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

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Manuscripts

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

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Key Words: Syphilis, neurosyphilis, epidemiology, tertiary syphilis

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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

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2
3 syphilis and clinical evaluation of cases for complications continues to be important in the
4
5 context of global resurgence of syphilis.
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13 **Keywords:** tertiary syphilis, neurosyphilis, Canada
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18 **Strengths and Limitations of this study:**
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- 20 • An important strength of our study was the consistent reporting of all cases with positive
21 syphilis serology over the 44 year period by laboratories as well as active follow up of all cases
22 by the provincial STI program.
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- 25 • Another strength of our study is the retrospective application of current case definitions to all
26 cases by 2 experienced STI clinicians.
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- 29 • One of the limitations to the retrospective review of data is the possibility of inaccurate
30 classification of cases due to insufficient available information.
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- 33 • Additional study limitations include changes in data collection practices over time.
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- 36 • Routine testing for HIV in cases of syphilis was also not conducted in earlier years and as such
37 the number of concurrent HIV infections may have been underestimated.
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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 lesions³ 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

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3 In the pre-antibiotic era, an estimated one third of untreated persons developed tertiary
4 syphilis¹⁴ with about 15% progressing to gummatous disease (1-46 years post-infection), 10% to
5 cardiovascular syphilis (20-30 years after infection), and 4-14% to late neurosyphilis (2-50 years
6 after infection).¹ After the introduction of penicillin in the 1940s, the number of cases of syphilis
7 plummeted in the United States, reaching a nadir in 2000.¹ Nowadays, tertiary syphilis is a rare
8 disease due to easy and effective treatment of infectious and latent syphilis. Antibiotic use for
9 other infections is also likely a factor.
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23 In Canada, syphilis (all stages) has been nationally notifiable since 1924. However national
24 reports only include data on infectious syphilis, since only these cases are of major public health
25 significance.¹⁵ In Alberta, all cases of syphilis, including tertiary and neuro-syphilis have been
26 notifiable to a centralized program under the Public Health Act since 1921. Syphilis rates have
27 fluctuated over the last fifty years with a rise in rates during outbreak periods. Since 2000, rates
28 of infectious syphilis have increased dramatically in Alberta (0.6/100,000 population in 2000 to
29 12.5/100,000 population in 2017), with the most recent resurgence among men who have sex
30 with men (MSM) and up to 30% of patients co-infected with HIV (personal communication
31 Jennifer Gratrix, Provincial STI Services, Alberta Health Services).¹⁶
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47 There are few data on the prevalence and characteristics of tertiary and neuro-syphilis cases in
48 the post antibiotic era. We are aware of only one study from the Netherlands which estimated
49 that 10-13% of all syphilis cases from 1999-2010 had neurosyphilis; these data were limited by
50 the fact that the diagnostic criteria used for neurosyphilis was based on hospital discharge
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3 diagnosis rather than clinical examination or laboratory criteria.¹⁷ We sought to determine the
4 prevalence and characteristics of reported cases of tertiary and neurosyphilis in Alberta from
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6 1973 onwards.
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10 11 12 13 **Methods**

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15 A retrospective review was conducted of all tertiary and neurosyphilis cases in Alberta (current
16 population 4.3 million) from 1973 to March 2017. All cases of syphilis are reportable by
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18 laboratories and clinicians to Provincial STI Services under the Alberta Public Health Act. Cases
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20 were classified as defined in Table 1.¹⁸
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28 Table 1: Case Definitions Used for Diagnosis of Neurosyphilis and Tertiary Syphilis (Adapted
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30 from¹⁹;
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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) <i>Asymptomatic</i>	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

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

(>1 year after infection) <i>Symptomatic</i>	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*
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*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

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6 Variables collected for analysis included demographics, sexual partners, HIV status (testing
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8 available since 1985²⁰ and recommended for all syphilis cases once serology available),
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10 diagnosis date, clinical parameters, symptoms, and treatment. Variables for cases diagnosed
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12 prior to 2004 were captured through chart review, while variables for cases diagnosed after
13
14 2004 were extracted from the provincial STI surveillance system. Client reported symptoms
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16 were broken into six categories (not mutually exclusive) based on system involvement: ocular
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18 (e.g. uveitis, retinal, vision loss), auditory (e.g. hearing loss, tinnitus), stroke, peripheral
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20 neuropathy (e.g. impaired gait, numbness), central nervous system (e.g. aphasia, ataxia), and
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22 cognitive impairment (e.g. dementia, psychosis).
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30 Treatment data was divided into 3 mutually exclusive categories based on the following
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32 minimum treatments: 1) penicillin G 3-4 million units IV q 4 h (18-24 million units/day) for 10 -
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34 14 days, 2) ceftriaxone 2 g IV/IM daily x 10-14 days, 3) Other, which included drugs like
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36 chloramphenicol, doxycycline, tetracycline, benzathine penicillin G- long acting, reduced doses
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38 of penicillin G or ceftriaxone.
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45 Analysis was stratified by stage of syphilis to compare early and late neurosyphilis by the
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47 previously listed variables using Chi-square or Fisher's exact for categorical variables and Mann-
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49 Whitney tests for continuous variables. Missing data was categorized as unknown and included
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51 in the analysis. As well, each syphilis stage was stratified by asymptomatic and symptomatic for
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53 comparison. Associations over time (collection decade) were analyzed using linear association.
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3 Significant changes in rates over time were assessed using a linear trend model. The
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5 significance was set at p -value of <0.05 . Data was analyzed using IBM SPSS Statistics version
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7 19.0 (IBM, Armonk, NY, USA). This study was approved by the University of Alberta Health
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9 Research Ethics Board (Approval Number: Pro00075972).
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15 ***Patient and Public Involvement***

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17 Patients were not involved in the design of this research study.
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23 **Results**

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25 A total of 254 cases were identified during the study period, of which 251 were neurosyphilis
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27 and 3 were cardiovascular (CV) cases; one case of CV syphilis was reported in each of the
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29 following years: 1976, 1979, and 1984. No cases of gummatous syphilis were reported during
30
31 this time period. The neurosyphilis cases were evenly divided as early (52.4%; $n=133$) and late
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33 (46.1%; $n=117$), with one additional case of unknown duration. Three individuals were
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35 diagnosed with two distinct episodes of neurosyphilis over the course of the reporting period.
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37 All three of these individuals were men who reported same sex partners, all six episodes were
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39 diagnosed between 2005 and 2014, and all categorized as early neurosyphilis. Two of these
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41 men were co-infected with HIV.
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50 Between 1975 and 2016, 8,874 total cases of syphilis were reported in Alberta. Of these, 4513
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52 (51%) were infectious (i.e. staged as primary, secondary, early latent) and 4361 (49%) were
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54 classified as non-infectious (i.e. late latent, tertiary). Over the time period, three outbreaks of
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3 infectious syphilis were identified (Figure 1). The first outbreak (defined as an increase in cases
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5 of two standard deviations above the baseline) occurred between 1981 and 1987, the second
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7 outbreak commenced in 2000 and declined in 2011, and a third outbreak began in 2015 and
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9 continues. Of the infectious syphilis cases, 2.8% (n=128) were staged as early neurosyphilis.
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11 When plotting the rate of early neurosyphilis cases against infectious syphilis cases, significant
12
13 rises were seen during the outbreak periods (outbreak #2, $p < 0.001$; Figure 2). Of the
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15 noninfectious syphilis cases staged during this time, 2.6% (115/4316) were staged with late
16
17 neurosyphilis. When plotting the rate of late neurosyphilis against infectious syphilis during the
18
19 outbreak periods, a significant rise in late neurosyphilis cases was also noted toward the end of
20
21 the outbreak periods (outbreak #1, $p = 0.04$, outbreak #2, $p = 0.02$).
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30 Early neurosyphilis cases were significantly younger, more likely to be Caucasian, born in
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32 Canada, diagnosed in recent decades (2010's), reported same sex partners, and HIV positive as
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34 compared to late neurosyphilis cases (Table 2).
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40 Table 2: Characteristics of Early and Late Neurosyphilis (Alberta, 1973 to March 2017; n=250)
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	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	40 (32-	47 (39-	44	0.02	45 (32-	64 (53-	58	<0.0	<0.001
Age	46)	55)	(36-		65)	75)	(45-	01	
(IQR)			54)				70)		
Gender									
Female	8 (28.6)	12 (11.4)	20	0.02	6 (12.8)	15 (21.4)	21	0.23	0.54
			(15.0				(17.9		
))		
Male	20 (71.4)	93 (88.6)	113		41 (87.2)	55 (78.6)	96		
			(85.0				(82.1		
))		
Ethnicity									
Indigeno	6 (21.4)	6 (5.7)	12	0.00	6 (12.8)	3 (4.3)	9	0.44	<0.001
us			(9.0)	1			(7.7)		
Caucasia	10 (35.7)	78 (74.3)	88		14 (29.8)	23 (32.9)	37		
n			(66.2				(31.6		
))		
Other	3 (10.7)	4 (3.8)	7		16 (34.0)	27 (38.6)	43		
			(5.3)				(36.8		
))		
Unknow	9 (32.1)	17 (16.2)	26		11 (23.4)	17 (24.3)	28		
n			(19.5				(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		7 (14.9)	18 (25.7)	25		

n			(35.3				(21.4		
))		
Decade									
of									
Diagnosi									
s									
1970's	1 (3.6)	1 (1.0)	2 (1.5)	0.00 1	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)	0.00	<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%;

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3 n=57) than late neurosyphilis cases (n=12; 17.1%; p<0.001). The first case of ocular syphilis was
4 reported in 1990 with the majority (66.7%; n=46) of cases being diagnosed between 2010 and
5
6 2017. The second most common (34.3%; n=60) manifestation of symptomatic neurosyphilis was
7
8 cognitive impairment with significantly more late neurosyphilis cases (55.7%; n=39) reporting
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10 these symptoms than early cases (20.0%; n=21; p<0.001). One-quarter of symptomatic cases
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12 reported peripheral involvement (26.9%; n=47), seven (4.0%) reported strokes and seven cases
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14 with central nervous system manifestations like ataxia, aphasia, and reduced level of
15
16 consciousness. Eleven (6.3%) cases reported auditory symptoms; all cases were diagnosed with
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18 early infection (p=0.003). Thirteen (7.4%) cases reported other symptoms like headache or no
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20 specific symptoms.
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30 Although the first HIV co-infected case was reported in 1986, over one-half (57.4%; n=35) of
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32 HIV co-infected cases were reported between 2010 and 2017. The majority (62.2%; n= 46) of
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34 cases with an unknown HIV status occurred between the 1970's and 1980's, prior to the clinical
35
36 availability of diagnostic serology. As well cases that had HIV test results were significantly
37
38 younger (47 years; IQR: 37-55) than cases without HIV test results (64 years; IQR: 44-70;
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40 p<0.001).
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47 Thirty-six (14.2%) of all the cases were diagnosed without a lumbar puncture result. Nearly all
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49 of these clinical cases (97.2%; n=35) were symptomatic. The remaining asymptomatic case was
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51 diagnosed based on an inadequate fall in RPR titres over time. There was no significant
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53 difference by HIV status for those who had and did not have a lumbar puncture (p=0.62).
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3 Clinical parameters by HIV status are outlined in Figure 3. Of the 2 HIV-positive and 6 HIV-
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5 negative cases with negative clinical parameters, all were symptomatic cases.
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10 The majority (74.4%; n=189) of all cases were treated with intravenous penicillin G.

