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Clinical Education Session



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ASHM SSHC 2019 HIV/Sexual Health Clinical Education Centre

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Syphilis

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Registrar SSHC
October 2020

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Approach

- January 2019- October 2020
- PubMed, Google Scholar
- Themes: congenital syphilis, neurosyphilis, ocular syphilis, point-of-care testing, alternative treatment regimes, vaccine development, pre and post exposure prophylaxis

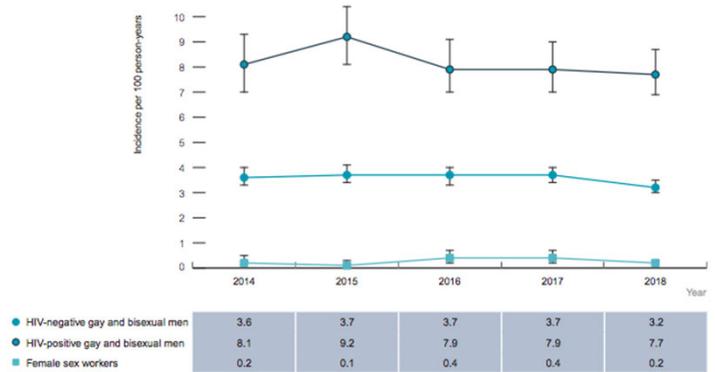
Objectives

- Describe current syphilis epidemiology in Australia
- Awareness of increasing rates of heterosexual syphilis in high income countries
- Recognize that sexual positioning may influence stage of syphilis at presentation
- Explore whether increasing rates of asymptomatic reinfection are due to increased frequency of testing, different disease manifestation or both
- Challenges of RPR interpretation in re-infection
- Possible future diagnostic test

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The Kirby Institute "National update on HIV, viral hepatitis and sexually transmissible infections in Australia: 2009–2018 (2020) pp 30-31

New syphilis cases in sexual health clinic attendees per 100 person (2014-2018):



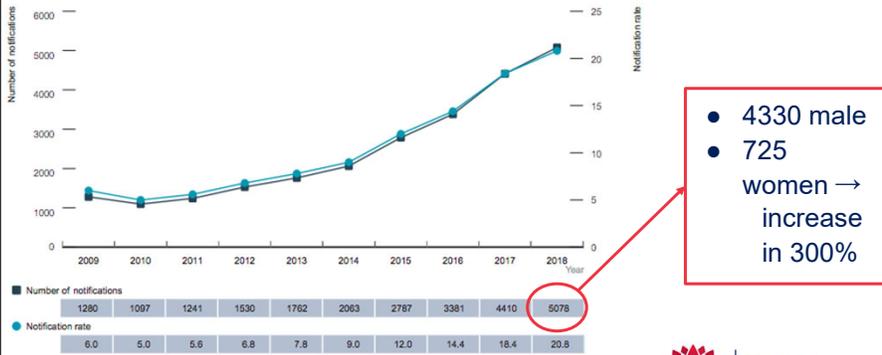
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Average number of syphilis tests among MSM in ACCESS network



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Infectious syphilis cases per 100 000 (2009-2018):



Why are rates increasing?



Infectious syphilis cases per 100 000 by Indigenous status (2009-2018):



Summary

Infectious syphilis in Australia

- sexual health clinic attendees' rates are fluctuating but stable and testing rates are increasing
- Overall rates are increasing particularly in:
 - women
 - 15-29 year old ATSI heterosexuals

Infectious Syphilis in high-income countries¹:

- Japan 2016: heterosexual rates higher than MSM
- United States: doubled in women between 2014-2018
- Western Europe: increasing rates in women

¹ Spiteri et al. (2019). The resurgence of syphilis in high-income countries in the 2000s: A focus on Europe. *Epidemiology and Infection*, 147

Kidd SE, Grey JA, Torrone EA, Weinstock HS, "Increased Methamphetamine, Injection Drug, and Heroin Use Among Women and Hetrosexual Men with Primary and Secondary Syphilis - United States, 2013-2017. *MMWR Morb Mortal Weekly Report*, 2019; 68(6): 144-148, DOI: 10.15585/mmwr.mm6806a4

Background

- United States during 2013-2017, the primary and secondary syphilis rate increased 72.7% nationally and 155.6% among women
- Drug use associated with sexual behaviours that increase risk of acquiring STIs

