also entered into a provincial surveillance database. Cases were classified as defined in Table 1.[17]

Table 1: Case Definitions Used for Diagnosis of Neurosyphilis and Tertiary Syphilis (Adapted from[17]:

Syphilis stage	Definition
Tertiary syphilis	Reactive treponemal serology together with characteristic late abnormalities of the cardiovascular system, bone, skin or other structures, in the absence of other known causes of these abnormalities and no clinical or laboratory evidence of neurosyphilis

Early Neurosyphilis (< 1 year after infection) *Asymptomatic*	Laboratory confirmation of primary, second or early latent syphilis and i) reactive CSF-VDRL in non-bloody CSF AND/OR ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes AND NO signs or symptoms of neurosyphilis
Early Neurosyphilis (< 1 year after infection) *Symptomatic*	Laboratory confirmation of primary, second or early latent syphilis and i) reactive CSF-VDRL in non-bloody CSF AND/OR ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes AND clinical signs or symptoms of neurosyphilis*
Late neurosyphilis (>1 year after infection) *Asymptomatic*	Reactive treponemal serology (not staged as primary, secondary or early latent syphilis) and i) reactive CSF-VDRL in non-bloody CSF AND/OR ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes

	AND NO clinical signs or symptoms of neurosyphilis
Late neurosyphilis (>1 year after infection) *Symptomatic*	Reactive treponemal serology (not staged as primary, secondary or early latent syphilis) and iii) reactive CSF-VDRL in non-bloody CSF AND/OR iv) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes AND clinical signs or symptoms of neurosyphilis*

*if ocular or otic signs or symptoms present with a normal CSF examination, patient was classified as symptomatic neurosyphilis (early or late)

Serological testing for syphilis changed during the study period, with reverse sequence syphilis screening (RSSS) using an enzyme immunoassay being introduced in September 2007; prior to this a quantitative Rapid Plasma Reagin (RPR) was used. Since the criteria for classifying neurosyphilis evolved over time, all neurosyphilis cases during the study period were reviewed by two STI physicians and classified into early asymptomatic, early symptomatic, late asymptomatic, late symptomatic neurosyphilis cases; disagreement between the classifications of cases was resolved by consensus between the two physicians (PS and AES).

Reported notification rates of other stages of syphilis prior to 2000 were obtained from historical surveillance reports from Alberta STI Services beginning in 1975. Population denominators were obtained through government population estimates.[18] An outbreak was defined as an increase in infectious syphilis cases of two standard deviations above the baseline (previous 5 year quarterly average) for the given time period.

Variables collected for analysis included demographics, sexual partners, HIV status (testing available since 1985[19] and recommended for all syphilis cases once serology available), diagnosis date, clinical parameters, symptoms, and treatment. Variables for cases diagnosed prior to 2004 were captured through chart review, while variables for cases diagnosed after 2004 were extracted from the provincial STI surveillance system. Client reported symptoms were broken into five categories (not mutually exclusive) based on system involvement: ocular (e.g. uveitis, retinal, vision loss), auditory (e.g. hearing loss, tinnitus), ataxia, cognitive impairment (e.g. dementia, psychosis), and other (aphasia, stroke, reduced level of consciousness, headache, and unspecified neurological symptoms).

Treatment data was divided into 3 mutually exclusive categories based on the following minimum treatments: 1) penicillin G 3-4 million units IV q 4 h (18-24 million units/day) for 10 - 14 days, 2) ceftriaxone 2 g IV/IM daily x 10-14 days, 3) Other, which included drugs like chloramphenicol, doxycycline, tetracycline, benzathine penicillin G- long acting, reduced doses of penicillin G or ceftriaxone.