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12 Asymptomatic late neurosyphilis cases were less likely to be treated with penicillin G (44.7%;
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14 n=21) as compared to late neurosyphilis (90.0%; n=63; p<0.001). There was a rise in the use of
15
16 ceftriaxone in late neurosyphilis treatment from no use in the 1970's to 1990's, to 12.5% (n=3)
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18 in 2000's and 31.1% (n=14) in the 2010's. Other drug combinations for neurosyphilis was
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20 highest in the 1970's (85.7%; n=6) and dropped to a low of 4.3% (n=1) in the 1990's.
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28 Discussion

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30 A review of the trends in reported cases of infectious syphilis from 1975 to 2016 in Alberta
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32 shows a cycling in the number of cases over time. During this time period, the first major
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34 outbreak of infectious syphilis occurred between 1981 and 1987, with the majority of cases
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36 between 1983 and 1985.²¹ A quiescent period of approximately two decades followed with a
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38 resurgence in infectious cases in 2000 followed by a decline in 2011 and then another rise in
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40 2015. These observations are consistent with a study of long term trends in reported primary
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42 and secondary syphilis cases in the United States which showed recurrent peaks and troughs in
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44 approximately 10-year cycles.²² This pattern of periodic resurgence of syphilis has variously
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46 been attributed to either failure to sustain control efforts, changing risk behaviours (such as
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48 crack cocaine use), and waxing and waning partial host immunity to infection at the population
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50 level.^{23,24} Interestingly, our province observed a 20-year gap between the outbreak in the mid
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3 1980s and the mid 2000s. The reasons for this prolonged gap are unclear but are likely multi-
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5 factorial including a well-established and sustained prevention and control program for STIs in
6
7 the province, emergence of HIV and the mass education that occurred during this time period.
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9
10 Our observed rising rates of infectious syphilis since the mid-2000s are consistent with many
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12 jurisdictions across Canada and the United States.^{15,25} The rise in late latent syphilis in 2007 has
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14 been attributed to the introduction of RSSS.²⁶
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20 Some studies have reported a rise in cases of neurosyphilis related to outbreaks of infectious
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22 syphilis. One possible explanation for this is that the overall rise in rates of infectious syphilis
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24 could potentially increase the pool of persons progressing to neurosyphilis and tertiary syphilis.
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26 For example, a study conducted in British Columbia, one of Alberta's neighboring provinces,
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28 reported that in the context of rising rates of infectious syphilis, the neurosyphilis rate was 0.03
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30 per 100,000 in 1992 and increased 27-fold to 0.8 per 100,000 in 2012.²⁷ Investigators from
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32 Guangdong province in China similarly reported an incidence rate increase in neurosyphilis
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34 cases from 0.21 cases per 100,000 persons in 2009 to 0.31 cases per 100,000 persons in 2014
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36 and in tertiary cases from 0.28 cases per 100,000 persons in 2009 to 0.36 cases per 100,000
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38 persons in 2014.²⁸ Neither of these studies, however, distinguished between early and late
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40 neurosyphilis cases. In our review, we observed a significant rise in early neurosyphilis during
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42 the outbreak periods and a significant decline after the outbreak periods, e.g. only one case
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44 was observed in 2012 after the second outbreak. We had expected to see a sustained increase
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46 in late neurosyphilis cases based on the hypothesis that the number of untreated infected
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48 persons with syphilis would increase over time but there was no significant increase during the
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3 overall observation period. Interestingly, a rise in late neurosyphilis cases was observed
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5 towards the end of the outbreak periods, perhaps due to heightened awareness and increased
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7 testing due to public health announcements during the outbreak periods.
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10 Early neurosyphilis cases were more likely to be younger, Caucasian, born in Canada, HIV
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12 positive and reporting same sex partners. These observations parallel the observed rise in
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14 infectious syphilis during the third outbreak and may also be related to selection bias since
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16 lumbar punctures were more likely to be performed in HIV positive persons in the early years,
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18 especially those with low CD₄ counts (<350) and/or RPR \geq 1:32 dilutions as recommended in the
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20 Canadian STI Guidelines.²⁹
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28 The most common manifestation (40%) of symptomatic neurosyphilis was ocular involvement
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30 with cases of early neurosyphilis more likely than cases of late neurosyphilis to have ocular
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32 involvement (54% vs 17%, $p < 0.001$). Two-thirds of ocular cases were reported between 2010
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34 and 2017, with 46.4% reported among MSM, similar to other studies.³⁰ Late neurosyphilis cases
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36 were more likely to be older, born outside of Canada and less likely to report same sex
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38 partners, paralleling the demographics of late latent cases of syphilis in our province (data not
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40 shown).
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47 Our study identified very few ($n=3$) cardiovascular cases of tertiary syphilis with all cases
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49 identified at the time of a diagnosis of aortic aneurysm. This likely represents an underestimate
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51 in the actual number of cases of CV syphilis as we suspect that most patients with aortic
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53 aneurysm or initial cardiovascular involvement do not have syphilis testing performed. In
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3 Alberta, the provincial STI program facilitates the assessment of all late stage syphilis cases by a
4 physician who then conducts a neurological and cardiovascular examination. A chest
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6 radiograph, recommended in the past in some jurisdictions to look for linear calcification of the
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8 ascending aorta, a radiological sign of syphilitic aortitis is not routinely done. Chest radiographs
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10 for the evaluation of CV syphilis in asymptomatic patients with LLS is of such low yield, that it is
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12 not routinely recommended.³¹ Neither clinical examination nor chest radiograph is likely to be
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14 sensitive enough to identify cases of CV syphilis and given the presumed rarity of this condition
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16 and that the treatment is the same as for LLS, further evaluations (e.g. echocardiograms) are
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18 not warranted.
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28 No cases of gummatous syphilis were reported during our study period. Although syphilitic
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30 gummas were reported in up to 15% cases in the pre-antibiotic era, it is possible that the
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32 widespread use of antibiotics for other conditions, which may indirectly treat or partially treat
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34 syphilis, has affected the occurrence.
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40 One of the strengths of our study is that there was consistent reporting of all cases with
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42 positive syphilis serology over time by laboratories and active follow up by the provincial STI
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44 program with health care providers. We were able to apply current case definitions
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46 retrospectively to all cases; however, one of the limitations to retrospective review of data is
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48 the possibility of inaccurate classification of cases. Our review by two experienced medical
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50 consultants resulted in only one case where insufficient information was available to classify
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52 the case with reasonable accuracy. Additional study limitations include changes in data
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3 collection practices over time. The information about gender of sex partners may have been
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5 inaccurate in earlier years due to stigma associated with same sex partners. Routine testing for
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7 HIV in cases of syphilis was also not conducted in earlier years and as such the number of
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9 concurrent HIV infections may be underestimated.
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15 In summary, our review of tertiary and neurosyphilis cases in Alberta over a 44-year period
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17 found that early and late neurosyphilis cases continue to occur in the context of cycling of
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19 infectious syphilis outbreaks. Ocular disease was the most common manifestation of
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21 neurosyphilis in our study. On the other hand, cardiovascular syphilis was extremely rare and
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23 no cases of gumma were identified. Ongoing identification of syphilis cases with prompt
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25 treatment and follow up continues to be important in the context of resurgence of infectious
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27 syphilis worldwide.
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35 **Author contributions:** TL reviewed hard copy records of all cases and conducted data entry into
36
37 an Excel file; PS and AS reviewed and re-classified all cases; JG conducted data analysis; JG and
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39 AS drafted initial versions of the manuscript; all authors helped develop the study design and
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41 reviewed drafts of the manuscript.
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58 [infections/canadian-guidelines-](https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections/canadian-guidelines-sexually-transmitted-infections-27.html)
59 [infections/canadian-guidelines-](https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections/canadian-guidelines-sexually-transmitted-infections-27.html)
60 [infections/canadian-guidelines-](https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections/canadian-guidelines-sexually-transmitted-infections-27.html)
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3 Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada,
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5 1975-2016)
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10 Figure 2. Rates of Early and Late Neurosyphilis during 2 Different Outbreak Periods with Linear
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12 Trend Line (Alberta, 1975-2016)
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17 Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases
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19 (Alberta, 1975-March 2017)
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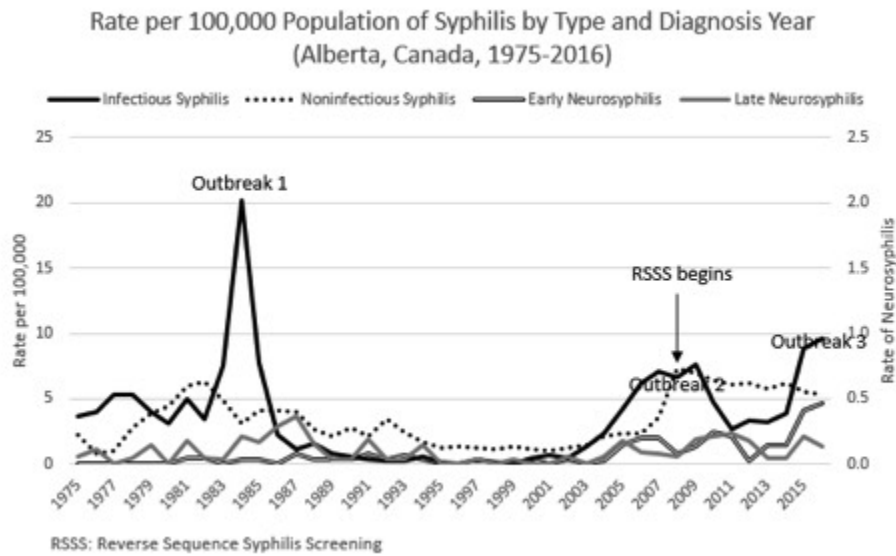


Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada, 1975-2016)

