

DIAGNOSIS AND MANAGEMENT OF GONORRHOEA AND SYPHILIS

APPENDIX



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APPENDIX

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1. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

1.1. Composition of the Guideline Development Group

Clinicians	Field of expertise, affiliations
Nicole Dekker, President of the GDG	General Practitioner, Domus Medica
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Tine Cornelissen	General practitioner
Tania Crucitti	Microbiologist Pharmacist, Institute of Tropical Medicine
Anne-Sophie De Cannière	General practitioner, vzw Pasop
Wouter Dhaeze	Afdeling preventie, agentschap zorg en gezondheid,
Els Dufraimont	Gynaecologist, Imelda Ziekenhuis
Régine Goemaes	Nurse practitioner midwife, VBOV
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Wim Vanden Berghe	Public Health scientist STI, Sciensano
Sandra Van den Eynde	SENSOA



1.2. Composition of the KCE expert team

KCE member	Specific role
Christophe Janssens	Program Director
Els Van Bruystegem	Project Facilitator
Vicky Jespers	Principal Investigator
Sabine Stordeur	Scientific research and methodological support
Anja Desomer	Scientific research
Nicolas Fairon	Information Specialist

1.3. External researchers involved in the guideline development

Subcontractor	Specific role
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Sedina Lewis	Research Fellow, National Guideline Centre, UK
Mark Perry	Senior Research Fellow, National Guideline Centre, UK



2. SEARCH STRATEGIES

2.1. General literature search

The search strategy focused on diagnosis and at-risk groups for treatable STIs (e.g. excluding herpes, warts). We performed a general search for STIs. Several more specific searches for HIV, chlamydia, gonorrhea, syphilis, hepatitis C and hepatitis B. To identify publications on risk groups we searched for men having sex with men, migrants, adolescents and young adults, and sex workers.

Search for guidelines and systematic reviews from 2005 – 2017 performed on August 1st, 2017 through Ovid MEDLINE, Cochrane and EMBASE.

2.1.1. Ovid MEDLINE

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Search Strategy:

1 exp Sexually Transmitted Diseases/ (319081)
2 "sexually transmitted disease*".ti,kw. (6376)
3 venereal disease*.ti,kw. (3767)
4 sexually transmitted infection*.ti,kw. (3602)
5 (STI or STIs).ab,ti,kw. (9476)
6 (STD or STDs).ab,ti,kw. (11569)
7 1 or 2 or 3 or 4 or 5 or 6 (328158)
8 HIV Infections/ (172519)
9 (Acquired Immunodeficiency Syndrome or HIV or AIDS or HIV infection).ti,kw. (233033)
10 8 or 9 (286989)
11 exp Chlamydia Infections/ (20090)
12 exp Gonorrhea/ (13770)

13 exp Syphilis/ (26723)
14 chlamydia.ti,kw. (14223)
15 (gonorrhea or gonorrhoea).ti,kw. (5585)
16 syphilis.ti,kw. (16534)
17 lymphogranuloma.ti,kw. (1242)
18 11 or 12 or 13 or 14 or 15 or 16 or 17 (64274)
19 exp Hepatitis B/ (53143)
20 Hepatitis B virus/ (23766)
21 "hepatitis b".ti,kw. (44277)
22 HBV.ti,kw. (7033)
23 19 or 20 or 21 or 22 (70581)
24 Hepatitis C, Chronic/ (21171)
25 Hepatitis C/ (36777)
26 "hepatitis c".ti,kw. (46248)
27 (hepatitis adj3 "non-a non-b").ti,kw. (1255)
28 hcv.ti,kw. (12665)
29 24 or 25 or 26 or 27 or 28 (71515)
30 7 or 10 or 18 or 23 or 29 (521753)
31 limit 30 to yr="2005 -Current" (233243)
32 limit 31 to systematic reviews (6524)
33 32 not editorial.pt. (6468)
34 33 not (animals/ not human/) (6459)
35 homosexuality, male/ (12715)
36 "homosexual males".ab,ti,kw. (402)
37 "homosexual men".ab,ti,kw. (3268)
38 "homosexual man".ab,ti,kw. (403)
39 "bisexual males".ab,ti,kw. (185)
40 "bisexual men".ab,ti,kw. (1952)
41 "bisexual man".ab,ti,kw. (76)



- 42 gay?.ab,ti,kw. (9045)
 43 MSM.ab,ti,kw. (7527)
 44 "Men Who Had Sex with Men".ab,ti,kw. (147)
 45 "men who have sex with other men".ab,ti,kw. (39)
 46 "Men Who Have Sex with Men".ab,ti,kw. (8460)
 47 "Men having Sex with Men".ab,ti,kw. (424)
 48 "Men having Sex with other Men".ab,ti,kw. (4)
 49 (men adj3 (having or had or have) adj1 sex adj3 men).ab,ti,kw. (9270)
 50 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or
 47 or 48 or 49 (26144)
 51 34 and 50 (339)
 52 remove duplicates from 51 (315)
 53 "Transients and Migrants"/ (9851)
 54 Refugees/ (8372)
 55 Undocumented Immigrants/ (97)
 56 migrant*.ab,ti,kw. (15900)
 57 immigrant*.ab,ti,kw. (21780)
 58 refugee?.ab,ti,kw. (8342)
 59 asylum seeker?.ab,ti,kw. (1131)
 60 53 or 54 or 55 or 56 or 57 or 58 or 59 (47537)
 61 34 and 60 (70)
 62 remove duplicates from 61 (66)
 63 adolescent/ (1864886)
 64 adolescent*.ab,ti,kw. (214404)
 65 teen?.ab,ti,kw. (9348)
 66 teenager?.ab,ti,kw. (12879)
 67 youth?.ab,ti,kw. (63093)
 68 young adult/ (623382)
 69 young?.ab,ti,kw. (421369)
 70 young adult?.ab,ti,kw. (74890)
 71 young *.kw. (4458)
 72 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 (2504597)
 73 34 and 72 (1001)
 74 remove duplicates from 73 (939)
 75 sex workers/ (1448)
 76 sex work/ (5752)
 77 prostitute?.ab,ti,kw. (2462)
 78 prostitution.ab,ti,kw. (1949)
 79 sex industry.ab,ti,kw. (258)
 80 sex industries.ab,ti,kw. (8)
 81 brothel?.ab,ti,kw. (417)
 82 hooker?.ab,ti,kw. (353)
 83 call girl?.ab,ti,kw. (13)
 84 streetwalker?.ab,ti,kw. (7)
 85 sex work*.ab,ti,kw. (5394)
 86 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 (11111)
 87 34 and 86 (149)
 88 remove duplicates from 87 (144)
- 2.1.2. Cochrane**
- Database: Cochrane Library (CDSR, DARE, HTA)
 Date Run: 01/08/17 10:54:09.123
 Warning: Problems were found with one or more of your search lines
 (specific lines are identified below). For best results, you should review and
 edit the search lines indicated
- | ID | Search Hits | |
|----|---------------------------------------|-------|
| #1 | [mh "Sexually Transmitted Diseases"] | 10903 |
| #2 | "sexually transmitted disease*":ti,kw | 1231 |
| #3 | venereal disease*:ti,kw | 61 |
| #4 | sexually transmitted infection*:ti,kw | 1374 |



#5	(STI or STIs):ab,ti,kw	736	#33	"homosexual males":ab,ti,kw	6
#6	(STD or STDs):ab,ti,kw	809	#34	"homosexual men":ab,ti,kw	83
#7	#1 or #2 or #3 or #4 or #5 or #6	12251	#35	"homosexual man":ab,ti,kw	0
#8	[mh "HIV Infections"]	9520	#36	"bisexual males":ab,ti,kw	6
#9	(Acquired Immunodeficiency Syndrome or HIV or AIDS or HIV infection):ti,kw	15596	#37	"bisexual men":ab,ti,kw	57
#10	#8 or #9	15596	#38	"bisexual man":ab,ti,kw	0
#11	[mh "Chlamydia Infections"]	670	#39	gay:ab,ti,kw or gays:ab,ti,kw	210
#12	[mh Gonorrhea]	448	#40	MSM:ab,ti,kw	382
#13	[mh Syphilis]	128	#41	"Men Who Had Sex with Men":ab,ti,kw	7
#14	chlamydia:ti,kw	1058	#42	"men who have sex with other men":ab,ti,kw	0
#15	(gonorrhea or gonorrhoea):ti,kw	893	#43	"Men Who Have Sex with Men":ab,ti,kw	455
#16	syphilis:ti,kw	341	#44	"Men having Sex with Men":ab,ti,kw	7
#17	lymphogranuloma:ti,kw	18	#45	"Men having Sex with other Men":ab,ti,kw	0
#18	#11 or #12 or #13 or #14 or #15 or #16 or #17	2092	#46	(men near/3 (having or had or have) near/1 sex near/3 men):ab,ti,kw	479
#19	[mh "Hepatitis B"]	2177	#47	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46	910
#20	[mh "Hepatitis B virus"]	772	#48	#31 and #47	475
#21	"hepatitis b":ti,kw	5855	#49	[mh "Transients and Migrants"]	68
#22	HBV:ti,kw	561	#50	migrant*:ab,ti,kw	227
#23	#19 or #20 or #21 or #22	6002	#51	immigrant*:ab,ti,kw	459
#24	[mh "Hepatitis C, Chronic"]	1624	#52	[mh Refugees]	89
#25	[mh "Hepatitis C"]	2676	#53	[mh "Undocumented Immigrants"]	0
#26	"hepatitis c":ti,kw	5881	#54	refugee*:ab,ti,kw	187
#27	(hepatitis near/3 "non-a non-b"):ti,kw	121	#55	asylum seeker*:ab,ti,kw	19
#28	hcv:ti,kw	1686	#56	#49 or #50 or #51 or #52 or #53 or #54 or #55	814
#29	#24 or #25 or #26 or #27 or #28	6714	#57	#31 and #56	60
#30	#7 or #10 or #18 or #23 or #29	30950	#58	[mh adolescent]	91247
#31	#7 or #10 or #18 or #23 or #29 Publication Year from 2005 to 2017	18453	#59	adolescent*:ab,ti,kw	114737
#32	[mh "homosexuality, male"]	298	#60	teen:ab,ti,kw or teens:ab,ti,kw	677



#61	teenager*:ab,ti,kw	503				#73	sex industry:ab,ti,kw	141
#62	youth:ab,ti,kw or youths:ab,ti,kw	3637				#74	sex industries:ab,ti,kw	10
#63	[mh "young adult"]	284				#75	brothel*:ab,ti,kw	9
#64	youngs:ab,ti,kw	3				#76	hooker*:ab,ti,kw	3
#65	young:ab,ti,kw	74070				#77	call girl*:ab,ti,kw	10
#66	"young adult*":ab,ti,kw	58738				#78	streetwalker*:ab,ti,kw	0
#67	young *:kw	80793				#79	sex work*:ab,ti,kw	2618
#68	#58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67	165600				#80	#70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79	2763
#69	#31 and #68	4288				#81	#31 and #80	307
#70	[mh "sex workers"]	43				[**Error**] ==> #82		
#71	[mh "sex work"]	90						
#72	prostitut*:ab,ti,kw	112						



2.1.3. Embase

No.	Query	Results
#82	#34 AND #81	43
#81	#70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80	12,328
#80	'sex worker':ab,ti OR 'sex workers':ab,ti	5,259
#79	'sex work':ab,ti	1,694
#78	streetwalker*:ab,ti	7
#77	'call girl':ab,ti OR 'call girls':ab,ti	9
#76	hooker*:ab,ti	491
#75	brothel*:ab,ti	433
#74	'sex industries':ab,ti	7
#73	'sex industry':ab,ti	258
#72	prostitut*:ab,ti	3,284
#71	'prostitution'/exp	8,786
#70	'sex worker'/exp	475
#69	#34 AND #68	327
#68	#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67	2,197,034
#67	'young adult':ab,ti OR 'young adults':ab,ti	91,291
#66	young*:ab,ti	724,940
#65	youth*:ab,ti	67,019
#64	teen*:ab,ti	34,072
#63	adolescent*:ab,ti	260,369
#62	'young adult'/exp	186,916
#61	'adolescent'/exp	1,433,533
#60	#34 AND #59	35



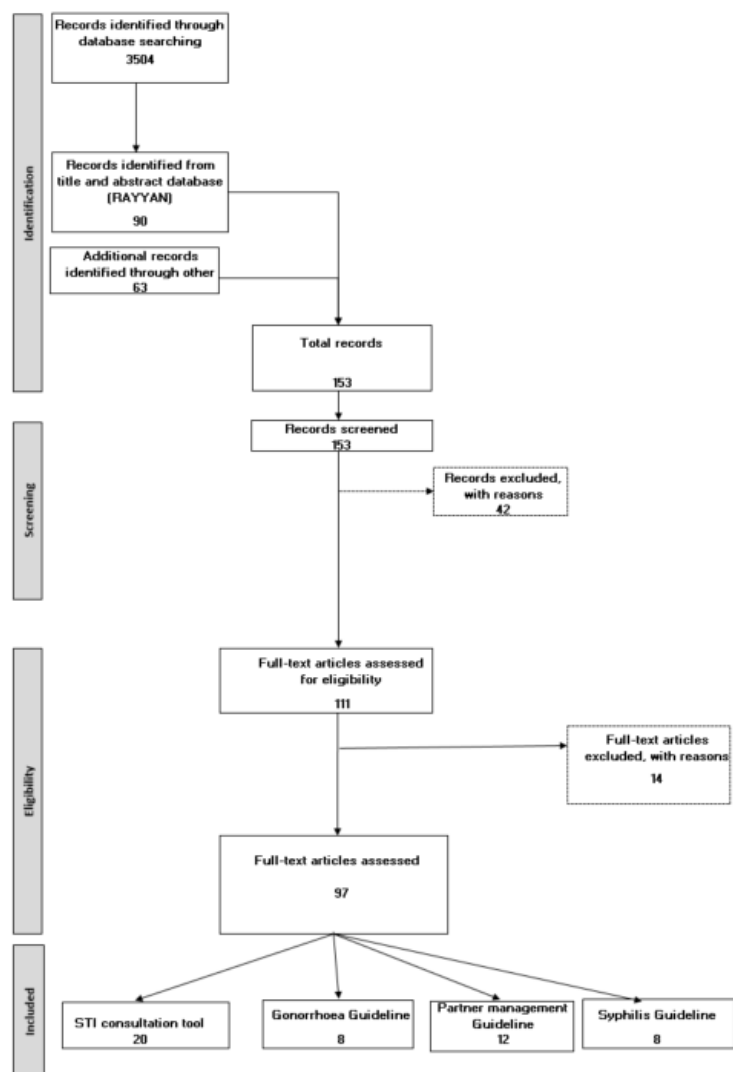
#59	#52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58	50,690
#58	'asylum seeker':ab,ti OR 'asylum seekers':ab,ti	1,242
#57	refugee*:ab,ti	8,354
#56	immigrant*:ab,ti	23,358
#55	migrant*:ab,ti	14,556
#54	'undocumented immigrant'/exp	270
#53	'refugee'/exp	9,877
#52	'migrant'/exp	28,731
#51	#34 AND #50	107
#50	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49	27,413
#49	(men NEAR/3 (having OR had OR have) NEAR/1 sex NEAR/3 men):ab,ti	10,959
#48	'men having sex with other men':ab,ti	7
#47	'men having sex with men':ab,ti	529
#46	'men who have sex with men':ab,ti	9,830
#45	'men who have sex with other men':ab,ti	51
#44	'men who had sex with men':ab,ti	179
#43	msm:ab,ti	10,141
#42	gay:ab,ti OR gays:ab,ti	9,090
#41	'bisexual males':ab,ti	187
#40	'bisexual man':ab,ti	79
#39	'bisexual men':ab,ti	1,941
#38	'homosexual men':ab,ti	3,380
#37	'homosexual man':ab,ti	455
#36	'homosexual males':ab,ti	439
#35	'homosexual male'/exp	5,932
#34	#33 NOT editorial:it	3,834
#33	#32 NOT [medline]/lim	4,102
#32	#31 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	15,559
#31	#30 AND ('meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review' OR 'guideline' OR 'practice guideline'/exp)	18,139
#30	#29 AND [2005-2018]/py	350,249



#29	#17 OR #22 OR #28	663,745
#28	#23 OR #24 OR #25 OR #26 OR #27	114,463
#27	hcv:ti	20,412
#26	(hepatitis NEAR/3 'non-a non-b'):ti	1,377
#25	'hepatitis c':ti	58,247
#24	'hepatitis c'/exp	95,291
#23	'hepatitis c, chronic'/exp	5,287
#22	#18 OR #19 OR #20 OR #21	116,602
#21	'hepatitis b virus'/exp	47,862
#20	hbv:ti	10,866
#19	'hepatitis b':ti	56,516
#18	'hepatitis b'/exp	86,607
#17	#5 OR #16	479,980
#16	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	465,297
#15	lymphogranuloma:ti	1,284
#14	'syphilis':ti	16,215
#13	gonorrhea:ti OR gonorrhoea:ti	5,551
#12	chlamydia:ti	15,827
#11	'acquired immunodeficiency syndrome':ti OR hiv:ti OR aids:ti	263,989
#10	'syphilis'/exp	31,043
#9	'gonorrhea'/exp	18,392
#8	'chlamydia sis'/exp	21,017
#7	'human immunodeficiency virus infection'/exp	342,701
#6	#1 OR #2 OR #3 OR #4 OR #5	107,208
#5	std:ab,ti OR stds:ab,ti OR sti:ab,ti OR stis:ab,ti	27,543
#4	'sexually transmitted infection':ti OR 'sexually transmitted infections':ti	3,389
#3	'venereal disease':ti OR 'venereal diseases':ti	2,507
#2	'sexually transmitted disease':ti OR 'sexually transmitted diseases':ti	4,921
#1	'sexually transmitted disease'/exp	95,089



2.1.4. Study flow for general literature search





2.2. Additional search for diagnosis of gonorrhoea

2.2.1. Medline

Date	11-01-18
Database	Medline
Search Strategy	exp gonorrhea/ exp Neisseria gonorrhoeae/ 1 or 2 exp "Sensitivity and Specificity"/ exp Diagnostic Errors/ 4 or 5 3 and 6
Note	Search replicate from Nelson et al.

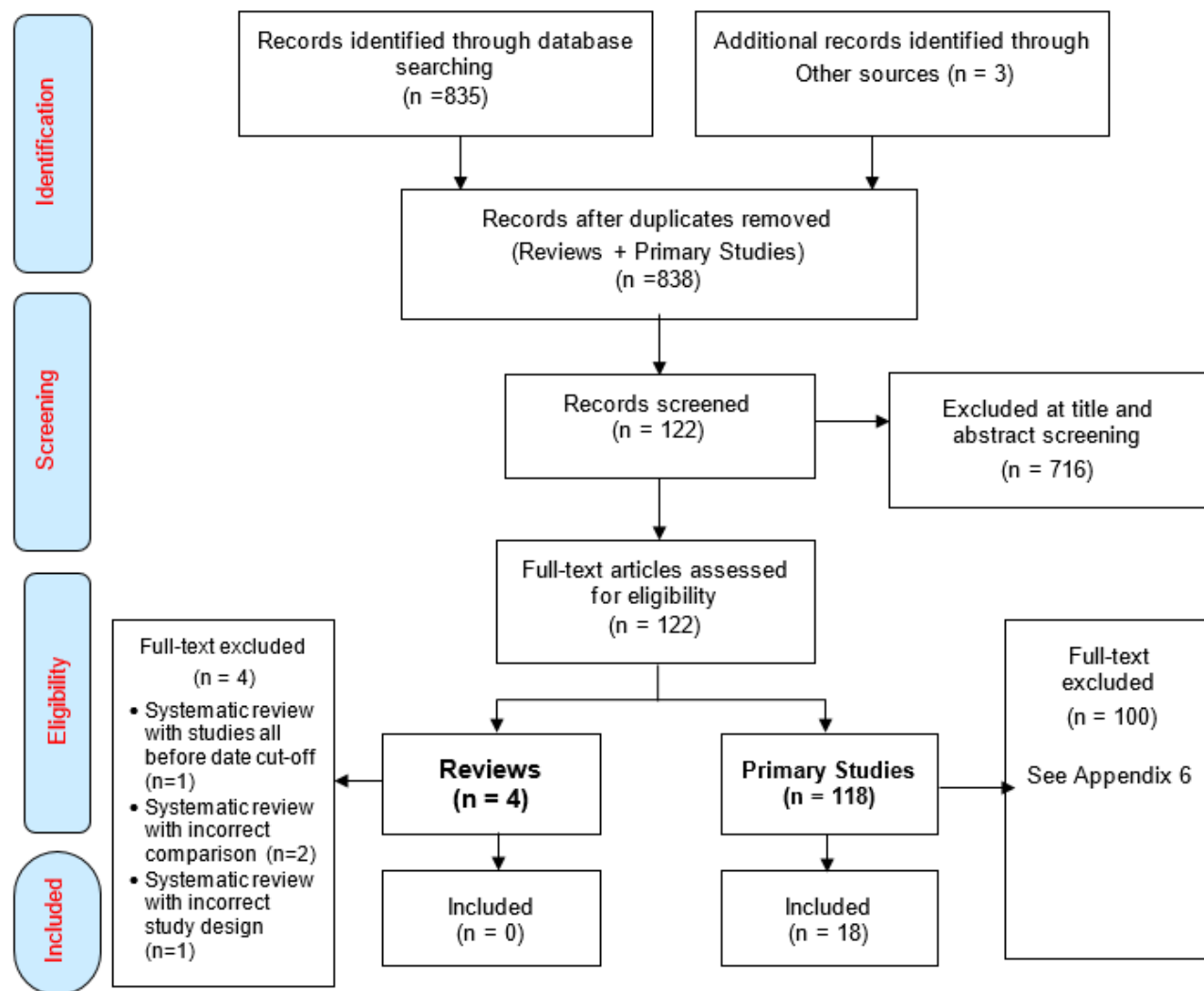
2.2.2. Central

Date	11-01-2018
Database	Central
Search Strategy	gonorrh* (sensitiv* or accurate* or accuracy or predict* or misdiagnos* or misinterpret* or ((diagnos* or detect* or discover*) near/5 (error* or erroneous* or fail* or bias*)) or (false* near/3 (positiv* or negativ*))) #1 and #2
Note	Search replicate from Nelson et al.



2.2.3. Study flow of selection of primary studies

Figure 1 – Study flow of selection of primary studies





2.2.4. Excluded studies

Table 1 – Table of excluded studies – diagnosis of gonorrhoea

Reference	Reason for exclusion
Alam 2012 ¹	Population and intervention do not match review protocol
Alexander 2008 ²	Intervention does not match review protocol
Armed Forces 2013 ³	Intervention does not match review protocol
Bachmann 2009 ⁴	Intervention does not match review protocol
Bachmann 2010 ⁵	Intervention does not match review protocol
Barbee 2014 ⁶	Study design does not match review protocol
Bartelsman 2014 ⁷	Study design does not match review protocol
Benzaken 2006 ⁸	Population does not match review protocol
Berry 2017 ⁹	Intervention does not match review protocol
Bhalla 2007 ¹⁰	Population does not match review protocol
Black 2009 ¹¹	Population does not match review protocol
Bromhead 2013 ¹²	Population does not match review protocol
Brook 2015 ¹³	Study design does not match review protocol
Bruce 2010 ¹⁴	Population does not match review protocol
Buchanan 2016 ¹⁵	Intervention does not match review protocol
Cheng 2011 ¹⁶	Intervention does not match review protocol
Cheng 2014 ¹⁷	Intervention does not match review protocol
Chernesky 2007 ¹⁸	Intervention does not match review protocol
Chernesky 2012 ¹⁹	Intervention does not match review protocol
Chernesky 2014 ²⁰	Outcomes do not match review protocol
Cook 2005 ²¹	Systematic review – all studies before date cut-off
Dewaaij 2015 ²²	Population and intervention do not match review protocol
Dize 2013 ²³	Intervention does not match review protocol
Dize 2016 ²⁴	Intervention does not match review protocol
Dona 2016 ²⁵	Intervention does not match review protocol



Downing 2010 ²⁶	Outcomes do not match review protocol
Field 2014 ²⁷	Study design does not match review protocol
Fontana 2005 ²⁸	Population does not match review protocol
Fowler 2013 ²⁹	Outcomes do not match review protocol
Geraats 2015 ³⁰	Intervention does not match review protocol
Ghanem 2006 ³¹	Intervention does not match review protocol
Gimenes 2014 ³²	Intervention does not match review protocol
Goire 2008 ³³	Outcomes do not match review protocol
Golden 2004 ³⁴	Outcomes do not match review protocol
Goldenberg 2012 ³⁵	Population does not match review protocol
Golparian 2013 ³⁶	Intervention does not match review protocol
Golparian 2015 ³⁷	Intervention does not match review protocol
Golparian 2015 ³⁸	Intervention does not match review protocol
Gueye 2014 ³⁹	Intervention does not match review protocol
Han 2014 ⁴⁰	Population and intervention do not match review protocol
Herring 2006 ⁴¹	Study design does not match review protocol
Hjelmevoll 2008 ⁴²	Intervention does not match review protocol
Ho 2009 ⁴³	Population does not match review protocol
Hopkins 2010 ⁴⁴	Intervention does not match review protocol
Kapala 2011 ⁴⁵	Study design and outcomes do not match review protocol
Kerndt 2011 ⁴⁶	Intervention does not match review protocol
Lee 2012 ⁴⁷	Population does not match review protocol
Leroy 2012 ⁴⁸	Intervention does not match review protocol
Lindan 2005 ⁴⁹	Population does not match review protocol
Lowe 2006 ⁵⁰	Intervention does not match review protocol
Luijt 2005 ⁵¹	Intervention does not match review protocol
Lunny 2005 ⁵²	Study design does not match review protocol
Marangoni 2015 ⁵³	Study design does not match review protocol



Martens 2013 ⁵⁴	Intervention does not match review protocol
McNally 2008 ⁵⁵	Outcomes do not match review protocol
McNicol 2013 ⁵⁶	Population and intervention do not match review protocol
Meyer 2016 ⁵⁷	Intervention does not match review protocol
Mohammed 2015 ⁵⁸	Study design does not match review protocol
Moncada 2015 ⁵⁹	Intervention does not match review protocol
Moss 2007 ⁶⁰	Population does not match review protocol
Mushanski 2012 ⁶¹	Intervention does not match review protocol
Nasution 2007 ⁶²	Population does not match review protocol
O'Callaghan 2010 ⁶³	Study design does not match review protocol
Papp 2007 ⁶⁴	Intervention does not match review protocol
Parra-Sanchez 2012 ⁶⁵	Intervention does not match review protocol
Parra-Sanchez 2016 ⁶⁶	Population does not match review protocol
Perry 2014 ⁶⁷	Intervention does not match review protocol
Peuchant 2015 ⁶⁸	Outcomes do not match review protocol
Pol 2011 ⁶⁹	Study design does not match review protocol
Pol 2013 ⁷⁰	Study design does not match review protocol
Pol 2015 ⁷¹	Study design does not match review protocol
Pope 2010 ⁷²	Intervention does not match review protocol
Rahimi 2013 ⁷³	Population does not match review protocol
Rahman 2014 ⁷⁴	Intervention does not match review protocol
Rockett 2010 ⁷⁵	Population does not match review protocol
Sachdev 2015 ⁷⁶	Population does not match review protocol
Samra 2011 ⁷⁷	Population does not match review protocol
Sanders 2014 ⁷⁸	Study design does not match review protocol
Serra-Pladevall 2015 ⁷⁹	Study design does not match review protocol
Sexton 2013 ⁸⁰	Intervention does not match review protocol
Shipitsyna 2008 ⁸¹	Population and intervention do not match review protocol



Shipitsyna 2009 ⁸²	Population does not match review protocol
Skovgaard 2012 ⁸³	Population and intervention do not match review protocol
Stampler 2008 ⁸⁴	Outcomes do not match review protocol
Sturm 2004 ⁸⁵	Population does not match review protocol
Suzuki 2004 ⁸⁶	Intervention does not match review protocol
Tabrizi 2005 ⁸⁷	Intervention does not match review protocol
Thielemans 2018 ⁸⁸	Intervention does not match review protocol
Thorley 2015 ⁸⁹	Study design does not match review protocol
Upton 2013 ⁹⁰	Intervention does not match review protocol
Ursi 2016 ⁹¹	Intervention does not match review protocol
Verma 2010 ⁹²	Population does not match review protocol
Verma 2012 ⁹³	Intervention does not match review protocol
Verma 2014 ⁹⁴	Study design does not match review protocol
Walsh 2011 ⁹⁵	Intervention does not match review protocol
Watchirs 2013 ⁹⁶	Systemic review – incorrect comparison
Wheeler 2005 ⁹⁷	Study design does not match review protocol
Whiley 2005 ⁹⁸	Population does not match review protocol
Whiley 2005 ⁹⁹	Population does not match review protocol
Wilson 2016 ¹⁰⁰	Study design does not match review protocol
Wilson 2016 ¹⁰¹	Study design does not match review protocol
Wind 2015 ¹⁰²	Intervention does not match review protocol
Wood 2007 ¹⁰³	Intervention does not match protocol
Yu 2016 ¹⁰⁴	Population does not match review protocol



2.3. Additional search for treatment of gonorrhea

2.3.1. Medline

Date	19-02-2018
Database	Medline
Search Strategy	gonorrhoea.mp. gonorrhea.mp. gonococcal.mp. or/1-3 ceftriaxone/ Ceftriaxone.ti,ab. or/5-6 4 and 7 limit 8 to yr="2015 -Current"
Note	On the 9 th of May we did a top up search replicating the same search strategy used in PubMed, limited to RCT's. gonorrhoea.mp. gonorrhea.mp. gonococcal.mp. or/1-3 (treat* or therap* or manag* or protocol or intervention* or procedure* or anti bacterial agent* or antibiotic* or resistance or pharmacological action or failure).ti,ab. Therapeutics/ or/5-6 4 and 7 randomized controlled trial.pt. controlled clinical trial.pt. randomi#ed.ti,ab. placebo.ab. randomly.ti,ab. Clinical Trials as topic.sh. trial.ti. 8 and 15 limit 16 to yr="2015 -Current"



2.3.2. Embase

Date	19-02-2018
Database	Embase
Search Strategy	gonorrhoea.mp. gonorrhea.mp. gonococcal.mp. or/1-3 ceftriaxone/ Ceftriaxone.ti,ab. or/5-6 4 and 7 limit 8 to yr="2015 -Current"
Note	On the 9 th of May we did a top up search replicating the same search strategy used in PubMed, limited to RCT's. gonorrhoea.mp. gonorrhea.mp. gonococcal.mp. or/1-3 (treat* or therap* or manag* or protocol or intervention* or procedure* or anti bacterial agent* or antibiotic* or resistance or pharmacological action or failure).ti,ab. therapy/ 5 or 6 4 and 7 random*.ti,ab. factorial*.ti,ab. (crossover* or cross over*).ti,ab. ((doubl* or singl*) adj blind*).ti,ab. (assign* or allocat* or volunteer* or placebo*).ti,ab. crossover procedure/ single blind procedure/ randomized controlled trial/ double blind procedure/ or/9-17 8 and 18 limit 19 to yr="2015 -Current"



2.3.3. Cochrane

Date	19-02-2018
Database	Cochrane-Wiley
Search Strategy	gonorrhoea:ti,kw,ab gonorrhea:ti,kw,ab gonococcal:ti,kw,ab 105-#3 MeSH descriptor: [Ceftriaxone] this term only Ceftriaxone:ti,kw,ab or #5-#6 #4 and #7 Publication Year from 2015 to 2018
Note On the 9 th of May we did a top up search replicating the same search strategy used in PubMed:	gonorrhoea:ti,kw,ab gonorrhea:ti,kw,ab gonococcal:ti,kw,ab or #1-#3 (treat* or therap* or manag* or protocol or intervention* or procedure* or anti bacterial agent* or antibiotic* or resistance or pharmacological action or failure):ti,ab MeSH descriptor: [Therapeutics] this term only or #5-#6 #4 and #7 Publication Year from 2015 to 2018

Date	22-02-2018
Database	PubMed
Search Strategy	((("gonorrhoea"[All Fields] OR "gonorrhea"[MeSH Terms] OR "gonorrhea"[All Fields]) OR gonorrhoeae[All Fields] OR ("gonorrhoea"[All Fields] OR "gonorrhea"[MeSH Terms] OR "gonorrhea"[All Fields]) OR ("neisseria gonorrhoeae"[MeSH Terms] OR ("neisseria"[All Fields] AND "gonorrhoeae"[All Fields]) OR "neisseria gonorrhoeae"[All Fields] OR "gonococcus"[All Fields]) OR ("gonorrhea"[MeSH Terms] OR "gonorrhea"[All Fields] OR "gonococcal"[All Fields])) AND ((("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR resistance[All Fields] OR ("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotics"[All Fields]) OR failure[All Fields]) AND (("2013/03/09"[PDAT] : "2018/02/22"[PDAT]) AND English[lang])



2.3.4. Study flow of selection of primary studies

In MEDLINE, Embase, PubMed and Cochrane 2047 potential relevant references were identified. After de-duplication 1884 references remained. Based on title and abstract 1876 studies were excluded resulting in 7 remaining studies (4 systematic reviews and 3 primary studies) from the update search.