Aim

- analyze primary and secondary syphilis data among women, MSW and MSM and assess percentage of cases who reported drug-related risk behaviours from 2013-2017

Methods

- retrospective cross-sectional study
- National Notifiable Diseases Surveillance System 2013 - 2017
- reported primary + secondary syphilis cases:
 - women, MSW and MSM
 - self reported behaviour: methamphetamine use, injection drug use, heroin use and sex with person who injects drugs

Results

Prevalence of drug related behaviours in Primary or Secondary Syphilis

Behavior during past 12 months	No. (%)				
	2013	2014	2015	2016	2017
Used methamphetamine					
Women	69 (6.2)	92 (6.8)	184 (10.6)	317 (13.7)	456 (16.6)
MSW	88 (5.0)	151 (7.4)	194 (7.6)	347 (11.1)	482 (13.3)
MSM	805 (9.2)	867 (8.7)	855 (7.5)	1,039 (7.9)	1,132 (8.0)
Total*	987 (7.9)	1,136 (7.9)	1,253 (7.4)	1,738 (8.5)	2,106 (9.6)
Had sex with person who injects drugs					
Women	64 (5.5)	113 (8.3)	135 (7.9)	217 (9.9)	325 (12.4)
MSW	64 (3.6)	119 (5.8)	167 (6.4)	201 (6.6)	325 (9.3)
MSM	368 (4.3)	495 (5.0)	537 (4.7)	594 (4.6)	725 (5.2)
Total*	499 (4.2)	734 (5.3)	847 (5.2)	1,015 (5.5)	1,380 (6.7)
Used injection drugs					
Women	44 (4.0)	81 (6.1)	119 (7.0)	179 (8.1)	281 (10.5)
MSW	48 (2.8)	78 (3.7)	96 (3.6)	152 (4.8)	230 (6.3)
MSM	288 (3.5)	365 (3.6)	345 (2.9)	406 (3.1)	514 (3.5)
Total*	388 (3.5)	534 (3.8)	569 (3.4)	745 (3.9)	1,042 (4.9)
Used heroin					
Women	23 (2.1)	42 (3.1)	59 (3.4)	109 (4.7)	156 (5.8)
MSW	15 (0.8)	37 (1.8)	44 (1.7)	66 (2.1)	97 (2.7)
MSM	57 (0.7)	49 (0.5)	78 (0.7)	102 (0.8)	117 (0.8)
Total*	95 (0.8)	131 (0.9)	182 (1.1)	279 (1.4)	375 (1.7)

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Conclusions

- Between 2013-2017:
 - rates of primary and secondary syphilis increased in both men and women
 - in people with primary and secondary syphilis:
 - drug use has increased in women and MSW
 - stable in MSM but not MSM with primary and secondary syphilis
- heterosexual syphilis and drug use - intersecting epidemics

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Cornelisse V, Chow E, Latimer R et al. "Getting to the Bottom of It: Sexual Positioning and Stage of Syphilis at Diagnosis, and Implications for Syphilis Screening". *Clinical Infectious Diseases*, 2020, 71(2):318-22. doi: 10.193/cid/ciz802

Background

- Syphilis rates continue to rise among MSM
- Need to diagnose and treat as early as possible.
- Stage of syphilis at diagnosis and treatment:
 - Primary syphilis → shorter duration of infectivity
 - Secondary syphilis → longer duration of infectivity

Hypothesis

- MSM who practice RASI are more likely to present with secondary syphilis than MSM who do not practice RASI

Method

- retrospective analysis, MSM primary + secondary syphilis 2008-2017
- univariable and multivariable logistic regression



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Results

559 MSM total

- Median age 32 years
- Median of 3 casual male partners
- Sexual positioning:
 - 429 (76.7%) versatile
 - 80 (14.3%) exclusive tops
 - 50 (8.9%) exclusive bottoms
- 90 (16.1%) PLHIV
- Stage of syphilis:
 - 338 (60.5%) primary:
 - exclusive tops → penile chancre (61/66, 92%)
 - 221 (39.5%) secondary