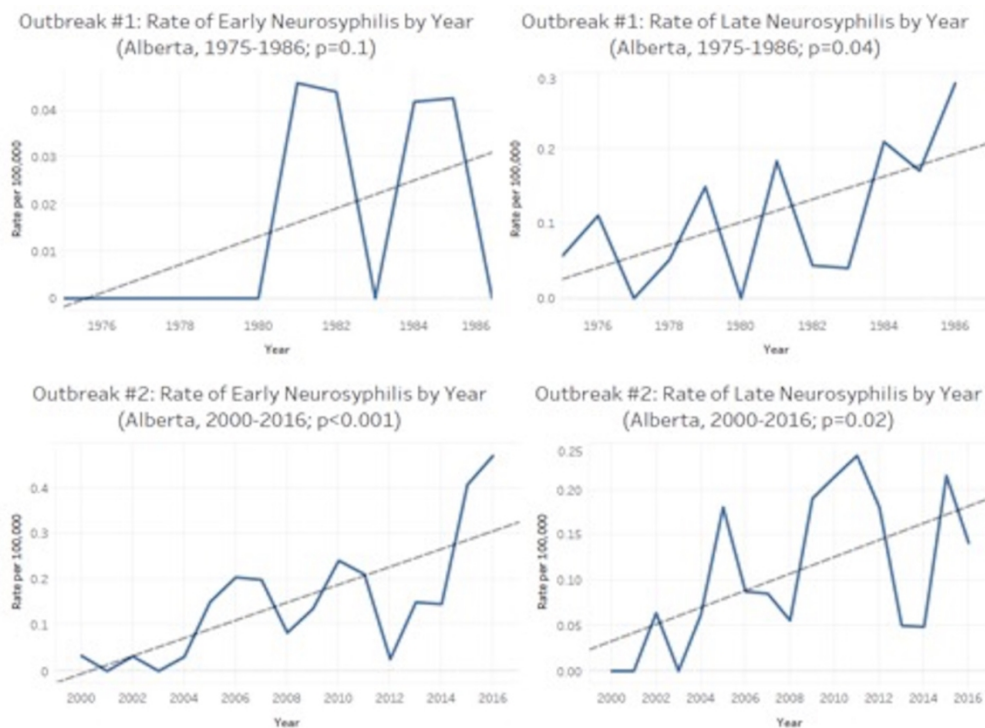


Figure 2. Rates of Early and Late Neurosyphilis during 2 Different Outbreak Periods with Linear Trend Line (Alberta, 1975-2016)

122x90mm (300 x 300 DPI)

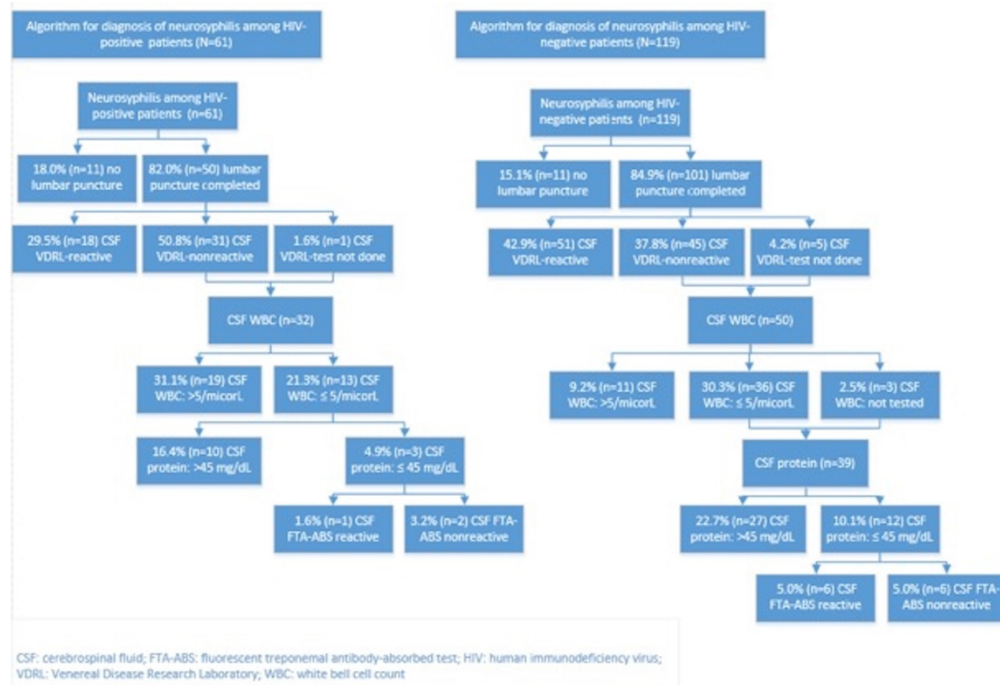


Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases (Alberta, 1975-March 2017)

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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Manuscripts

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

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Key Words: Syphilis, neurosyphilis, epidemiology, tertiary syphilis

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1 **Abstract**

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

4 **Methods:** A retrospective review of all neurosyphilis and tertiary syphilis cases reported in
5 Alberta from 1973 to March 2017 was undertaken and cases classified into early neurosyphilis,
6 late neurosyphilis and cardiovascular syphilis. Variables collected included demographics,
7 sexual partners, HIV status, clinical parameters, symptoms and treatment and distributions
8 were compared between early versus late neurosyphilis and asymptomatic versus symptomatic
9 cases (stratified by early versus late stage). Data was analyzed using IBM SPSS Statistics Version
10 19.0.

11 **Results:** 254 cases were identified; 251 were neurosyphilis and 3 were cardiovascular. No cases
12 of gummatous syphilis were reported. Early neurosyphilis accounted for 52.4% (n=133) and
13 46.1% (n=117) were late neurosyphilis cases; one (0.4%) case with unknown duration. Three
14 outbreaks of infectious syphilis were identified during the study period and a concurrent rise in
15 both early and late neurosyphilis was observed during the outbreak periods. The most
16 common manifestation of symptomatic neurosyphilis was ocular involvement which was more
17 likely in early neurosyphilis. Relative to late neurosyphilis cases, early neurosyphilis cases were
18 more likely to be younger, Caucasian, born in Canada, HIV positive and reporting same sex
19 partners while late neurosyphilis cases were more likely to be older, born outside of Canada
20 and less likely to report same sex partners.

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

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3 23 Cardiovascular syphilis cases were extremely rare. Ongoing identification of new cases of
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5 24 syphilis and clinical evaluation of cases for complications continues to be important in the
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8 25 context of global resurgence of syphilis.
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15 28 **Keywords:** tertiary syphilis, neurosyphilis, Canada
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20 30 **Strengths and Limitations of this study:**
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- 22
23 31 • An important strength of our study was the consistent reporting of all cases with positive
24
25 32 syphilis serology over the 44 year period by laboratories as well as active follow up of all cases
26
27 33 by the provincial STI program.
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29 34 • Another strength of our study is the retrospective application of current case definitions to all
30
31 35 cases by 2 experienced STI clinicians.
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34 36 • One of the limitations to the retrospective review of data is the possibility of inaccurate
35
36 37 classification of cases due to insufficient available information.
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38 38 • Additional study limitations include changes in testing policies and practices, as well as changes
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40 39 in social norms over time.
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43 40 • Routine testing for HIV in cases of syphilis was also not conducted in earlier years and as such
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45 41 the number of concurrent HIV infections may have been underestimated.
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3 46 **Manuscript**

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6 47 **Background**

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8 48 Syphilis, caused by *Treponema pallidum* subspecies *pallidum*, passes through a series of stages,
9
10 49 including primary, secondary, latent, and tertiary syphilis if left untreated.¹ Based on data from
11
12
13 50 the pre-antibiotic era, about a third of persons with untreated latent syphilis will develop late
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15 51 neurosyphilis, cardiovascular syphilis or gummatous syphilis.² Gummatous syphilis is
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17
18 52 characterized by the development of indolent granulomatous lesions³ which typically affect the
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20 53 skin, liver, and bone but can also involve other parts of the body.⁴ Syphilitic aortitis is the most
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23 54 common manifestation of cardiovascular syphilis and typically involves the ascending aorta.⁴⁻⁶
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27 56 Neurosyphilis can occur at any stage of syphilis.^{1,7} It is classified into early and late forms.¹ Early
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29
30 57 neurosyphilis affects the cerebrospinal fluid (CSF), cerebral blood vessels, and meninges more
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32
33 58 often than the brain or spinal cord parenchyma. Typically, manifestations occur within weeks to
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35 59 a few years after primary infection and may occur at the same time as primary or secondary
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38 60 syphilis, or may be asymptomatic. Manifestations may include meningitis with or without
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41 61 cranial nerve involvement, meningovascular disease or stroke. Late neurosyphilis can remain
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44 62 asymptomatic or progress to meningovascular syphilis, tabes dorsalis, or general paresis. Late
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47 63 neurosyphilis is extremely rare in the antibiotic era and usually occurs years to decades after
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50 64 primary infection.^{1,8} HIV infection may affect the natural course of disease as atypical
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53 65 presentations and rapid progression of syphilis in HIV positive individuals has been reported.⁹⁻¹³
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3 67 In the pre-antibiotic era, an estimated one third of untreated persons developed tertiary
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5 68 syphilis with about 15% progressing to gummatous disease (1-46 years post-infection), 10% to
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8 69 cardiovascular syphilis (20-30 years after infection), and 4-14% to late neurosyphilis (2-50 years
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10 70 after infection).¹ After the introduction of penicillin in the 1940s, the number of cases of syphilis
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12 71 plummeted in the United States, reaching a nadir in 2000.¹ Nowadays, tertiary syphilis is a rare
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14 72 disease due to easy and effective treatment of infectious and latent syphilis. Antibiotic use for
15
16 73 other infections is also likely a factor.
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22 75 In Canada, syphilis (all stages) has been nationally notifiable since 1924. However national
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24 76 reports only include data on infectious syphilis, since only these cases are of major public health
25
26 77 significance.¹⁴ In Alberta, all cases of syphilis, including tertiary and neuro-syphilis have been
27
28 78 notifiable to a centralized program under the Public Health Act since 1921. Syphilis notification
29
30 79 rates have fluctuated over the last fifty years with a rise in notification rates during outbreak
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32 80 periods. Since 2000, notification rates of infectious syphilis have increased dramatically in
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34 81 Alberta (0.6/100,000 population in 2000 to 12.5/100,000 population in 2017), with the most
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36 82 recent resurgence among men who have sex with men (MSM) and up to 30% of patients co-
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38 83 infected with HIV (personal communication Jennifer Gratrix, Provincial STI Services, Alberta
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40 84 Health Services).¹⁵
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50 86 There are few data on the prevalence and characteristics of tertiary and neuro-syphilis cases in
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52 87 the post antibiotic era. We are aware of only one study from the Netherlands which estimated
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54 88 that 10-13% of all syphilis cases from 1999-2010 had neurosyphilis; these data were limited by
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89 the fact that the diagnostic criteria used for neurosyphilis was based on hospital discharge
 90 diagnosis rather than clinical examination or laboratory criteria.¹⁶ We sought to determine the
 91 notification rate and characteristics of reported cases of tertiary and neurosyphilis in Alberta
 92 from 1973 onwards.