Systematic reviews: Of the 4 remaining reviews; 1 systematic review (Cochrane review) was included as background information only as the included primary studies were extracted separately. The remaining 3 systematic reviews were excluded with reason (Table 2).

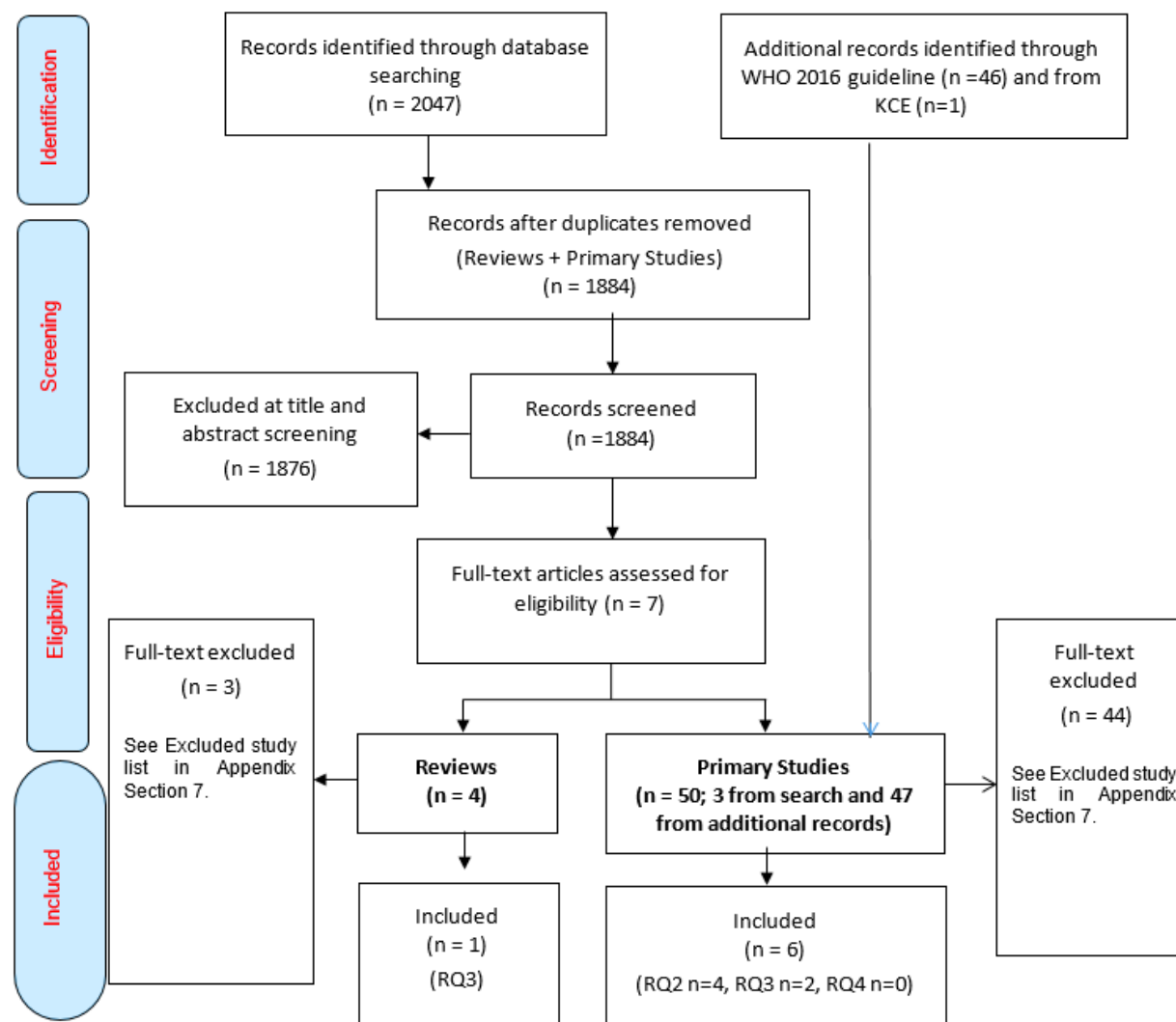
Primary studies: In addition to the 3 primary studies selected there was an additional 47 primary studies selected through other methods for consideration.

Of these 50 studies, 6 studies were included and 44 studies were excluded with reason (Table 2).

On 09/05/18 another search was conducted in Medline, Embase and Cochrane using the same search strategy as PubMed. 272 studies were identified and 95 remained after deduplication. No one of these studies was included.



Figure 2 – Study flow of selection of systematic reviews and primary studies





2.3.5. Excluded studies

Table 2 – Table of excluded studies – Treatment of gonorrhoea

Reference	Reason for exclusion
Aplasca De Los Reyers 2001 ¹⁰⁶	Population does not match review protocol
Baddour 1992 ¹⁰⁷	Intervention does not match review protocol
Bai 2012 ¹⁰⁸	Systematic review – all studies before date cut-off
Bignell 2013 ¹⁰⁹	Systematic review – all studies before date cut-off
Brittain 2016 ¹¹⁰	Study design does not match review protocol
Bryan 1990 ¹¹¹	Population does not match review protocol
Calderon 1988 ¹¹²	Population does not match review protocol
Collier 1984 ¹¹³	Intervention does not match review protocol
Covino 1990 ¹¹⁴	Intervention does not match review protocol
Covino 1993 ¹¹⁵	Intervention does not match review protocol
Dixon 1986 ¹¹⁶	Comparison does not match review protocol
Duancic 1974 ¹¹⁷	Intervention does not match review protocol
Handsfield 1981 ¹¹⁸	Intervention does not match review protocol
Handsfield 1983 ¹¹⁹	Intervention does not match review protocol
Handsfield 1991 ¹²⁰	Intervention does not match review protocol
Handsfield 1994 ¹²¹	Intervention does not match review protocol
Hathorn 2014 ¹²²	Study design does not match review protocol
Hook 1993 ¹²³	Intervention does not match review protocol
Hook 1997 ¹²⁴	Intervention does not match review protocol
Hook 2015 ¹²⁵	Study design does not match review protocol
Judson 1983 ¹²⁶	Intervention does not match review protocol
Karney 1977 ¹²⁷	Study design does not match review protocol
Khaki 2007 ¹²⁸	Population and study design does not match review protocol
Kim 1984 ¹²⁹	Population does not match review protocol
Korting 1989 ¹³⁰	Intervention does not match review protocol



Kouri 1989 ¹³¹	Population does not match review protocol
Lassus 1990 ¹³²	Intervention does not match review protocol
Lule 1994 ¹³³	Population does not match review protocol
McCormack 1993 ¹³⁴	Intervention does not match review protocol
Megran 1990 ¹³⁵	Intervention does not match review protocol
Meheus 1984 ¹³⁶	Population does not match review protocol
Mogabgab 1994 ¹³⁷	Intervention does not match review protocol
Odugbemi 1993 ¹³⁸	Population and study design does not match review protocol
Pabst 1989 ¹³⁹	Intervention does not match review protocol
Panikabutra 1983 ¹⁴⁰	Population does not match review protocol
Panikabutra 1985 ¹⁴¹	Population does not match review protocol
Panikabutra 1988 ¹⁴²	Population does not match review protocol
Pedersen 1972 ¹⁴³	Intervention does not match review protocol
Plourde 1992 ¹⁴⁴	Population does not match review protocol
Portilla 1992 ¹⁴⁵	Intervention does not match review protocol
Rompalo 1993 ¹⁴⁶	Intervention does not match review protocol
Rustomjee 2002 ¹⁴⁷	Population does not match review protocol
Sham Ur 2009 ¹⁴⁸	Population does not match review protocol
Smith 1993 ¹⁴⁹	Intervention does not match review protocol
Steingrimsson 1990 ¹⁵⁰	Population does not match review protocol
Steingrimsson 1994 ¹⁵¹	Intervention does not match review protocol
Zajdowicz 1983 ¹⁵²	Intervention does not match review protocol



2.4. Additional search for diagnosis of syphilis

2.4.1. Medline

Date	26-03-2018
Database	Medline
Search Strategy	exp Treponema pallidum/ exp Syphilis/di 1 or 2 exp "Sensitivity and Specificity"/ 3 and 4 exp Diagnostic Errors/ 3 and 6 5 or 7 (fals\$ adj3 (positiv\$ or negativ\$)).mp. 3 and 9 (accura\$ or inaccura\$ or (predict\$ adj5 (value\$ or able or abilit\$ or capab\$ or effectiv\$ or unable or inabilit\$ or incapab\$ or ineffect\$ or correct\$))).mp. 3 and 11 8 or 10 or 12 (20163* or 20164* or 20165* or 20166* or 20167* or 20168* 20169* 201610* 201611* 201612* or 2017* or 2018*).ed,dc. 13 and 14



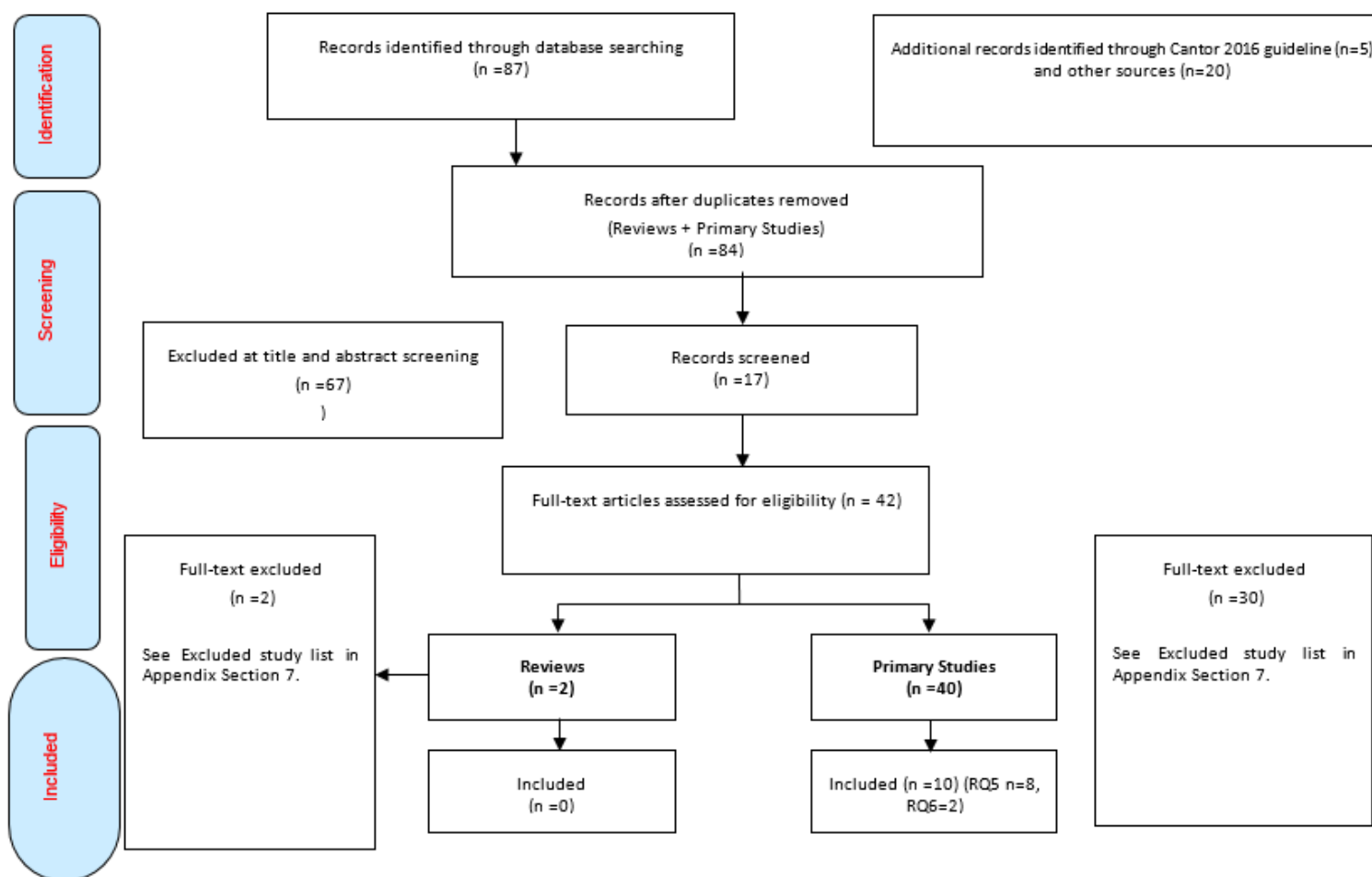
2.4.2. Cochrane

26-03-2018	
Database	Cochrane
Search Strategy	<p>syphil*</p> <p>treponema pallidum</p> <p>{or #1-#2}D</p> <p>MeSH descriptor: [Sensitivity and Specificity] explode all trees</p> <p>MeSH descriptor: [Diagnostic Errors] explode all trees</p> <p>(diagnos* near/3 (mistak* or error* or erroneous*))</p> <p>(fals* near/3 (positiv* or negativ*))</p> <p>(accura* or inaccura* or (predict* near/5 (value* or able or abilit* or capab* or effectiv* or unable or inabilit* or incapab* or ineffect* or correct*)))</p> <p>{or #4-#8}</p> <p>#3 and #9 Publication Year from 2016 to 2018</p>



2.4.3. Study flow of selection of systematic reviews and primary studies

Figure 3 – Study flow of selection of systematic reviews and primary studies – diagnosis of syphilis





2.4.4. Excluded studies

Table 3 – Table of excluded studies – Diagnosis of syphilis

Reference	Reason for exclusion
Castro 2014 ¹⁵³	Study design does not match protocol
Causer 2015 ¹⁵⁴	Study design does not match protocol
CDC 2011 ¹⁵⁵	Intervention does not match review protocol
Dekeukeleire 2017 ¹⁵⁶	Population does not match review protocol
Enders 2015 ¹⁵⁷	Study design does not match protocol
Gama 2017 ¹⁵⁸	Population does not match review protocol
Gratrix 2012 ¹⁵⁹	Study design does not match protocol
Gliddon 2017 ¹⁶⁰	Population does not match review protocol
Guinard 2013 ¹⁶¹	Study design does not match protocol
Herbst 2017 ¹⁶²	Intervention does not match review protocol
Huh 2016 ¹⁶³	Population does not match review protocol
Humphries 2014 ¹⁶⁴	Study design does not match protocol
Hunter 2013 ¹⁶⁵	Intervention does not match review protocol
Jun 2016 ¹⁶⁶	Population does not match review protocol
Juarez 2007 ¹⁶⁷	Population does not match review protocol
Koek 2006 ¹⁶⁸	Intervention does not match review protocol
Kremastinou 2016 ¹⁶⁹	Intervention does not match review protocol
Li 2016 ¹⁷⁰	Population does not match review protocol
Li 2016 ¹⁷¹	Population does not match review protocol
Li 2016 ¹⁷²	Population does not match review protocol
Lipinsky 2012 ¹⁷³	Population does not match review protocol
Maple 2010 ¹⁷⁴	Intervention does not match review protocol
Marks 2016 ¹⁷⁵	Population does not match review protocol
Nakku 2016 ¹⁷⁶	Population does not match review protocol
Owusu-Edusei ¹⁷⁷	Study design does not match protocol
Owusu-Edusei ¹⁷⁸	Outcomes do not match protocol
Palmer 2003 ¹⁷⁹	Intervention does not match review protocol



Park 2011 ¹⁸⁰	Intervention does not match review protocol
Sommese 2016 ¹⁸¹	Intervention does not match review protocol
Sommese 2016 ¹⁸²	Intervention does not match review protocol
Wheeler 2004 ¹⁸³	Study design does not match protocol
Xiao 2017 ¹⁸⁴	Population does not match review protocol

2.5. Additional search for treatment of syphilis

2.5.1. Medline

Date	19-04-2018
Database	Medline
Search Strategy	syphilis/ or syphilis.ti,ab. Treponema pallidum/ or treponema pallidum.ti,ab. Treponemal Infections/ or Treponemal Infections.ti,ab. or/1-3 (therapy or treatment or drugs or "prevention and control").ti,ab. 4 and 5 (201303* or 201304* or 201305* or 201306* or 201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015* or 2016* or 2017* or 2018*).ed,dc. 6 and 7 mit 8 to English language
Note	A top up was conducted for French and Dutch language



2.5.2. Embase

Date	19-04-2018
Database	Embase
Search Strategy	syphilis/ or syphilis.ti,ab. Treponema pallidum/ or treponema pallidum.ti,ab. treponematosi/ or Treponemal Infections.ti,ab. or/1-3 (therapy or treatment or drugs or "prevention and control").ti,ab. 4 and 5 (201303* or 201304* or 201305* or 201306* or 201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015* or 2016* or 2017* or 2018*).ed,dc. 6 and 7 limit 8 to English language
Note	A top up was conducted for French and Dutch language

2.5.3. Cochrane

Date	19-04-2018
Database	Cochrane
Search Strategy	MeSH descriptor: [Syphilis] this term only syphilis:ti,ab MeSH descriptor: [Treponema pallidum] this term only Treponema pallidum:ti,ab MeSH descriptor: [Treponemal Infections] explode all trees {or #1-#5} (therapy or treatment or drugs or "prevention and control"):ti,ab #6 and #7 Publication Year from 2013 to 2018

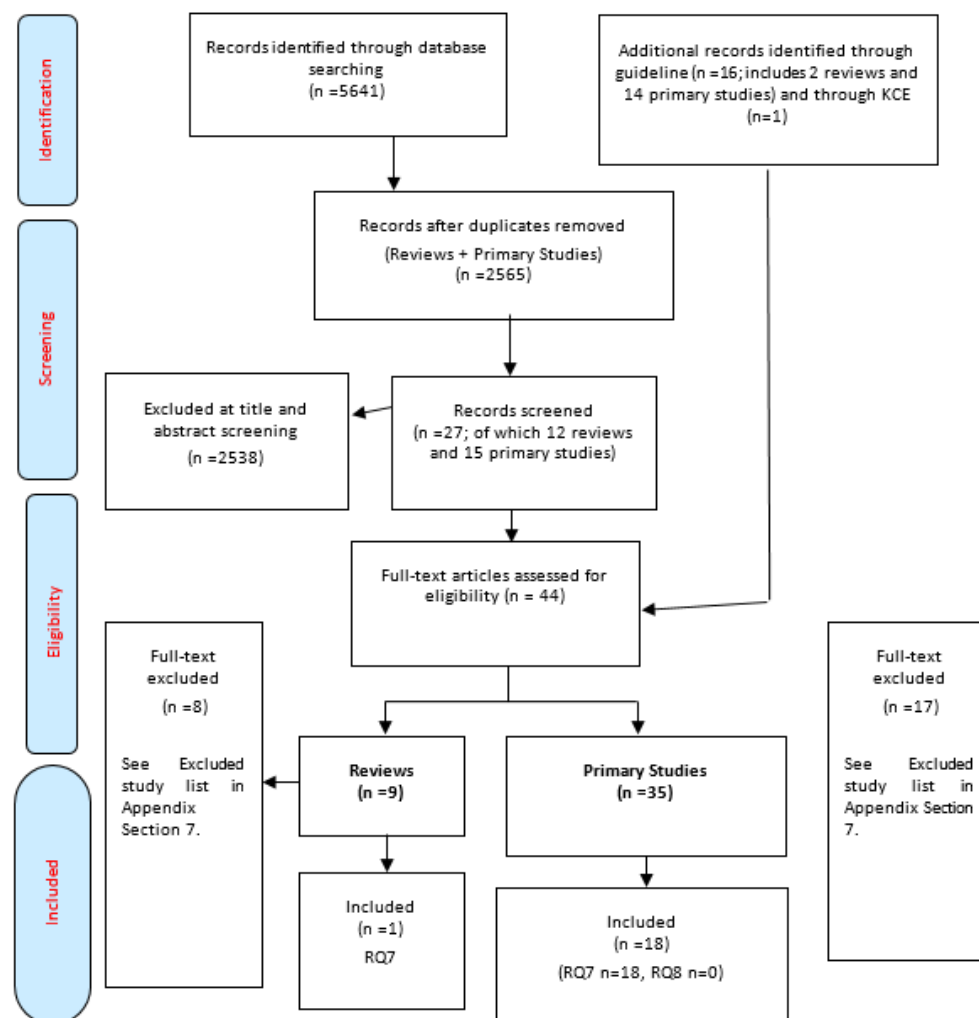


2.5.4. Pubmed

Date	19-04-2018
Database	PubMed
Search Strategy	((("syphilis"[MeSH Terms] OR "syphilis"[All Fields]) OR ("treponema pallidum"[MeSH Terms] OR ("treponema"[All Fields] AND "pallidum"[All Fields]) OR "treponema pallidum"[All Fields])) OR ("treponemal infections"[MeSH Terms] OR ("treponema"[All Fields] AND "infections"[All Fields]) OR "treponemal infections"[All Fields])) AND (("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "drugs"[All Fields]) OR "prevention and control"[All Fields]) AND (("2013/03/01"[PDAT] : "2018/04/19"[PDAT]) AND English[lang])
Note	A top up was conducted for French and Dutch language



Figure 4 – Study flow of selection of systematic reviews and primary studies – treatment of syphilis





2.5.5. Excluded studies

Table 4 – Table of excluded studies – Treatment of syphilis

Reference	Reason for exclusion
Blank 2011 ¹⁸⁵	Review - study design does not match review protocol.
Clement 2014 ¹⁸⁶	Review - study design does not match review protocol.
Cousins 2012 ¹⁸⁷	Study design does not match review protocol.
Drago 2015 ¹⁸⁸	Study design does not match review protocol.
Dufty 2014 ¹⁸⁹	Review - study design does not match review protocol.
Farhi 2009 ¹⁹⁰	Outcomes do not match review protocol.
Fatkenheuer 2017 ¹⁹¹	Study design does not match review protocol.
Ganesan 2015 ¹⁹²	Study design does not match review protocol.
Hopkins 2009 ¹⁹³	Study design does not match review protocol.
Li 2018 ¹⁹⁴	Review - study design does not match review protocol.
Li 2014 ¹⁹⁵	Study design does not match review protocol.
Liang 2016 ¹⁹⁶	Review - study design does not match review protocol.
Liu 2017 ¹⁹⁷	Review - study design does not match review protocol.
O'Mahony 2012 ¹⁹⁸	Study design does not match review protocol.
Riedner 2005 ¹⁹⁹	Population does not match review protocol.
Spornraft-Ragaller 2011 ²⁰⁰	Study design does not match review protocol.
Psomas 2012 ²⁰¹	Study design does not match review protocol.
Sena 2011 ²⁰²	Study design does not match review protocol.
Sena 2015 ²⁰³	Review - study design does not match review protocol.
Tsai 2014 ²⁰⁴	Outcome does not match review protocol.
Taiwan HIV and syphilis study group 2013 ²⁰⁵	Study design does not match review protocol.
Uslu 2017 ²⁰⁶	Study design does not match review protocol.
Vanbrussel 2015 ²⁰⁷	Study design does not match review protocol.
Warwick 2009 ²⁰⁸	Comparison does not match review protocol.
Yang 2015 ²⁰⁹	Review - study design does not match review protocol.



3. GUIDELINES IDENTIFIED

3.1. Topic: diagnosis and/or management of gonorrhoea

Country/Organization	Reference	Search date limits
Canada	Canadian STI guidelines 2010 -supplements 2014 & 2016	
Europe	Bignell C, et al. 2013 International Journal of STD & AIDS 24(2):85-92 - 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults	2008-2012
International / WHO	WHO guidelines for the treatment of Neisseria gonorrhoeae 2016	2004- 2015
UK / BASHH	UK national guideline for gonorrhoea laboratory testing, 2012	2006-2010
UK / IUSTI	Bignell C, et al. 2011 International Journal of STD & AIDS 22(10):541-7 - UK national guideline for the management of gonorrhoea in adults, 2011	2005-2009
USA / CDC	Workowski KA, et al. 2015 Morbidity & Mortality Weekly Report. Recommendations & Reports 64(RR-03):1-137 - Sexually transmitted diseases treatment guidelines, 2015.	2004-2014
USA / CDC	Kidd S, Workowski K. Clin. Infect. Dis. - Volume 61, Issue 8, pp. 15 - published 2015-01-01. Management of Gonorrhea in Adolescents and Adults in the United States	2008-2013
USA / USPSTF	LeFevre ML, et al. 2014 Annals of Internal Medicine 161(12):902-10 - Screening for Chlamydia and gonorrhea: U.S. Preventive Services Task Force recommendation statement	2004-2014
	Nelson HD, Zakher B, Cantor A, Deagas M, Pappas M. Screening for Gonorrhea and Chlamydia: Systematic Review to Update the U.S. Preventive Services Task Force Recommendations. Evidence Synthesis No. 115. AHRQ Publication No. 13-05184-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.	