Analysis was stratified by stage of syphilis to compare early and late neurosyphilis by the previously listed variables using Chi-square or Fisher's exact for categorical variables and Mann-Whitney tests for continuous variables. Missing data was categorized as unknown and included in the analysis. As well, each syphilis stage was stratified by asymptomatic and symptomatic for comparison. The significance was set at a two-sided *p*-value of <0.05. A sensitivity analysis to verify univariate findings by cases diagnosed pre- and post-2000 was considered; however, small cell sizes precluded the inclusion of early neurosyphilis and changes to syphilis screening in 2007 increasing the diagnosis of late latent syphilis cases were already known. Data was analyzed using IBM SPSS Statistics version 19.0 (IBM, Armonk, NY, USA). This study was approved by the University of Alberta Health Research Ethics Board (Approval Number: Pro00075972).

Patient and Public Involvement

Patients were not involved in the design of this research study.

Results

A total of 254 cases were identified during the study period, of which 251 were neurosyphilis and 3 were cardiovascular (CV) cases; one case of CV syphilis was reported in each of the following years: 1976, 1979, and 1984. No cases of gummatous syphilis were reported during this time period. The neurosyphilis cases were evenly divided as early (52.4%; n=133) and late (46.1%; n=117), with one additional case of unknown duration. Three individuals were

diagnosed with two distinct episodes of neurosyphilis over the course of the reporting period. All three of these individuals were men who reported same sex partners, all six episodes were diagnosed between 2005 and 2014, and all categorized as early neurosyphilis. Two of these men were co-infected with HIV.

Between 1975 and 2016, 8,874 total cases of syphilis were reported in Alberta. Of these, 4,513 (51%) were infectious (i.e. staged as primary, secondary, early latent) and 4,361 (49%) were classified as non-infectious (i.e. late latent, tertiary). Over the time period, three outbreaks of infectious syphilis were identified (Figure 1). The first outbreak occurred between 1981 and 1987, the second outbreak commenced in 2000 and declined in 2011, and a third outbreak began in 2015 and continues. Of the infectious syphilis cases, 2.8% (n=128) were staged as early neurosyphilis. When plotting the notification rate of early neurosyphilis cases, increases in the rate were found at corresponding times to infectious syphilis outbreaks #2 and #3 (Figure 2). Of the noninfectious syphilis cases staged during this time, 2.6% (115/4316) were staged with late neurosyphilis. Similarly, for late neurosyphilis, peaks in notification rates were found shortly after outbreak #1 and outbreak #2 (Figure 2).

Early neurosyphilis cases were significantly younger, more likely to be Caucasian, born in Canada, diagnosed in recent decades (2010's), reported same sex partners, and HIV positive as compared to late neurosyphilis cases (Table 2).

Table 2: Characteristics of Early and Late Neurosyphilis (Alberta, 1973 to March 2017; n=250)

	Early Neurosyphilis	Late Neurosyphilis	Compar

	Asymptomatic (n=28)	Symptomatic (n=105)	Total (n=133)	p-Value	Asymptomatic (n=47)	Symptomatic (n=70)	Total (n=117)	p-Value	ison of Early and Late p-Value
Median Age (IQR)	40 (32-46)	47 (39-55)	44 (36-54)	0.02	45 (32-65)	64 (53-75)	58 (45-70)	<0.001	<0.001
Gender									
Female	8 (28.6)	12 (11.4)	20 (15.0)	0.02	6 (12.8)	15 (21.4)	21 (17.9)	0.23	0.54
Male	20 (71.4)	93 (88.6)	113 (85.0)		41 (87.2)	55 (78.6)	96 (82.1)		
Ethnicity									
Indigenous	6 (21.4)	6 (5.7)	12 (9.0)	0.001	6 (12.8)	3 (4.3)	9 (7.7)	0.44	<0.001