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Results

	Primary, n = 338			Secondary, n = 221			Univariable			Multivariable 1			Multivariable 2			
	Total, N = 559	n	%	95% CI	n	%	95% CI	OR	95% CI	P	aOR	95% CI	P	aOR	95% CI	P
Condoms for RAI with CSP																
No RAI with CSP	134	103	76.9	68.8-83.7	31	23.1	16.3-31.2	2.80	1.76-4.46	<.001	3.90	2.25-6.74	<.001
Always use condoms	131	72	55.0	46.0-63.7	59	45.0	36.3-54.0	1.00	0.66-1.51	.987	1.59	0.87-2.89	0.128
Not always use condoms	280	151	53.9	47.9-59.9	129	46.1	40.1-52.1	Ref	Ref
Condoms for IAI with CSP																
No IAI with CSP	108	64	59.3	49.4-68.6	44	40.7	31.4-50.6	0.87	0.55-1.37	.547	0.49	0.29-0.84	0.01
Always use condoms	134	74	55.2	46.4-63.8	60	44.8	36.2-53.6	0.69	0.46-1.04	.077	0.49	0.27-0.90	0.02
Not always use condoms	301	191	63.5	57.7-68.9	110	36.5	31.1-42.3	Ref	Ref
Sexual positioning																
Versatile	429	250	58.3	53.4-63.0	179	41.7	37.0-46.6	Ref	Ref
Exclusive top	80	66	82.5	72.4-90.1	14	17.5	9.9-27.6	3.41	1.86-6.26	<.001	3.34	1.81-6.16	<.001
Exclusive bottom	50	22	44.0	30.0-58.7	28	56.0	41.3-70.0	0.62	0.34-1.11	.106	0.63	0.35-1.14	.124

Discussion

Summary:

- IASI → primary syphilis
- RASI → secondary syphilis
- anorectal chancres less noticeable than penile chancres

Clinical Implications:

- strategies to improve detection in MSM RASI

Marra C, Maxwell C et al. 'Previous Syphilis Alters the Course of Subsequent Episodes of Syphilis'. *Clinical Infectious Diseases*, 2020, 71(5): 1243-1247. DOI <http://doi.org/10.1093/cid/ciz943>

Background

- Repeat episodes of syphilis in the same individual are increasing
- Individuals with repeat episodes of syphilis are often asymptomatic.

Clinical Question

- Is this due to increased frequency of serological testing?
- Or due to differences in disease manifestations in individuals with repeat episodes?
- Or both?



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Methods

Participants:

- Seattle, Washington 1996-2014. 701 participants enrolled in a study of CSF abnormalities.
- evidence of syphilis + concern for neurosyphilis

Clinical Procedures

- standardized medical history and examination
- blood draw and lumbar puncture:
 - CSF: white blood cell + VDRL
 - Serum RPR
 - T.pallidum in blood
 - rRNA in CSF
- medical and public health records reviewed

Statistical Methods

- 'index' episode = analysis episode
- odds ratios with 95% confidence intervals were determined using logistic regression



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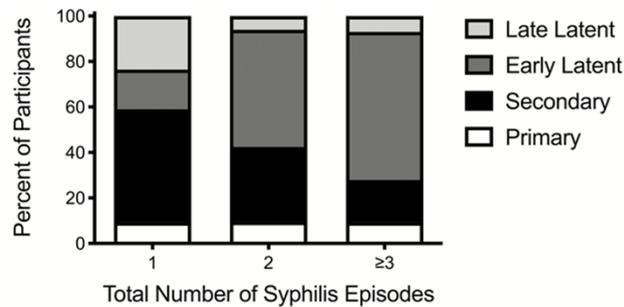
Results

Characteristic	Value
Male	687 (98.0)
Men who have sex with men	656 (95.6) ^a
Age, y	39 (33–46)
Persons living with human immunodeficiency virus	558 (79.6)
Index episode stage	
Primary	67 (9.6)
Secondary	292 (41.7)
Early latent	222 (31.7)
Late latent	120 (17.1)
Serum rapid plasma reagin titer	64 (32–256)
Treated for the index episode of syphilis before entry	338 (48.2)
<i>Treponema pallidum</i> DNA detected in blood	175 (26.5) ^b
<i>T. pallidum</i> rRNA detected in CSF	86 (12.7) ^c
CSF white blood cells >20/uL or reactive CSF- Venereal Disease Research Laboratory test	144 (21.2) ^c

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Results

Figure 1. Syphilis stage at the index episode among individuals with 1, 2, or ≥3 total episodes of syphilis.