3.2. Topic: diagnosis and/or management of syphilis

Country/Organization	Reference	Search date limits
Canada	Canadian STI guidelines 2010 -supplements 2014 & 2016	
Europe / IUSTI	Janier M, et al. 2014 Journal of the European Academy of Dermatology & Venereology 28(12):1581-93 - 2014 European guideline on the management of syphilis.	2008-2014
International / WHO	WHO guidelines for the treatment of Treponema pallidum (syphilis) 2016	Up to 2016
International / WHO	WHO guideline on syphilis screening and treatment for pregnant women 2016	Up to 2016
UK / BASHH	Kingston M, et al. 2016 International Journal of STD & AIDS 27(6):421-46 - UK national guidelines on the management of syphilis 2015	2007-2014
USA / USPSTF	USPSTF. 2016 Jama 315(21):2321-7 - Screening for Syphilis Infection in Nonpregnant Adults and Adolescents: US Preventive Services Task Force Recommendation Statement Cantor A, Nelson HD, Daeges M, Pappas M. Screening for Syphilis in Nonpregnant Adolescents and Adults: Systematic Review to Update the 2004 U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 136. AHRQ Publication No. 14-05213-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2016	2004-2016
USA / CDC	Ghanem KG 2015 Clinical Infectious Diseases 61(8):15 - Management of Adult Syphilis: Key Questions to Inform the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines	2008-2013
USA / CDC	Workowski KA, et al. 2015 Morbidity & Mortality Weekly Report. Recommendations & Reports 64(RR-03):1-137 - Sexually transmitted diseases treatment guidelines, 2015.	2004-2014



4. GUIDANCE DOCUMENTS AND CONSULTATION ALGORITHMS FOR THE TOOL

Table 5 – Retrieved documents for the consultation tool

Country	Format	Document	Year	Internet link
Belgium	Guidance	Domus Medica Praktijktool Seksueel Overdraagbare infecties: aanpak in de huisartsenpraktijk	2017	https://www.domusmedica.be/documentatie/downloads/praktijkdocumenten/richtlijnen/1332-praktijktool-seksueel-overdraagbare-infecties-aanpak-in-de-huisartsenpraktijk.html
	Tool	Domus Medica Advies HIV-screening door huisartsen	2017	https://www.domusmedica.be/varia/docman-alles/publiek/praktijkdocumenten/steekkaarten-en-andere-hulpmiddelen/bloed-bloedvormende-organen-en-immuunstelsel/1328-advies-hiv-screening-door-huisartsen.html
	Guidance	Ghapro & Pasop Leidraad voor medische consultaties bij sekswerkers	2014	http://www.ghapro.be/nl/ghapro-publicaties_andere.html
	Tool	Ghapro & Pasop samenvattingsschema uit leidraad	2014	http://www.ghapro.be/nl/ghapro-publicaties_andere.html
	Guidance	BABCOP Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk en steekkaart	2012	https://upb-avb.be/nl/news/antibioticagids-van-bapcoc-nieuwe-editie/
Netherlands	Guidance	NHG Standaard M82: Het SOA consult	2013	https://www.nhg.org/standaarden/samenvatting/het-soa-consult https://www.nhg.org/standaarden/ volledig/nhg-standaard-het-soa-consult
	Tool	NHG: Beslisboom soa-consult		https://www.nhg.org/sites/default/files/content/nhg_org/uploads/standaard/download/beslisboomkaart_a4_formaat_opwebsites_plaatsen_versie_nov_2013.pdf
	Guidance	Nederlandse Vereniging voor Dermatologie en Venereologie Multidisciplinaire Richtlijn Seksueel Overdraagbare Aandoeningen voor de 2e Lijn	2018	https://www.nhg.org/sites/default/files/content/nhg_org/uploads/multidisciplinaire_richtlijn_soa_herziening_2018.pdf
UK	Guideline	BASHH National guideline for consultations requiring sexual history taking	2013	https://www.bashhguidelines.org/current-guidelines/sexual-history-taking-and-sti-testing/ https://www.bashhguidelines.org/media/1078/sexual-history-taking-guideline-2013-2.pdf ;
	Guidance	BASHH CEG guidance on tests for sexually transmitted infections	2015	https://www.bashhguidelines.org/media/1084/sti-testing-tables-2015-dec-update-4.pdf



Australia	Guideline	Australian sexually transmitted infection & HIV testing guidelines for asymptomatic men who have sex with men	2014	https://www.clinicalguidelines.gov.au/portal/2489/australian-sexually-transmitted-infection-and-hiv-testing-guidelines-2014-asymptomatic
	Tool	Quick guide to STI testing. Who? Why? Which? What?	2017	http://ww2.health.wa.gov.au/Silver-book
	Tool	Quick reference to STI management	2017	http://ww2.health.wa.gov.au/Silver-book
	Tool	STI/HIV testing tool Australia New South Wales	2017	https://stipu.nsw.gov.au/gp/hiv-and-sti-clinical-management/
Europe	Guideline	European guideline for the organization of a consultation for sexually transmitted infections	2012	http://journals.sagepub.com/doi/abs/10.1258/ijsa.2012.012115?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&
US	Summary	CDC: Screening Recommendations and Considerations Referenced in 2015 STD Treatment Guidelines and Original Sources	2015	https://www.cdc.gov/std/tg2015/screening-recommendations.htm
	Summary	CDC: Pocked guide - Sexually transmitted diseases treatment guidelines	2015	https://www.cdc.gov/std/tg2015/default.htm
	Summary	CDC: Wall chart - Sexually transmitted diseases treatment guidelines	2015	https://www.cdc.gov/std/tg2015/default.htm
	Guideline	CDC and Prevention: Sexually Transmitted Diseases Treatment Guidelines	2015	https://www.cdc.gov/std/tg2015/default.htm
Canada	Guideline	Canadian guidelines on STIs	2010 updates 2016	https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections.html



5. GUIDANCE DOCUMENTS FOR PARTNER MANAGEMENT

Table 6 – Retrieved documents for the partner management

Country	Format	Document	Year	Internetlink
Belgium	Guidance	Domus Medica Praktijktool Seksueel Overdraagbare infecties: aanpak in de huisartsenpraktijk	2017	https://www.domusmedica.be/documentatie/downloads/praktijkdocumenten/richtlijnen/1332-praktijktool-seksueel-overdraagbare-infecties-aanpak-in-de-huisartsenpraktijk.html
	Tool	Domus Medica Advies HIV-screening door huisartsen	2017	https://www.domusmedica.be/varia/docman-alles/publiek/praktijkdocumenten/steekkaarten-en-andere-hulpmiddelen/b-bloed-bloedvormende-organen-en-immuunstelsel/1328-advies-hiv-screening-door-huisartsen.html
	Guidance	Ghapro & Pasop Leidraad voor medische consultaties bij sekswerkers	2014	http://www.ghapro.be/nl/ghapro-publicaties_andere.html
	Tool	Ghapro & Pasop samenvattingsschema uit leidraad	2014	http://www.ghapro.be/nl/ghapro-publicaties_andere.html
	Guidance	BABCOP Belgische gids voor anti-intectieuze behandeling in de ambulante praktijk en steekkaart	2012	https://upb-avb.be/nl/news/antibioticagids-van-bapcoc-nieuwe-editie/
Netherlands	Guidance	NHG Standaard M82: Het SOA consult	2013	https://www.nhg.org/standaarden/samenvatting/het-soa-consult https://www.nhg.org/standaarden/volledig/nhg-standaard-het-soa-consult
	Tool	NHG: Beslisboom soa-consult		https://www.nhg.org/sites/default/files/content/nhg_org/uploads/standaard/download/beslisboomkaart_a4_formaat_opwebsites_plaatsen_versie_nov_2013.pdf
	Guidance	Nederlandse Vereniging voor Dermatologie en Venereologie Multidisciplinaire Richtlijn Seksueel Overdraagbare Aandoeningen voor de 2e Lijn	2018	https://www.nhg.org/sites/default/files/content/nhg_org/uploads/multidisciplinaire_richtlijn_soa_herziening_2018.pdf
UK	Guideline	BASHH National guideline for consultations requiring sexual history taking	2013	https://www.bashhguidelines.org/current-guidelines/sexual-history-taking-and-sti-testing/ https://www.bashhguidelines.org/media/1078/sexual-history-taking-guideline-2013-2.pdf
	Guidance	BASHH CEG guidance on tests for sexually transmitted infections	2015	https://www.bashhguidelines.org/media/1084/sti-testing-tables-2015-dec-update-4.pdf



Australia	Guideline	Australasian contact tracing guidelines for primary care practitioners	2011	http://contacttracing.ashm.org.au/
	Guideline	Australian sexually transmitted infection & HIV testing guidelines for asymptomatic men who have sex with men	2014	https://www.clinicalguidelines.gov.au/portal/2489/australian-sexually-transmitted-infection-and-hiv-testing-guidelines-2014-asymptomatic
	Tool	Quick guide to STI testing. Who? Why? Which? What?	2017	http://ww2.health.wa.gov.au/Silver-book
	Tool	Quick reference to STI management	2017	http://ww2.health.wa.gov.au/Silver-book
	Tool	STI/HIV testing tool Australia New South Wales	2017	https://stipu.nsw.gov.au/gp/hiv-and-sti-clinical-management/
Europe	Guideline	European guideline for the organization of a consultation for sexually transmitted infections	2012	http://journals.sagepub.com/doi/abs/10.1258/ijisa.2012.012115?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&
US	Summary	CDC: Screening Recommendations and Considerations Referenced in 2015 STD Treatment Guidelines and Original Sources	2015	https://www.cdc.gov/std/tg2015/screening-recommendations.htm
	Summary	CDC: Pocked guide - Sexually transmitted diseases treatment guidelines	2015	https://www.cdc.gov/std/tg2015/default.htm
	Summary	CDC: Wall chart - Sexually transmitted diseases treatment guidelines	2015	https://www.cdc.gov/std/tg2015/default.htm
	Guideline	CDC and Prevention: Sexually Transmitted Diseases Treatment Guidelines	2015	https://www.cdc.gov/std/tg2015/default.htm
Canada	Guideline	Canadian guidelines on STIs	2010 update s 2016	https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections.html



6. QUALITY APPRAISAL

6.1. Quality appraisal tools

6.1.1. Guidelines

The AGREE II evaluation score was used to critically appraise guidelines retrieved (Table 7).

Table 7 – AGREE II instrument

Critical appraisal of clinical practice guidelines - AGREE II

Domain 1. Scope and Purpose

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Domain 2. Stakeholder Involvement

4. The guideline development group includes individuals from all the relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.

Domain 3. Rigour of Development

7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.

Domain 4. Clarity of Presentation

**Critical appraisal of clinical practice guidelines - AGREE II**

15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.

Domain 5. Applicability

18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/ or auditing criteria.

Domain 6. Editorial Independence

22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

Table 8 – AGREE II scores of retrieved guidelines for the diagnosis and/or the management of gonorrhoea

Country/ Organization	Title	Standardised Score /100						Final Appraisal /10	Inclusion / exclusion
		Scope	Stakeholder involvement	Rigour of development	Clarity	Applicability	Editorial Independence		
Canada	Canadian STI guidelines 2010 - supplements 2014 & 2016	89	61	57	97	54	25	6.4	excluded
Europe	Bignell C, et al. 2013 International Journal of STD & AIDS 24(2):85-92 - 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults	94	72	60	89	42	100	7.6	included
International / WHO	WHO guidelines for the treatment of Neisseria gonorrhoeae 2016	100	53	95	100	81	100	8.8	included
UK / BASHH	UK national guideline for gonorrhoea laboratory testing, 2012	100	83	70	78	48	100	8.0	included



UK / BASHH	Bignell C, et al. 2011 International Journal of STD & AIDS 22(10):541-7 - UK national guideline for the management of gonorrhoea in adults, 2011	100	78	61	75	21	100	7.3	excluded
USA / CDC	Workowski KA, et al. 2015 Morbidity & Mortality Weekly Report. Recommendations & Reports 64(RR-03):1-137 - Sexually transmitted diseases treatment guidelines, 2015.	83	64	77	78	71	100	7.9	included
USA / USPSTF	LeFevre ML, et al. 2014 Annals of Internal Medicine 161(12):902-10 - Screening for Chlamydia and gonorrhea: U.S. Preventive Services Task Force recommendation statement	100	64	91	86	69	100	8.5	included
	Nelson HD, Zakher B, Cantor A, Deagas M, Pappas M. Screening for Gonorrhea and Chlamydia: Systematic Review to Update the U.S. Preventive Services Task Force Recommendations. Evidence Synthesis No. 115. AHRQ Publication No. 13-05184-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.								
USA/CDC	Kidd S, Workowski K. Clin. Infect. Dis. - Volume 61, Issue 8, pp. 15 - published 2015-01-01. Management of Gonorrhea in Adolescents and Adults in the United States	100	56	84	86	63	100	8.1	included


Table 9 – AGREE scores of retrieved guidelines for the diagnosis and/or the management of syphilis

Country / Organization	Title	Standardised Score /100						Final Appraisal /10	Inclusion / Exclusion
		Scope	Stakeholder involvement	Rigour of development	Clarity	Applicability	Editorial Independence		
Canada	Canadian STI guidelines 2010 -supplements 2014 & 2016	89	61	57	97	54	25	6.4	excluded
Europe / IUSTI	Janier M, et al. 2014 Journal of the European Academy of Dermatology & Venereology 28(12):1581-93 - 2014 European guideline on the management of syphilis.	58	72	60	78	69	100	7.3	Included for the reason of the adapted reverse algorithm
International / WHO	WHO guidelines for the treatment of Treponema pallidum (syphilis) 2016	100	56	93	100	88	100	8.9	included
International / WHO	WHO guideline on syphilis screening and treatment for pregnant women 2016	94	58	91	100	85	100	8.8	included
UK / BASHH	Kingston M, et al. 2016 International Journal of STD & AIDS 27(6):421-46 - UK national guidelines on the management of syphilis 2015	83	83	78	86	77	100	8.5	included
USA / CDC	Workowski KA, et al. 2015 Morbidity & Mortality Weekly Report. Recommendations & Reports 64(RR-03):1-137 - Sexually transmitted diseases treatment guidelines, 2015	83	64	77	78	71	100	7.9	included
USA / CDC	Ghanem KG 2015 Clinical Infectious Diseases 61(8):15 - Management of Adult Syphilis: Key Questions to Inform the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines	92	61	88	83	71	100	8.2	included
USA / USPSTF	USPSTF. 2016 Jama 315(21):2321-7 - Screening for Syphilis Infection in Nonpregnant Adults and Adolescents: US Preventive	100	64	94	81	67	100	8.4	included



Services Task Force Recommendation Statement

Cantor A, Nelson HD, Daeges M, Pappas M. Screening for Syphilis in Nonpregnant Adolescents and Adults: Systematic Review to Update the 2004 U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 136. AHRQ Publication No. 14-05213-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2016

6.1.2. Diagnostic accuracy studies

The quality assessment tool used for the quality assessment of diagnostic accuracy studies was QUADAS 2 Tool (Table 10).

Table 10 – QUADAS 2 tool: Risk of bias and applicability judgments

Domain 1: Patient selection	
A. Risk of bias	
Describe methods of patient selection:	
• Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear
• Was a case-control design avoided?	Yes/No/Unclear
• Did the study avoid inappropriate exclusions?	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting):	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) (if more than 1 index test was used, please complete for each test)	
A. Risk of bias	



Describe the index test and how it was conducted and interpreted:

- | | |
|---|----------------|
| • Were the index test results interpreted without knowledge of the results of the reference standard? | Yes/No/Unclear |
| • If a threshold was used, was it pre-specified? | Yes/No/Unclear |

Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
---	------------------------

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
---	---------------------------

Domain 3: Reference standard

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted:

- | | |
|---|----------------|
| • Is the reference standard likely to correctly classify the target condition? | Yes/No/Unclear |
| • Were the reference standard results interpreted without knowledge of the results of the index test? | Yes/No/Unclear |

Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
--	------------------------

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
---	---------------------------

Domain 4: Flow and timing

A. Risk of bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):

Describe the time interval and any interventions between index test(s) and reference standard:

- | | |
|---|----------------|
| • Was there an appropriate interval between index test(s) and reference standard? | Yes/No/Unclear |
| • Did all patients receive a reference standard? | Yes/No/Unclear |
| • Did patients receive the same reference standard? | Yes/No/Unclear |
| • Were all patients included in the analysis? | Yes/No/Unclear |

Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR
--	------------------------



6.1.2.1. Quality appraisal of selected primary studies for diagnosis

Table 11 – Methodological quality of the included primary studies for diagnosis of gonorrhoea– QUADAS 2

Study	RISK OF BIAS				APPLICABILITY CONCERNS			OVERALL
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	GRADE rating*
Chernesky 2005								Serious risk of bias
Cosentino 2012								No serious risk of bias
Fang 2012								Very serious risk of bias
Gaydos 2010								No serious risk of bias
Gaydos 2013								Serious risk of bias
Masek 2009								Very serious risk of bias
Moncada 2004								Serious risk of bias
Moncada 2009								Serious risk of bias
Ota 2009								Serious risk of bias
Rumyantseva 2015								Serious risk of bias
Schachter 2005								Very serious risk of bias
Schachter 2008								Very serious risk of bias
Sultan 2016								Serious risk of bias
Stewart 2012								No serious risk of bias
Taylor 2012								Serious risk of bias
Van Der Pol 2012a								No serious risk of bias
Van Der Pol 2012b								Very serious risk of bias



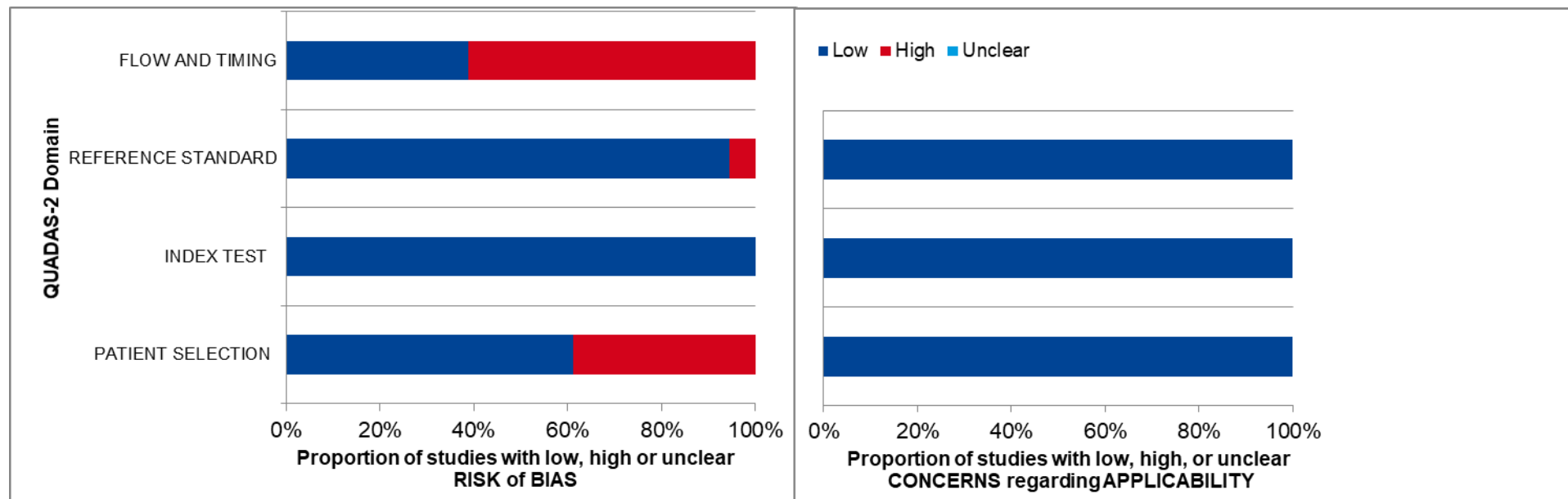
Van Der Pol 2017



😊 Low Risk 😞 High Risk ? Unclear Risk

*Overall rating chosen by: One high risk of bias criteria rating would lead to a serious risk of bias GRADE rating. Two high risk of bias criteria ratings would produce a very serious risk of bias. All smiley faces would mean no serious risk of bias

Figure 5 – Risk of bias summary graph for studies diagnosis gonorrhoea





6.1.3. Primary studies for therapeutic interventions

To assess risk of bias of randomised controlled trials, we used Cochrane Collaboration's tool (Table 13).

Table 13 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting

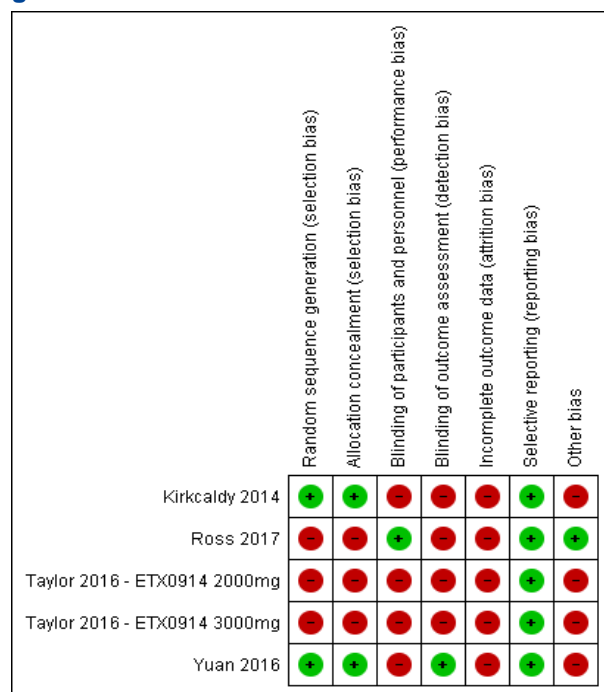


Domain	Support for judgement	Review authors' judgement
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

Key: Criteria rated as + =Low risk or - =High risk

6.1.3.1. Quality appraisal of selected primary studies for treatment of gonorrhoea

Figure 6 – Risk of bias summary of RCTs for treatment of gonorrhoea in adults – outcome: number cured



Key: + =Low risk and - =High risk

Figure 7 – Risk of bias graph of RCTs for treatment of gonorrhoea in adults – outcome: number cured

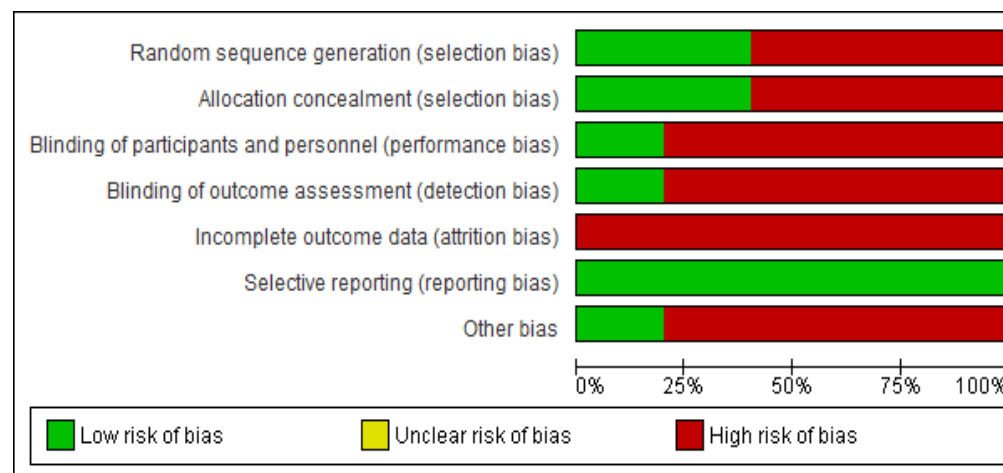




Figure 8 – Risk of bias summary of RCTs for treatment of gonorrhoea in adults – outcome: adverse events

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kirkcaldy 2014	+	+	-	-	-	+	+
Yuan 2016	+	+	-	+	-	+	+

Key: + = Low risk and - = High risk

Figure 9 – Risk of bias graph of RCTs for treatment of gonorrhoea in adults – outcome: adverse events

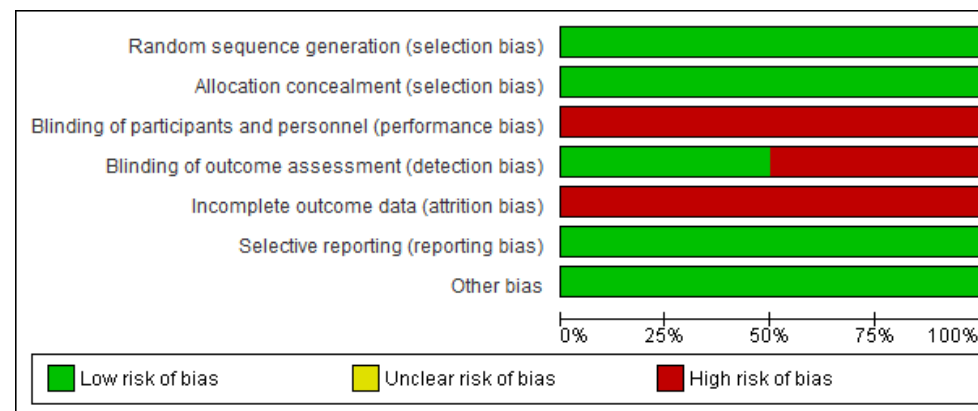
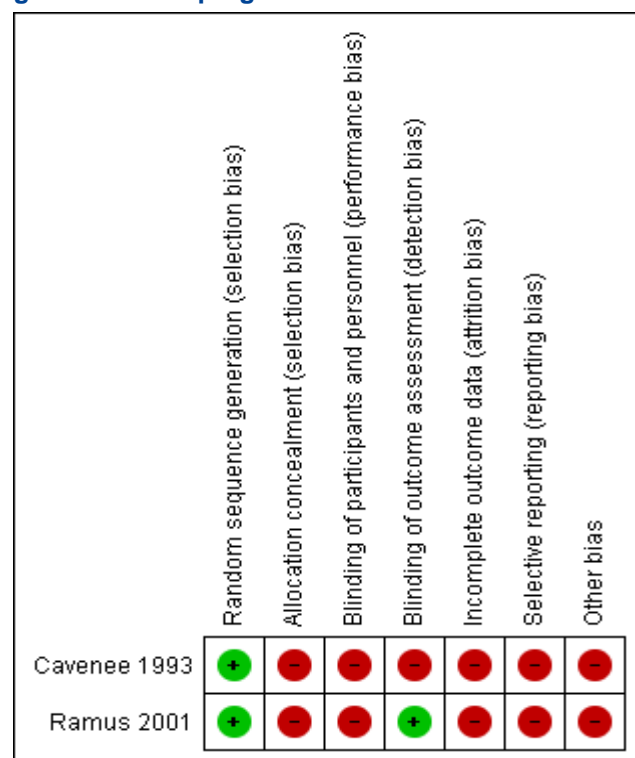




Figure 10 – Risk of bias summary of RCTs for treatment of gonorrhoea in pregnant women – outcome: number cured



Key: + = Low risk and - = High risk

Figure 11 – Risk of bias graph of RCTs treatment of gonorrhoea in pregnant women – outcome: number cured

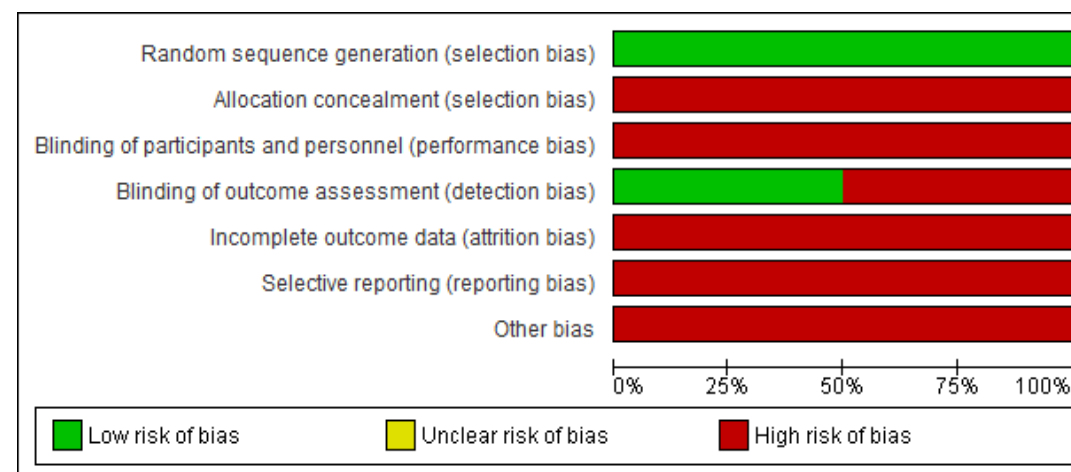
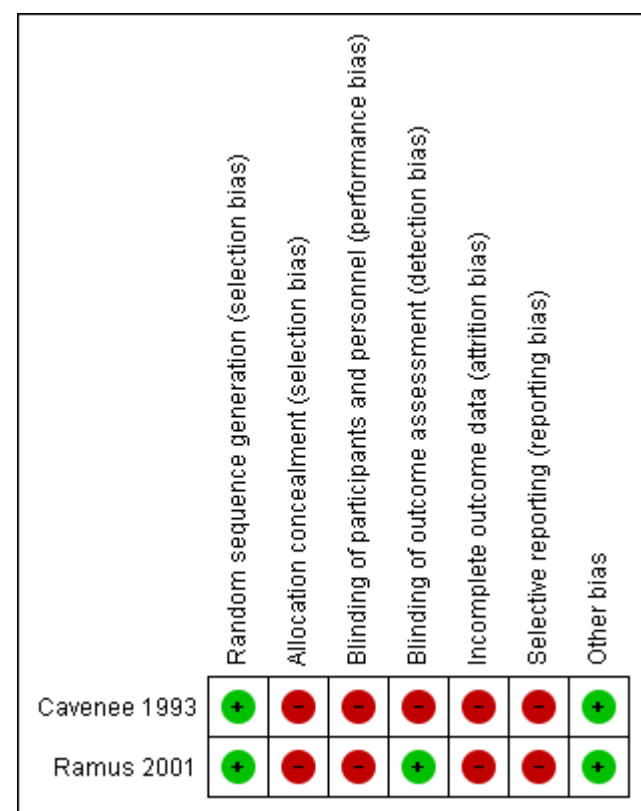


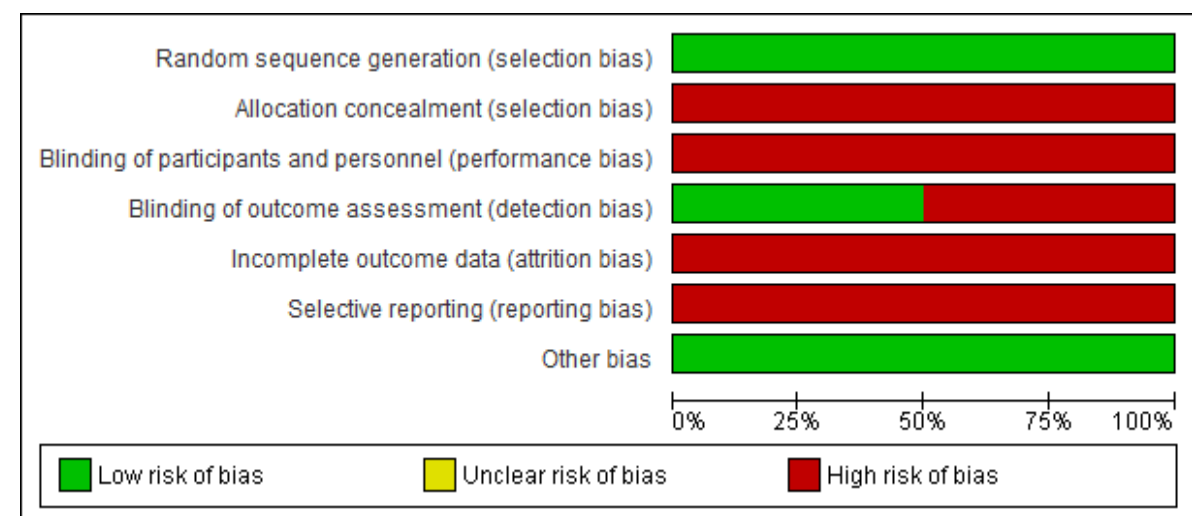


Figure 12 – Risk of bias summary of RCTs for treatment of gonorrhoea in pregnant women – outcome: adverse events



Key: + = Low risk and - = High risk

Figure 13 – Risk of bias summary graph of RCTs for treatment of gonorrhoea in pregnant women – outcome: adverse events





6.1.3.2. Quality appraisal of selected primary studies for treatment of syphilis

Figure 14 – Risk of bias summary of RCTs (treatment of syphilis in adults – serological response)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Andrade 2017	+	-	-	-	+	+	+
Cao 2017	-	-	-	-	+	+	+
Drago 2016	-	-	-	-	-	+	+
Hook 2002	+	-	-	+	-	+	+
Hook 2010	-	-	-	-	-	+	+
Liu 2017	+	-	-	-	+	+	+
Riedner 2005	+	+	-	+	+	+	+
Rolfs 1997	+	+	+	+	-	+	+
Smith 2004	-	-	-	-	-	+	+

Key: + = Low risk and - = High risk

Figure 15 – Risk of bias graph of RCTs (treatment of syphilis – serological response)

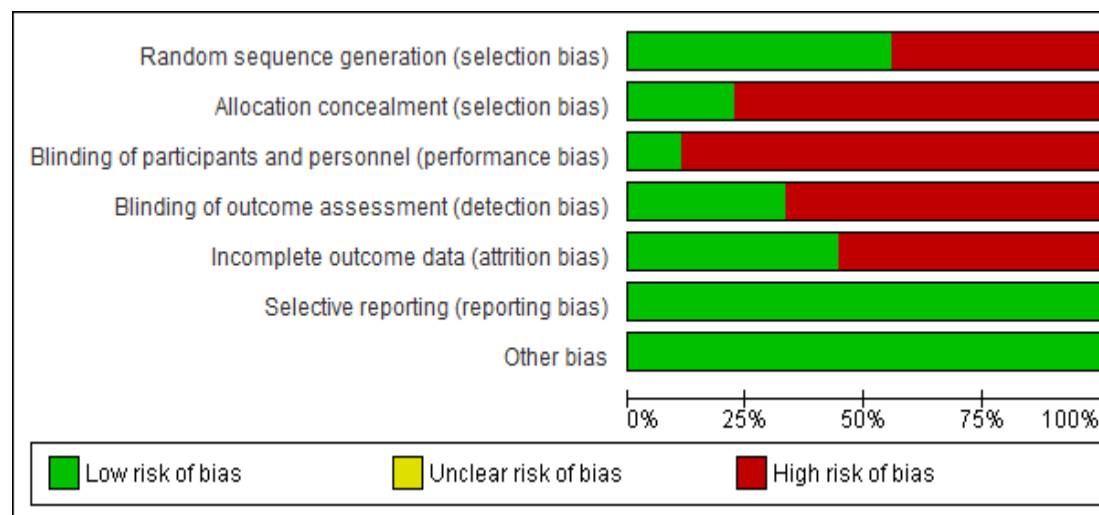



Table 14 – Quality appraisal of selected primary studies (cohort studies)

Domains	Options	Costa 2016	Ghanem 2006	Salado-Rasmussens 2016	Shao 2016
Domain 1: Selection bias					
• Can selection bias be sufficiently excluded?	Yes/No/Insufficient info to assess	No. Unbalanced number in each group. No significant baseline differences.	No. Unbalanced number in each group. Baseline characteristics differ for HIV and stage of syphilis although not statistically significant.	No. Groups unbalanced due to retrospective design. CD4 cell count and proportion on cART were different at baseline between groups.	No. Unbalanced number in each group. Baseline differences for stage of syphilis. Statistical differences not provided.
• Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?	Yes/No/Insufficient info to assess	Author reports that sex, age, and other confounders did not affect response to treatment.	Multivariate analysis not done as sample size too small.	No. There is no discussion of confounding factors.	No. Confounding factors not taken into account in analysis. Baseline differences were present for stage of syphilis.
Domain 2: Detection bias					
• Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?	Yes/No/Insufficient info to assess	Yes.	Yes	Yes.	Yes.
• Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?	Yes/No/Insufficient info to assess	Yes for primary outcome.	Yes for primary outcome.	Yes.	Yes.