94 **Methods**

95 A retrospective review was conducted of all tertiary and neurosyphilis cases in Alberta (current
 96 population 4.3 million) from 1973 (when syphilis data was first available by staging) to March
 97 2017 (most recent cases staged at time of data collection). All cases of syphilis are reportable by
 98 laboratories and clinicians to Provincial STI Services under the Alberta Public Health Act. A
 99 paper chart was created for each syphilis case containing laboratory results, medical
 100 correspondence, syphilis-relevant history, clinical findings, and staging. Cases diagnosed since
 101 2000 were also entered into a provincial surveillance database. Cases were classified as defined
 102 in Table 1.¹⁷

104 Table 1: Case Definitions Used for Diagnosis of Neurosyphilis and Tertiary Syphilis (Adapted
 105 from¹⁷:

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

<p>Early Neurosyphilis (< 1 year after infection) <i>Asymptomatic</i></p>	<p>Laboratory confirmation of primary, second or early latent syphilis and</p> <ul style="list-style-type: none"> i) reactive CSF-VDRL in non-bloody CSF <p>AND/OR</p> <ul style="list-style-type: none"> ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes <p>AND</p> <p>NO signs or symptoms of neurosyphilis</p>
<p>Early Neurosyphilis (< 1 year after infection) <i>Symptomatic</i></p>	<p>Laboratory confirmation of primary, second or early latent syphilis and</p> <ul style="list-style-type: none"> i) reactive CSF-VDRL in non-bloody CSF <p>AND/OR</p> <ul style="list-style-type: none"> ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes <p>AND</p> <p>clinical signs or symptoms of neurosyphilis*</p>
<p>Late neurosyphilis (>1 year after infection) <i>Asymptomatic</i></p>	<p>Reactive treponemal serology (not staged as primary, secondary or early latent syphilis) and</p> <ul style="list-style-type: none"> i) reactive CSF-VDRL in non-bloody CSF <p>AND/OR</p> <ul style="list-style-type: none"> 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) <i>Symptomatic</i>	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*

106

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

109

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

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6 118 Reported notification rates of other stages of syphilis prior to 2000 were obtained from
7
8 119 historical surveillance reports from Alberta STI Services beginning in 1975. Population
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10 120 denominators were obtained through government population estimates.¹⁸ An outbreak was
11
12 121 defined as an increase in infectious syphilis cases of two standard deviations above the baseline
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15 122 for the given time period.

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20 124 Variables collected for analysis included demographics, sexual partners, HIV status (testing
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22 125 available since 1985¹⁹ and recommended for all syphilis cases once serology available),
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25 126 diagnosis date, clinical parameters, symptoms, and treatment. Variables for cases diagnosed
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27 127 prior to 2004 were captured through chart review, while variables for cases diagnosed after
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30 128 2004 were extracted from the provincial STI surveillance system. Client reported symptoms
31
32 129 were broken into five categories (not mutually exclusive) based on system involvement: ocular
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35 130 (e.g. uveitis, retinal, vision loss), auditory (e.g. hearing loss, tinnitus), ataxia, cognitive
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37 131 impairment (e.g. dementia, psychosis), and other (aphasia, stroke, reduced level of
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40 132 consciousness, headache, and unspecified neurological symptoms).

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45 134 Treatment data was divided into 3 mutually exclusive categories based on the following
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47 135 minimum treatments: 1) penicillin G 3-4 million units IV q 4 h (18-24 million units/day) for 10 -
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49 136 14 days, 2) ceftriaxone 2 g IV/IM daily x 10-14 days, 3) Other, which included drugs like
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52 137 chloramphenicol, doxycycline, tetracycline, benzathine penicillin G- long acting, reduced doses
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55 138 of penicillin G or ceftriaxone.

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6 140 Analysis was stratified by stage of syphilis to compare early and late neurosyphilis by the
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8 141 previously listed variables using Chi-square or Fisher's exact for categorical variables and Mann-
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10 142 Whitney tests for continuous variables. Missing data was categorized as unknown and included
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13 143 in the analysis. As well, each syphilis stage was stratified by asymptomatic and symptomatic for
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15 144 comparison. The significance was set at a two-sided p -value of <0.05 . A sensitivity analysis was
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18 145 conducted to determine if associations between early and late neurosyphilis were directionally
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20 146 consistent over time by analyzing associations with gender, ethnicity, country of birth, and
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23 147 sexual partners by decades. Data was analyzed using IBM SPSS Statistics version 19.0 (IBM,
24
25 148 Armonk, NY, USA). This study was approved by the University of Alberta Health Research Ethics
26
27
28 149 Board (Approval Number: Pro00075972).

150

151 ***Patient and Public Involvement***

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

153

154 **Results**

155 A total of 254 cases were identified during the study period, of which 251 were neurosyphilis
156 and 3 were cardiovascular (CV) cases; one case of CV syphilis was reported in each of the
157 following years: 1976, 1979, and 1984. No cases of gummatous syphilis were reported during
158 this time period. The neurosyphilis cases were evenly divided as early (52.4%; $n=133$) and late
159 (46.1%; $n=117$), with one additional case of unknown duration. Three individuals were
160 diagnosed with two distinct episodes of neurosyphilis over the course of the reporting period.

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3 161 All three of these individuals were men who reported same sex partners, all six episodes were
4
5 162 diagnosed between 2005 and 2014, and all categorized as early neurosyphilis. Two of these
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8 163 men were co-infected with HIV.
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12
13 165 Between 1975 and 2016, 8,874 total cases of syphilis were reported in Alberta. Of these, 4,513
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15 166 (51%) were infectious (i.e. staged as primary, secondary, early latent) and 4,361 (49%) were
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17
18 167 classified as non-infectious (i.e. late latent, tertiary). Over the time period, three outbreaks of
19
20 168 infectious syphilis were identified (Figure 1). The first outbreak occurred between 1981 and
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23 169 1987, the second outbreak commenced in 2000 and declined in 2011, and a third outbreak
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25 170 began in 2015 and continues. Of the infectious syphilis cases, 2.8% (n=128) were staged as early
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28 171 neurosyphilis. When plotting the notification rate of early neurosyphilis cases, increases in the
29
30 172 rate were found at corresponding times to infectious syphilis outbreaks #2 and #3 (Figure 2). Of
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32 173 the noninfectious syphilis cases staged during this time, 2.6% (115/4316) were staged with late
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35 174 neurosyphilis. Similarly, for late neurosyphilis, peaks in notification rates were found shortly
36
37 175 after outbreak #1 and outbreak #2 (Figure 2).
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40 176 Early neurosyphilis cases were significantly younger, more likely to be Caucasian, born in
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42 177 Canada, diagnosed in recent decades (2010's), reported same sex partners, and HIV positive as
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44
45 178 compared to late neurosyphilis cases (Table 2).
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47 179 Sensitivity analysis found similar directionally associations for gender, country of birth, and
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49
50 180 ethnicity for early neurosyphilis. Throughout the decades, cases reporting same sex partners
51
52 181 had the highest proportion of cases, except during the 2000's. Consistent directional
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55 182 associations were found for gender and sexual partners. During the 2000's, missing values for
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183 ethnicity and country of birth were the lowest, causing the other ethnicity and non-Canadian
 184 born to their highest proportions during the 5 decades.

185 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									

Indigeno us	6 (21.4)	6 (5.7)	12 (9.0)	0.00 1	6 (12.8)	3 (4.3)	9 (7.7)	0.44	<0.001
Caucasia n	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)		
Unknow n	9 (32.1)	17 (16.2)	26 (19.5)		11 (23.4)	17 (24.3)	28 (23.9)		
Municip ality									
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
Edmont on	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 n	7 (25.0)	40 (38.1)	47 (35.3)		7 (14.9)	18 (25.7)	25 (21.4)		
Decade of Diagnos is									
1970's	1 (3.6)	1 (1.0)	2 (1.5)	0.00 1	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)	0.00 2	<0.001
Same Sex	14 (50.0)	52 (49.5)	66 (49.6)		11 (23.4)	5 (7.1)	16 (13.7)		

Unknow n	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)	<0.0 01	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)		
Unknow n	6 (21.4)	7 (6.7)	13 (9.8)		20 (42.6)	37 (52.9)	57 (48.7)		
Treatme nt									
Penicilli n G	22 (78.6)	82 (78.1)	104 (78.2)	0.87	21 (44.7)	63 (90.0)	84 (71.8)	<0.0 01	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)		

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

193

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

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

204 Table 3: Manifestations of Early and Late Symptomatic Neurosyphilis (Alberta, 1973 to March
 205 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

206 • *Aphasia, reduced level of consciousness, headache, unspecified neurological symptoms

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

212
 213 Thirty-six (14.2%) of all the cases were diagnosed without a lumbar puncture result. Nearly all
 214 of these clinical cases (97.2%; n=35) were symptomatic. The remaining asymptomatic case was
 215 diagnosed based on an inadequate fall in RPR titres over time. There was no significant
 216 difference by HIV status for those who had and did not have a lumbar puncture (p=0.62).