Caucasian	10 (35.7)	78 (74.3)	88 (66.2)		14 (29.8)	23 (32.9)	37 (31.6)		
Other	3 (10.7)	4 (3.8)	7 (5.3)		16 (34.0)	27 (38.6)	43 (36.8)		
Unknown	9 (32.1)	17 (16.2)	26 (19.5)		11 (23.4)	17 (24.3)	28 (23.9)		
Municipality									
Calgary	9 (32.1)	32 (30.5)	41 (30.8)	0.62	10 (21.3)	22 (31.4)	32 (27.4)	0.46	0.59
Edmonton	15 (53.6)	48 (45.7)	63 (47.4)		28 (59.6)	35 (50.0)	63 (53.8)		
Other	4 (14.3)	25 (23.8)	29 (21.8)		9 (19.1)	13 (18.6)	22 (18.8)		

Country of Birth									
Canada	16 (57.1)	56 (53.3)	72 (54.1)	0.23	23 (48.9)	16 (22.9)	39 (33.3)	0.01	<0.001
Outside of Canada	5 (17.9)	9 (8.6)	14 (10.5)		17 (36.2)	36 (51.4)	53 (45.3)		
Unknown	7 (25.0)	40 (38.1)	47 (35.3)		7 (14.9)	18 (25.7)	25 (21.4)		
Decade of Diagnosis									
1970's	1 (3.6)	1 (1.0)	2 (1.5)	0.001	4 (8.5)	1 (1.4)	5 (4.3)	0.29	<0.001
1980's	6 (21.4)	3 (2.9)	9 (6.8)		13 (27.7)	15 (21.4)	28 (23.9)		

1990's	3 (10.7)	5 (4.8)	8 (6.0)		6 (12.8)	9 (12.7)	15 (12.8)		
2000's	8 (28.6)	28 (26.7)	36 (27.1)		4 (8.5)	20 (28.6)	24 (20.5)		
2010's	10 (35.7)	68 (64.8)	78 (58.6)		20 (42.6)	25 (35.7)	45 (38.5)		
Sexual Partners									
Heterosexual	12 (42.9)	46 (43.8)	58 (43.6)	1.00	30 (63.8)	38 (54.3)	68 (58.1)	0.002	<0.001
Same Sex	14 (50.0)	52 (49.5)	66 (49.6)		11 (23.4)	5 (7.1)	16 (13.7)		
Unknown	2 (7.1)	7 (6.7)	9 (6.8)		6 (12.8)	27 (38.6)	33 (28.2)		

HIV Status									
Negative	5 (17.9)	68 (64.8)	73 (54.9)	<0.001	19 (40.4)	27 (38.6)	46 (39.3)	0.31	<0.001
Positive	17 (60.7)	30 (28.6)	47 (35.3)		8 (17.0)	6 (8.6)	14 (12.0)		
Unknown	6 (21.4)	7 (6.7)	13 (9.8)		20 (42.6)	37 (52.9)	57 (48.7)		
Treatment									
Penicillin G	22 (78.6)	82 (78.1)	104 (78.2)	0.87	21 (44.7)	63 (90.0)	84 (71.8)	<0.001	0.43
Ceftriaxone	3 (10.7)	14 (13.3)	17 (12.8)		12 (25.5)	5 (7.1)	17 (14.5)		

Other	3 (10.7)	9 (8.6)	12 (9.0)		14 (29.8)	2 (2.9)	16 (13.7)		

Among early neurosyphilis cases, 79.0% (n=105) were symptomatic; symptomatic cases were more likely to be older, male, Caucasian, recently diagnosed (2010's), and HIV negative compared to asymptomatic cases. Among late neurosyphilis cases, 59.8% (n=70) were symptomatic; symptomatic cases were more likely to be older, born outside of Canada, and treated with intravenous penicillin G, and less likely to have a same sex partner as compared to asymptomatic cases.