Domains	Options	Costa 2016	Ghanem 2006	Salado-Rasmussens 2016	Shao 2016
<ul style="list-style-type: none"> Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? 	Yes/No/Insufficient info to assess	Retrospective design.	Retrospective design.	Retrospective design.	Retrospective design.
<ul style="list-style-type: none"> Is the assessment of outcome made blind to exposure status? 	Yes/No/Insufficient info to assess	No.	No.	No.	No.
<ul style="list-style-type: none"> If no to question 6, does this have an impact on the assessment of the outcome? 	Yes/No/ Not possible in this type of exposure /Insufficient info to assess	No. Serological response reported.	No. Serological response reported.	No. Serological response reported.	No. Serological response reported.
<ul style="list-style-type: none"> Is the follow-up sufficiently long to measure all relevant outcomes? 	Yes/No/Insufficient info to assess	Yes.	Yes	Yes.	Yes.
Domain 3: Attrition bias					
<ul style="list-style-type: none"> Can selective loss-to-follow-up be sufficiently excluded? 	Yes/No/Insufficient info to assess	Insufficient info to assess.	Insufficient info to assess.	Insufficient info to assess.	Insufficient info to assess.


Table 15 – Quality appraisal of selected primary studies (cohort studies) continued

Domains	Options	Tsai 2014	Xiao 2017	Yang 2016	Yang 2014
Domain 1: Selection bias					
<ul style="list-style-type: none"> Can selection bias be sufficiently excluded? 	Yes/No/Insufficient info to assess	No. Unbalanced number in each group. Baseline characteristics similar except for patients with secondary and early latent syphilis.	No. Unbalanced groups as one treatment only given if patient allergic to penicillin or refuse injection. No significant baseline differences.	No. Unbalanced number in each group. Baseline characteristics differ for a number of criteria, including: secondary syphilis, CD4 count, PVL, prior syphilis, taking cART and mean log ₁₀ PVL.	Yes. No significant baseline differences.
<ul style="list-style-type: none"> Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? 	Yes/No/Insufficient info to assess	Multivariate analysis to assess associations to serological response.	No. Authors discuss limitations of confounding factors but not taken into account in the analysis. Baseline comparable.	Multivariate analysis to assess associations to serological response.	Insufficient info to assess. Multivariate analysis used but unclear which factors were considered as only those associated with serological response are stated.
Domain 2: Detection bias					
<ul style="list-style-type: none"> Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? 	Yes/No/Insufficient info to assess	Yes.	Yes.	Yes.	Yes.



Domains	Options	Tsai 2014	Xiao 2017	Yang 2016	Yang 2014
<ul style="list-style-type: none"> Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? 	Yes/No/Insufficient info to assess	Yes for primary outcome.	Yes for primary outcome.	Yes for primary outcome.	Yes.
<ul style="list-style-type: none"> Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? 	Yes/No/Insufficient info to assess	Retrospective design.	Retrospective design.	Retrospective design.	Yes
<ul style="list-style-type: none"> Is the assessment of outcome made blind to exposure status? 	Yes/No/Insufficient info to assess	No.	No.	No.	No.
If no to question 6, does this have an impact on the assessment of the outcome?	Yes/No/ Not possible in this type of exposure /Insufficient info to assess	No. Serological response reported.	No. Serological response reported.	No. Serological response reported.	No. Serological response reported.
<ul style="list-style-type: none"> Is the follow-up sufficiently long to measure all relevant outcomes? 	Yes/No/Insufficient info to assess	Yes.	Yes.	Yes.	Yes.
Domain 3: Attrition bias					
<ul style="list-style-type: none"> Can selective loss-to-follow-up be sufficiently excluded? 	Yes/No/Insufficient info to assess	Insufficient info to assess.	Insufficient info to assess.	Insufficient info to assess.	Yes.


Table 16 – Quality appraisal of selected primary studies (cohort studies) continued

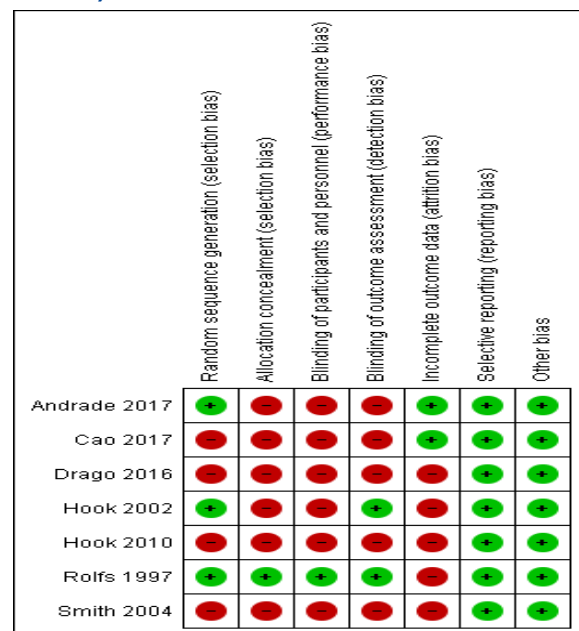
Domains	Options	Wong 2008
Domain 1: Selection bias		
• Can selection bias sufficiently be excluded?	Yes/No/Insufficient info to assess	No. Unbalanced numbers in each group. No significant baseline differences.
• Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?	Yes/No/Insufficient info to assess	No. Authors discuss limitations of confounding factors but not taken into account in the analysis. No significant baseline differences.
Domain 2: Detection bias		
• Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?	Yes/No/Insufficient info to assess	Yes.
• Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?	Yes/No/Insufficient info to assess	Yes for primary outcome.
• Is the likelihood that some eligible subjects might have the	Yes/No/Insufficient info to assess	Retrospective design.



Domains	Options	Wong 2008
outcome at the time of enrolment assessed and taken into account in the analysis?		
<ul style="list-style-type: none"> Is the assessment of outcome made blind to exposure status? 	Yes/No/Insufficient info to assess	No.
If no to question 6, does this have an impact on the assessment of the outcome?	Yes/No/ Not possible in this type of exposure /Insufficient info to assess	No. Serological response reported.
<ul style="list-style-type: none"> Is the follow-up sufficiently long to measure all relevant outcomes? 	Yes/No/Insufficient info to assess	Yes.
Domain 3: Attrition bias		
<ul style="list-style-type: none"> Can selective loss-to-follow-up be sufficiently excluded? 	Yes/No/Insufficient info to assess	Insufficient information to assess.



Figure 16 – Risk of bias summary of RCTs (treatment of syphilis in adults – adverse events)



Key: + = Low risk and - = High risk

Figure 17 – Risk of bias graph of RCTs (treatment of syphilis – adverse events)

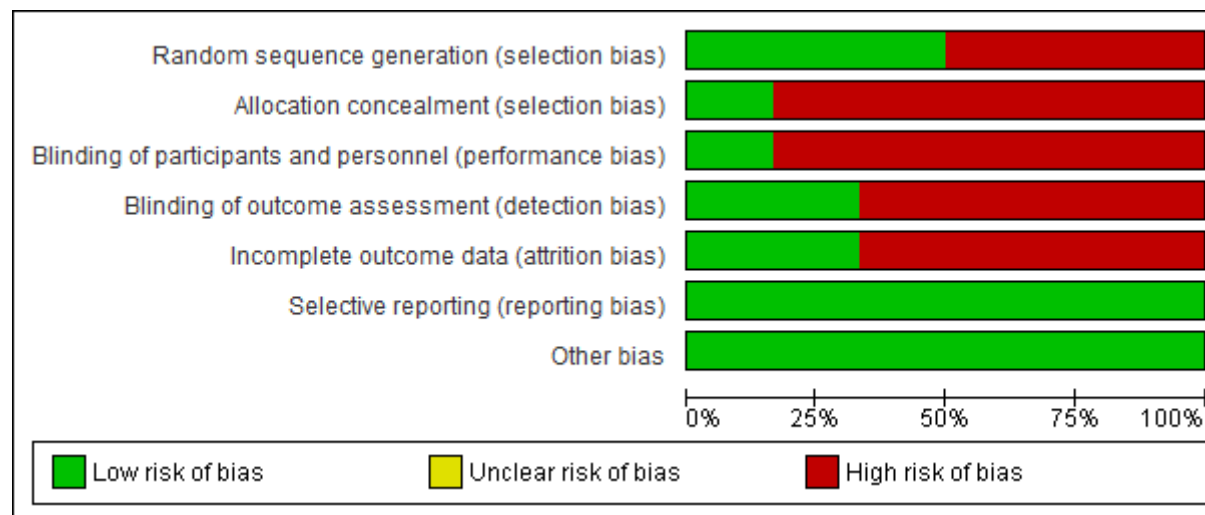
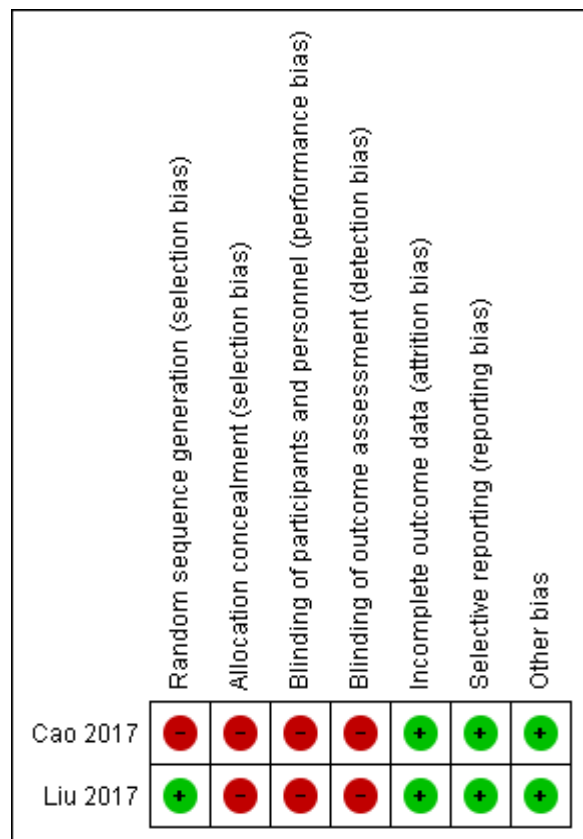


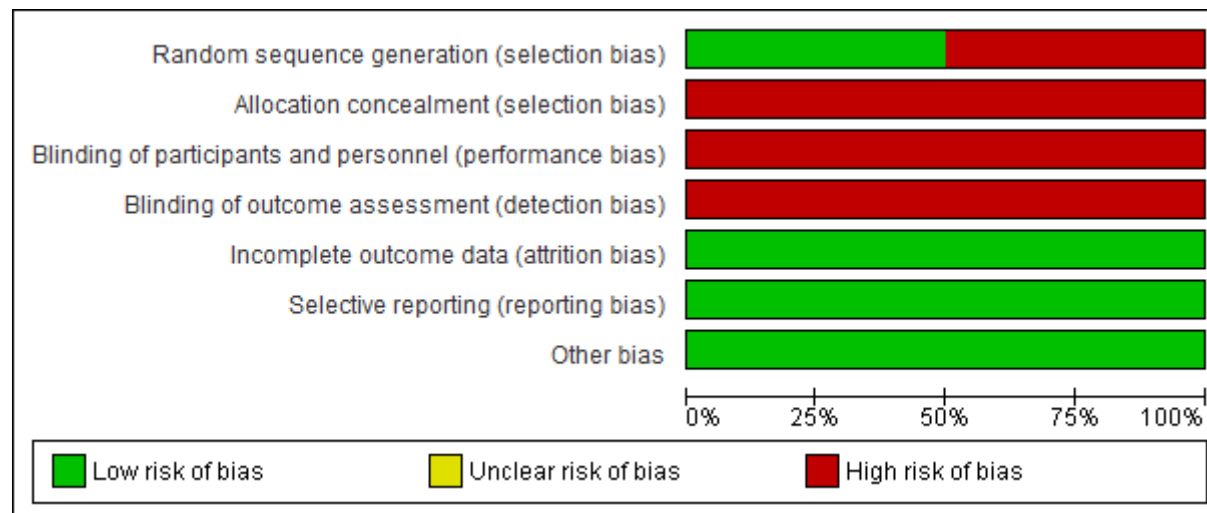


Figure 18 – Risk of bias summary of RCTs (treatment of syphilis in adults – clinical cure)



Key: + = Low risk and - = High risk

Figure 19 – Risk of bias graph of RCTs (treatment of syphilis – clinical cure)





7. EVIDENCE TABLES BY CLINICAL QUESTION

7.1. Diagnosis of gonorrhea

7.1.1. Nucleic acid amplification Tests (NAATs) and culture

7.1.1.1. Individual studies

Table 17 – Evidence table of diagnostic studies regarding the diagnosis of gonorrhoea

Men

Ability of New APTIMA CT and APTIMA GC Assays to Detect Chlamydia trachomatis and Neisseria gonorrhoeae in Male Urine and Urethral Swabs. Chernesky 2005 ²¹⁰	
Methods	
• Design	Prospective multicenter study.
• Source of funding and competing interest	Not stated.
• Setting	6 STI clinics in Canada (Hamilton, Ontario) and United States (New Orleans, Birmingham, Jacksonville, Pittsburgh and San Francisco).
• Sample size	Enrolled 1322 men.
• Time interval between tests	Not reported.
• Statistical analysis	Sensitivity, specificity, positive predictive value and negative predictive value were calculated.
Patient characteristics	
• Eligibility criteria	Men between the ages of 15 – 77 years from 6 sexually transmitted disease clinics from October 2002 to January 2003. Excluded if they could not concurrently provide a first void urine of the first 25 ml of micturition and two physician-collected urethral swabs, if they had urinated within 1 hour, if they had taken antibiotics within the last 21 days or if they could not provide a valid informed consent.
• Patient characteristics	Mean age 28.5 years 62.2% non-Hispanic black, 24.6% white.
• Prevalence of disease	Not stated in general population. 13.8% prevalence in the study.
Interventions	



- | | |
|-------------------------------------|--|
| • TMA NG – urethral sample | Transcription mediated amplification (TMA) - urethra: Aptima NG test <ul style="list-style-type: none"> - GenProbe APTIMA GC - Positive result if both urethral swab and first catch urine positive on one or more of 2 NAATs; or positive on both tests for 1 or more specimen type - Blinding not reported. |
| • TMA NG – first catch urine | TMA – first catch urine: Aptima NG test <ul style="list-style-type: none"> - GenProbe APTIMA GC - What (including the provider's name if applicable), by whom and how, when - Positive result if both urethral swab and first catch urine positive on one or more of 2 NAATs; or positive on both tests for 1 or more specimen type - Blinding not reported. |
| • Reference standard | TMA and strand displacement assay (SDA) <ul style="list-style-type: none"> - GenProbe Aptima Combo 2 and BD ProbeTec energy transfer amplified DNA assay - Blinding not reported. |

Results

- | | |
|---------------------------------------|--|
| • TMA NG – urethral swab | TP: 182
FP: 31
FN: 1
TN: 1103
Sensitivity: 99.5% (97-100)
Specificity: 97.3% (96.1-98.1)
PPV: 85.4%
NPV: 99.3%
PLR: 36.38*
NLR: 0.01* |
| • TMA – NG – first catch urine | TP: 181
FP: 8
FN: 2
TN: 1130
Sensitivity: 98.9% (96.1-99.9)
Specificity: 99.3% (98.6-99.7)
PPV: 95.8%
NPV: 99.8%
PLR: 140.70* |



NLR: 0.01*

* Calculated using Review Manager

Limitations and other comments

- **Limitations** Serious risk of bias (patient flow and timing and unclear blinding).
No serious applicability/indirectness.
Figures given for TP, TN, FN, and FP do not add up to total population.
- **Authors' conclusion** The authors concluded that the TMA NG assay performed very well on first catch urine and urethral swabs from men.

Evaluation of Self-collected Glans and Rectal Swabs for Men Who Have Sex with Men for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae by Use of Nucleic Acid amplification Tests. Moncada 2009²¹¹

Methods

- **Design** Prospective cross-sectional study.
- **Source of funding and competing interest** This work was supported in part by each of the manufacturers of the diagnostic tests: Becton Dickinson Co. and Gen-Probe Inc.
- **Setting** A city sexually transmitted disease clinic in San Francisco, California, USA.
- **Sample size** Enrolled = 907 men
Results reported for n=882 for N. gonorrhoeae - reasons for drop outs not reported.
- **Time interval between tests** Not reported.
- **Statistical analysis** Sensitivity, specificity, positive predictive value and negative predictive value were calculated.

Patient characteristics

- **Eligibility criteria** Men who have sex with men who were attending the city sexually transmitted disease clinic were enrolled.
Subjects who had urinated within the previous one hour or who had received antibiotic therapy within the previous 21 days were excluded. Each participant provided self-collected rectal swab, first catch urine and finally clinician collected rectal swab specimens at the clinic visit.
- **Patient characteristics** Enrolled = 907 men
Symptomatic men 469 (51.7%) and asymptomatic men 438 (48.3%).
Results provided for 882 men without reason for drop outs.
- **Prevalence of disease** Prevalence estimation of the disease in the general population – not reported.



Study prevalence 9.4% (83/882).

Interventions

- TMA Combo – self and clinician collected**

Transcription-mediated amplification test (TMA):

 - Aptima Combo 2 (AC2), Gen-Probe Inc.
 - After sample self-collection was completed, the clinician examined the patient and obtained, in a randomized order, a rectal swab specimen for culture and the NAATs.
 - Technologists performing the tests were blinded to the results of any of the other tests.
- SDA BD ProbeTec – self and clinician collected**

Strand displacement amplification test (SDA):

 - ProbeTec; Becton Dickinson Company
 - After sample self-collection was completed, the clinician examined the patient and obtained, in a randomized order, a rectal swab specimen for culture and the NAATs.
 - Technologists performing the tests were blinded to the results of any of the other tests.
- Culture**

Culture:

 - Clinician obtained a rectal swab specimen for culture in a randomised order.
 - Cotton swabs for culture were streaked onto Thayer-Martin plates. They were immediately placed in candle jars and the jars were incubated at 36°C. At the end of each day cultures were transported into the San Francisco Public Health laboratory for final identification of the organism present.
 - Blinding not reported.
- Reference standard**

A true positive result was defined as a culture positive result, two or more positive nucleic acid amplification test (NAAT) results, or a single NAAT-positive result confirmed by an alternate amplification method (Aptima N. gonorrhoeae test).

 - Specimens that were uniquely positive by one NAAT received additional testing by another NAAT targeting alternate primers. Aptima N. Gonorrhoeae assay (Gen-rProbe Inc) which detects a region of the 16s rRNA different from that which AC2 detects was performed.

Results

- | | | |
|---|-----------------------------|------------------------------|
| TMA Combo – self collected rectal swab | <i>N. gonorrhoea</i> | <i>C. trachomatis</i> |
| | TP: 70 | TP: 54 |
| | FP: 0 | FP: 12 |
| | FN: 13 | FN: 0 |
| | TN: 799 | TN: 841 |
| | Sensitivity: 84.3% | Sensitivity: 81.8% |
| | Specificity: 100% | Specificity: 100% |
| | PPV: 100%* | |
| | NPV: 98.4%* | |
| | PLR: Not reported | |



	NLR: 0.1566*	
• TMA Combo – clinician collected rectal swab	<i>N. gonorrhoea</i> TP: 65 FP: 2 FN: 18 TN: 797 Sensitivity: 78.3% Specificity: 99.8% PPV: 97.0%* NPV: 97.8%* PLR: 312.86* NLR: 0.22*	<i>C. trachomatis</i> TP: 46 FP: 19 FN: 3 TN: 838 Sensitivity: 71.2% Specificity: 99.5%
• SDA BD ProbeTec – self collected rectal swab	<i>N. gonorrhoea</i> TP: 64 FP: 6 FN: 19 TN: 793 Sensitivity: 77.1% Specificity: 99.3% PPV: 91.4%* NPV: 97.7%* PLR: 102.68* NLR: 0.23*	<i>C. trachomatis</i> TP: 27 FP: 39 FN: 0 TN: 841 Sensitivity: 40.9% Specificity: 100%
• SDA BD ProbeTec – clinician collected rectal swab	<i>N. gonorrhoea</i> TP: 56 FP: 0 FN: 27 TN: 799 Sensitivity: 67.5% Specificity: 100.0% PPV: 100.0%* NPV: 96.7%* PLR: Not reported	<i>C. trachomatis</i> TP: 29 FP: 37 FN: 11 TN: 840 Sensitivity: 43.9% Specificity: 99.9%



	NLR: 0.33*	
• Culture – clinician collected rectal swab	<i>N. gonorrhoea</i> TP: 29 FP: 0 FN: 54 TN: 799 Sensitivity: 34.9% Specificity: 100.0% PPV: 100.0%* NPV: 93.7%* PLR: Not reported NLR:0.6506*	<i>C. trachomatis</i> TP: 12 FP: 54 FN: 0 TN: 837 Sensitivity: 18.2% Specificity: 100%

*Calculated using Review Manger

Limitations and other comments

- **Limitations** Serious risk of bias in patient flow and timing (unclear dropouts).
No serious applicability/indirectness.
- **Authors' conclusion** The authors concluded that self-collected rectal swabs from men sleeping with men are valid specimens for the detection of gonorrhoeae by SDA and AC2. The performance characteristics of the NAATs varied on the basis of the patient's symptoms, the prevalence, and the collection method used.

Detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in pharyngeal and rectal specimens using the BD Probetec ET system, the Gen-Probe Aptima Combo 2 assay and culture. Ota 2009²¹²

Methods

- **Design** Prospective cohort study
- **Source of funding and competing interest** Funding not reported and no competing interests.
- **Setting** Hassle Free Men's Clinic in Toronto, Canada
- **Sample size** 248 participants recruited, data collection was complete in 100% of study participants.
Details about the number of patients needed for the study was not reported.



• Time interval between tests	Not reported
• Statistical analysis	Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated.
Patient characteristics	
• Eligibility criteria	Male subjects presenting for symptomatic testing or asymptomatic screening for sexually transmitted infections between 1 December 2006 and 31 January 2008. Subjects were also eligible if they were presenting to receive treatment as an STI contact.
	Exclusion criteria: Subjects were excluded if their sexual contact was exclusively with women or if they were less than 18 years of age
• Patient characteristics	No baseline characteristics reported
• Prevalence of disease	Prevalence in the study = 8.7% (pharyngeal 8.1%, rectal 11.7%, urethral 6.8%)
Interventions	
• SDA BD ProbeTec - pharyngeal specimen	BD Probetec ET system (SDA) <ul style="list-style-type: none"> - NAAT that is based on strand displacement amplification technology. A fluorescent-labelled detector probe is used to detect amplified GC DNA. An inhibitor control was performed with every test. - Blinding not reported
• SDA BD ProbeTec - rectal specimen	BD Probetec ET system (SDA) <ul style="list-style-type: none"> - NAAT that is based on strand displacement amplification technology. A fluorescent-labelled detector probe is used to detect amplified GC DNA. An inhibitor control was performed with every test. - Blinding not reported
• Reference standard	Aptima Combo 2 (AC2) (TMA) and culture were used to determine true positives. <ul style="list-style-type: none"> - A "true positive" was defined as: (1) positive culture, (2) positive PT and AC2 at the same site or (3) a single positive NAAT and detection of the same organism by any method at another site (that is, pharynx, rectum or urethra). - The Aptima Combo 2 is a NAAT that is based on transcription-mediated amplification and involves replication of specific regions of 16S rRNA. A fluorescent-labelled detector probe is used to detect rRNA amplification product sequences. - GC culture specimens were plated on to New York City agar and incubated in CO₂ at 37°C and held for 72 hours. - Identification was confirmed by characteristic colonial morphology and Gram stain; positive oxidase, negative ortho-nitrophenyl-b-galactoside (ONPG), evidence of CTA glucose fermentation and lack of CTA maltose or sucrose fermentation. The Accuprobe (Gen-Probe, San Diego, CA, USA) Neisseria gonorrhoeae culture identification test was used to confirm identification. - Blinding (investigator) to clinical information and/or to index test results not reported.
Results	
• SDA BD ProbeTec - pharyngeal specimen	TP: 19 FP: 4 FN: 1 TN: 224



	Sensitivity: 95.0% Specificity: 98.2% PPV: 82.6% NPV: 99.6% PLR: 54.15* NLR: 0.051*
<ul style="list-style-type: none">• TMA Combo - pharyngeal specimen (<i>reference standard</i>)	TP: 19 FP: 1 FN: 1 TN: 227 Sensitivity: 95.0% Specificity: 99.6% PPV: 95.0% NPV: 99.6% PLR: 216.60* NLR: 0.050*
<ul style="list-style-type: none">• Culture - pharyngeal specimen (<i>reference standard</i>)	TP: 0 FP: Not estimable (insufficient data provided) FN: 20 TN: Not estimable (insufficient data provided) Sensitivity: 0% Specificity: Not estimable (insufficient data provided) PPV: Not estimable NPV: 91.9% PLR: Not estimable NLR: Not estimable
<ul style="list-style-type: none">• SDA BD ProbeTec - rectal specimen	TP: 27 FP: 0 FN: 2 TN: 219 Sensitivity: 93.1% Specificity: 100.0% PPV: 100.0%



	NPV: 99.1% PLR: Not estimable NLR: 0.069*
<ul style="list-style-type: none"> TMA Combo - rectal specimen (reference standard) 	TP: 29 FP: 0 FN: 0 TN: 219 Sensitivity: 100.0% Specificity: 100.0% PPV: 100.0% NPV: 100.0% PLR: Not estimable NLR: Not estimable
<ul style="list-style-type: none"> Culture - rectal specimen (reference standard) 	TP: 12 FP: Not estimable (insufficient data provided) FN: 17 TN: Not estimable (insufficient data provided) Sensitivity: Not estimable (insufficient data provided) Specificity: Not estimable (insufficient data provided) PPV: NA NPV: 92.8% PLR: Not estimable NLR: Not estimable
	*Calculated using Review Manager
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	Serious risk of bias due to patient selection. No serious applicability/indirectness. Study reported in Nelson 2014 systematic review using sub-group analysis of women without symptoms suggestive of bacterial STI, whereas whole cohort figures reported here.
<ul style="list-style-type: none"> Authors' conclusion 	The authors concluded that SDA and TMA combo detected gonorrhoea in clinician-collected pharyngeal and rectal samples in men who have sex with men with superior sensitivity compared to culture.