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3 217 Clinical parameters by HIV status are outlined in Figure 3. Of the 2 HIV-positive and 6 HIV-
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6 218 negative cases with negative clinical parameters, all were symptomatic cases.
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10 220 The majority (74.4%; n=189) of all cases were treated with intravenous penicillin G.
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13 221 Asymptomatic late neurosyphilis cases were less likely to be treated with penicillin G (44.7%;
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15 222 n=21) as compared to symptomatic late neurosyphilis (90.0%; n=63; p<0.001). There was a rise
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18 223 in the use of ceftriaxone in late neurosyphilis treatment from no use in the 1970's to 1990's, to
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20 224 12.5% (n=3) in 2000's and 31.1% (n=14) in the 2010's. Other drug combinations for
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23 225 neurosyphilis was highest in the 1970's (85.7%; n=6) and dropped to a low of 4.3% (n=1) in the
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25 226 1990's.
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30 228 **Discussion**

31
32 229 A review of the trends in reported cases of infectious syphilis from 1975 to March, 2017 in
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35 230 Alberta shows a cycling in the number of cases over time. During this time period, the first
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37 231 major outbreak of infectious syphilis occurred between 1981 and 1987, with the majority of
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40 232 cases between 1983 and 1985.²⁰ A quiescent period of approximately two decades followed
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42 233 with a resurgence in infectious cases in 2000 followed by a decline in 2011 and then another
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45 234 rise in 2015. These observations are consistent with a study of long term trends in reported
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47 235 primary and secondary syphilis cases in the United States which showed recurrent peaks and
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50 236 troughs in approximately 10-year cycles.²¹ This pattern of periodic resurgence of syphilis has
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52 237 variously been attributed to either failure to sustain control efforts, changing risk behaviours
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55 238 (such as crack cocaine use), and waxing and waning partial host immunity to infection at the
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3 239 population level.^{22,23} Interestingly, our province observed a 20-year gap between the outbreak
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5 240 in the mid 1980s and the mid 2000s. The reasons for this prolonged gap are unclear but are
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8 241 likely multi-factorial including a well-established and sustained prevention and control program
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10 242 for STIs in the province, emergence of HIV and the mass education that occurred during this
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13 243 time period. This theory is supported by declining notification rates of gonorrhoea and chlamydia
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15 244 until 1998 and then subsequent rises to current rates.²⁴ Our observed rising notification rates of
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18 245 infectious syphilis since the mid-2000s are consistent with many jurisdictions across Canada and
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20 246 the United States.^{14,25} The rise in late latent syphilis in 2007 has been attributed to the
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23 247 introduction of RSSS.²⁶
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27 249 Some studies have reported a rise in cases of neurosyphilis related to outbreaks of infectious
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30 250 syphilis. One possible explanation for this is that the overall rise in notification rates of
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33 251 infectious syphilis could potentially increase the pool of persons progressing to neurosyphilis
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35 252 and tertiary syphilis. For example, a study conducted in British Columbia, one of Alberta's
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38 253 neighboring provinces, reported that in the context of rising rates of infectious syphilis, the
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40 254 neurosyphilis rate was 0.03 per 100,000 in 1992 and increased 27-fold to 0.8 per 100,000 in
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42 255 2012.²⁷ Investigators from Guangdong province in China similarly reported an incidence rate
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45 256 increase in neurosyphilis cases from 0.21 cases per 100,000 persons in 2009 to 0.31 cases per
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47 257 100,000 persons in 2014 and in tertiary cases from 0.28 cases per 100,000 persons in 2009 to
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50 258 0.36 cases per 100,000 persons in 2014.²⁸ Neither of these studies, however, distinguished
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52 259 between early and late neurosyphilis cases. In our review, we observed a significant rise in early
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55 260 neurosyphilis during the outbreak periods and a significant decline after the outbreak periods,
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3 261 e.g. only one case was observed in 2012 after the second outbreak. We had expected to see a
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6 262 sustained increase in late neurosyphilis cases based on the hypothesis that the number of
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8 263 untreated infected persons with syphilis would increase over time but there was no significant
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10 264 increase during the overall observation period. Interestingly, a rise in late neurosyphilis cases
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13 265 was observed towards the end of the outbreak periods, perhaps due to heightened awareness
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15 266 and increased testing due to public health announcements during the outbreak periods and
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17 267 also because late (tertiary) neurosyphilis can occur as soon as two years post-infection.¹
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20 268 Although individuals diagnosed with late symptomatic neurosyphilis are not infectious and
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23 269 therefore not of concern from a public health perspective, these individuals would benefit from
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25 270 screening and appropriate treatment for syphilis to prevent complications of tertiary syphilis.¹
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30 272 Early neurosyphilis cases were more likely to be younger, Caucasian, born in Canada, HIV
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32 273 positive and reporting same sex partners. These observations parallel the observed rise in
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34 274 infectious syphilis during the third outbreak and may also be related to selection bias since
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36 275 lumbar punctures were more likely to be performed in HIV positive persons in the early years,
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38 276 especially those with low CD₄ counts (<350) and/or RPR \geq 1:32 dilutions as recommended in the
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40 277 Canadian STI Guidelines.²⁹ In addition, most clinicians providing care to HIV positive individuals
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43 278 in Alberta would have offered regular syphilis screening in HIV positive individuals, as endorsed
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45 279 for several years in the U.S. Department of Health and Human Services guidelines.³⁰
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52 281 The most common manifestation (40%) of symptomatic neurosyphilis was ocular involvement
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54 282 with cases of early neurosyphilis more likely than cases of late neurosyphilis to have ocular
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3 283 involvement (54% vs 17%, $p < 0.001$). Two-thirds of ocular cases were reported between 2010
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5 284 and 2017, with 46.4% reported among MSM, similar to other studies.³¹ Late neurosyphilis cases
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7
8 285 were more likely to be older, born outside of Canada and less likely to report same sex
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10 286 partners, paralleling the demographics of late latent cases of syphilis in our province (data not
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12
13 287 shown).

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17 289 Our study identified very few ($n=3$) cardiovascular cases of tertiary syphilis with all cases
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19 290 identified at the time of a diagnosis of aortic aneurysm. This likely represents an underestimate
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21 291 in the actual number of cases of CV syphilis as we suspect that most patients with aortic
22
23 292 aneurysm or initial cardiovascular involvement do not have syphilis testing performed. In
24
25 293 Alberta, the provincial STI program facilitates the assessment of all late stage syphilis cases by a
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27 294 physician who then conducts a neurological and cardiovascular examination. A chest
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29
30 295 radiograph, recommended in the past in some jurisdictions to look for linear calcification of the
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32 296 ascending aorta, a radiological sign of syphilitic aortitis is not routinely done. Chest radiographs
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34 297 for the evaluation of CV syphilis in asymptomatic patients with LLS is of such low yield, that it is
35
36 298 not routinely recommended.³² Neither clinical examination nor chest radiograph is likely to be
37
38 299 sensitive enough to identify cases of CV syphilis and given the presumed rarity of this condition
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40 300 and that the treatment is the same as for LLS, further evaluations (e.g. echocardiograms) are
41
42 301 not warranted.

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45 303 No cases of gummatous syphilis were reported during our study period. Although syphilitic
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47 304 gummas were reported in up to 15% cases in the pre-antibiotic era, it is possible that the
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3 305 widespread use of antibiotics for other conditions, which may indirectly treat or partially treat
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5 306 syphilis, has affected the occurrence.
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10 308 One of the strengths of our study is that there was consistent reporting of all cases with
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12 309 positive syphilis serology over time by laboratories and active follow up by the provincial STI
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14 310 program with health care providers. We were able to apply current case definitions
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16 311 retrospectively to all cases; however, one of the limitations to retrospective review of data is
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18 312 the possibility of inaccurate classification of cases. Our review by two experienced medical
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20 313 consultants resulted in only one case where insufficient information was available to classify
21
22 314 the case with reasonable accuracy. Additional study limitations include changes in and quality
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24 315 of data collection practices over time, with improved data quality over time. The information
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26 316 about gender of sex partners may have been inaccurate in earlier years due to stigma
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28 317 associated with same sex partners. Routine testing for HIV in cases of syphilis was also not
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30 318 conducted in earlier years and as such the number of concurrent HIV infections may be
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32 319 underestimated.
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42 321 In summary, our review of tertiary and neurosyphilis cases in Alberta over a 44-year period
43
44 322 found that early and late neurosyphilis cases continue to occur in the context of cycling of
45
46 323 infectious syphilis outbreaks. Ocular disease was the most common manifestation of
47
48 324 neurosyphilis in our study. On the other hand, cardiovascular syphilis was extremely rare and
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50 325 no cases of gumma were identified. Ongoing identification of syphilis cases with prompt
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3 326 treatment and follow up continues to be important in the context of resurgence of infectious
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6 327 syphilis worldwide.

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10 329 **Author contributions:** TL reviewed hard copy records of all cases and conducted data entry into
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12
13 330 an Excel file; PS and AS reviewed and re-classified all cases; JG conducted data analysis; JG and
14
15 331 AS drafted initial versions of the manuscript; TL, PS, RC, JG, LB, RR, BR and AES helped develop
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18 332 the study design and reviewed drafts of the manuscript.

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3 436 Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada,
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10 439 Figure 2. Rates of Early and Late Neurosyphilis during 2 Different Outbreak Periods with Linear
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13 440 Trend Line (Alberta, 1975-2016)

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18 442 Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases
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20 443 (Alberta, 1975-March 2017)

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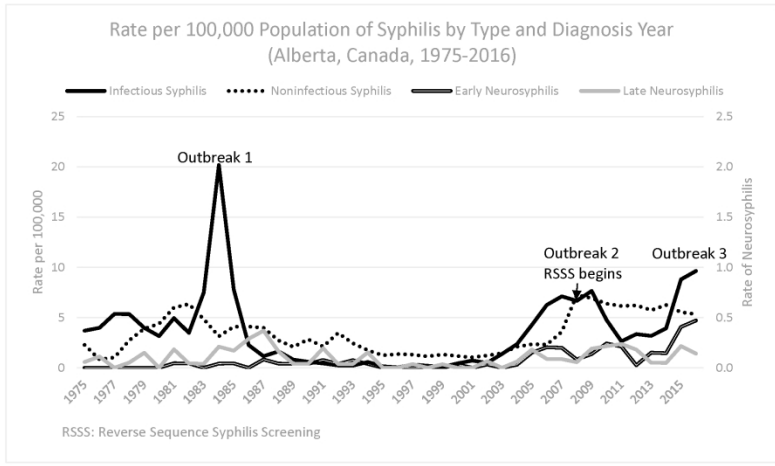


Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada, 1975-2016)

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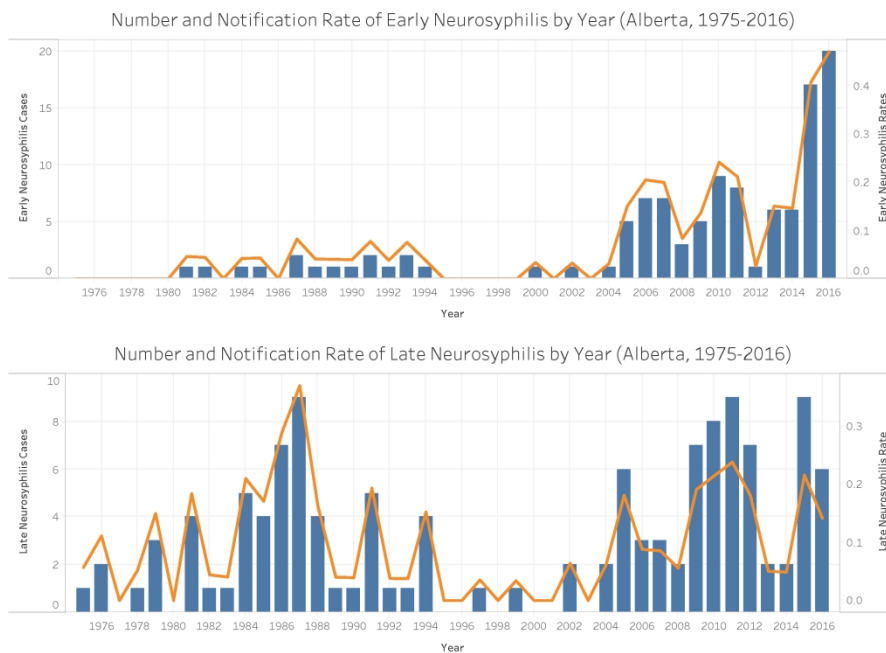