The majority (79.9%; n=139) of symptomatic cases reported a single manifestation. The most common clinical manifestation of the symptomatic cases (41.1%; n=72) was ocular involvement; early neurosyphilis cases were more likely to have ocular involvement than late neurosyphilis cases (Table 3). The first case of ocular syphilis was reported in 1990 with the majority (68.1%; n=49) of cases being diagnosed between 2010 and 2017. The second most common (33.7%; n=59) manifestation of symptomatic neurosyphilis was cognitive impairment with significantly more late neurosyphilis cases reporting these symptoms than early cases. Twelve (6.9 %) cases reported auditory symptoms and 10.9% (n=19) reported ataxia. Nearly one-third (29.7%; n=52) of cases reported other symptoms including aphasia, stroke, reduced level of consciousness, headache, and unspecified neurological symptoms.

Table 3: Manifestations of Early and Late Symptomatic Neurosyphilis (Alberta, 1973 to March 2017; n=175)

Manifestation	Early Neurosyphilis (n=105)	Late Neurosyphilis (n=70)	P-Value
Ocular	59 (56.2)	13 (18.6)	<0.001
Cognitive Impairment	20 (19.0)	39 (55.7)	<0.001
Ataxia	9 (8.6)	10 (14.3)	0.23
Auditory	10 (9.5)	2 (2.9)	0.13
Other*	30 (28.6)	22 (31.4)	0.69

- *Aphasia, reduced level of consciousness, headache, unspecified neurological symptoms

Although the first HIV co-infected case was reported in 1986, over one-half (57.4%; n=35) of HIV co-infected cases were reported between 2010 and 2017. The majority (62.2%; n= 46) of cases with an unknown HIV status occurred between the 1970's and 1980's, prior to the clinical availability of diagnostic serology. Cases that had HIV test results were significantly younger (47 years; IQR: 37-55) than cases without HIV test results (64 years; IQR: 44-70; p<0.001).

Thirty-six (14.2%) of all the cases were diagnosed without a lumbar puncture result. Nearly all of these clinical cases (97.2%; n=35) were symptomatic. The remaining asymptomatic case was diagnosed based on an inadequate fall in RPR titres over time. There was no significant difference by HIV status for those who had and did not have a lumbar puncture (p=0.62). Clinical parameters by HIV status are outlined in Figure 3. Of the 2 HIV-positive and 6 HIV-negative cases with negative clinical parameters, all were symptomatic cases.

The majority (74.4%; n=189) of all cases were treated with intravenous penicillin G. Asymptomatic late neurosyphilis cases were less likely to be treated with penicillin G (44.7%; n=21) as compared to symptomatic late neurosyphilis (90.0%; n=63; p<0.001). There was a rise in the use of ceftriaxone in late neurosyphilis treatment from no use in the 1970's to 1990's, to 12.5% (n=3) in 2000's and 31.1% (n=14) in the 2010's. Other drug combinations for neurosyphilis was highest in the 1970's (85.7%; n=6) and dropped to a low of 4.3% (n=1) in the 1990's.

Discussion

A review of the trends in reported cases of infectious syphilis from 1975 to March, 2017 in Alberta shows a cycling in the number of cases over time. During this time period, the first major outbreak of infectious syphilis occurred between 1981 and1987, with the majority of cases between 1983 and 1985.[20] A quiescent period of approximately two decades followed with a resurgence in infectious cases in 2000 followed by a decline in 2011 and then another rise in 2015. These observations are consistent with a study of long term trends in reported primary and secondary syphilis cases in the United States which showed recurrent peaks and troughs in approximately 10-year cycles.[21] This pattern of periodic resurgence of syphilis has variously been attributed to either failure to sustain control efforts, changing risk behaviours (such as crack cocaine use), and waxing and waning partial host immunity to infection at the population level.[22,23] Interestingly, our province observed a 20-year gap between the outbreak in the mid 1980s and the mid 2000s. The reasons for this prolonged gap are unclear but are

likely multi-factorial including a well-established and sustained prevention and control program for STIs in the province, emergence of HIV and the mass education that occurred during this time period. This theory is supported by declining notification rates of gonorrhea and chlamydia until 1998 and then subsequent rises to current rates.[24] Our observed rising notification rates of infectious syphilis since the mid-2000s are consistent with many jurisdictions across Canada and the United States.[14,25] The rise in late latent syphilis in 2007 has been attributed to the introduction of RSSS.[26]