Nucleic Acid Amplification Tests in the Diagnosis of Chlamydial and Gonococcal Infections of the Oropharynx and Rectum in Men Who Have Sex With Men. Schachter 2008 ²¹³

Methods

• Design	Prospective cohort study
• Source of funding and competing interest	Funding not reported. Supported in part by each of the manufacturers of the diagnostic tests: Roche Molecular Systems (Branchburg, NJ), Becton, Dickinson and Co. (Sparks, MD), and Gen-Probe Inc. (San Diego, CA).
• Setting	San Francisco City STD Clinic
• Sample size	Total participants = 1,110 Number of participants required and details about any un-evaluable specimen was not reported.
• Time interval between tests	Not reported
• Statistical analysis	Sensitivity and specificity were calculated.

Patient characteristics

• Eligibility criteria	Men who have sex with men presenting at the STI clinic. Exclusion criteria not reported.
• Patient characteristics	Median age: 35.4 years Sexual orientation: 91% homosexual, 8% bisexual HIV status: 25% HIV positive Symptomatic: yes – 60.5%, no – 39.5%
• Prevalence of disease	Prevalence in the study = 8.7% (pharyngeal 8.1%, rectal 11.7%, urethral 6.8%)

Interventions

• SDA BD ProbeTec oropharyngeal specimen	- Becton Dickinson's ProbTec Assay (SDA) - Specimen was inoculated into M4 tubes and further inoculated into an AC2 specimen transport tube then processed. - Blinding (technologists) to clinical information and/or to index test results was reported
• TMA Combo - oropharyngeal specimen	- APTIMA Combo 2 assay (AC2) (TMA) - Specimen was inoculated into M4 tubes and further inoculated into an AC2 specimen transport tube then processed.



	- Blinding (technologists) to clinical information and/or to index test results was reported
• Culture - oropharyngeal specimen	- Inoculated Thayer-Martin plates were incubated at 36°C in 5% CO ₂ for 48 hours. Presumptive NG colonies were Gram stained, oxidase tested and sub-cultured onto chocolate agar. Pure cultures were confirmed by carbohydrate reaction tests. - Blinding (technologists) to clinical information and/or to index test results was reported.
• SDA BD ProbeTec - rectal specimen	Becton Dickinson's ProbTec Assay (SDA) - Specimen was inoculated into M4 tubes and further inoculated into an AC2 specimen transport tube then processed. - Blinding (technologists) to clinical information and/or to index test results was reported
• TMA Combo - rectal specimen	- APTIMA Combo 2 assay (AC2) (TMA) - Specimen was inoculated into M4 tubes and further inoculated into an AC2 specimen transport tube then processed. - Blinding (technologists) to clinical information and/or to index test results was reported.
• Culture - rectal specimen	- Inoculated Thayer-Martin plates were incubated at 36°C in 5% CO ₂ for 48 hours. Presumptive NG colonies were Gram stained, oxidase tested and sub-cultured onto chocolate agar. Pure cultures were confirmed by carbohydrate reaction tests. - Blinding (technologists) to clinical information and/or to index test results was reported.
• Reference standard	- True positives were defined as culture positive or AC2/PCR positive or A2/SDA positive or a single NAAT positive confirmed by an alternate NAAT - Blinding (technologists) to clinical information and/or to index test results was reported.

Results

• SDA BD ProbeTec - oropharyngeal specimen	<i>N. gonorrhoea</i> TP: 58 FP: 11 FN: 8 TN: 1000 Sensitivity: 87.9% Specificity: 98.9% PPV: 84%* NPV: 99.2%* PLR: 80.77* NLR: 0.99*	<i>C. trachomatis</i> TP: 6 FP: 1 FN: 0 TN: 1103 Sensitivity: 85.7% Specificity: 100%
• TMA Combo - oropharyngeal specimen	<i>N. gonorrhoea</i> TP: 58 FP: 23 FN: 8	<i>C. trachomatis</i> TP: 7 FP: 0 FN: 4



		TN: 988 Sensitivity: 87.9% Specificity: 97.7% PPV: 71.60%* NPV: 99.20%* PLR: 38.63* NLR: 0.12*	TN: 1099 Sensitivity: 100% Specificity: 99.6%
• Culture specimen	- oropharyngeal	<i>N. gonorrhoea</i> TP: 36 FP: 0 FN: 30 TN: 1011 Sensitivity: 54.5% Specificity: 100.0% PPV: 100%* NPV: 97.1%* PLR: Not estimable NLR: 0.45*	<i>C. trachomatis</i> TP: 4 FP: 3 FN: 0 TN: 1103 Sensitivity: 57.1% Specificity: 100%
• SDA BD ProbeTec specimen	- rectal	<i>N. gonorrhoea</i> TP: 69 FP: 1 FN: 9 TN: 998 Sensitivity: 88.5% Specificity: 99.9% PPV: 98.6%* NPV: 99.1%* PLR: 883.7* NLR: 0.12*	<i>C. trachomatis</i> TP: 41 FP: 5 FN: 2 TN: 1062 Sensitivity: 89.1% Specificity: 99.8%
• TMA Combo specimen	- rectal	<i>N. gonorrhoea</i> TP: 72	<i>C. trachomatis</i> TP: 43



	FP: 13 FN: 6 TN: 986 Sensitivity: 92.3% Specificity: 98.7% PPV: 84.7%* NPV: 99.4%* PLR: 0.85* NLR: 0.99*	FP: 3 FN: 24 TN: 1040 Sensitivity: 93.5% Specificity: 97.7%
<ul style="list-style-type: none"> Culture - rectal specimen 	<p><i>N. gonorrhoea</i></p> TP: 38 FP: 0 FN: 40 TN: 999 Sensitivity: 48.7% Specificity: 100.0% PPV: 100%* NPV: 96%* PLR: Not estimable NLR: 0.51*	<p><i>C. trachomatis</i></p> TP: 18 FP: 28 FN: 0 TN: 1064 Sensitivity: 39.1% Specificity: 100%
*Calculated using Review Manager		
Limitations and other comments		
<ul style="list-style-type: none"> Limitations 	<p>Very serious risk of bias due to patient selection, flow and timing.</p> <p>No serious applicability/indirectness.</p> <p>Use of PCR was discontinued after a preliminary evaluation of the first 205 men where the results for oropharyngeal swabs showed 78.9% specificity. This result was deemed unacceptable as 39/51 (76.5%) of the PCR positives were false positives. The sensitivity of PCR at this preliminary evaluation was 60.0% (12/20).</p>	
<ul style="list-style-type: none"> Authors' conclusion 	<p>Authors felt that it is feasible to use clinician collected oropharyngeal and rectal specimens for the identification of <i>C. Trachomatis</i> and <i>N. gonorrhoea</i> by AC2 (TMA Combo) or SDA. There are limitations with PCR assays.</p>	



The “3 in 1” Study: Pooling Self-Taken Pharyngeal, Urethral, and Rectal Samples into a Single Sample for Analysis for Detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in Men Who Have Sex with Men. Sultan 2016.²¹⁴

Methods

• Design	Prospective cross-sectional study.
• Source of funding and competing interest	Funded by local NHS bodies, Camden provider Services, and Guy's and St Thomas; NHS foundation Trust. The funders had no role in study design, data collection and interpretation or the decision to submit the work for publication.
• Setting	Sexual Health and HIV clinics for the Mortimer market Centre (site 1) and Guy's Hospital and St Thomas' Hospital (site 2) in the UK between October 2012 and August 2013. Two different collection methods for pooled samples were evaluated. Method A at site 1 and method B at site 2. All men underwent triple site testing (pharyngeal, urine/urethral and rectal specimens). Half way through the study, both sites switched to method B because early results suggested that method B was more effective and easier for clinic and laboratory staff members.
• Sample size	Authors calculated that assuming prevalence to be 10% among symptomatic men that a sample size of 1400 men would be required. N=1064
• Time interval between tests	Not reported.
• Statistical analysis	Sensitivity was reported without actual figures so could not be checked and no additional calculations could be done in Review Manager. Negative predictive value was reported for the overall results only.

Patient characteristics

• Eligibility criteria	Men having sex with men over 18 years of age were eligible to participate if they (i) requested testing for STIs, (ii) reported recent sexual contact with either trachomatis or gonorrhoeae or (iii) reported symptoms suggesting an STI. Patients were ineligible if they declined to participate or had received any antibiotics in the previous 4 weeks.
• Patient characteristics	Median age (interquartile range): 37 years (31-44) Symptomatic=72%; HIV positive=42%; reported having an STI in last year=47%.
• Prevalence of disease	Authors estimate 10% prevalence. Study prevalence 27%.

Interventions

• TMA Combo – pooled self-collected sample	Transcription mediated amplification (TMA): - Aptima Combo 2 (AC2) - Pooled self-collected samples from pharyngeal, urine/urethral and rectal specimens. - Blinding (investigator) not reported.
• TMA Combo – SOC	Transcription mediated amplification (TMA): - Aptima Combo 2 (AC2)



	<ul style="list-style-type: none"> - Testing from individual sites which are the current standard of care (SOC) testing. - Samples from pharyngeal, urine/urethral and rectal specimens. - Pharyngeal and rectal specimens collected by clinicians in a standardized way. - Allocation of the order of collection of specimens for each test was randomized and determined using previously prepared sealed envelopes, with the exception of urethral swab specimens, which were always obtained prior to voiding of urine. - Blinding (investigator) not reported.
• Reference standard	<p>True positive result defined as (i) positive culture results from any site, (ii) positive results from any anatomical site, confirmed using the respective aptima single-analyte assay or (iii) positive results from the pooled sample using the AC2 confirmed using the respective Aptima single-analyte assay.</p> <p>Negative results from any individual site using the AC2 were considered negative.</p> <ul style="list-style-type: none"> - Culture used Thayer-martin selective medium and incubated in 10% CO₂ at 37 °C for 48 h.

Results

• TMA Combo - Pooled sample	<p><i>N. gonorrhoea</i></p> <p>Overall: Sensitivity: 89.9% (85.8-93.1) and NPV: 96% (95-98)</p> <p>Method A: Sensitivity: 87.5% (81.5-92.1)</p> <p>Method B: Sensitivity: 93.2% (87.1-97.0)</p> <p>Pooled excluding pharynx: Sensitivity: 94.4% (90.6-97.0) By anatomical site of infection:</p> <p>Urethra: Sensitivity: = 97.9% (93.9-99.6)</p> <p>Rectum: Sensitivity: = 93.4% (88.5-96.7)</p> <p>Pharynx: Sensitivity: = 89.1% (83.1-93.5)</p>	<p><i>C. trachomatis</i></p> <p>Overall: Sensitivity: 91.9% (86.5-95.6)</p> <p>Method A: Sensitivity: 90.9% (82.9-96.0)</p> <p>Method B: Sensitivity: 93.1% (84.5-97.7)</p> <p>Pooled excluding pharynx: Sensitivity: 94.2% (89.2-97.3) By anatomical site of infection:</p> <p>Urethra: Sensitivity: = 98.6% (92.6-100.0)</p> <p>Rectum: Sensitivity: = 92.1% (85.0-96.5)</p> <p>Pharynx: Sensitivity: = 69.2% (38.6-90.9)</p>
• TMA Combo - SOC testing	<p><i>N. gonorrhoea</i></p> <p>Overall: Sensitivity: 98.6% (96.4-99.6) and NPV: 99% (99-100)</p> <p>Method A: Sensitivity: 98.8% (95.8-99.9)</p> <p>Method B: Sensitivity: 98.3% (94.0-99.8)</p> <p>Pooled excluding pharynx: Sensitivity: 98.3% (95.6-99.5)</p>	<p><i>C. trachomatis</i></p> <p>Overall: Sensitivity: 96.3% (92.2-98.6)</p> <p>Method A: Sensitivity: 97.8% (92.3-99.7)</p> <p>Method B: Sensitivity: 94.5% (86.6-98.5)</p> <p>Pooled excluding pharynx: Sensitivity: 96.2% (91.9-98.6)</p>



Limitations and other comments

- Limitations**

Methods A and B: Patients were asked to place self-taken urethral swabs into a universal container (method A) or directly into the AC2 urine tube (method B). For method A, after removal of 2ml of urine, both self-taken swabs were added to the first void urine sample to produce the pooled specimen. For method B, the self-taken swabs were swirled and compressed against the inner wall of the tube, to release swab material into the C2 urine tube, and then were removed and discarded. The 2ml of urine was then added to this AC2 tube to form the method B pooled specimen.

Serious risk of bias (patient flow and timing and unclear blinding).
No serious applicability/indirectness.
- Authors' conclusion**

The authors concluded that the sensitivity for pooled testing was significantly lower than standard of care testing. However, this increased when pharynx-only infections were excluded

Evaluation of the Roche Cobas CT/NG Test for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae in Male Urine. Taylor 2012²¹⁵

Methods

- Design**

Prospective cohort study – men recruited for VENUS trial.
- Source of funding and competing interest**

Study supported by Roche Molecular Systems.
- Setting**

11 geographically distinct specimen collection sites, including OB/GYN practices, family planning and STD clinics.
- Sample size**

N=790 screened; with n=768 enrolled.
Reasons for exclusions: withdrew consent after enrollment=3, errors in sample collection and/or storage=9, invalid cobas CT test results after the initial and repeated testing=10.
- Time interval between tests**

Tests done performed at 4 testing sites in the US. Time frames not reported.
- Statistical analysis**

Sensitivity, specificity, positive predictive value and negative predictive value were calculated.

Patient characteristics

- Eligibility criteria**

Men who were 14 years or older and willing and able to provide written, informed consent.
Participants were excluded if they had been previously enrolled in the study or used antimicrobials active against gonorrhoea during the preceding 21 days.
- Patient characteristics**

Mean age: 55% ≤30y
Ethnicity: Non-Hispanic 82.7%, Hispanic 15.1%, Unknown 2.2%.
Race: African-American/black 82.7%, Caucasian/white 32.9%, Other 1.3%, American Indian/Alaskan native 0.4%, Native Hawaiian/Pacific Islander 0.1%, Unknown 0.1%



Asymptomatic 61.5%, Symptomatic 38.5%.			
• Prevalence of disease	71 (9.2%) had gonorrhoea in this study.		
Interventions			
• PCR C4800 - first catch urine	Roche C4800 Cobas Amplicor CT/NG test: <ul style="list-style-type: none">- Roche C4800 Cobas Amplicor CT/NG test - polymerase chain reaction amplification occurs (PCR)- Site: first catch urine sample.- Blinding not reported.		
• TMA Combo - first catch urine	TMA - Gen-Probe Aptima Combo 2 (AC2) assay.		
• TMA Combo - urethral swab	<ul style="list-style-type: none">- Site: first catch urine sample and urethral swab.- Blinding not reported.		
• SDA BD Qx - first catch urine	SDA - Becton Dickinson (BD) ProbeTec CT/GC Q assay		
• SDA - urethral swab	<ul style="list-style-type: none">- Site: first catch urine sample and urethral swab.- Blinding not reported.		
• Reference standard	Patient infected status: <ul style="list-style-type: none">- Positive if at least 2 NAATs with different target regions gave a positive result in the urethral swab and /or the urine specimen.- Site: first catch urine sample and urethral swabs.- Blinding (investigator) to clinical information and/or to index test results not reported.		
Results			
• PCR C4800 - first catch urine	<table><tr><td><i>N. gonorrhoea</i> TP: 71 FP: 2 FN: 0 TN: 695 Sensitivity: 100% (94.9-100) Specificity: 99.7% (99.0-99.9) PPV: 97.3%* NPV: 100%* PLR: Not reported NLR: Not reported</td><td><i>C. trachomatis</i> TP: 123 FP: 3 FN: 3 TN: 639 Sensitivity: 97.6% (93.2-99.2) Specificity: 99.5% (98.6-99.8)</td></tr></table>	<i>N. gonorrhoea</i> TP: 71 FP: 2 FN: 0 TN: 695 Sensitivity: 100% (94.9-100) Specificity: 99.7% (99.0-99.9) PPV: 97.3%* NPV: 100%* PLR: Not reported NLR: Not reported	<i>C. trachomatis</i> TP: 123 FP: 3 FN: 3 TN: 639 Sensitivity: 97.6% (93.2-99.2) Specificity: 99.5% (98.6-99.8)
<i>N. gonorrhoea</i> TP: 71 FP: 2 FN: 0 TN: 695 Sensitivity: 100% (94.9-100) Specificity: 99.7% (99.0-99.9) PPV: 97.3%* NPV: 100%* PLR: Not reported NLR: Not reported	<i>C. trachomatis</i> TP: 123 FP: 3 FN: 3 TN: 639 Sensitivity: 97.6% (93.2-99.2) Specificity: 99.5% (98.6-99.8)		
• TMA Combo - first catch urine	<table><tr><td><i>N. gonorrhoea</i> TP: 71 FP: 0</td><td><i>C. trachomatis</i> TP: 120 FP: 7</td></tr></table>	<i>N. gonorrhoea</i> TP: 71 FP: 0	<i>C. trachomatis</i> TP: 120 FP: 7
<i>N. gonorrhoea</i> TP: 71 FP: 0	<i>C. trachomatis</i> TP: 120 FP: 7		



	FN: 0 TN: 697 Sensitivity: 100% (94.9-100.0) Specificity: 100% (99.5-100.0) PPV: 100%* NPV: 100%* PLR: Not reported NLR: Not reported	FN: 4 TN: 644 Sensitivity: 96.8% (92.0-98.7) Specificity: 98.9% (97.8-99.5)
• TMA Combo - urethral swab	<i>N. gonorrhoea</i> TP: 70 FP: 1 FN: 1 TN: 696 Sensitivity: 98.6% (92.4-99.8) Specificity: 99.9% (99.2-100.0) PPV: 98.6%* NPV: 99.9%* PLR: 687.18* NLR: 0.01*	<i>C. trachomatis</i> TP: 117 FP: 7 FN: 7 TN: 644 Sensitivity: 94.4% (88.8-97.2) Specificity: 98.9% (97.8-99.5)
• SDA BD Qx - first catch urine	<i>N. gonorrhoea</i> TP: 71 FP: 2 FN: 0 TN: 695 Sensitivity: 100% (94.9-100.0) Specificity: 99.7% (99.0-99.9) PPV: 97%* NPV: 100%* PLR: 348.50* NLR: 0.00	<i>C. trachomatis</i> TP: 122 FP: 6 FN: 2 TN: 646 Sensitivity: 98.4% (94.3-99.6) Specificity: 99.2% (98.2-99.7)
• SDA BD Qx - urethral swab	<i>N. gonorrhoea</i> TP: 71 FP: 1	<i>C. trachomatis</i> TP: 113 FP: 4



	FN: 0 TN: 696 Sensitivity: 100.0% (94.9-100.0) Specificity: 99.9% (99.2-100.0) PPV: 98.6%* NPV: 100%* PLR: 697.00* NLR: 0.00*	FN: 11 TN: 647 Sensitivity: 91.1% (84.8-95.0) Specificity: 99.4% (98.4-99.8)
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* Calculated using Review Manager

Limitations and other comments	
• Limitations	Serious risk of bias (patient flow and timing and unclear blinding). No serious applicability/indirectness.
• Authors' conclusion	The authors concluded that in both symptomatic and asymptomatic men, the c4800 offers high sensitivity, specificity, PPV and NPV for detection of <i>N. gonorrhoea</i> and <i>C. trachomatis</i> in urine specimens.

Clinical Evaluation of the BD ProbeTec *Neisseria gonorrhoeae* Q Amplified DNA Assay on the BD Viper System With XTR Technology. Van Der Pol 2012b ²¹⁶

Methods	
• Design	Prospective multicenter study
• Source of funding and competing interest	Funding not reported. Supported by BD Diagnostics, Sparks, MD.
• Setting	Participants were enrolled from 7 geographically diverse sites (type of setting not reported)
• Sample size	Total number of participants = 1,768 (6,284 specimens) (available for analysis) 1,846 participants enrolled in the study – 74 participants were excluded due to inclusion/exclusion criteria violations, transport/storage errors, and for protocol deviations in specimen collection or aliquoting. Details about the number of patients needed for the study was not reported.
• Time interval between tests	Not reported
• Statistical analysis	Sensitivity and specificity were calculated.



Patient characteristics	
• Eligibility criteria	Men and women between the ages of 16 to 64 years who presented with urogenital symptoms or were being screened for chlamydia (CT) and gonorrhoea (GC) were enrolled between November 26, 2007 and March 21, 2008. Asymptomatic male enrolment continued until November 20, 2008.
	Exclusion criteria not reported
• Patient characteristics	Sex: 994 women (56%); 774 men (44%) Symptomatic: Yes - 554 women (55%); 257 men (33%) (<i>Genitourinary symptoms suggestive of a sexually transmitted infection (burning/pain upon urination, abnormal discharge, coital pain/difficulty/bleeding, testicular, or scrotum pain/swelling)</i>)
• Prevalence of disease	Prevalence in the study = 14.5% in men and 6.5% for women.
Interventions	
• SDA –BD Qx urethral swab	BD <i>N. gonorrhoea</i> Qx Amplified DNA Assay (GCQ) (SDA) <ul style="list-style-type: none"> - Urethral swabs were stored up to 14 days before testing. - The GCQ assay targets the Pilin gene within the genome of <i>N. gonorrhoea</i>, which is also the gene targeted by the PT assay - Blinding not reported
• SDA –BD Qx - urine specimen	BD <i>N. gonorrhoea</i> Qx Amplified DNA Assay (GCQ) (SDA) <ul style="list-style-type: none"> - The GCQ assay targets the Pilin gene within the genome of <i>N. gonorrhoea</i>, which is also the gene targeted by the PT assay - Blinding not reported
• Reference standard	<p>APTIMA Combo 2 assay (AC2) (TMA) and BD ProbeTec™ ET GC Amplified DNA Assay (PT) (SDA-PT) were used for reference standards.</p> <p>Patient infected status (PIS) for evaluation of GCQ performance was based on the reference swab and urine specimen results obtained using the PT assay (DNA target) and AC2 assay (16S rRNA target) which allowed for 4 reference results, 2 from each system. A participant was infected with <i>N. gonorrhoeae</i> if a minimum of 1 positive result was reported by each of the reference NAAT assays (i.e., a positive from both the PT assay and AC2 assay)</p> <p>Specimens: 1 urethral swab using each manufacturer's sample collection device, first-catch urine. The reference method was randomised at the collection stage to either the PT or the AC2 assay</p> <p>Blinding (investigator) to clinical information and/or to index test results not reported.</p>
Results - Male population	
• SDA – BD Qx - urethral swab (reference standard)	TP: 112 FP: 6 FN: 0 TN: 647



	Sensitivity: 100% (96.8-100.0) Specificity: 99.1% (98.0-99.7) PPV: 95%* NPV: 100%* PLR: 108.83* NLR: Not estimable
• SDA – BD ProbeTec - urethral swab	TP: 106 FP: 2 FN: 1 TN: 621 Sensitivity: 99.1% (94.9-100.0) Specificity: 99.7% (98.8-100.0) PPV: 98.2%* NPV: 99.8%* PLR: 308.59* NLR: 0.0094*
• TMA Combo - urethral swab (reference standard)	TP: 98 FP: 7 FN: 0 TN: 611 Sensitivity: 100.0% (96.3-100.0) Specificity: 98.9% (97.7-99.5) PPV: 93.3%* NPV: 100%* PLR: 88.29* NLR: Not estimable
• SDA BD Qx - urine specimen	TP: 112 FP: 6 FN: 0 TN: 656 Sensitivity: 100.0% (96.8-100.0) Specificity: 99.1% (98.0-99.7) PPV: 95%*



	NPV: 100%*
	PLR: 110.33*
	NLR: Not estimable
<ul style="list-style-type: none"> • SDA- BD ProbeTec - urine specimen (<i>reference standard</i>) 	TP: 112 FP: 3 FN: 3 TN: 649 Sensitivity: 97.4% (92.6-99.5) Specificity: 99.5% (98.7-99.9) PPV: 97.4%* NPV: 99.5%* PLR: 211.7* NLR: 0.026*
<ul style="list-style-type: none"> • TMA Combo- urine specimen (<i>reference standard</i>) 	TP: 112 FP: 6 FN: 0 TN: 655 Sensitivity: 100.0% (96.8-100.0) Specificity: 99.1% (98.0-99.7) PPV: 94.9%* NPV: 100%* PLR: 110.17* NLR: Not estimable
	*Calculated using Review Manager
Limitations and other comments	
<ul style="list-style-type: none"> • Limitations 	Very serious risk of bias due to patient selection and patient flow and timing. There was also a lack of blinding. No serious applicability/indirectness. Study reported in Nelson 2014 systematic review using sub-group analysis of women without symptoms suggestive of bacterial STI, whereas whole cohort figures reported here.
<ul style="list-style-type: none"> • Authors' conclusion 	Use of the GCQ assay for the detection of <i>N. gonorrhoeae</i> provides highly reliable diagnosis of symptomatic or asymptomatic infection for men.


Combined Testing for Chlamydia, Gonorrhea, and Trichomonas by Use of the BD Max CT/GC/TV Assay with Genitourinary Specimen Types. Van Der Pol 2017 ²¹⁷
Methods

- **Design** Prospective cohort study
- **Source of funding and competing interest** Funding for this project was provided by BD Diagnostics. B.V.D.P. (primary author) reports receiving consulting fees, honoraria, or research support from Atlas Genetics, BD Diagnostics, Beckman Coulter, Cepheid, Rheonix, and Roche Molecular Diagnostics. S.N.T. (fourth author) reports receiving research support or honoraria from BD Diagnostics, Hologic, Cepheid, Beckman Coulter, ELITech, and Roche Molecular Diagnostics. E.W.H. (fifth author) reports that he has received research support for this project and others from BD Diagnostics, Cepheid, and Roche Molecular. He has also received honoraria from Roche Molecular and Cepheid. All other authors have no financial disclosures to report.
- **Setting** Eight STI, family planning, and OB/GYN clinics located throughout the United States (five of these sites recruited men – 3 STI clinics, 2 family planning clinic and 1 other clinic type)
- **Sample size** Total number of participants recruited = 908. 16 were subsequently found to have not met inclusion/exclusion criteria and were excluded. Due to noncompliance with specimen collection or unavailable CT/GC comparator results, 62 and 52 men did not have specimens tested, respectively.
Final sample size = 840
Details about the number of patients needed for the study was not reported.
- **Time interval between tests** Not reported
- **Statistical analysis** Sensitivity and specificity were calculated.

Patient characteristics

- **Eligibility criteria** Men presenting for routine STI symptom evaluation or screening and being of appropriate age to provide informed consent for research. Exclusion criteria: the use of antibiotics, including metronidazole/tinidazole within the previous 14 days, having urinated within 1 hour prior to recruitment.
- **Patient characteristics** Details not reported
- **Prevalence of disease** Prevalence in the study: 12.9%

Interventions

- **PCR Max- urine specimen** BD Max GC assay (PCR)
 - The MAX assay is a TaqMan-based PCR assay that utilizes target-specific primers and probes to perform simultaneous amplification and detection of amplified products using quenchers and fluorophores.
 - Blinding not reported
- **Reference standard** For men, a composite infection standard was used since urethral swabs and urine capture infection at the same body site. Infections were defined by positive results from ≥ 2 of the 3 assays performed on the 4 specimens (for 2 specimens [1 urethral swab and 1 urine specimen], the CTQ/GCQ assay was performed). CTQ assay results alone did not define an infection, as at least one other assay-positive result was required.



Results - Male population

• PCR Max- urine specimen

N. gonorrhoea

TP: 107

FP: 0

FN: 1

TN: 732

Sensitivity: 99.1% (94.9-99.8)

Specificity: 100% (99.5-100)

PPV: 100%*

NPV: 99.9%*

PLR: Not estimable

NLR: 0.0093*

C. trachomatis

TP: 69

FP: 2

FN: 1

TN: 378

Sensitivity: 98.6% (92.3-99.7)

Specificity: 99.5% (98.1-99.9)

*Calculated using Review Manager

Limitations and other comments

• Limitations

No serious risk of bias. However, there was limited results for male participants
No serious applicability/indirectness.

Study reported in Nelson 2014 systematic review using sub-group analysis of women without symptoms suggestive of bacterial STI, whereas whole cohort figures reported here.