Figure 2. Rates of Early and Late Neurosyphilis during 2 Different Outbreak Periods with Linear Trend Line (Alberta, 1975-2016)

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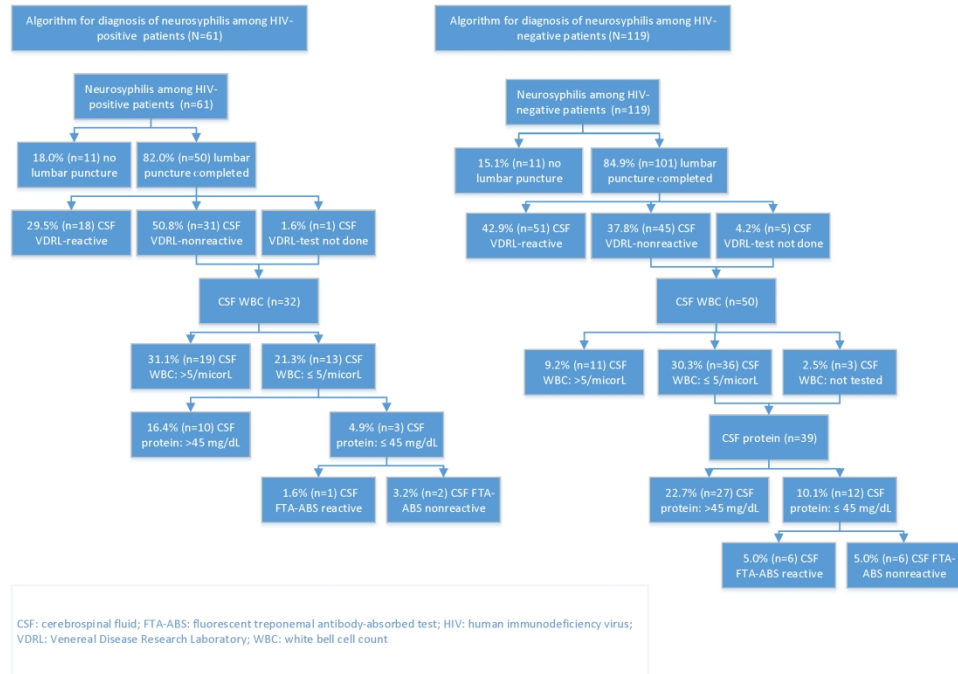


Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases (Alberta, 1975-March 2017)

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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Manuscripts

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

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Key Words: Syphilis, neurosyphilis, epidemiology, tertiary syphilis

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1 **Abstract**

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

4 **Methods:** A retrospective review of all neurosyphilis and tertiary syphilis cases reported in
5 Alberta from 1973 to March 2017 was undertaken and cases classified into early neurosyphilis,
6 late neurosyphilis and cardiovascular syphilis. Variables collected included demographics,
7 sexual partners, HIV status, clinical parameters, symptoms and treatment and distributions
8 were compared between early versus late neurosyphilis and asymptomatic versus symptomatic
9 cases (stratified by early versus late stage). Data was analyzed using IBM SPSS Statistics Version
10 19.0.

11 **Results:** 254 cases were identified; 251 were neurosyphilis and 3 were cardiovascular. No cases
12 of gummatous syphilis were reported. Early neurosyphilis accounted for 52.4% (n=133) and
13 46.1% (n=117) were late neurosyphilis cases; one (0.4%) case with unknown duration. Three
14 outbreaks of infectious syphilis were identified during the study period and a concurrent rise in
15 both early and late neurosyphilis was observed during the outbreak periods. The most
16 common manifestation of symptomatic neurosyphilis was ocular involvement which was more
17 likely in early neurosyphilis. Relative to late neurosyphilis cases, early neurosyphilis cases were
18 more likely to be younger, Caucasian, born in Canada, HIV positive and reporting same sex
19 partners..

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

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3 23 syphilis and clinical evaluation of cases for complications continues to be important in the
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6 24 context of global resurgence of syphilis.
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13 27 **Keywords:** tertiary syphilis, neurosyphilis, Canada
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18 29 **Strengths and Limitations of this study:**
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- 20 30
- 21 • An important strength of our study was the consistent reporting of all cases with positive
22 31 syphilis serology over the 44 year period by laboratories as well as active follow up of all cases
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24 32 by the provincial STI program.
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27 33 • Another strength of our study is the retrospective application of current case definitions to all
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29 34 cases by 2 experienced STI clinicians.
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31 35 • One of the limitations to the retrospective review of data is the possibility of inaccurate
32
33 36 classification of cases due to insufficient available information.
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36 37 • Additional study limitations include changes in testing policies and practices, as well as changes
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38 38 in social norms over time.
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40 39 • Routine testing for HIV in cases of syphilis was also not conducted in earlier years and as such
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42 40 the number of concurrent HIV infections may have been underestimated.
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3 46 **Manuscript**

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6 47 **Background**

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8 48 Syphilis, caused by *Treponema pallidum* subspecies *pallidum*, passes through a series of stages,
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10 49 including primary, secondary, latent, and tertiary syphilis if left untreated.¹ Based on data from
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12
13 50 the pre-antibiotic era, about a third of persons with untreated latent syphilis will develop late
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15 51 neurosyphilis, cardiovascular syphilis or gummatous syphilis.² Gummatous syphilis is
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18 52 characterized by the development of indolent granulomatous lesions³ which typically affect the
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20 53 skin, liver, and bone but can also involve other parts of the body.⁴ Syphilitic aortitis is the most
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23 54 common manifestation of cardiovascular syphilis and typically involves the ascending aorta.⁴⁻⁶
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27 56 Neurosyphilis can occur at any stage of syphilis.^{1,7} It is classified into early and late forms.¹ Early
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30 57 neurosyphilis affects the cerebrospinal fluid (CSF), cerebral blood vessels, and meninges more
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33 58 often than the brain or spinal cord parenchyma. Typically, manifestations occur within weeks to
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35 59 a few years after primary infection and may occur at the same time as primary or secondary
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38 60 syphilis, or may be asymptomatic. Manifestations may include meningitis with or without
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41 61 cranial nerve involvement, meningovascular disease or stroke. Late neurosyphilis can remain
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44 62 asymptomatic or progress to meningovascular syphilis, tabes dorsalis, or general paresis. Late
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47 63 neurosyphilis is extremely rare in the antibiotic era and usually occurs years to decades after
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50 64 primary infection.^{1,8} HIV infection may affect the natural course of disease as atypical
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53 65 presentations and rapid progression of syphilis in HIV positive individuals has been reported.⁹⁻¹³
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3 67 In the pre-antibiotic era, an estimated one third of untreated persons developed tertiary
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5 68 syphilis with about 15% progressing to gummatous disease (1-46 years post-infection), 10% to
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8 69 cardiovascular syphilis (20-30 years after infection), and 4-14% to late neurosyphilis (2-50 years
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10 70 after infection).¹ After the introduction of penicillin in the 1940s, the number of cases of syphilis
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12 71 plummeted in the United States, reaching a nadir in 2000.¹ Nowadays, tertiary syphilis is a rare
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14 72 disease due to easy and effective treatment of infectious and latent syphilis. Antibiotic use for
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16 73 other infections is also likely a factor.
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22 75 In Canada, syphilis (all stages) has been nationally notifiable since 1924. However national
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24 76 reports only include data on infectious syphilis, since only these cases are of major public health
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26 77 significance.¹⁴ In Alberta, all cases of syphilis, including tertiary and neuro-syphilis have been
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28 78 notifiable to a centralized program under the Public Health Act since 1921. Syphilis notification
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30 79 rates have fluctuated over the last fifty years with a rise in notification rates during outbreak
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32 80 periods. Since 2000, notification rates of infectious syphilis have increased dramatically in
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34 81 Alberta (0.6/100,000 population in 2000 to 12.5/100,000 population in 2017), with the most
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36 82 recent resurgence among men who have sex with men (MSM) and up to 30% of patients co-
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38 83 infected with HIV (personal communication Jennifer Gratrix, Provincial STI Services, Alberta
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40 84 Health Services).¹⁵
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50 86 There are few data on the prevalence and characteristics of tertiary and neuro-syphilis cases in
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52 87 the post antibiotic era. We are aware of only one study from the Netherlands which estimated
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54 88 that 10-13% of all syphilis cases from 1999-2010 had neurosyphilis; these data were limited by
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89 the fact that the diagnostic criteria used for neurosyphilis was based on hospital discharge
 90 diagnosis rather than clinical examination or laboratory criteria.¹⁶ We sought to determine the
 91 notification rate and characteristics of reported cases of tertiary and neurosyphilis in Alberta
 92 from 1973 onwards.

94 **Methods**

95 A retrospective review was conducted of all tertiary and neurosyphilis cases in Alberta (current
 96 population 4.3 million) from 1973 (when syphilis data was first available by staging) to March
 97 2017 (most recent cases staged at time of data collection). All cases of syphilis are reportable by
 98 laboratories and clinicians to Provincial STI Services under the Alberta Public Health Act. A
 99 paper chart was created for each syphilis case containing laboratory results, medical
 100 correspondence, syphilis-relevant history, clinical findings, and staging. Cases diagnosed since
 101 2000 were also entered into a provincial surveillance database. Cases were classified as defined
 102 in Table 1.¹⁷

104 Table 1: Case Definitions Used for Diagnosis of Neurosyphilis and Tertiary Syphilis (Adapted
 105 from¹⁷:

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

<p>Early Neurosyphilis (< 1 year after infection) <i>Asymptomatic</i></p>	<p>Laboratory confirmation of primary, second or early latent syphilis and</p> <ul style="list-style-type: none"> i) reactive CSF-VDRL in non-bloody CSF <p>AND/OR</p> <ul style="list-style-type: none"> ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes <p>AND</p> <p>NO signs or symptoms of neurosyphilis</p>
<p>Early Neurosyphilis (< 1 year after infection) <i>Symptomatic</i></p>	<p>Laboratory confirmation of primary, second or early latent syphilis and</p> <ul style="list-style-type: none"> i) reactive CSF-VDRL in non-bloody CSF <p>AND/OR</p> <ul style="list-style-type: none"> ii) elevated CSF leukocytes (>5/micro) and/or elevated CSF protein (>45 mg/dL) in the absence of other known causes <p>AND</p> <p>clinical signs or symptoms of neurosyphilis*</p>
<p>Late neurosyphilis (>1 year after infection) <i>Asymptomatic</i></p>	<p>Reactive treponemal serology (not staged as primary, secondary or early latent syphilis) and</p> <ul style="list-style-type: none"> i) reactive CSF-VDRL in non-bloody CSF <p>AND/OR</p> <ul style="list-style-type: none"> 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) <i>Symptomatic</i>	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*