Some studies have reported a rise in cases of neurosyphilis related to outbreaks of infectious syphilis. One possible explanation for this is that the overall rise in notification rates of infectious syphilis could potentially increase the pool of persons progressing to neurosyphilis and tertiary syphilis. For example, a study conducted in British Columbia, one of Alberta's neighboring provinces, reported that in the context of rising rates of infectious syphilis, the neurosyphilis rate was 0.03 per 100,000 in 1992 and increased 27-fold to 0.8 per 100,000 in 2012.[27] Investigators from Guangdong province in China similarly reported an incidence rate increase in neurosyphilis cases from 0.21 cases per 100,000 persons in 2009 to 0.31 cases per 100,000 persons in 2014 and in tertiary cases from 0.28 cases per 100,000 persons in 2009 to 0.36 cases per 100,000 persons in 2014.[28] Neither of these studies, however, distinguished between early and late neurosyphilis cases. In our review, we observed a significant rise in early neurosyphilis during the outbreak periods and a significant decline after the outbreak periods, e.g. only one case was observed in 2012 after the second outbreak. We had expected to see a sustained increase in late neurosyphilis cases based on the hypothesis that the number of

untreated infected persons with syphilis would increase over time but there was no significant increase during the overall observation period. Interestingly, a rise in late neurosyphilis cases was observed towards the end of the outbreak periods, perhaps due to heightened awareness and increased testing due to public health announcements during the outbreak periods and also because late (tertiary) neurosyphilis can occur as soon as two years post-infection.[1] Although individuals diagnosed with late symptomatic neurosyphilis are not infectious and therefore not of concern from a public health perspective, these individuals would benefit from screening and appropriate treatment for syphilis to prevent complications of tertiary syphilis.[1]

Early neurosyphilis cases were more likely to be younger, Caucasian, born in Canada, HIV positive and reporting same sex partners. These observations parallel the observed rise in infectious syphilis during the third outbreak and may also be related to selection bias since lumbar punctures were more likely to be performed in HIV positive persons in the early years, especially those with low CD_4 counts (<350) and/or RPR $\geq$ 1:32 dilutions as recommended in the Canadian STI Guidelines.[29] In addition, most clinicians providing care to HIV positive individuals in Alberta would have offered regular syphilis screening in HIV positive individuals, as endorsed for several years in the U.S. Department of Health and Human Services guidelines.[30]

The most common manifestation (40%) of symptomatic neurosyphilis was ocular involvement with cases of early neurosyphilis more likely than cases of late neurosyphilis to have ocular involvement (54% vs 17%, p<0.001). Two-thirds of ocular cases were reported between 2010 and 2017, with 46.4% reported among MSM, similar to other studies.[31] Late neurosyphilis cases

were more likely to be older, born outside of Canada and less likely to report same sex partners, paralleling the demographics of late latent cases of syphilis in our province (data not shown).

Our study identified very few (n=3) cardiovascular cases of tertiary syphilis with all cases identified at the time of a diagnosis of aortic aneurysm. This likely represents an underestimate in the actual number of cases of CV syphilis as we suspect that most patients with aortic aneurysm or initial cardiovascular involvement do not have syphilis testing performed. In Alberta, the provincial STI program facilitates the assessment of all late stage syphilis cases by a physician who then conducts a neurological and cardiovascular examination. A chest radiograph, recommended in the past in some jurisdictions to look for linear calcification of the ascending aorta, a radiological sign of syphilitic aortitis is not routinely done. Chest radiographs for the evaluation of CV syphilis in asymptomatic patients with LLS is of such low yield, that it is not routinely recommended.[32] Neither clinical examination nor chest radiograph is likely to be sensitive enough to identify cases of CV syphilis and given the presumed rarity of this condition and that the treatment is the same as for LLS, further evaluations (e.g. echocardiograms) are not warranted.