• Authors' conclusion

MAX performance was equivalent to the performances of currently available platforms used in many centralized reference laboratories. The MAX platform provided high sensitivity and specificity using vaginal or endocervical swabs or urine specimens. In many U.S. settings, given the broad utility of the platform based on current and future menus, the MAX offers a potential solution for small to medium laboratories

**Women**

Evaluation of Self-Collected Vaginal Swab, First Void Urine, and Endocervical Swab Specimens for the Detection of Chlamydia Trachomatis and Neisseria Gonorrhoeae in Adolescent Females. Fang 2008. ²¹⁸

Methods

- | | |
|---|---|
| • Design | Part of the prospective longitudinal study on hormone contraceptive use, ectopy and sexually transmitted infection acquisition. |
| • Source of funding and competing interest | Funded by NICHD RO1 HD37785-04. |
| • Setting | Urban Adolescent Clinic in an academic institution in USA. |
| • Sample size | 350 recruited and provided specimens at baseline and then every 6 months for testing.
342 participants and 1079 baseline and semi-annual visits had test results (including indeterminate results described as when the trachomatis, gonorrhoea and separate amplification control were all negative, indicating inhibition of amplification). |
| • Time interval between tests | All specimens were stored in a refrigerator at 2-8 degrees C prior to transfer in an insulated cooler to the main laboratory within 4 days of collection and were processed according to the manufacturer instructions. |
| • Statistical analysis | Sensitivity, specificity, positive predictive value and negative predictive value were calculated. |

Patient characteristics

- | | |
|----------------------------------|--|
| • Eligibility criteria | Healthy female adolescents were eligible to participate if they were 12-18 years old, sexually active, and not currently pregnant or pregnant in the last 3 months. Participants were recruited over a period of 5 years from 2001-2006 and followed up every 6 months. |
| • Patient characteristics | Age (median) = 16 years
12-14 years=14.9%
15-16 years =41.7%
17-18 years =43.4%

Race/ethnicity: (7 missing)
African American: 95.9%
Hispanic: 0.6%
Caucasian: 0.9%
Other: 2.6%

Age at sexual debut: median=14 years, missing =9.
Lifetime number of sexual partners: median=4, missing =9. |
| • Prevalence of disease | Study population high prevalence.
Study prevalence: 11.7 per 100 women. |



Interventions

- SDA BD ProbeTec – self collected vaginal swab**
 Strand Displacement assay (SDA) from self-collected vaginal swab
 - BDProbeTEC ET Amplified DNA Assay (BD Biosciences, Sparks, MD) to detect trachomatis and gonorrhoeae infections.
 - Blinding (investigator) not reported.
- SDA BD ProbeTec – first void urine**
 Strand Displacement assay (SDA) from first void urine
 - BDProbeTEC ET Amplified DNA Assay (BD Biosciences, Sparks, MD) to detect trachomatis and gonorrhoeae infections.
 - Blinding (investigator) not reported.
- SDA BD ProbeTec – provider collected endocervical**
 Strand Displacement assay (SDA) from provider collected endocervical
 - BDProbeTEC ET Amplified DNA Assay (BD Biosciences, Sparks,) MD to detect trachomatis and gonorrhoeae infections.
 - Blinding (investigator) not reported.
- Reference standard**
 A positive result:
 - A positive result from at least two of the three specimens collected from the same subject at the same study visit was considered a true positive.
 - Blinding (investigator) not reported.

Results

- SDA BD ProbeTec – self collected vaginal swab**
 TP: 44
 FP: 6
 FN: 0
 TN: 980
 Sensitivity: 100%
 Specificity: 94.7% (this calculates to 99% in Review Manager)
 PPV: 88.0%
 NPV: 95.2%
 PLR: Not reported
 NLR: Not reported
 Number of indeterminate results that fell into true positive category=0
 Number of indeterminate results that fell into true negative category=49
 Indeterminate results falling into either true positive or true negative category were included in sensitivity, specificity, PPV and NPV calculations in the study.
- SDA BD ProbeTec – first void urine**
 TP: 39
 FP: 1
 FN: 4
 TN: 996
 Sensitivity: 88.6% (this calculates to 99% in Review Manager)



	<p>Specificity: 96.2% (this calculates to 100% in Review Manager)</p> <p>PPV: 95.1%</p> <p>NPV: 96.0%</p> <p>PLR: Not reported</p> <p>NLR: Not reported</p> <p>Number of indeterminate results that fell into true positive category=1</p> <p>Number of indeterminate results that fell into true negative category=38</p> <p>Indeterminate results falling into either true positive or true negative category were included in sensitivity, specificity, PPV and NPV calculations in the study.</p>
<ul style="list-style-type: none">• SDA BD ProbeTec – provider collected endocervical	<p>TP: 42</p> <p>FP: 0</p> <p>FN: 2</p> <p>TN: 1032</p> <p>Sensitivity: 95.5%</p> <p>Specificity: 99.7%</p> <p>PPV: 100%</p> <p>NPV: 99.5%</p> <p>PLR: Not reported</p> <p>NLR: Not reported</p> <p>Number of indeterminate results that fell into true positive category= 0</p> <p>Number of indeterminate results that fell into true negative category= 3</p> <p>Indeterminate results falling into either true positive or true negative category were included in sensitivity, specificity, PPV and NPV calculations in the study.</p>
Limitations and other comments	
<ul style="list-style-type: none">• Limitations	<p>Very serious risk of bias (patient selection, patient flow and timing, unclear blinding and reference standard used).</p> <p>No serious applicability/indirectness.</p> <p>Diagnostic accuracy results based on subject visits rather than individual participants.</p> <p>Reference standard uses two positive tests to provide a true positive result which may underestimate true prevalence when one test had a positive (could have been a true result) these would have been interpreted as a false positive.</p> <p>Indeterminate results included in the analysis.</p>
<ul style="list-style-type: none">• Authors' conclusion	<p>Authors conclude that vaginal sampling performed by the women themselves was the most sensitive approach (compared to endocervical and first flow urine) and could be another non-invasive alternative in addition to first flow urine in screening (if it was FDA approved).</p>



Performance of Three Nucleic Acid Amplification Tests for Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* by Use of Self-Collected Vaginal Swabs Obtained via an Internet-Based Screening Program. Masek 2009²¹⁹

• Design	Prospective longitudinal study.
• Source of funding and competing interest	Contribution of some of the diagnostic kits from the manufacturers. Funded by the HIV Prevention Trials Network (HPTN), NIH, NIAID, Baltimore City Health Department and Family Planning Council Region III, Philadelphia, PA.
• Setting	Internet based self-screening program for samples mailed to the laboratory for testing between July 2004 and November 2007. Stage 1 consisted of the first 500 samples from July 2004 to August 2005 and samples were tested by 3 NAATs. Stage 2 consisted of the second 500 samples which were received from August 2005 to November 2007 but were tested by only two NAATs.
• Sample size	1000 self-collected vaginal swabs mailed to the laboratory.
• Time interval between tests	Not reported.
• Statistical analysis	Sensitivity, specificity, negative predictive value and positive predictive values were calculated.
Patient characteristics	
• Eligibility criteria	Women who accessed the Internet based self-screening website.
• Patient characteristics	No patient characteristics were reported.
• Prevalence of disease	Study population prevalence 5/500 (1.0%)
Interventions	
• SDA BD ProbeTec	Strand Displacement Amplification (SDA): <ul style="list-style-type: none"> - Becton Dickinson ProbeTec - Blinding (investigator) not reported.
• TMA Combo	Transcription Mediated Amplification (TMA): <ul style="list-style-type: none"> - Gen-Probe Aptima Combo 2 - Blinding (investigator) not reported.
• PCR Roche	PCR <ul style="list-style-type: none"> - Roche Amplicor - Roche Molecular Diagnostics, Indianapolis, IN, USA. - Blinding (investigator) not reported.
• Reference standard	Gold standard defined as patient infected status as two or more positive NAAT results. When only two NAATs were used the discordant specimens were tested by another standalone Aptima NAAT, either rACT or AGC (GenProbe Inc) which targets alternative gene sequences. : <ul style="list-style-type: none"> - Blinding (investigator) not reported.



Results		
• SDA BD ProbeTec	<i>N. gonorrhoea</i>	<i>C. trachomatis</i>
	TP: 4 FP: 0 FN: 1 TN: 495 Sensitivity: 80.0% (28.4-99.5) Specificity: 100.0% (99.6-100) PPV: 100.0% (39.8-100.0) NPV: 99.8 % (98.9-99.9) PLR: Not reported NLR: 0.200*	TP: 75 FP: 17 FN: 0 TN: 908 Sensitivity: 81.5% (72.1-88.9) Specificity: 100.0% (99.6-100)
• TMA Combo	<i>N. gonorrhoea</i>	<i>C. trachomatis</i>
	TP: 5 FP: 0 FN: 0 TN: 495 Sensitivity: 100.0% (47.8-100.0) Specificity: 100.0% (99.3-100.0) PPV: 100.0% (47.8-100.0) NPV: 100.0% (99.3-100.0) PLR: Not reported NLR: 0.000*	TP: 92 FP: 0 FN: 0 TN: 908 Sensitivity: 100.0% (96.1-100) Specificity: 100.0% (99.6-100)
• PCR Roche On the first 500 samples	<i>N. gonorrhoea</i>	<i>C. trachomatis</i>
	TP: 5 FP: 6 FN: 0 TN: 489 Sensitivity: 100.0% (47.8-100.0) Specificity: 98.8% (97.4-99.6) PPV: 45.5% (16.7-76.6) NPV: 100.0% (99.2-100.0)	TP: 46 FP: 0 FN: 3 TN: 451 Sensitivity: 100.0% (92.3-100) Specificity: 99.3% (98.1-99.9)



PLR: 82.5 *

NLR:0.00*

*Calculated using Review Manager

Limitations and other comments

- Limitations**
 Very serious risk of bias due to patient flow (drop outs not reported) and patient selection (no information on patient selection, baseline characteristics or eligibility).
 No serious applicability/indirectness.
 Only stage 1 included in analysis (first 500 samples) as stage 2 only tested with 2 NAATs and did not have an appropriate reference standard.
- Authors' conclusion**
 Authors conclude that NAATs perform well for detection of *N. gonorrhoea* and *C. trachomatis* with self-obtained vaginal swabs shipped in a dry state to a laboratory and the most superior assay was Aptima Combo 2.

The Effect of Urine Testing in Evaluations of the Sensitivity of the Gen-Probe Aptima Combo 2 assay on Endocervical Swabs for Chlamydia trachomatis and Neisseria gonorrhoeae: The Infected Patient Standard Reduces Sensitivity of Single Site Evaluation. Moncada 2004 ²²⁰

Methods

- Design**
 Prospective cohort study
- Source of funding and competing interest**
 Funding not reported. Study was supported by Gen-Probe Inc. (San Diego, California)
- Setting**
 Seven geographically diverse clinic sites across the United States. Locations were in Stockton and San Francisco, CA, Birmingham, AL, Baltimore, MD, Jacksonville, FL, Houston, TX and New Orleans, LA. Patients were seen at STF, family planning and obstetrics and gynaecology clinics with high and low prevalence of NG infections
- Sample size**
 Total participants = 1,489 (all specimens were evaluable)
 Details about the number of patients needed for the study were not reported.
- Time interval between tests**
 Not reported
- Statistical analysis**
 Sensitivity and specificity were calculated.

Patient characteristics

- Eligibility criteria**
 Symptomatic and asymptomatic female patients from March to August 2000.
 Exclusion criteria not reported.
- Patient characteristics**
 Symptomatic: Yes – 59.8% (890/1489), No – 40.2% (599/1489)
- Prevalence of disease**
 Prevalence in the study = 8.7%



Interventions		
<ul style="list-style-type: none">• TMA Combo - endocervical specimen	APTIMA Combo 2 Assay (AC2) (TMA) <ul style="list-style-type: none">- Specimens were tested according to the Gen-Probe's specifications.- Specimens were tested within 7 days of collection- Blinding not reported	
<ul style="list-style-type: none">• LCR - endocervical specimen	Ligase Chain Reaction Assay (LCR) <ul style="list-style-type: none">- The targets are the Opa gene of NG- Specimens were tested in batches within 4 days of collection- Blinding not reported	
<ul style="list-style-type: none">• Culture - endocervical specimen	<ul style="list-style-type: none">- Thayer-Martin plates were read within 48 hours.- Oxidase-positive colonies yielding Gram-negative diplococci were sub-culture to chocolate agar plates.- Isolates were confirmed as NG by either sugar utilisation tests, fluorescent antibody or HNID	
<ul style="list-style-type: none">• Reference standard	NG true-positives were defined by endocervical specimens that were either culture-positive or positive with both the LCR and AC2 amplification tests.	
Results		
<ul style="list-style-type: none">• TMA Combo - endocervical specimen	<i>N. gonorrhoea</i> TP: 127 FP: 19 FN: 1 TN: 1342 Sensitivity: 99.2% Specificity: 98.6% PPV: 87%* NPV: 99.9%* PLR: 71.07* NLR: 0.0079*	<i>C. trachomatis</i> TP: 182 FP: 32 FN: 1 TN: 1196 Sensitivity: 99.4% Specificity: 97.4%
<ul style="list-style-type: none">• LCR - endocervical specimen	<i>N. gonorrhoea</i> TP: 123 FP: 4 FN: 5 TN: 1357 Sensitivity: 96.1%	<i>C. trachomatis</i> TP: 175 FP: 7 FN: 8 TN: 1221 Sensitivity: 95.6%



		Specificity: 99.7% PPV: 96.9%* NPV: 99.6%* PLR: 327.0* NLR: 0.039*	Specificity: 99.4%
•	Culture specimen - endocervical	<i>N. gonorrhoea</i> TP: 110 FP: 0 FN: 18 TN: 1361 Sensitivity: 85.9% Specificity: 100% PPV: Not estimable NPV: 99%* PLR: Not estimable NLR: 0.14*	
		*Calculated using Review Manager	
•	PCR - endocervical specimen		<i>C. trachomatis</i> TP: 175 FP: 9 FN: 8 TN: 1219 Sensitivity: 95.6% Specificity: 99.3%
Limitations and other comments			
•	Limitations	<p>Serious risk of bias due to patient selection. There was also a lack of blinding.</p> <p>No serious applicability/indirectness.</p> <p>Study also reports an 'infected patient standard' – a patient was considered infected with NG when either the culture result was positive or there was a least 1 LCR-positive (with endocervical swab or first-catch urine sample) and 1 AC2-positive (endocervical or first-catch urine sample) test result. The results were not reported in this evidence review as it is unclear how many endocervical swabs or first-catch urine samples were tested.</p>	



- **Authors' conclusion** Results confirm that the AC2 assay is highly sensitive and specific DNA amplification assay for the detection of NG and CT in endocervical specimens.

Vaginal Swabs Are the Specimens of Choice When Screening For Chlamydia trachomatis and Neisseria gonorrhoeae: Results From a Multicenter Evaluation of the APTIMA Assays for Both Infections. Schachter 2005 ²²¹

Methods

- **Design** Prospective cohort study
- **Source of funding and competing interest** Study funded by Gen-Probe Inc. (San Diego, California)
- **Setting** STD, obstetrics and gynaecology, teen, and family planning clinics – 9 centres in North America
- **Sample size** Total enrolled participants = 1,464
14 participants were not included in analysis – missing results
Details about the number of patients needed for the study was not reported.
- **Time interval between tests** Not reported
- **Statistical analysis** Sensitivity and specificity were calculated.

Patient characteristics

- **Eligibility criteria** Symptomatic and asymptomatic female patients attending STD clinic, obstetrics and gynaecology, teen, and family planning clinics. Exclusion criteria not reported.
- **Patient characteristics** Age - mean (SD): 26.1 (7.3) years
Age – range: 15-71 years
Symptomatic: Yes – 56% (818/1464), No – 44% (646/1464)
Ethnic origin: Black – 59.5%, White – 10.6%, Hispanic – 24.6%, Asian – 3.0%, Other/unknown – 2.2%
- **Prevalence of disease** Prevalence in the study = 5.4%

Interventions

- **TMA Combo - vaginal specimen** APTIMA Combo 2 Assay (AC2) (TMA2)
 - Specimen collection methods: patient-collected and clinician-collected
 - Specimens were tested according to the manufacturer's specification.
 - Blinding not reported
- **TMA NG - vaginal specimen** APTIMA GC Assay (TMA)
 - Specimen collection methods: patient-collected and clinician-collected



- Specimens were tested according to the manufacturer's specification.
- Blinding not reported

- **Reference standard** True positives were defined as positive results with BDProbeTec ET System GC Assay (BD) or AC2 when specimens were tested.

Results

- **TMA Combo - vaginal specimen (patient-collected)**

TP: Not estimable (insufficient data reported)
FP: Not estimable (insufficient data reported)
FN: Not estimable (insufficient data reported)
TN: Not estimable (insufficient data reported)
Sensitivity: 98.7% *
Specificity: 99.6% *
PPV: Not estimable (insufficient data reported)
NPV: Not estimable (insufficient data reported)
PLR: Not estimable (insufficient data reported)
NLR: Not estimable (insufficient data reported)

* These sensitivities and specificities were reported in the study without actual figures therefore we could not check results or work out any of the other diagnostic outcomes.
- **TMA Combo - vaginal specimen (clinician-collected)**

TP: Not estimable (insufficient data reported)
FP: Not estimable (insufficient data reported)
FN: Not estimable (insufficient data reported)
TN: Not estimable (insufficient data reported)
Sensitivity: 96.2% *
Specificity: 99.4% *
PPV: Not estimable (insufficient data reported)
NPV: Not estimable (insufficient data reported)
PLR: Not estimable (insufficient data reported)
NLR: Not estimable (insufficient data reported)

* These sensitivities and specificities were reported in the study without actual figures therefore we could not check results or work out any of the other diagnostic outcomes.
- **TMA NG - vaginal specimen (patient-collected)**

TP: Not estimable (insufficient data reported)
FP: Not estimable (insufficient data reported)



	<p>FN: Not estimable (insufficient data reported)</p> <p>TN: Not estimable (insufficient data reported)</p> <p>Sensitivity: 96.1% *</p> <p>Specificity: 99.3% *</p> <p>PPV: Not estimable (insufficient data reported)</p> <p>NPV: Not estimable (insufficient data reported)</p> <p>PLR: Not estimable (insufficient data reported)</p> <p>NLR: Not estimable (insufficient data reported)</p> <p>* These sensitivities and specificities were reported in the study without actual figures therefore we could not check results or work out any of the other diagnostic outcomes.</p>
<ul style="list-style-type: none"> TMA NG - vaginal specimen (clinician-collected) 	<p>TP: Not estimable (insufficient data reported)</p> <p>FP: Not estimable (insufficient data reported)</p> <p>FN: Not estimable (insufficient data reported)</p> <p>TN: Not estimable (insufficient data reported)Not reported</p> <p>Sensitivity: 96.2% *</p> <p>Specificity: 99.3% *</p> <p>PPV: Not estimable (insufficient data reported)</p> <p>NPV: Not estimable (insufficient data reported)</p> <p>PLR: Not estimable (insufficient data reported)</p> <p>NLR: Not estimable (insufficient data reported)</p> <p>* These sensitivities and specificities were reported in the study without actual figures therefore we could not check results or work out any of the other diagnostic outcomes.</p>
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	<p>Very serious risk of bias due to patient selection, flow and timing.</p> <p>No serious applicability/indirectness.</p>
<ul style="list-style-type: none"> Authors' conclusion 	<p>Sensitivities and specificities for vaginal swab specimens in the AGC assays were quite high, there was no difference seen between the performances of the tests for the patient-collected or clinician collected specimens. A subset of patients in the study were asked about the ease of collection and specimen preference, a large majority found it easy to collect and preferred vaginal swab to methods such as first-catch urine sample collection (this is discussed further in another study referenced within this study)</p>



Assessment of self-taken swabs versus clinician taken swab cultures for diagnosing gonorrhoea in women: single centre, diagnostic accuracy study. Stewart 2012²²²

Methods

- **Design** Prospective cross-sectional study.
- **Source of funding and competing interest** Funding of extra diagnostic reagents and equipment needed for the study was provided by Gen-Probe.
- **Setting** Single centre, sexual health clinic in urban setting, Leeds, UK (enrolled between March 2009 and January 2010).
- **Sample size** 3976 recruited but losses due to incomplete data (n=3) and some missing results (n=114) despite full demographic data. 3859 with complete data and results.
- **Time interval between tests** Samples taken on same visit.
- **Statistical analysis** Sensitivity, specificity, positive predictive value and negative predictive value were calculated.

Patient characteristics

- **Eligibility criteria** Women who wished to be tested for STIs were given an information leaflet about the study and those consenting were recruited. Exclusion criteria: women who used antibiotics in the preceding 28 days and were unable or unwilling to perform a self-taken swab or have the standard examination and swabs performed by clinicians.
- **Patient characteristics** Women aged 16 years or older, attending the clinic for sexually transmitted infection testing for a new visit.

Of 3973 with complete data:
Mean age: 25 years (range 16-59)
Self-reported ethnicity was white in 80%, black 9%, mixed 7% and other 4%.
Previous diagnosis of STI = 37%
Contact with a partner recently diagnosed with an STI = 7%
At least one symptom suggestive of bacterial STI = 42%
Clinical diagnosis of cervicitis = 5%
Clinical diagnosis of pelvic inflammatory disease = 4%
- **Prevalence of disease** Study prevalence 2.5%.

Interventions

- **TMA Combo - vulvovaginal swab (self taken)** Vulvovaginal swab self-taken with Transcription Mediated Amplification (TMA):
 - Aptima Combo 2 (AC2) assay by Gen-Probe uses transcription mediated amplification technology in which ribosomal RNA target regions from N gonorrhoeae are amplified.
 - Results are either positive or negative for N gonorrhoeae.



	- Laboratory staff performing the AC2 assay were blinded to the gonococcal culture results.
• TMA Combo - endocervical swab (clinician taken)	Endocervical swab by clinician with TMA: <ul style="list-style-type: none"> - Aptima Combo 2 (AC2) assay by Gen-Probe uses transcription mediated amplification technology in which ribosomal RNA target regions from N gonorrhoeae are amplified. - Results are either positive or negative for N gonorrhoeae. - Laboratory staff performing the AC2 assay were blinded to the gonococcal culture results.
• Culture	Urethral and endocervix swab by clinician for culture <ul style="list-style-type: none"> - Inoculated directly on to selective gonococcal agar plates and incubated at 37 degrees in 5% carbon dioxide until they were transported to the department where incubation continued. The plates were read at 24 and 48 hand colonies with suspected N gonorrhoeae were confirmed biologically. - Culture results were either positive or negative. - Laboratory staff performing the AC2 assay were blinded to the gonococcal culture results.
• Reference standard	Patient infected status defined as one or more of the following: a positive culture with biochemical confirmation for N gonorrhoeae, or a positive AC2 result from the endocervical or vulvovaginal swabs that was also confirmed by the Aptima GC test.

Results

• TMA Combo - vulvovaginal swab (self taken)	TP: 95 FP: 0 FN: 1 TN: 3763 Sensitivity: 99% (94-100) Specificity: 100% PPV: 1.0000* NPV: 0.9997* PLR: NR NLR: 0.0104*
• TMA Combo - endocervical swab (clinician taken)	TP: 92 FP: 0 FN: 4 TN: 3763 Sensitivity: 96% (90-98) Specificity: 100% PPV: 100.0%* NPV: 99.9%*



	PLR: NR NLR: 0.0417*
• Culture	TP: 78 FP: 0 FN: 18 TN: 3763 Sensitivity: 81% (72-88) Specificity: 100% PPV: 1.0000* NPV: 0.9952* PLR: NR NLR: 0.1875*
	* Calculated using Review Manager

Limitations and other comments

• Limitations	Low risk of bias. No serious applicability/indirectness.
• Authors' conclusion	The authors concluded that vulvovaginal swabs taken by women themselves and tested by AC2 (a NAAT) were significantly more sensitive at detecting gonorrhoea than culture with urethral and endocervical samples taken by clinicians, and are equivalent to endocervical swabs analysed by AC2.

Performance of the cobas CT/NG Test Compared to the Aptima AC2 and Viper CTQ/GCQ Assays for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae. Van Der Pol, 2012a ²²³

Methods

• Design	Prospective multicenter study
• Source of funding and competing interest	Study was funded by Roche Molecular Systems, Pleasanton, CA. B. Van Der Pol discloses consulting honoraria or research funding received from Abbott Molecular, BD Diagnostics, and Roche Molecular Systems. E. W. Hook III has received research support from Roche Molecular Systems, BD Diagnostics, Gen-Probe, Siemens, and Cepheid.
• Setting	Number of participating centres was not reported. The specimen collection sites were geographically diverse and included obstetrics-gynecology practices, family planning clinics, and STD clinics.



<ul style="list-style-type: none">Sample size	<p>Total number of participants = 4,316 (for testing of <i>C. trachomatis</i> and <i>N. gonorrhoeae</i>)</p> <p>4,479 participants enrolled in the study - 17 = excluded because they did not meet the inclusion criteria or did not provide appropriate consent; 146 = non-evaluable because of errors in specimen collection, transport, and storage.</p> <p>Among evaluable subjects, 351 specimens = non-evaluable for the <i>N. gonorrhoeae</i> primary analysis: specimen was not available for testing or because a specimen was repeatedly inhibitory (IC failure)</p> <p>Details about the number of patients needed for the study was not reported.</p>
<ul style="list-style-type: none">Time interval between tests	Not reported
<ul style="list-style-type: none">Statistical analysis	Sensitivity, specificity and positive predictive value (PPV) were calculated.
Patient characteristics	
<ul style="list-style-type: none">Eligibility criteria	<p>Females at least 14 years of age and being eligible for routine <i>C. trachomatis</i>/<i>N. gonorrhoeae</i> screening according to the routine practices at each enrolment site.</p> <p>Exclusion criteria: previously enrolled in the study, use of antimicrobial agents active against <i>C. trachomatis</i> or <i>N. gonorrhoeae</i> during the preceding 21 days, use of Replens, a vaginal lubricant (Lil' Drug Store Products, Inc., Cedar Rapids, IA), within the previous 3 days, (iv) history of hysterectomy, or contraindication to Pap test/cervical sampling.</p>
<ul style="list-style-type: none">Patient characteristics	<p>This study evaluated the diagnostic accuracy of the cobas 4800 system for <i>C. trachomatis</i> as well as <i>N. gonorrhoeae</i> in sexually active females aged ≥ 14 years.</p> <p>Overall baseline characteristics were reported for both of these STIs as well as disease prevalence for the individual infections (disease prevalence for <i>C. trachomatis</i> is not reported as it is not relevant for this evidence report).</p> <p><u>Overall baseline</u></p> <p>Median age, 25 years</p> <p>Race: Black – 1,860 (43.1%), White – 2,089 (48.4%), Asian/Pacific islander – 122 (2.8%), Other – 245 (5.7%), Hispanic – 955 (22.1%)</p> <p>Symptomatic: Yes – 2,024 (46.9%), No – 2,292 (53.1%)</p> <p>Clinical type: Family planning – 1,762 (40.8%), Obstetrics-gynaecology – 1,079 (25%), STD – 1,475 (34.2%)</p> <p><u>Prevalence for <i>N. gonorrhoeae</i> (% [95% CI])</u></p> <p>Race: Black – 2.9% (2.2-3.7%), White – 0.7% (0.4-1.1%), Asian/Pacific islander – 0.8% (0.1-4.5%), Other – 0.4% (0.1-2.3%), Hispanic – 0.4% (0.2-1.1)</p> <p>Symptomatic: Yes – 2.3% (1.7-3.0%), No – 1.0% (0.7-1.5)</p>



	Clinical type: Family planning – 1.6% (1.1-2.3), Obstetrics-gynaecology – 0.1% (0.0-0.5), STD – 2.7% (2.0-3.7)
• Prevalence of disease	Prevalence in the study = 1.6%
Interventions	
• PCR C4800 - endocervical specimen	Roche cobas 4800 system (PCR) <ul style="list-style-type: none"> - The c4800 uses a dual-target approach – automated amplification system - <i>N. gonorrhoeae</i> primers NG514 and NG519 target a sequence of approximately 190 nucleotides from a highly conserved direct repeat region of <i>N. gonorrhoeae</i> called DR-9 - Blinding not reported
• PCR C4800- urine specimen	Roche cobas 4800 system (PCR) <ul style="list-style-type: none"> - The c4800 uses a dual-target approach – automated amplification system - <i>N. gonorrhoeae</i> primers NG514 and NG519 target a sequence of approximately 190 nucleotides from a highly conserved direct repeat region of <i>N. gonorrhoeae</i> called DR-9 - Blinding not reported
• Reference standard	APTIMA Combo 2 assay (AC2) (TMA) and BD Viper ProbeTec GC Qx amplified DNA assay (GCQ) (SDA) used to determine patient infection status (PIS). PIS was defined as being infected with <i>N. gonorrhoeae</i> if at least 2 NAATs with different target regions gave positive results in the endocervical swab and/or the urine specimen.
	Specimens were collected in the following order: first-catch urine; 3 endocervical swabs using each manufacturer's sample collection device (in randomised order)

Results		
• PCR C4800 - endocervical specimen	<i>N. gonorrhoea</i> TP: 65 FP: 2 FN: 3 TN: 4,182 Sensitivity: 95.6% (87.8-98.5) Specificity: 100.0% (99.8-100) PPV (hypothetical): 93.8-99.9% (97%*) NPV: 99.9% ²⁵¹ PLR: 1999.71* NLR: 0.044*	<i>C. trachomatis</i> TP: 240 FP: 7 FN: 22 TN: 3,984 Sensitivity: 91.6% (87.6-94.4) Specificity: 99.8% (99.6-99.9)



<ul style="list-style-type: none"> TMA Combo- endocervical specimen (<i>reference standard</i>) 	<i>N. gonorrhoea</i> TP: 69 FP: 1 FN: 0 TN: 4,239 Sensitivity: 100.0% (94.7-100) Specificity: 100.0% (99.9-100) PPV: 98.6%* NPV: 100%* PLR: 4240* NLR: Not estimable	<i>C. trachomatis</i> TP: 254 FP: 32 FN: 9 TN: 4,016 Sensitivity: 96.6% (93.6-98.2) Specificity: 99.2% (98.9-99.4)
<ul style="list-style-type: none"> SDA BD Qx- endocervical specimen (<i>reference standard</i>) 	<i>N. gonorrhoea</i> TP: 66 FP: 9 FN: 4 TN: 4,207 Sensitivity: 94.3% (86.2-97.8) Specificity: 99.8% (99.6-99.9) PPV: 88%* NPV: 99.9%* PLR: 441.70* NLR: 0.06*	<i>C. trachomatis</i> TP: 255 FP: 14 FN: 13 TN: 4,004 Sensitivity: 95.1% (91.9-97.1) Specificity: 99.7% (99.4-99.8)
<ul style="list-style-type: none"> PCR C4800- urine specimen 	<i>N. gonorrhoea</i> TP: 64 FP: 3 FN: 1 TN: 4,210 Sensitivity: 98.5% (91.8-99.7) Specificity: 99.9% (99.8-100) PPV: 95.5%* NPV: 99.9%* PLR: 1382.7* NLR: 0.015*	<i>C. trachomatis</i> TP: 251 FP: 10 FN: 21 TN: 3,997 Sensitivity: 92.3% (88.5-94.9) Specificity: 99.8% (99.5-99.9)



<ul style="list-style-type: none"> TMA Combo- urine specimen (reference standard) 	<i>N. gonorrhoea</i> TP: 62 FP: 3 FN: 2 TN: 4,245 Sensitivity: 96.9% (89.3-99.1) Specificity: 99.9% (99.8-100) PPV: 95.4%* NPV: 100.0%* PLR: 1372.0* NLR: 0.031*	<i>C. trachomatis</i> TP: 250 FP: 19 FN: 11 TN: 4,029 Sensitivity: 95.8% (92.6-97.6) Specificity: 99.5% (99.3-99.7)
<ul style="list-style-type: none"> SDA BD Qx- urine specimen (reference standard) 	<i>N. gonorrhoea</i> TP: 64 FP: 3 FN: 2 TN: 4,223 Sensitivity: 97.0% (89.6-99.2) Specificity: 99.9% (99.8-100) PPV: 95.5%* NPV: 100%* PLR: 1366.0* NLR: 0.030*	<i>C. trachomatis</i> TP: 253 FP: 9 FN: 14 TN: 4,015 Sensitivity: 94.8% (91.4-96.9) Specificity: 99.8% (99.6-99.9)
*Calculated using Review Manager		
Limitations and other comments		
<ul style="list-style-type: none"> Limitations 	No serious risk of bias. No serious applicability/indirectness.	
	Study reported in Nelson 2014 systematic review using sub-group analysis of women without symptoms suggestive of bacterial STI, whereas whole cohort figures reported here.	
<ul style="list-style-type: none"> Authors' conclusion 	PCR performance was equivalent to other currently available FDA-approved assays for the detection of <i>N. gonorrhoea</i> and <i>C. trachomatis</i> infections in women. Performance was not affected by the presence or absence of symptoms, making this a useful assay	



for both screening and diagnosis. The system is suitable for use in a routine clinical laboratory because of the limited hands-on requirements, relatively rapid time to results, and throughput of approximately 388 samples per 9-hour shift.