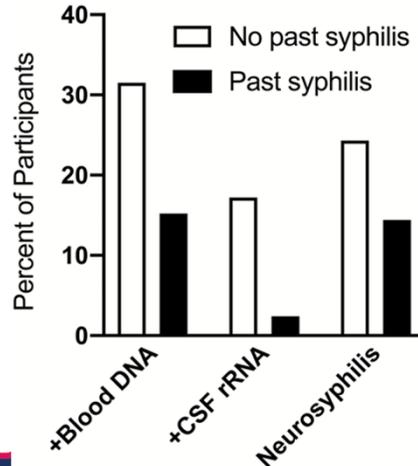


Number of participants	1	2	≥3
Primary	42	16	8
Secondary	224	55	16
Early latent	79	86	56
Late latent	106	10	6

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Results

Figure 2. Proportions of participants with and without previous syphilis who had detectable *Treponema pallidum* DNA in blood or rRNA in CSF or neurosyphilis.



Results

Factor	<i>Treponema pallidum</i> DNA Detected in Blood		<i>Treponema pallidum</i> rRNA Detected in Cerebrospinal Fluid	
	OR (95% CI), P Value	aOR (95% CI), P Value	OR (95% CI), P Value	aOR (95% CI), P Value
Previous syphilis (any stage)	0.39 (.25-0.60), <.001	0.13 (.08-.23), <.001	0.12 (.05-.30), <.001	0.06 (.02-.17), <.001
Previous late latent syphilis	0.47 (.29-.77), .002	NI*	0.74 (.41-1.33), .31	NI*
Treated for the index episode of syphilis before entry	0.05 (.03-.09), <.001	0.02 (.01-.05), <.001	0.10 (.05-.20), <.001	0.07 (.04-.16), <.001
Serum rapid plasma reagin (per 2-fold titer increase)	1.25 (1.15-1.36), <.001	1.33 (1.20-1.48), <.001	1.34 (1.20-1.50), <.001	1.50 (1.30-1.73), <.001
Stage (early vs late)	2.00 (1.18-3.38), .01	5.84 (3.06-11.16), <.001	1.0 (.55-1.81), .99	NI*
People living with HIV vs people not living with HIV	1.84 (1.15-2.95), .01	NI*	0.81 (.47-1.39), .45	NI*

- odds of detection of *t.pallidum* DNA in blood:
 - lower in previous syphilis, late latent, treatment prior to study entry date
 - higher for every 2-fold increase in RPR, early stage syphilis and PLHIV
- odds of detection of *t.pallidum* rRNA in CSF:
 - lower in previous syphilis, treatment prior to study entry date
 - higher for every 2-fold increase in RPR

Discussion

Summary

- previous syphilis attenuates clinical and laboratory manifestations of infection with syphilis
- repeat syphilis
 - asymptomatic, not explained by testing frequency
 - lower odds of detecting t.pallidum DNA in blood and rRNA in CSF
 - lower odds of neurosyphilis

Clinical implications

- vaccine potential
- testing frequency in at risk groups

Harjanto R, Smith D et al. "Utility of rapid plasmin reagin titres in assessing treatment response and re-infection for infectious syphilis". *Sexual Health*, 2020, 17(4) pp 330-336, doi: 10.1071/SH20043

Background

- RPR is mainstay in syphilis diagnosis and treatment monitoring
- Serological cure: four-fold decline in titre within 6 months of treatment
- RPR decline varies between patients:
 - Seroreversion: non reactive titre of <1:1
 - Serofast: plateau at a titre after appropriate decline; or
- RPR interpretation can be difficult:

blunted serological response or serofast state?

vs

reinfection or treatment failure?

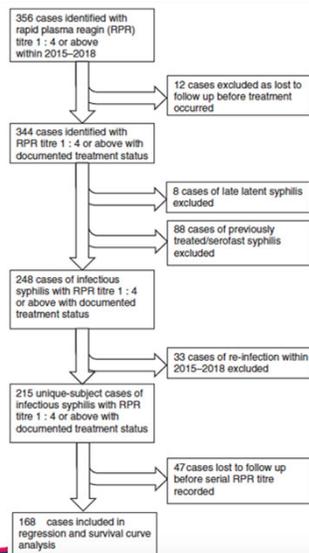
Aims

- Evaluate changes in RPR following syphilis diagnosis and treatment

Hypotheses

- Four-fold decline may be > 6 months following treatment
- Time to serofast state may be >12 months following treatment

Methods



- retrospective case file review of records from the Albion Centre, Sydney
- all samples tested at SAVID laboratories of NSW Health