No cases of gummatous syphilis were reported during our study period. Although syphilitic gummas were reported in up to 15% cases in the pre-antibiotic era, it is possible that the widespread use of antibiotics for other conditions, which may indirectly treat or partially treat syphilis, has affected the occurrence.

One of the strengths of our study is that there was consistent reporting of all cases with positive syphilis serology over time by laboratories and active follow up by the provincial STI program with health care providers. We were able to apply current case definitions retrospectively to all cases; however, one of the limitations to retrospective review of data is the possibility of inaccurate classification of cases. Our review by two experienced medical consultants resulted in only one case where insufficient information was available to classify the case with reasonable accuracy. Additional study limitations include changes in and quality of data collection practices over time, with improved data quality over time. The information about gender of sex partners may have been inaccurate in earlier years due to stigma associated with same sex partners. Routine testing for HIV in cases of syphilis was also not conducted in earlier years and as such the number of concurrent HIV infections may be underestimated.

In summary, our review of tertiary and neurosyphilis cases in Alberta over a 44-year period found that early and late neurosyphilis cases continue to occur in the context of cycling of infectious syphilis outbreaks. Ocular disease was the most common manifestation of neurosyphilis in our study. On the other hand, cardiovascular syphilis was extremely rare and no cases of gumma were identified. Ongoing identification of syphilis cases with prompt treatment and follow up continues to be important in the context of resurgence of infectious syphilis worldwide.

Author contributions: TL reviewed hard copy records of all cases and conducted data entry into an Excel file; PS and AS reviewed and re-classified all cases; JG conducted data analysis; JG and AS drafted initial versions of the manuscript; TL, PS, RC, JG, LB, RR, BR and AES helped develop the study design and reviewed drafts of the manuscript.

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Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada, 1975-2016)

Figure 2. Number and Notification Rate of Early and Late Neurosyphilis by Year (Alberta, 1975-2016)

Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases (Alberta, 1975-March 2017)

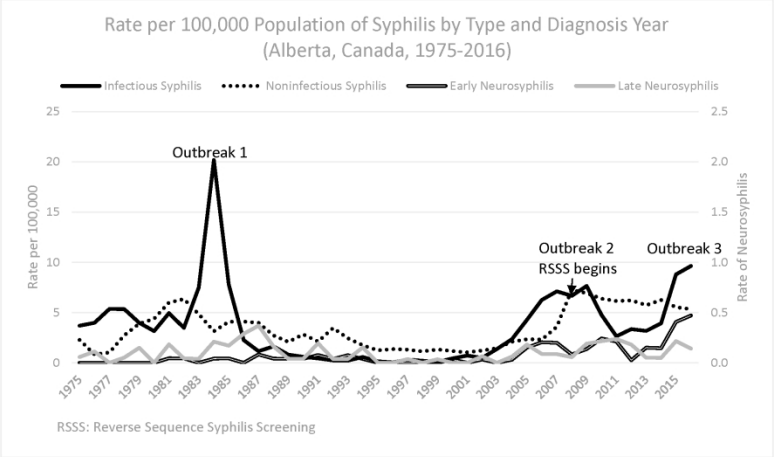

Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada, 1975-2016)

215x279mm (300 x 300 DPI)