Clinical Evaluation of the BD ProbeTec *Neisseria gonorrhoeae* Q Amplified DNA Assay on the BD Viper System With XTR Technology. Van Der Pol 2012b ²¹⁶

Methods

- **Design** Prospective multicenter study
- **Source of funding and competing interest** Supported by BD Diagnostics, Sparks, MD.
- **Setting** Participants were enrolled from 7 geographically diverse sites (type of setting not reported)
- **Sample size** Total number of participants = 1,768 (6,284 specimens) (available for analysis)

1,846 participants enrolled in the study – 74 participants were excluded due to inclusion/exclusion criteria violations, transport/storage errors, and for protocol deviations in specimen collection or aliquoting.

Details about the number of patients needed for the study was not reported.
- **Time interval between tests** Not reported
- **Statistical analysis** Sensitivity and specificity were calculated.

Patient characteristics

- **Eligibility criteria** Men and women between the ages of 16 to 64 years who presented with urogenital symptoms or were being screened for chlamydia (CT) and gonorrhoea (GC) were enrolled between November 26, 2007 and March 21, 2008. Asymptomatic male enrolment continued until November 20, 2008.

Exclusion criteria not reported
- **Patient characteristics** Sex: **994 women (56%)**; 774 men (44%)

Symptomatic: Yes - **554 women (55%)**; 257 men (33%) (*Genitourinary symptoms suggestive of a sexually transmitted infection (burning/pain upon urination, abnormal discharge, coital pain/difficulty/bleeding, testicular, or scrotum pain/swelling)*)
- **Prevalence of disease** Prevalence in the study = 14.5% in men and 6.5% for women.

Interventions

- **SDA BD Qx - endocervical swab** BD *N. gonorrhoea* Qx Amplified DNA Assay (GCQ) (SDA)
- Endocervical swabs were stored up to 14 days before testing.



	<ul style="list-style-type: none"> - The GCQ assay targets the Pilin gene within the genome of <i>N. gonorrhoea</i> , which is also the gene targeted by the PT assay - Blinding not reported
<ul style="list-style-type: none"> • SDA BD Qx - vaginal swab 	BD <i>N. gonorrhoea</i> Qx Amplified DNA Assay (GCQ) (SDA) <ul style="list-style-type: none"> - Vaginal swabs were stored for up to 7days before testing. - The GCQ assay targets the Pilin gene within the genome of <i>N. gonorrhoea</i> , which is also the gene targeted by the PT assay - Blinding not reported
<ul style="list-style-type: none"> • SDA BD Qx - urine 	BD <i>N. gonorrhoea</i> Qx Amplified DNA Assay (GCQ) (SDA) <ul style="list-style-type: none"> - The GCQ assay targets the Pilin gene within the genome of <i>N. gonorrhoea</i> , which is also the gene targeted by the PT assay - Blinding not reported
<ul style="list-style-type: none"> • Reference standard 	<p>APTIMA Combo 2 assay (AC2) (TMA) and BD ProbeTec™ ET GC Amplified DNA Assay (PT) (SDA-PT) were used for reference standards. Patient infected status (PIS) for evaluation of GCQ performance was based on the reference swab and urine specimen results obtained using the PT assay (DNA target) and AC2 assay (16S rRNA target) which allowed for 4 reference results, 2 from each system. A participant was infected with <i>N. gonorrhoeae</i> if a minimum of 1 positive result was reported by each of the reference NAAT assays (i.e., a positive from both the PT assay and AC2 assay)</p> <p>Specimens: 1 endocervical swab using each manufacturer's sample collection device and first-catch urine. Blinding (investigator) to clinical information and/or to index test results not reported.</p>

Results - Female population

<ul style="list-style-type: none"> • SDA BD Qx - endocervical swab 	TP: 64 FP: 3 FN: 1 TN: 924 Sensitivity: 98.5% (91.7-100.0) Specificity: 99.7% (99.1-99.9) PPV: 95.5%* NPV: 99.9%* PLR: 304.25* NLR: 0.015*
<ul style="list-style-type: none"> • SDA- BD ProbeTec - endocervical (used as reference standard) 	TP: 64 FP: 6 FN: 2 TN: 908



	Sensitivity: 97.0% (89.5-99.6) Specificity: 99.3% (98.6-99.8) PPV: 91.4%* NPV: 99.8%* PLR: 147.72* NLR: 0.03*
<ul style="list-style-type: none"> TMA Combo- endocervical swab (<i>reference standard</i>) 	TP: 65 FP: 5 FN: 1 TN: 918 Sensitivity: 98.5% (91.8-100.0) Specificity: 99.5% (98.7-99.8) PPV: 92.9%* NPV: 99.9%* PLR: 181.80* NLR: 0.015*
<ul style="list-style-type: none"> SDA BD Qx - vaginal specimen (<i>self collected</i>) 	TP: 65 FP: 8 FN: 0 TN: 920 Sensitivity: 100.0% (94.5-100.0) Specificity: 99.1% (98.3-99.6) PPV: 89.0%* NPV: 100.0%* PLR: 116.00* NLR: Not estimable
<ul style="list-style-type: none"> 	<i>No reference standard data for vaginal specimen</i>
<ul style="list-style-type: none"> SDA BD Qx - urine specimen 	TP: 64 FP: 3 FN: 1 TN: 925 Sensitivity: 98.5% (91.7-100.0) Specificity: 99.7% (99.1-99.9)



	PPV: 95.5%* NPV: 99.9%* PLR: 304.57* NLR: 0.015*
• SDA- BD ProbeTec - urine specimen <i>(reference standard)</i>	TP: 59 FP: 4 FN: 7 TN: 915 Sensitivity: 89.4% (79.4-95.6) Specificity: 99.6% (98.9-99.9) PPV: 93.7%* NPV: 99.2%* PLR: 205.38* NLR: 0.11*
• TMA Combo - urine specimen <i>(reference standard)</i>	TP: 58 FP: 0 FN: 8 TN: 927 Sensitivity: 87.9% (77.5-94.6) Specificity: 100.0% (99.6-100) PPV: 100%* NPV: 99.1%* PLR: Not estimable NLR: 0.12*
*Calculated using Review Manager	
Limitations and other comments	
• Limitations	Very serious risk of bias due to patient selection and patient flow and timing. There was also a lack of blinding. No serious applicability/indirectness.
• Authors' conclusion	Use of the GCQ assay for the detection of N. gonorrhoeae provides highly reliable diagnosis of symptomatic or asymptomatic infection for women.


Combined Testing for Chlamydia, Gonorrhea, and Trichomonas by Use of the BD Max CT/GC/TV Assay with Genitourinary Specimen Types. Van Der Pol 2017 ²¹⁷
Methods

- **Design** Prospective cohort study
- **Source of funding and competing interest** Funding for this project was provided by BD Diagnostics. B.V.D.P. (primary author) reports receiving consulting fees, honoraria, or research support from Atlas Genetics, BD Diagnostics, Beckman Coulter, Cepheid, Rheonix, and Roche Molecular Diagnostics. S.N.T. (fourth author) reports receiving research support or honoraria from BD Diagnostics, Hologic, Cepheid, Beckman Coulter, ELITech, and Roche Molecular Diagnostics. E.W.H. (fifth author) reports that he has received research support for this project and others from BD Diagnostics, Cepheid, and Roche Molecular. He has also received honoraria from Roche Molecular and Cepheid. All other authors have no financial disclosures to report.
- **Setting** Eight STI, family planning, and obstetrics and gynaecology clinics located throughout the United States
- **Sample size** Total number of participants recruited = 2,166. One participant did not meet eligibility requirements and 51 chose to stop participation prior to collection of all sample. Specimens excluded from analyses due to specimen handling or comparator testing protocol deviations at one study site included 278, 281, and 260 vaginal samples, endocervical samples, and urine specimens, respectively.

Details about the number of patients needed for the study was not reported.
- **Time interval between tests** Not reported
- **Statistical analysis** Sensitivity and specificity were calculated.

Patient characteristics

- **Eligibility criteria** Women presenting for routine STI symptom evaluation or screening and being of appropriate age to provide informed consent for research.

Exclusion criteria: the use of antibiotics, including metronidazole/tinidazole within the previous 14 days, having urinated within 1 hour prior to recruitment, and additionally for women hysterectomy or use of contraceptive foams or jellies within 8 hours of recruitment.
- **Patient characteristics** Median age of 2,144 participants was 26 years (range: 16-23)
47% of women were enrolled from sexually transmitted disease (STD) clinics, 44.5% from family planning clinics, 4.2% from obstetric/gynaecologic (OB/GYN) clinics, and 4.4% from other clinical setting
- **Prevalence of disease** Prevalence in the study: 2.3%

Interventions

- **PCR Max - urine specimen** BD Max GC assay (PCR)
 - The MAX assay is a TaqMan-based PCR assay that utilizes target-specific primers and probes to perform simultaneous amplification and detection of amplified products using quenchers and fluorophores.
 - Blinding not reported



- | | |
|--|--|
| <ul style="list-style-type: none"> PCR Max - endocervical specimen | BD Max GC assay (PCR) <ul style="list-style-type: none"> - The MAX assay is a TaqMan-based PCR assay that utilizes target-specific primers and probes to perform simultaneous amplification and detection of amplified products using quenchers and fluorophores. - Blinding not reported |
| <ul style="list-style-type: none"> PCR Max - vaginal specimen | BD Max GC assay (PCR) <ul style="list-style-type: none"> - The MAX assay is a TaqMan-based PCR assay that utilizes target-specific primers and probes to perform simultaneous amplification and detection of amplified products using quenchers and fluorophores. - Blinding not reported |
| <ul style="list-style-type: none"> Reference standard | BD N. gonorrhoea Qx Amplified DNA Assay (GCQ) (SDA) and Hologic Aptima Combo 2 (AC2) (TMA) were used for the reference standard. The patient infection status (PIS) defined gonococcal infections based on the positive results of the two comparator assays using results from both endocervical swabs and urine specimens. At least one positive result, from either sample type, was required from each assay in order to categorize a participant as infected.
Blinding (investigator) to clinical information and/or to index test results not reported. |

Results - Female population

- | | | |
|--|---|--|
| <ul style="list-style-type: none"> PCR Max - urine sample | <i>N. gonorrhoea</i>
TP: 44
FP: 5
FN: 2
TN: 1798
Sensitivity: 95.7% (85.5-98.8)
Specificity: 99.7% (99.4-99.9)
PPV: 90%*
NPV: 100%*
PLR: 344.9*
NLR: 0.04* | <i>C. trachomatis</i>
TP: 130
FP: 12
FN: 8
TN: 1699
Sensitivity: 91.5% (85.8-95.1)
Specificity: 99.5% (99.1-99.8) |
| <ul style="list-style-type: none"> PCR Max - endocervical specimen | <i>N. gonorrhoea</i>
TP: 42
FP: 1
FN: 2
TN: 1779
Sensitivity: 95.5% (84.9-98.7)
Specificity: 99.9% (99.7-100)
PPV: 98%*
NPV: 100%* | <i>C. trachomatis</i>
TP: 132
FP: 6
FN: 13
TN: 1680
Sensitivity: 95.7% (90.8-98.0)
Specificity: 99.2% (98.7-99.6) |



	PLR: 1699*	
	NLR: 0.05*	
• PCR Max - vaginal specimen	<i>N. gonorrhoea</i> TP: 42 FP: 3 FN: 2 TN: 1789 Sensitivity: 95.5% (84.9-98.7) Specificity: 99.8% (99.5-99.9) PPV: 93.3%* NPV: 100%* PLR: 570.18* NLR: 0.046*	<i>C. trachomatis</i> TP: 140 FP: 1 FN: 23 TN: 1672 Sensitivity: 99.3% (96.1-99.9) Specificity: 98.6% (98.0-99.1)
	*Calculated using Review Manager	
Limitations and other comments		
• Limitations	No serious risk of bias. No serious applicability/indirectness.	
• Authors' conclusion	MAX/PCR performance was equivalent to the performances of currently available platforms used in many centralized reference laboratories. The MAX platform provided high sensitivity and specificity using vaginal or endocervical swabs or urine specimens. In many U.S. settings, given the broad utility of the platform based on current and future menus, the MAX offers a potential solution for small to medium laboratories.	



7.1.1.2. Men and women

Use of Nucleic Acid Amplification Testing for Diagnosis of Anorectal Sexually Transmitted Infections. Cosentino 2012. ²²⁴

Methods

- **Design** Prospective cross-sectional study.
- **Source of funding and competing interest** Gen-Probe provided the reagents for T. vaginalis and M. genitalium testing, but they were not involved in the design of the study, analysis, and interpretation of the data and preparation or approval of the manuscript. The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases with cofunding from the national institute of child Health and human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. The project described was supported by the national Institutes of Health through grants.
- **Setting** Recruited from the Allegheny County Health Department, Magee-Women's Hospital of University of Pittsburgh Medical Center (UPMC) or the Pittsburgh AIDS Center for Treatment, U.S.A.
- **Sample size** 500 participants of those 497 had complete evaluable swab sample sets. Two participants were excluded because they enrolled twice. One participant excluded because she admitted that the self-obtained swab was taken from the vagina. Males n=225 and females n=272.
- **Time interval between tests** Samples were transported to the laboratory within 24 hours. Once at the laboratory, specimens were processed as recommended in the package insert for each product.
- **Statistical analysis** Sensitivity, specificity, positive predictive value and negative predictive value were calculated.

Patient characteristics

- **Eligibility criteria** Participants aged 18-64 years attending the two sites between May 2009 and March 2010 who reported having had at least one lifetime episode of receptive anal intercourse. Participants were excluded if they had taken oral antibiotics in the past 7 days or used a rectal douche or other rectal product in the previous 24 hours.
- **Patient characteristics**

Number of males/females: 225/272

Age (median [range] years):
Total: 29 (18-64); Males: 40 (18-63); Females: 27 (18-64)

Race:
Males: Black 32.4%; White 64.9%; Other 2.7%
Females: Black 58.5%; White 37.1%; Other 4.4%

Collection:
Males: Clinician collected 40.4%; self-collected 59.6%
Females: Clinician collected 32.7%; self-collected 67.3%



<ul style="list-style-type: none">• Prevalence of disease	The study reports a prevalence of 4.2%.	
Interventions		
<ul style="list-style-type: none">• TMA Combo – rectal swab	Aptima (AC2): <ul style="list-style-type: none">- GenProbe- Rectal swabs where participant could chose to have clinician collected or self-collected- Specimens were transported to the laboratory within 24 hours.- Blinding (investigator) not reported.	
<ul style="list-style-type: none">• SDA BD ProbeTec– rectal swab	Describe the evaluated test(s): <ul style="list-style-type: none">- Becton Dickinson Probetec- Rectal swabs where participant could chose to have clinician collected or self-collected- Specimens were transported to the laboratory within 24 hours.- Blinding (investigator) not reported.	
<ul style="list-style-type: none">• Culture – rectal swab	Culture test: <ul style="list-style-type: none">- Charcoal swab for the culture detection was stored at ambient temperature and inoculated onto Modified Thayer Martin media within 24 hours of collection.- Identification was based on gram stain, oxidase test, and the GonoGen II (Becton –Dickinson, Sparks, MD) identification system.- Rectal swabs where participant could chose to have clinician collected or self-collected- Blinding not reported.	
<ul style="list-style-type: none">• Reference standard	True positive if it was positive by culture or by two positive molecular tests (SDA and AC2). <ul style="list-style-type: none">- Discordant results between SDA and AC2, the Aptima GC assay which targets different nucleic acid sequences, was used as the confirmatory test.- Blinding (investigator) not reported.	
Results		
<ul style="list-style-type: none">• TMA Combo – rectal swab	<i>N. gonorrhoea</i> TP: 21 FP: 0 FN: 0 TN: 478 Sensitivity: 100.0% Specificity: 100.0% PPV: 100.0%* NPV: 100.0%* PLR: Not reported	<i>C. trachomatis</i> TP: 41 FP: 0 FN: 1 TN: 455 Sensitivity: 100.0% Specificity: 99.8%



NLR: 0.000*	
<ul style="list-style-type: none">• SDA BD ProbeTec – rectal swab	<div><div><div><i>N. gonorrhoea</i></div><div>TP: 16</div><div>FP: 0</div><div>FN: 5</div><div>TN: 478</div><div>Sensitivity: 76.2%</div><div>Specificity: 100.0%</div><div>PPV: 100.0%*</div><div>NPV: 99.0%*</div><div>PLR: Not reported</div><div>NLR: 0.2381*</div></div><div><div><i>C. trachomatis</i></div><div>TP: 23</div><div>FP: 18</div><div>FN: 0</div><div>TN: 456</div><div>Sensitivity: 56.1%</div><div>Specificity: 100.0%</div></div></div>
<ul style="list-style-type: none">• Culture – rectal swab	<div><div><div>TP: 5</div><div>FP: 0</div><div>FN: 16</div><div>TN: 478</div><div>Sensitivity: 23.8%</div><div>Specificity: 100.0%</div><div>PPV: 100.0%*</div><div>NPV: 96.8%*</div><div>PLR:</div><div>NLR: 0.7619*</div></div><div>* Calculated using Review Manager</div></div>
Limitations and other comments	
<ul style="list-style-type: none">• Limitations	<div>Result table reports 21 positives and 478 uninfected which totals 499 but study total reported as n=497.</div> <div>No serious risk of bias.</div> <div>No serious applicability/indirectness.</div>
<ul style="list-style-type: none">• Authors' conclusion	<div>Authors reported that samples for culture were held for up to 24 hours prior to processing, which may have resulted in loss of viability during transport.</div> <div>Authors conclude that AC2 assay had high sensitivity and specificity for detection of <i>N. gonorrhoea</i> and <i>C. trachomatis</i> from rectal swabs.</div>


Performance of the Abbott RealTime CT/NG for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae. Gaydos 2010²²⁵
Methods

- **Design** Prospective cross-sectional study.
- **Source of funding and competing interest** Study funded by Abbott Molecular, Des Plaines, IL, USA.
- **Setting** Multicentre study (16 geographically diverse sites including high and low prevalence sites).
- **Sample size** N=3832 symptomatic and asymptomatic male and female subjects
- **Time interval between tests** Not reported. All tests done on one visit.
- **Statistical analysis** Sensitivity and specificity were reported without actual figures so could not be checked and no additional calculations could be done in Review Manager.

Patient characteristics

- **Eligibility criteria**

People 18 years of age or older, had been sexually active within the past 6 months, and met one or more of the following criteria: seeking screening for STI and/or a medical check-up, seeking treatment for STI-related symptoms, had sexual contact with an infected partner, had been previously treated for an STI and/or had a history of STIs, or had a new sexual partner(s), multiple sexual partners, or reported inconsistent condom use.

Exclusion criteria: ineligible if reported suing or having completed antimicrobial therapy within 21 days of enrolment, being unable or unwilling to provide the appropriate specimens, having voided within 1 h of specimen collection or having insufficient medical and/or sexual history to document the information required for the study.

Female subjects had 10 specimens collected (one self-collected vaginal swab, one urine sample divided into three aliquots, four endocervical swabs and two clinician-collected swabs). Male subjects had 6 specimens collected (three urethral swabs and one urine sample divided into three aliquots).
- **Patient characteristics**

Male: 1818 (47.44%), Female: 2014 (52.56%)

African-American 67.12%; American Indian (Alaska Native) 0.29%; American Indian (Alaska native)/African-American 0.10%; Asian 0.73%; Caucasian 31.26%; Caucasian/Asian 0.03%; Unknown 0.47%

Ethnicity: Hispanic/Latino 15.06%; Non-Hispanic/Latino 84.94%
- **Prevalence of disease** Study prevalence in women 3.8% and in men 16.7%.

Interventions

- **PCR XPert** Polymerase Chain Reaction assay (PCR):
 - Abbott RealTime CT/NG assay, a multiplex realtime assay. Target for gonorrhoeae is the Opa gene.
 - Performed on Abbott m2000 system.
 - Blinding (investigator) not reported.
- **TMA Combo** Transcription mediated amplification (TMA) test:



	<ul style="list-style-type: none"> - Aptima Combo 2 assay (AC2), by GenProbe - Blinding (investigator) not reported.
• SDA ProbeTec	Strand displacement amplification (SDA): <ul style="list-style-type: none"> - ProbeTec ET CT/GC assay, Becton Dickinson - Blinding (investigator) not reported.
• Reference standard	Patient infected status (PIS): <ul style="list-style-type: none"> - The PIS was determined based on the combined results from the reference assays. - Aptima Combo 2 assay (TMA), the ProbeTec assay (SDA), and the culture were used as the reference assays. - Culture used modified Thayer Martin medium for isolation and three clinical laboratories conducted culture testing. - A female subject was defined as infected if a minimum of one positive result reported by each of the reference NAATs (gen-Probe, Becton Dickinson). A male subject was defined as infected if a minimum of two positive results were reported by the reference NAAT. If the culture was positive, the subject was defined as infected regardless of NAAT results. - NAAT testing performed by ICON Laboratories according to comparator assay package inserts. - Blinding (investigator) not reported.

Results

• PCR XPert - overall	<i>N. gonorrhoea</i> Sensitivity: 96.9% (95.4-98.1) Specificity: 99.7% (99.6-99.8)	<i>C. trachomatis</i> Sensitivity: 92.4% (90.7-94.0) Specificity: 99.2% (99.0-99.4)
• PCR XPert - endocervical	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 87.1% (70.2-96.4) Specificity: 99.7% (99.0-100) <u>Asymptomatic:</u> Sensitivity: 91.3% (72.0-98.9) Specificity: 100.0% (99.5-100.0)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 87.7% (78.5-93.94) Specificity: 99.7% (98.9-100) <u>Asymptomatic:</u> Sensitivity: 80.9% (66.7-90.9) Specificity: 99.4% (98.4-99.8)
• PCR XPert – clinician collected vaginal	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 96.8% (83.3-99.9) Specificity: 99.9% (99.2-100.0) <u>Asymptomatic:</u> Sensitivity: 95.7% (78.1-99.9) Specificity: 99.4% (98.5-99.8)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 92.5% (84.4-97.2) Specificity: 98.8% (97.6-99.5) <u>Asymptomatic:</u> Sensitivity: 87.2% (74.3-95.2) Specificity: 99.1% (98.0-99.7)



• PCR XPert – self collected vaginal	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 96.7% (82.8-99.9) Specificity: 99.7% (98.9-100.0) <u>Asymptomatic:</u> Sensitivity: 95.7% (78.1-99.9) Specificity: 100% (99.4-100.0)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 94.7% (86.9-98.5) Specificity: 99.0% (97.9-99.6) <u>Asymptomatic:</u> Sensitivity: 84.8% (71.1-73.7) Specificity: 98.9% (97.7-99.6)
• PCR XPert – female urine	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 93.8% (79.2-99.2) Specificity: 99.7% (99.0-100.0) <u>Asymptomatic:</u> Sensitivity: 87.0% (66.4-97.2) Specificity: 99.6% (98.7-99.9)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 92.6% (84.6-97.2) Specificity: 99.5% (98.7-99.9) <u>Asymptomatic:</u> Sensitivity: 95.7% (85.2-99.5) Specificity: 99.2% (98.2-99.7)
• PCR XPert - urethral	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 99.2% (97.0-99.9) Specificity: 99.3% (98.3-99.8) <u>Asymptomatic:</u> Sensitivity: 81.8% (48.2-99.7) Specificity: 99.8% (99.1-100.0)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 93.3% (86.6-96.5) Specificity: 98.3% (97.0-99.1) <u>Asymptomatic:</u> Sensitivity: 88.6% (80.1-94.4) Specificity: 99.1% (97.9-99.7)
• PCR XPert – male urine	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 98.8% (96.4-99.7) Specificity: 99.5% (98.5-99.9) <u>Asymptomatic:</u> Sensitivity: 100.0% (71.5-100.0) Specificity: 100.0% (99.4-100.0)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 97.3% (93.7-99.1) Specificity: 99.7% (98.9-100.0) <u>Asymptomatic:</u> Sensitivity: 97.8% (92.3-99.7) Specificity: 99.6% (98.7-100.0)
• TMA Combo - overall	<i>N. gonorrhoea</i> Sensitivity: 96.1% (94.3-97.4) Specificity: 99.5% (99.3-99.7)	<i>C. trachomatis</i> Sensitivity: 94.5% (92.9-95.9) Specificity: 99.0% (98.7-99.2)
• TMA Combo - endocervical	<i>N. gonorrhoea</i>	<i>C. trachomatis</i>



	<u>Symptomatic:</u> Sensitivity: 90.6% (75.0-98.0) Specificity: 99.4% (98.6-99.8) <u>Asymptomatic:</u> Sensitivity: 90.9% (70.8-98.9) Specificity: 99.7% (99.0-100.0)	<u>Symptomatic:</u> Sensitivity: 91.4% (83.0-96.5) Specificity: 99.4% (98.5-99.8) <u>Asymptomatic:</u> Sensitivity: 78.7% (64.3-89.3) Specificity: 98.6% (97.4-99.4)
• TMA Combo – clinician collected vaginal	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 93.8% (79.2-99.2) Specificity: 99.3% (98.4-99.8) <u>Asymptomatic:</u> Sensitivity: 95.7% (78.1-99.9) Specificity: 99.7% (98.9-100.0)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 92.6% (84.6-97.2) Specificity: 98.7% (97.5-99.4) <u>Asymptomatic:</u> Sensitivity: 85.1% (71.7-93.8) Specificity: 98.2% (96.8-99.1)
• TMA Combo – female urine	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 84.4% (67.2-94.7) Specificity: 99.6% (98.8-99.9) <u>Asymptomatic:</u> Sensitivity: 82.6% (61.2-95.0) Specificity: 99.4% (98.5-99.8)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 93.8% (86.2-98.0) Specificity: 99.4% (98.5-99.8) <u>Asymptomatic:</u> Sensitivity: 93.5% (82.1-98.6) Specificity: 99.2% (98.2-99.8)
• TMA Combo - urethral	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 99.2% (97.0-99.9) Specificity: 99.2% (98.1-99.7) <u>Asymptomatic:</u> Sensitivity: 81.8% (48.2-97.7) Specificity: 99.7% (98.9-100.0)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 98.4% (95.3-99.7) Specificity: 98.5% (97.2-99.3) <u>Asymptomatic:</u> Sensitivity: 91.2% (83.4-96.1) Specificity: 99.1% (98.0-99.7)
• TMA Combo – male urine	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 97.9% (95.2-99.3) Specificity: 99.7% (98.8-100.0) <u>Asymptomatic:</u> Sensitivity: 100.0% (71.5-100.0)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 99.5% (97.0-100.0) Specificity: 99.4% (98.4-99.8) <u>Asymptomatic:</u> Sensitivity: 98.9% (94.0-100.0)



	Specificity: 99.5% (98.7-99.9)	Specificity: 99.5% (98.5-99.9)
• SDA BD ProbeTec - overall	<i>N. gonorrhoea</i> Sensitivity: 92.0% (88.7-94.6) Specificity: 97.3% (96.8-97.8)	<i>C. trachomatis</i> Sensitivity: 90.3% (87.4-92.7) Specificity: 99.5% (99.2-99.7)
• SDA BD ProbeTec - endocervical	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 87.5% (71.0-96.5) Specificity: 99.6% (98.8-99.9) <u>Asymptomatic:</u> Sensitivity: 91.3% (72.0-98.9) Specificity:98.9% (97.8-99.6)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 88.8% (79.7-94.7) Specificity: 99.1% (98.0-99.7) <u>Asymptomatic:</u> Sensitivity: 78.3% (63.6-89.1) Specificity: 99.8% (99.1-100.0)
• SDA BD ProbeTec – female urine	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity:76.7% (57.7-90.1) Specificity: 95.6% (93.7-97.0) <u>Asymptomatic:</u> Sensitivity: 85.7% (63.7-97.0) Specificity:96.9% (95.3-98.1)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 90.9% (82.2-96.3) Specificity: 99.7% (98.8-100.0) <u>Asymptomatic:</u> Sensitivity: 91.3% (79.2-97.6) Specificity: 99.7% (98.8-100.0)
• SDA BD ProbeTec – male urine	<i>N. gonorrhoea</i> <u>Symptomatic:</u> Sensitivity: 94.9% (91.3-97.3) Specificity: 97.0% (95.2-98.2) <u>Asymptomatic:</u> Sensitivity: 100.0% (69.2-100.0) Specificity:95.7% (93.8-97.2)	<i>C. trachomatis</i> <u>Symptomatic:</u> Sensitivity: 91.0% (85.7-94.7) Specificity: 99.0% (97.9-99.6) <u>Asymptomatic:</u> Sensitivity: 95.5% (88.9-98.8) Specificity: 99.4% (98.4-99.9)
• Survey for females on self-collected vaginal swab (2009 responded out of 2014)	<u>Most preferred by respondents:</u> Self-collected vaginal swab: 30.51% Urine specimen: 26.18% Least preferred clinician collected vaginal swab: 13.89% No preference: 29.87%	
Limitations and other comments		
• Limitations	No serious risk of bias.	