106

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

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

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6 118 Reported notification rates of other stages of syphilis prior to 2000 were obtained from
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8 119 historical surveillance reports from Alberta STI Services beginning in 1975. Population
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10 120 denominators were obtained through government population estimates.¹⁸ An outbreak was
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13 121 defined as an increase in infectious syphilis cases of two standard deviations above the baseline
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15 122 (previous 5 year quarterly average) for the given time period.
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20 124 Variables collected for analysis included demographics, sexual partners, HIV status (testing
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22 125 available since 1985¹⁹ and recommended for all syphilis cases once serology available),
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25 126 diagnosis date, clinical parameters, symptoms, and treatment. Variables for cases diagnosed
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27 127 prior to 2004 were captured through chart review, while variables for cases diagnosed after
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30 128 2004 were extracted from the provincial STI surveillance system. Client reported symptoms
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32 129 were broken into five categories (not mutually exclusive) based on system involvement: ocular
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35 130 (e.g. uveitis, retinal, vision loss), auditory (e.g. hearing loss, tinnitus), ataxia, cognitive
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37 131 impairment (e.g. dementia, psychosis), and other (aphasia, stroke, reduced level of
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40 132 consciousness, headache, and unspecified neurological symptoms).
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45 134 Treatment data was divided into 3 mutually exclusive categories based on the following
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47 135 minimum treatments: 1) penicillin G 3-4 million units IV q 4 h (18-24 million units/day) for 10 -
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50 136 14 days, 2) ceftriaxone 2 g IV/IM daily x 10-14 days, 3) Other, which included drugs like
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52 137 chloramphenicol, doxycycline, tetracycline, benzathine penicillin G- long acting, reduced doses
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55 138 of penicillin G or ceftriaxone.
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6 140 Analysis was stratified by stage of syphilis to compare early and late neurosyphilis by the
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8 141 previously listed variables using Chi-square or Fisher's exact for categorical variables and Mann-
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10 142 Whitney tests for continuous variables. Missing data was categorized as unknown and included
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13 143 in the analysis. As well, each syphilis stage was stratified by asymptomatic and symptomatic for
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15 144 comparison. The significance was set at a two-sided p -value of <0.05 . A sensitivity analysis to
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17 145 verify univariate findings by cases diagnosed pre- and post-2000 was considered; however,
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20 146 small cell sizes precluded the inclusion of early neurosyphilis and changes to syphilis screening
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23 147 in 2007 increasing the diagnosis of late latent syphilis cases were already known. Data was
24
25 148 analyzed using IBM SPSS Statistics version 19.0 (IBM, Armonk, NY, USA). This study was
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28 149 approved by the University of Alberta Health Research Ethics Board (Approval Number:
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30 150 Pro00075972).

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34 35 152 ***Patient and Public Involvement***

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37 153 Patients were not involved in the design of this research study.
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41 42 155 **Results**

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45 156 A total of 254 cases were identified during the study period, of which 251 were neurosyphilis
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47 157 and 3 were cardiovascular (CV) cases; one case of CV syphilis was reported in each of the
48
49
50 158 following years: 1976, 1979, and 1984. No cases of gummatous syphilis were reported during
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52 159 this time period. The neurosyphilis cases were evenly divided as early (52.4%; $n=133$) and late
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54 160 (46.1%; $n=117$), with one additional case of unknown duration. Three individuals were

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3 161 diagnosed with two distinct episodes of neurosyphilis over the course of the reporting period.
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5 162 All three of these individuals were men who reported same sex partners, all six episodes were
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7 163 diagnosed between 2005 and 2014, and all categorized as early neurosyphilis. Two of these
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9 164 men were co-infected with HIV.
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15 166 Between 1975 and 2016, 8,874 total cases of syphilis were reported in Alberta. Of these, 4,513
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17 167 (51%) were infectious (i.e. staged as primary, secondary, early latent) and 4,361 (49%) were
18

19 168 classified as non-infectious (i.e. late latent, tertiary). Over the time period, three outbreaks of
20

21 169 infectious syphilis were identified (Figure 1). The first outbreak occurred between 1981 and
22

23 170 1987, the second outbreak commenced in 2000 and declined in 2011, and a third outbreak
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25 171 began in 2015 and continues. Of the infectious syphilis cases, 2.8% (n=128) were staged as early
26

27 172 neurosyphilis. When plotting the notification rate of early neurosyphilis cases, increases in the
28

29 173 rate were found at corresponding times to infectious syphilis outbreaks #2 and #3 (Figure 2). Of
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31 174 the noninfectious syphilis cases staged during this time, 2.6% (115/4316) were staged with late
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33 175 neurosyphilis. Similarly, for late neurosyphilis, peaks in notification rates were found shortly
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35 176 after outbreak #1 and outbreak #2 (Figure 2).
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38 177 Early neurosyphilis cases were significantly younger, more likely to be Caucasian, born in
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40 178 Canada, diagnosed in recent decades (2010's), reported same sex partners, and HIV positive as
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42 179 compared to late neurosyphilis cases (Table 2).
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44

45 180 Table 2: Characteristics of Early and Late Neurosyphilis (Alberta, 1973 to March 2017; n=250)
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	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	Comparison 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

Caucasia n	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 n	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)	0.00	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)	0.00 2	<0.001
Same Sex	14 (50.0)	52 (49.5)	66 (49.6)		11 (23.4)	5 (7.1)	16 (13.7)		
Unknow n	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)	<0.0 01	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)	<0.0 01	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)		
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182 Among early neurosyphilis cases, 79.0% (n=105) were symptomatic; symptomatic cases were
 183 more likely to be older, male, Caucasian, recently diagnosed (2010's), and HIV negative
 184 compared to asymptomatic cases. Among late neurosyphilis cases, 59.8% (n=70) were
 185 symptomatic; symptomatic cases were more likely to be older, born outside of Canada, and
 186 treated with intravenous penicillin G, and less likely to have a same sex partner as compared to
 187 asymptomatic cases.

188

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

199 Table 3: Manifestations of Early and Late Symptomatic Neurosyphilis (Alberta, 1973 to March
 200 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

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

207
 208 Thirty-six (14.2%) of all the cases were diagnosed without a lumbar puncture result. Nearly all
 209 of these clinical cases (97.2%; n=35) were symptomatic. The remaining asymptomatic case was
 210 diagnosed based on an inadequate fall in RPR titres over time. There was no significant
 211 difference by HIV status for those who had and did not have a lumbar puncture (p=0.62).

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

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6 215 The majority (74.4%; n=189) of all cases were treated with intravenous penicillin G.
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8 216 Asymptomatic late neurosyphilis cases were less likely to be treated with penicillin G (44.7%;
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10 217 n=21) as compared to symptomatic late neurosyphilis (90.0%; n=63; p<0.001). There was a rise
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12 218 in the use of ceftriaxone in late neurosyphilis treatment from no use in the 1970's to 1990's, to
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14 219 12.5% (n=3) in 2000's and 31.1% (n=14) in the 2010's. Other drug combinations for
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16 220 neurosyphilis was highest in the 1970's (85.7%; n=6) and dropped to a low of 4.3% (n=1) in the
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18 221 1990's.
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25 223 **Discussion**

26
27 224 A review of the trends in reported cases of infectious syphilis from 1975 to March, 2017 in
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29 225 Alberta shows a cycling in the number of cases over time. During this time period, the first
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31 226 major outbreak of infectious syphilis occurred between 1981 and 1987, with the majority of
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33 227 cases between 1983 and 1985.²⁰ A quiescent period of approximately two decades followed
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35 228 with a resurgence in infectious cases in 2000 followed by a decline in 2011 and then another
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37 229 rise in 2015. These observations are consistent with a study of long term trends in reported
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39 230 primary and secondary syphilis cases in the United States which showed recurrent peaks and
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41 231 troughs in approximately 10-year cycles.²¹ This pattern of periodic resurgence of syphilis has
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43 232 variously been attributed to either failure to sustain control efforts, changing risk behaviours
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45 233 (such as crack cocaine use), and waxing and waning partial host immunity to infection at the
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47 234 population level.^{22,23} Interestingly, our province observed a 20-year gap between the outbreak
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54 235 in the mid 1980s and the mid 2000s. The reasons for this prolonged gap are unclear but are
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3 236 likely multi-factorial including a well-established and sustained prevention and control program
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6 237 for STIs in the province, emergence of HIV and the mass education that occurred during this
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8 238 time period. This theory is supported by declining notification rates of gonorrhoea and chlamydia
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10 239 until 1998 and then subsequent rises to current rates.²⁴ Our observed rising notification rates of
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12 240 infectious syphilis since the mid-2000s are consistent with many jurisdictions across Canada and
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15 241 the United States.^{14,25} The rise in late latent syphilis in 2007 has been attributed to the
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17 242 introduction of RSSS.²⁶
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23 244 Some studies have reported a rise in cases of neurosyphilis related to outbreaks of infectious
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25 245 syphilis. One possible explanation for this is that the overall rise in notification rates of
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27 246 infectious syphilis could potentially increase the pool of persons progressing to neurosyphilis
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30 247 and tertiary syphilis. For example, a study conducted in British Columbia, one of Alberta's
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32 248 neighboring provinces, reported that in the context of rising rates of infectious syphilis, the
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34 249 neurosyphilis rate was 0.03 per 100,000 in 1992 and increased 27-fold to 0.8 per 100,000 in
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37 250 2012.²⁷ Investigators from Guangdong province in China similarly reported an incidence rate
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39 251 increase in neurosyphilis cases from 0.21 cases per 100,000 persons in 2009 to 0.31 cases per
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42 252 100,000 persons in 2014 and in tertiary cases from 0.28 cases per 100,000 persons in 2009 to
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44 253 0.36 cases per 100,000 persons in 2014.²⁸ Neither of these studies, however, distinguished
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47 254 between early and late neurosyphilis cases. In our review, we observed a significant rise in early
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49 255 neurosyphilis during the outbreak periods and a significant decline after the outbreak periods,
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52 256 e.g. only one case was observed in 2012 after the second outbreak. We had expected to see a
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54 257 sustained increase in late neurosyphilis cases based on the hypothesis that the number of
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3 258 untreated infected persons with syphilis would increase over time but there was no significant
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6 259 increase during the overall observation period. Interestingly, a rise in late neurosyphilis cases
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8 260 was observed towards the end of the outbreak periods, perhaps due to heightened awareness
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11 261 and increased testing due to public health announcements during the outbreak periods and
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13 262 also because late (tertiary) neurosyphilis can occur as soon as two years post-infection.¹

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15 263 Although individuals diagnosed with late symptomatic neurosyphilis are not infectious and
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18 264 therefore not of concern from a public health perspective, these individuals would benefit from
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20 265 screening and appropriate treatment for syphilis to prevent complications of tertiary syphilis.¹

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25 267 Early neurosyphilis cases were more likely to be younger, Caucasian, born in Canada, HIV
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28 268 positive and reporting same sex partners. These observations parallel the observed rise in
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30 269 infectious syphilis during the third outbreak and may also be related to selection bias since
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32 270 lumbar punctures were more likely to be performed in HIV positive persons in the early years,
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35 271 especially those with low CD₄ counts (<350) and/or RPR \geq 1:32 dilutions as recommended in the
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37 272 Canadian STI Guidelines.²⁹ In addition, most clinicians providing care to HIV positive individuals
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40 273 in Alberta would have offered regular syphilis screening in HIV positive individuals, as endorsed
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42 274 for several years in the U.S. Department of Health and Human Services guidelines.³⁰

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46
47 276 The most common manifestation (40%) of symptomatic neurosyphilis was ocular involvement
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50 277 with cases of early neurosyphilis more likely than cases of late neurosyphilis to have ocular
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52 278 involvement (54% vs 17%, $p < 0.001$). Two-thirds of ocular cases were reported between 2010
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54 279 and 2017, with 46.4% reported among MSM, similar to other studies.³¹ Late neurosyphilis cases

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3 280 were more likely to be older, born outside of Canada and less likely to report same sex
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6 281 partners, paralleling the demographics of late latent cases of syphilis in our province (data not
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8 282 shown).