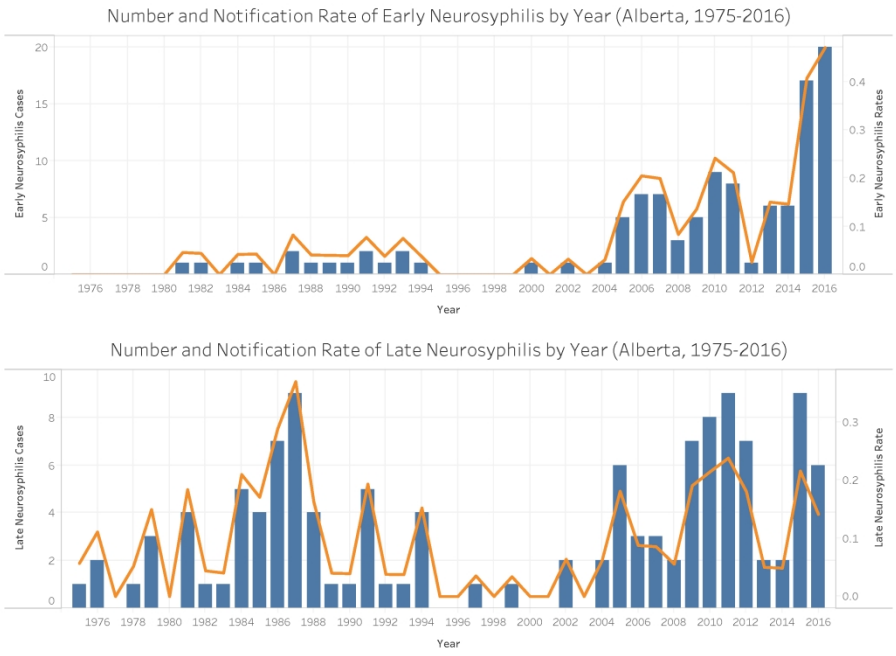

Figure 2. Rates of Early and Late Neurosyphilis during 2 Different Outbreak Periods with Linear Trend Line (Alberta, 1975-2016)

279x215mm (300 x 300 DPI)

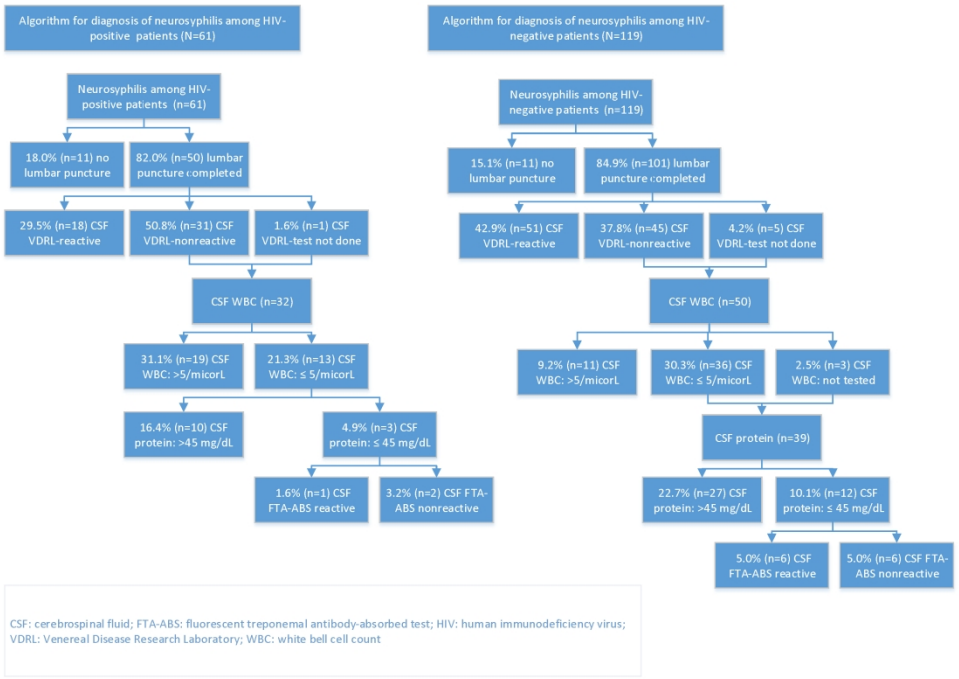

Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases (Alberta, 1975-March 2017)

279x215mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	

		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 2 8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.