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13 284 Our study identified very few (n=3) cardiovascular cases of tertiary syphilis with all cases
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15 285 identified at the time of a diagnosis of aortic aneurysm. This likely represents an underestimate
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18 286 in the actual number of cases of CV syphilis as we suspect that most patients with aortic
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20 287 aneurysm or initial cardiovascular involvement do not have syphilis testing performed. In
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23 288 Alberta, the provincial STI program facilitates the assessment of all late stage syphilis cases by a
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25 289 physician who then conducts a neurological and cardiovascular examination. A chest
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28 290 radiograph, recommended in the past in some jurisdictions to look for linear calcification of the
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30 291 ascending aorta, a radiological sign of syphilitic aortitis is not routinely done. Chest radiographs
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33 292 for the evaluation of CV syphilis in asymptomatic patients with LLS is of such low yield, that it is
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35 293 not routinely recommended.³² Neither clinical examination nor chest radiograph is likely to be
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38 294 sensitive enough to identify cases of CV syphilis and given the presumed rarity of this condition
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40 295 and that the treatment is the same as for LLS, further evaluations (e.g. echocardiograms) are
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42 296 not warranted.

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47 298 No cases of gummatous syphilis were reported during our study period. Although syphilitic
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50 299 gummas were reported in up to 15% cases in the pre-antibiotic era, it is possible that the
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52 300 widespread use of antibiotics for other conditions, which may indirectly treat or partially treat
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54 301 syphilis, has affected the occurrence.

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6 303 One of the strengths of our study is that there was consistent reporting of all cases with
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8 304 positive syphilis serology over time by laboratories and active follow up by the provincial STI
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10 305 program with health care providers. We were able to apply current case definitions
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12 306 retrospectively to all cases; however, one of the limitations to retrospective review of data is
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14 307 the possibility of inaccurate classification of cases. Our review by two experienced medical
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16 308 consultants resulted in only one case where insufficient information was available to classify
17
18 309 the case with reasonable accuracy. Additional study limitations include changes in and quality
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20 310 of data collection practices over time, with improved data quality over time. The information
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22 311 about gender of sex partners may have been inaccurate in earlier years due to stigma
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24 312 associated with same sex partners. Routine testing for HIV in cases of syphilis was also not
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26 313 conducted in earlier years and as such the number of concurrent HIV infections may be
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28 314 underestimated.
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37 316 In summary, our review of tertiary and neurosyphilis cases in Alberta over a 44-year period
38
39 317 found that early and late neurosyphilis cases continue to occur in the context of cycling of
40
41 318 infectious syphilis outbreaks. Ocular disease was the most common manifestation of
42
43 319 neurosyphilis in our study. On the other hand, cardiovascular syphilis was extremely rare and
44
45 320 no cases of gumma were identified. Ongoing identification of syphilis cases with prompt
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47 321 treatment and follow up continues to be important in the context of resurgence of infectious
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49 322 syphilis worldwide.
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3 324 **Author contributions:** TL reviewed hard copy records of all cases and conducted data entry into
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5
6 325 an Excel file; PS and AS reviewed and re-classified all cases; JG conducted data analysis; JG and
7
8 326 AS drafted initial versions of the manuscript; TL, PS, RC, JG, LB, RR, BR and AES helped develop
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10 327 the study design and reviewed drafts of the manuscript.
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3 434 Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada,
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10 437 Figure 2. Number and Notification Rate of Early and Late Neurosyphilis by Year (Alberta, 1975-
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18 440 Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases
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20 441 (Alberta, 1975-March 2017)

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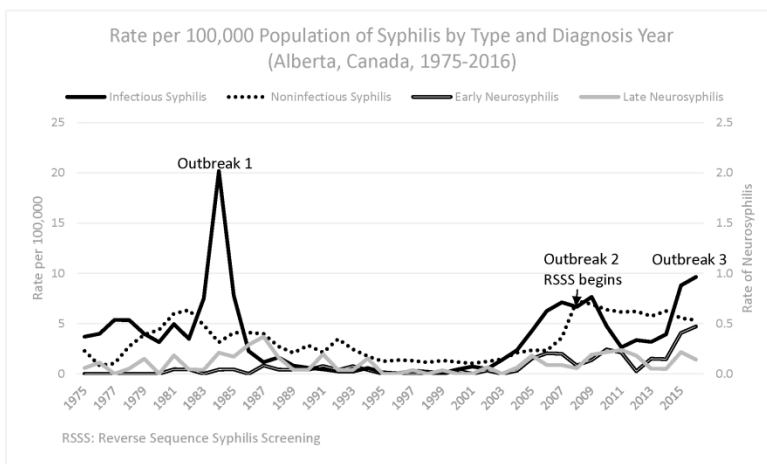


Figure 1. Rate per 100,000 Population of Syphilis by Type and Diagnosis Year (Alberta, Canada, 1975-2016)

215x279mm (300 x 300 DPI)

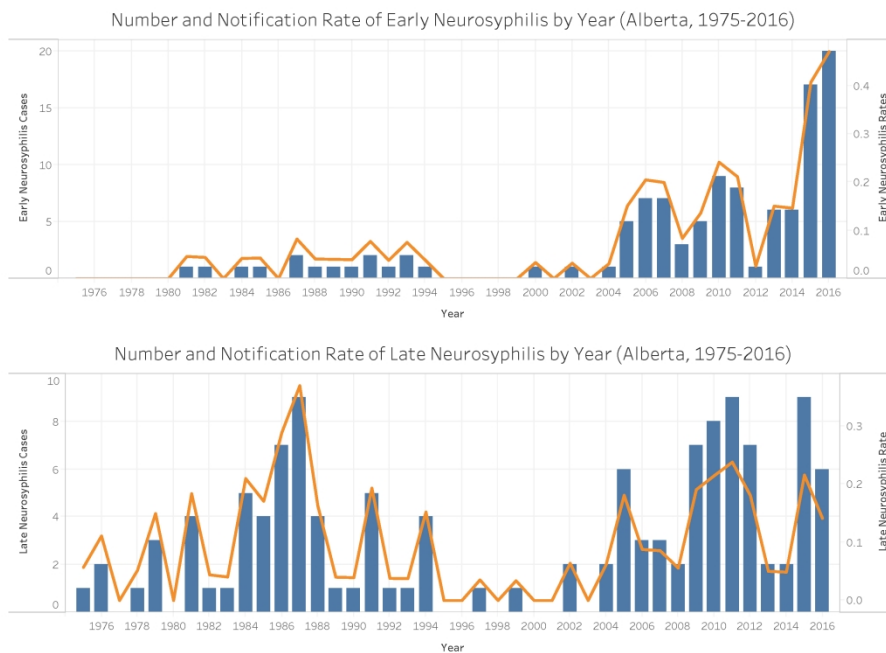


Figure 2. Rates of Early and Late Neurosyphilis during 2 Different Outbreak Periods with Linear Trend Line (Alberta, 1975-2016)

279x215mm (300 x 300 DPI)

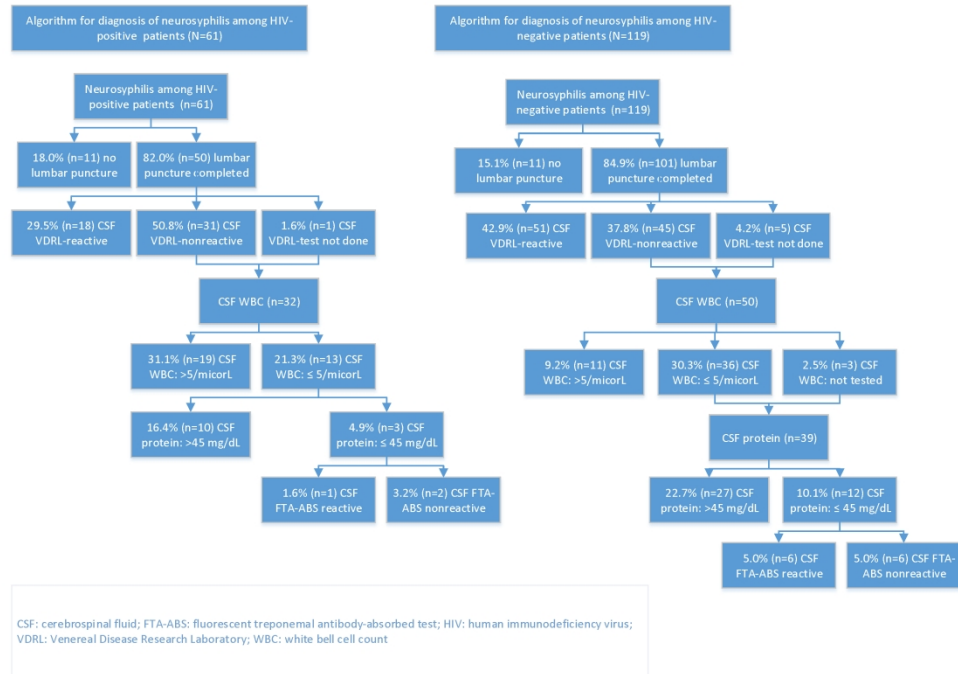


Figure 3: Algorithm of diagnosis of neurosyphilis among HIV-positive and HIV-negative cases (Alberta, 1975-March 2017)

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.