No serious applicability/indirectness.

- **Authors' conclusion** Nucleic acid amplification tests are the most sensitive assays available to date for detecting chlamydia and gonorrhoea in clinical specimens. Above this conclusion, authors conclude that the Abbott RealTime Ct/NG assay performed on the m2000 platform was highly accurate, reproducible, sensitive and specific.

Performance of the Cepheid CT/NG Xpert Rapid PCR Test for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae. Gaydos 2013²²⁶

Methods

- **Design** Prospective cohort study
- **Source of funding and competing interest** This study was funded by Cepheid (Sunnyvale, CA).

C.A.G. (primary author) was also funded by grant from the National Institute of Biomedical Imaging and Bioengineering (NIBIB). C.A.G. has received research support, honoraria, or consulting fees from the following sponsors: Abbott Molecular Diagnostics, BD Diagnostics, Cepheid, Gen-Probe, and Roche Diagnostics. B.V.D.P has received honoraria, consulting fees, or research support from the following sponsors: Abbott Molecular Diagnostics, BD Diagnostics, Beckman Coulter, Cepheid, and Roche Diagnostics. Another study author, E.W.H. received research support, honoraria, research support, or consulting fees from Cepheid, Abbott Molecular Diagnostics, BD Diagnostics, Gen-Probe Hologic, Roche Diagnostics, and Cempra Pharmaceuticals.
- **Setting** Multi-centre (number of centres included is not reported), obstetrics and gynaecology (OB-GYN), sexually transmitted disease (STD), teen, public health, or family planning clinics, USA and UK, (urban/rural setting details is not reported)
- **Sample size** Sample size was calculated using the following statistical plan: sensitivity (both genders, all matrix) required $\geq 95\%$, and specificity (both genders, all matrix) required $\geq 98\%$. The required sample size calculations assumed that subjects would be enrolled from sites with an approximate prevalence range of 3% to 7% for N. gonorrhoeae. For each site, male prevalence rates were assumed to be 2% higher than for females.
Total participants = 3,109
- **Time interval between tests** Not reported
- **Statistical analysis** Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Patient characteristics

- **Eligibility criteria** Age of ≥ 14 years, sexual activity within the past 6 months, and attending a participating clinic for reasons appropriate for sexual health screening.



	Exclusion criteria: having received antimicrobial therapy within 21 days preceding enrolment and (for females) a history of hysterectomy.
• Patient characteristics	<p>This study evaluated the diagnostic accuracy of the Xpert Rapid PCR Test for <i>C. trachomatis</i> as well as <i>N. gonorrhoeae</i> in sexually active people aged ≥14 years.</p> <p>Overall baseline characteristics were reported for both of these STIs as well as disease prevalence for the individual infections (disease prevalence for <i>C. trachomatis</i> is not reported as it is not relevant for this evidence report).</p> <p><u>Overall baseline</u></p> <p>Sex: Female – 1,722 (55.4%), Male – 1,387 (44.6%)</p> <p>Symptomatic: Yes – 839 (27.0%), No – 2,270 (73.0%)</p> <p>Clinic type: Family planning – 510 (16.4%), Public health – 969 (31.2%), STD – 206 (6.6%), Other – 1,424 (45.8%)</p> <p><u>Prevalence for <i>N. gonorrhoeae</i> (% [95% CI])</u></p> <p>Sex: Female – 1.3 (0.9-2.0), Male – 3.6 (2.7-4.7)</p> <p>Symptomatic: Yes – 6.7 (5.1-8.6), No – 0.7 (0.4-1.2)</p> <p>Clinic type: Family planning – 2.0 (0.9-3.6), Public health – 5.2 (3.9-6.7), STD – 2.9 (1.1-6.2), Other – 0.5 (0.2-1.0)</p>
• Prevalence of disease	Study prevalence = 1.3% for females; 3.6% for males
Interventions	
• PCR Xpert - vaginal swab (patient-collected)	<p>GeneXpert CT/NG (Xpert) assay (PCR)</p> <ul style="list-style-type: none"> - The GeneXpert system combines sample preparation with real-time PCR amplification and detection functions for fully integrated and automated nucleic acid analysis. - Steps of the assay: transfer 300 µl of prepared sample into the large hole in the cartridge, dispense elution reagent into the small hole in the cartridge, and insert the cartridge into Xpert platform and start the assay - Results reported as positive or negative or indeterminate (reading is invalid, error, or no result obtained) Indeterminate samples were re-tested using a new aliquot of specimen and a new Xpert cartridge. - Testing was performed according to the assay package inserts of the manufacturer (Cepheid). - Blinding not reported
• PCR Xpert - endocervical swab	<p>GeneXpert CT/NG (Xpert) assay (PCR)</p> <ul style="list-style-type: none"> - The GeneXpert system combines sample preparation with real-time PCR amplification and detection functions for fully integrated and automated nucleic acid analysis. - Steps of the assay: transfer 300 µl of prepared sample into the large hole in the cartridge, dispense elution reagent into the small hole in the cartridge, and insert the cartridge into Xpert platform and start the assay



	<ul style="list-style-type: none"> - Results reported as positive or negative or indeterminate (reading is invalid, error, or no result obtained) Indeterminate samples were re-tested using a new aliquot of specimen and a new Xpert cartridge. - Testing was performed according to the assay package inserts of the manufacturer (Cepheid). - Blinding not reported
<ul style="list-style-type: none"> • PCR Xpert – urine sample 	<p>GeneXpert CT/NG (Xpert) assay (PCR)</p> <ul style="list-style-type: none"> - One sample for each male and female participant - The GeneXpert system combines sample preparation with real-time PCR amplification and detection functions for fully integrated and automated nucleic acid analysis. - Steps of the assay: transfer 300 µl of prepared sample into the large hole in the cartridge, dispense elution reagent into the small hole in the cartridge, and insert the cartridge into Xpert platform and start the assay - Results reported as positive or negative or indeterminate (reading is invalid, error, or no result obtained) Indeterminate samples were re-tested using a new aliquot of specimen and a new Xpert cartridge. - Testing was performed according to the assay package inserts of the manufacturer (Cepheid). - Blinding not reported
<ul style="list-style-type: none"> • Reference standard 	<p>APTIMA Combo 2 assay (AC2) (TMA) and BDProbeTec N. gonorrhoeae amplified DNA assays (BDPT) (SDA) used to determine patient infection status (PIS). Patients for this trial were defined as infected for each specimen type if a minimum of one positive result was reported by each of the two comparator NAAT assays for that specimen type; thus, two comparator positives are required for that specimen type, at least one from each comparator assay</p> <p>Specimens used: endocervical swabs (used to determine patients infection status (PIS) and urine specimen for each female participant; urethral swabs for male participants (used to determine PIS)</p>

Results

<ul style="list-style-type: none"> • PCR Xpert - vaginal swab (patient-collected) 	<p><i>N. gonorrhoea</i></p> <p>TP: 22 FP: 2 FN: 0 TN: 1689 Sensitivity: 100% (87.3-100) Specificity: 99.9% (99.6-100) PPV: 91.7% NPV: 100% PLR: 845.5* NLR: Not estimable</p>	<p><i>C. trachomatis</i></p> <p>TP: 78 FP: 10 FN: 1 TN: 1624 Sensitivity: 98.7% (93.1-100) Specificity: 99.4% (98.9-99.7)</p>
<ul style="list-style-type: none"> • PCR Xpert - endocervical swab 	<p><i>N. gonorrhoea</i></p> <p>TP: 22</p>	<p><i>C. trachomatis</i></p> <p>TP: 76</p>



FP: 0	FP: 7
FN: 0	FN: 2
TN: 1688	TN: 1625
Sensitivity: 100% (87.3-100)	Sensitivity: 97.4% (91.0-99.7)
Specificity: 100 (99.8-100)	Specificity: 99.6% (99.1-99.8)
PPV: 100%	
NPV: 100%	
PLR: Not estimable	
NLR: Not estimable	

Results by gender

<ul style="list-style-type: none"> PCR Xpert - urine sample (female) 	<i>N. gonorrhoea</i> TP: 22 FP: 1 FN: 1 TN: 1694 Sensitivity: 95.6% (78.1-99.9) Specificity: 99.9% (99.7-100) PPV: 95.6% NPV: 99.9% PLR: 1621.3* NLR: 0.044*	<i>C. trachomatis</i> TP: 80 FP: 3 FN: 2 TN: 1633 Sensitivity: 97.6% (91.5-99.7) Specificity: 99.8% (99.5-100)
<ul style="list-style-type: none"> PCR Xpert - urine sample (male) 	<i>N. gonorrhoea</i> TP: 49* FP: 1* FN: 1* TN: 1335* Sensitivity: 98.0% (89.4-99.9) Specificity: 99.9% (99.6-100) PPV: 98.0% NPV: 99.9% PLR: 1309.3* NLR: 0.02*	<i>C. trachomatis</i> TP: 79 FP: 1 FN: 2 TN: 1304 Sensitivity: 97.5% (91.4-99.7) Specificity: 99.9% (99.6-100)



*Calculated using Review Manager

Limitations and other comments

- **Limitations**

Serious risk of bias due to patient flow and timing.
No serious applicability/indirectness.
Study reported in Nelson 2014 systematic review using sub-group analysis of women without symptoms suggestive of bacterial STI, whereas whole cohort figures reported here.
- **Authors' conclusion**

Data demonstrated that the presence or absence of symptoms has little impact on test performance. *N. gonorrhoeae* infections are regularly asymptomatic, particularly in women for *N. gonorrhoeae*, there was no statistical difference in test sensitivity for men or women for any sample type when participants were stratified based on symptoms.
Nucleic acid amplification tests are the most sensitive assays available to date for detecting chlamydia and gonorrhoea in clinical specimens, and the Xpert assay adds to the group of commercially available assays that are available to laboratories as choices for superior diagnostic performance.

Evaluation of the new AmpliSens multiplex real-time PCR assay for simultaneous detection of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, and *Trichomonas vaginalis*. Rumyantseva 2015 ²²⁷

Methods

- **Design**

Prospective cohort study
- **Source of funding and competing interest**

Funding not reported.
This study was supported by the Orebro County Council Research Committee and the Foundation for Medical Research at Orebro University Hospital, Sweden.
- **Setting**

Single centre, STI clinic, Orebro University Hospital, Sweden
- **Sample size**

Total participants = 1,261 (females = 707; males = 554)
Biological specimens collected = males (n = 554), and first-void urine (n = 498) or vaginal swabs (n = 209) were collected from all females.
Details not reported for any un-evaluable specimens (all specimens were analysed).
- **Time interval between tests**

Not reported
- **Statistical analysis**

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Patient characteristics

- **Eligibility criteria**

Consecutive attendees in the STI clinic, from May 2012 to January 2013, provided written consent
Exclusion criteria not reported
- **Patient characteristics**

Age:



	Females (range): 18-65 years (median: 29 years) Males (range): 21-80 years (median: 32 years)
• Prevalence of disease	Study prevalence = 0.3% among females and 0.4% among males
Interventions	
• PCR Ampli - vaginal swab	AmpliSens multiplex real-time (PCR) assay <ul style="list-style-type: none"> - Testing conducted following manufacturer's instruction - Blinding to reference test results reported
• PCR Ampli - urine specimen	AmpliSens multiplex real-time (PCR) assay <ul style="list-style-type: none"> - Testing conducted following manufacturer's instruction - Blinding to reference test results reported
• Reference standard	APTIMA Combo 2 assay (AC2) (TMA) <ul style="list-style-type: none"> - Testing of specimen within 1 week after specimen collection on the PANTHER platform - Specimens were subsequently frozen prior to testing with the reference standard - Blinding to the results of the index test not reported
Results	
• PCR Ampli- vaginal swab	TP: 0 FP: 0 FN: 0 TN: 209 Sensitivity: Could not be calculated due to lack of positive specimens Specificity: 100% (98.2-100) PPV: Could not be calculated due to lack of positive specimens NPV: 100% (98.2-100) PLR: Not estimable NLR: Not estimable
Results by gender (urine samples)	
• PCR Ampli - urine sample (female)	TP: 2 FP: 0 FN: 0 TN: 496 Sensitivity: 100% (19.3-100) Specificity: 100% (99.2-100) PPV: 100% (19.3-100)



	NPV: 100% (99.2-100) PLR: Not estimable NLR: Not estimable
<ul style="list-style-type: none"> • PCR Ampli - urine sample (male) 	TP: 2 FP: 0 FN: 0 TN: 552 Sensitivity: 100% (19.3-100) Specificity: 100% (99.3-100) PPV: 100% (19.3-100) NPV: 100% (99.3-100) PLR: Not estimable NLR: Not estimable
Limitations and other comments	
<ul style="list-style-type: none"> • Limitations 	Serious risk of bias due to patient flow and timing. No serious applicability/indirectness.
<ul style="list-style-type: none"> • Authors' conclusion 	The PCR assay demonstrated high clinical and analytical sensitivity and excellent specificity for the detection of <i>N. gonorrhoeae</i> . It is simple and quick to perform as well as cheaper compared to many international STI diagnostics NAATs.

7.2. Treatment of gonorrhoea

7.2.1. Sexually active women and men including adolescents

Table 18 – Evidence table of intervention studies for the treatment of gonorrhoea in sexually active women and men

The Efficacy and Safety of Gentamicin Plus Azithromycin and Gemifloxacin Plus Azithromycin as Treatment of Uncomplicated Gonorrhoea. Kirkcaldy 2014 ²²⁸	
Methods	
<ul style="list-style-type: none"> • Design 	RCT; Authors described as randomized, multisite, open-label, non-comparative trial.
<ul style="list-style-type: none"> • Source of funding and competing interest 	Supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health. All authors reported no conflict of interest.
<ul style="list-style-type: none"> • Setting 	Multicentre: 5 outpatient sexually transmitted disease clinic sites in Alabama, California, Maryland, and Pennsylvania, USA.
<ul style="list-style-type: none"> • Sample size 	664 participants with suspected gonorrhoea were assessed for eligibility, 614 were randomized and 603 received the study medication. Of those randomized and treated, 119 were found to be ineligible and 117 were due to negative enrollment cultures. Participants included in per protocol analysis n=401.



	Study anticipated a cure rate of 97% and allowed a 10% drop out rate. The target sample size was 250 infected participants per group. An independent safety monitoring committee meeting in August 2012 recommended halting enrollment because continued participant accrual to targeted enrollment of 500 infected participants would be highly unlikely to alter the results.
• Duration and follow-up	At 10-17 days after treatment the participants provided a follow-up culture to determine microbiologic cure defined as a negative culture.
• Statistical analysis	<p>Primary analysis used the per protocol population, which included all infected participants who (1) satisfied inclusion and exclusion criteria, (2) were randomised and treated, (3) returned for follow-up within 10-17 days and (4) had an evaluable follow-up culture result.</p> <p>Modified Intention to Treat (mITT) sensitivity analysis included all infected participants who satisfied inclusion and exclusion criteria and were randomised and treated. For the purposes of the mITT analysis, participants who were lost to follow up, vomited within 1 hour or whose follow-up culture were not evaluable were considered to have failed treatment (not cured).</p> <p>Adverse events were calculated on the patients in the per-protocol population and the safety population (all patients who received at least one dose of study medication, including those that vomited within one hour of drug administration).</p> <p>Relative risks calculated by reviewer using Review Manager.</p>
Patient characteristics	
• Eligibility criteria	<p>Men and women aged 15-60 years diagnosed with uncomplicated urogenital gonorrhoea were enrolled between May 2010 and November 2012.</p> <p>Initially eligible if they (1) were suspected to be infected with urethral or cervical <i>N. gonorrhoeae</i> and (2) were willing to abstain from sexual intercourse or use condoms until follow-up was complete.</p>
• Exclusion criteria	<p>Major exclusion criteria were age < 15 years or > 60 years, having a history of renal insufficiency, hepatic insufficiency, cardiac arrhythmia, neuromuscular disorders, rheumatoid arthritis, or tendon disorders; prior receipt of kidney, lung or heart transplants; pregnancy or lactation; allergy or prior adverse reaction to macrolides, aminoglycosides, or fluoroquinolones; concomitant infection requiring systemic antimicrobial therapy (besides chlamydia); receipt of systemic or intravaginal antimicrobials within 30 days of study enrolment, or current use of corticosteroids, immunosuppressive therapy, or cardiac antiarrhythmic medication; and clinically diagnosed abdominal pain related to PID, testicular pain, epididymitis, disseminated gonococcal infection, or genital ulcer disease. Women diagnosed with bacterial vaginosis (BV) at enrolment were enrolled if they were willing to defer BV treatment until the follow-up visit. Women who did not wish to defer BV treatment were withdrawn from the study.</p> <p>Culture specimens were collected and participants later found to have negative enrolment cervical or urethral cultures were deemed ineligible and were discontinued from the study.</p>
• Patient & disease characteristics	<p>Randomised: Group 1: n=309; Group 2: n=305</p> <p>Included in modified ITT analysis: Group 1: n=247; Group 2: n=237</p> <p>Included in per protocol analysis: Group 1: n=202; Group 2: n=199</p> <ul style="list-style-type: none"> - Excluded: 45 vs. 38 - Median age (IQR): Group 1: 26 (22-35) vs. Group 2: 29 (22-36)



- Sex women: Group 1: 9.4% vs Group 2: 10.6%
- MSM: Group 1: 67 (33.2%) vs Group 2: 77 (38.7%)
- MSW (men having sex exclusively with women): Group 1: 116 (57.4%) vs Group 2: 101 (50.8%)

Additional infections diagnosed:

- Pharyngeal gonorrhoea: Group 1: 10 (5%) vs Group 2: 15 (17.5%)
- Rectal gonorrhoea: Group 1: 1 (0.5%) vs Group 2: 5 (2.5%)

Interventions

- **Intervention group (1)**

Group 1: Gentamicin 240 mg intramuscularly (or 5mg/kg if ≤ 45 kg) plus azithromycin 2 g orally. The gentamicin 240mg, 2 separate 3-mL injections of 40mg/mL solution were administered. Azithromycin was provided as four 500-mg tablets.

A small snack was provided prior to medication administration. Participants were observed for at least 30 minutes after administration and were instructed to return to the clinic immediately if vomiting occurred within 30 minutes of departing the clinic. Those who vomited within 1 hour were discontinued from the study.
- **Control group (2)**

Group 2: gemifloxacin 320 mg orally plus azithromycin 2 g given simultaneously as single oral dose. Azithromycin was provided as four 500-mg tablets.

A small snack was provided prior to medication administration. Participants were observed for at least 30 minutes after administration and were instructed to return to the clinic immediately if vomiting occurred within 30 minutes of departing the clinic. Those who vomited within 1 hour were discontinued from the study.

Results

- **Microbiological cure for patients with urogenital gonorrhoea**

Per Protocol analysis:
Group 1: 202/202 (100%; lower 1-sided exact 95% CI bound, 98.5%) vs Group 2: 198/199 (99.5%; lower 1-sided exact 95% CI bound, 97.6%)
RR: 1.01 (95% CI, 0.99 to 1.02)*

MITT sensitivity analysis:
Group 1: 83.8% (lower 1-sided exact 95% CI bound, 80.0%) vs Group 2: 84.4% (lower 1-sided exact 95% CI bound, 80.5%)
- **Microbiological cure for patients with pharyngeal (n=25) and rectal gonorrhea (n=6)**

Pharyngeal gonorrhoea
Group 1: 10/10 (100%) vs Group 2: 15/15 (100%)

Rectal gonorrhoea
Group 1: 1/1 (100%) vs Group 2: 5/5 (100%)



<ul style="list-style-type: none"> Adverse events – tolerability (mild, moderate and severe combined) 	<p>Nausea: Group 1: 56/202 (27.7%) vs Group 2: 74/199 (37.2%); RR: 0.75 (0.56 to 0.99)</p> <p>Vomiting: Group 1: 15/202 (7.4%) vs Group 2: 10/199 (5.0%); RR: 1.48 (0.68 to 3.21)</p> <p>Abdominal pain: Group 1: 15/202 (7.4%) vs Group 2: 21/199 (10.6%); RR: 0.70 (0.37 to 1.33)</p> <p>Diarrhoea: Group 1: 39/202 (19.3%) vs Group 2: 46/199 (23.1%); RR: 0.84 (0.57 to 1.22)</p> <p>Injection site pain: Group 1: 2/202 (1.0%) vs Group 2: 0/199 (0%); Peto OR: 7.32 (0.46 to 117.39)</p> <p>Fatigue: Group 1: 4/202 (2.0%) vs Group 2: 6/199 (3.0%); RR: 0.66 (0.19 to 2.29)</p> <p>Dizziness: Group 1: 7/202 (3.5%) vs Group 2: 7/199 (3.5%); RR: 0.99 (0.35 to 2.76)</p> <p>Tendon disorder/tendonitis: Group 1: 1/202 (0.5%) vs Group 2: 3/199 (1.5%); RR: 0.33 (0.3 to 3.13)</p>
<ul style="list-style-type: none"> Compliance 	Not reported.
<ul style="list-style-type: none"> Antimicrobial susceptibility of pretreatment <i>Neisseria gonorrhoeae</i> isolates <ul style="list-style-type: none"> Per protocol analysis (n=421) 	<p>Percentage of isolates at or above minimum inhibitory concentration breakpoint:</p> <p>Azithromycin=0.5%</p> <p>Cefixime=1.4%</p> <p>Ceftriaxone=1.2%</p> <p>Gemifloxacin = 17.1%</p> <p>Gentamicin = 0%</p> <p>Ciprofloxacin = 24.5%</p> <p>Penicillin=23.0%</p> <p>Tetracycline=24.2%</p>
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	<p>Very serious risk of bias due to high risk of performance bias, detection bias and attrition bias.</p> <p>Cultures were used to diagnose gonorrhoea and the previous review found that this test had a low sensitivity. This could have resulted in missed cases of gonorrhoea and an overestimation of this outcome.</p>
<ul style="list-style-type: none"> Authors conclusion 	The combinations of azithromycin plus gentamicin or gemifloxacin exhibit excellent efficacy for treatment of uncomplicated urogenital gonorrhoea. These combinations may be helpful for patients with severe cephalosporin allergy.

The efficacy and safety of gentamicin for the treatment of genital, pharyngeal and rectal gonorrhoea: a randomised controlled trial. Ross 2017²²⁹

Methods

<ul style="list-style-type: none"> Design 	Conference abstract for a randomized controlled trial.
<ul style="list-style-type: none"> Source of funding and competing interest 	Not reported.
<ul style="list-style-type: none"> Setting 	Multi-centre, 14 sexual health clinics in England.



• Sample size	N=720. Patients randomized: Group 1: n=358 vs Group 2: n=362 Primary outcome data available: Group 1: n=292 vs Group 2: n=306 The study had 90% power to detect non-inferiority with a lower CI for an absolute risk difference of 5%.
• Duration and follow-up	Data collection completed in March 2017. Follow-up 2 weeks after treatment.
• Statistical analysis	Clearance of gonorrhoea reported (microbiological cure) and adjusted risk difference.
Patient characteristics	
• Eligibility criteria	Participants with genital, pharyngeal or rectal gonorrhoea. Diagnosis of gonorrhoea was based on a positive nucleic acid amplification test (NAAT) or gram stained smear on microscopy.
• Exclusion criteria	Not reported.
• Patient & disease characteristics	Baseline characteristics of both groups reported to be well balanced (no details provided). Sex of participants not reported.
Interventions	
• Group 1 – gentamicin	Gentamicin 240mg + azithromycin 1g - Single intramuscular injection.
• Group 2 – ceftriaxone	Ceftriaxone 500mg + azithromycin 1g - Single intramuscular injection.
Results	
• Microbiological cure based on NAAT	Group 1: 267/292 (91%) vs Group 2: 299/306 (98%) Adjusted risk difference -6.4% (95% CI -10.4%, -2.4%) Pre-specified sensitivity analyses supported this result (detail not provided).
• Microbiological cure by site	Genital: Group 1: 94% vs Group 2: 98% Pharynx: Group 1: 80% vs Group 2: 96% Rectum: Group 1: 90% vs Group 2: 98%
• Adverse events	Study reported that frequency of side effects was similar between treatment groups. No details on type of side effects.
• Compliance	Not reported.
• Microbial resistance	Not reported.
Limitations and other comments	



- **Limitations** Very serious risk of bias due to selection bias, detection bias and attrition bias.
- **Authors conclusion** Gentamicin is not non-inferior to ceftriaxone for the treatment of gonorrhoea.

A Phase II trial of single dose oral ETX0914 (AZD0914) for treatment of uncomplicated urogenital gonorrhoea. Taylor 2016²³⁰

Methods

- **Design** Conference abstract for a multi-centre Phase II trial (RCT).
- **Source of funding and competing interest** Not reported.
- **Setting** Not reported.
- **Sample size** 179 participants were enrolled, randomized and treated.
- **Duration and follow-up** Enrolled and treated from November 2014 to December 2015.
Test-of-cure visit occurred at 6+2 days to evaluate microbiological cure by culture, clinical cure and safety.
A follow-up safety visit also occurred at 31+2 days.
- **Statistical analysis** Microbiological cure and adverse events were reported.

Patient characteristics

- **Eligibility criteria** Individuals with signs and symptoms of urogenital gonorrhoea, confirmed urogenital gonorrhoea in the past 14 days or who had sexual contact with an individual diagnosed with gonorrhoea in the past 14 days were eligible for enrolment.
- **Exclusion criteria** Not reported.
- **Patient & disease characteristics** 167 men and 12 women.
At baseline: 141/179 had positive urogenital cultures (132 urethral and 9 cervical)

Interventions

- **Group 1 – ETX0914 2000mg** ETX0914 orally 2000 mg
 - Novel spiropyrimidinetrione antibiotic that unlike any marketed antibiotic inhibits deoxyribonucleic acid biosynthesis by accumulation of double strand cleavages.
 - Randomised approximately 70:70:40 (Group 1: Group 2: Group 3)
- **Group 2 – ETX0914 3000mg** ETX0914 orally 3000 mg
 - Novel spiropyrimidinetrione antibiotic that unlike any marketed antibiotic inhibits deoxyribonucleic acid biosynthesis by accumulation of double strand cleavages.
 - Randomised approximately 70:70:40 (Group 1: Group 2: Group 3)
- **Group 3 – Ceftriaxone 500mg** Ceftriaxone 500mg in single intramuscular injection.



- Randomised approximately 70:70:40 (Group 1: Group 2: Group 3)

Results

- **Microbiological cure for uncomplicated urogenital gonorrhoea by culture** Per protocol population:
Group 1: 48/49 (98%) vs Group 2: 47/47 (100%) vs Group 3: 21/21 (100%)*
**Microbiological cure outcome only reported for 117 participants but there are no details what this protocol entails.*
- **Adverse events** Total: 21/179 (20 mild and 1 moderate)
Authors reported that the most common ETX0914 related adverse events were gastrointestinal.
- **Compliance** Not reported.
- **Microbial resistance** Not reported.

Limitations and other comments

- **Limitations** Very serious risk of bias due to selection bias, performance bias, detection bias and attrition bias.
Cultures were used to diagnose gonorrhoea and the diagnostics review found that this test had a low sensitivity. This could have resulted in missed cases of gonorrhoea and an overestimation of this outcome.
- **Authors conclusion** Single-dose oral ETX0914 was safe and effective in eradicating gonorrhoea from urogenital sites and shows promise for treatment of uncomplicated gonorrhoea.

Randomized controlled clinical trial on the efficacy of fosfomycin trometamol for uncomplicated gonococcal urethritis in men. Yuan 2016¹⁰⁵

Methods

- **Design** RCT
- **Source of funding and competing interest** Supported by the Hospital Research Foundation of Dujiangyan Medical Center. All authors report no conflicts of interest relevant to this article.
- **Setting** Dujiangyan Medical Center, Chengdu, China
- **Sample size** A clinically acceptable margin of 10% and calculated that the sample size in each treatment group should be 59 at a 5% ($\alpha = 0.05$) level of significance and 80% ($\beta = 0.20$) power.

Patients initially randomized = 152
Patients that received interventions after randomization (n=146): intervention group = 72; ceftriaxone group = 74

Fosfomycin group = Excluded from analysis (n = 5) (Took other antibiotics during study: 2; No follow-up tests: 3)



	Ceftriaxone group = Excluded from analysis (n = 4) (Took other antibiotics during study: 3; No follow-up tests: 1)
	<p>Patients evaluable (per-protocol analysis) = 126 (fosfomycin = 62; ceftriaxone = 64)</p> <p>60 in the fosfomycin group and 61 in the ceftriaxone group completed all aspects of the study, and five patients (two patients in the intervention group and three in the control group) discontinued intervention because of unsuccessful treatment. Therefore, 126 patients were included in the per-protocol analyses.</p>
• Duration and follow-up	Follow-up: 7-14 days after treatment
• Statistical analysis	A 95% confidence interval for the treatment difference in clinical and microbiologic cure rates between the two regimens was calculated, and if it lays above the noninferiority margin value, then noninferiority was deemed to have been established.
Patient characteristics	
• Eligibility criteria	Men >18 years old who presented with lower urinary tract symptoms or associated mucopurulent urethral discharge attributed to urethritis with confirmed urethral <i>N. gonorrhoeae</i> infection between 1 st September 2013 and 31 st August 2015 were included in this study. For the study, a Gram stain of urethral secretions that demonstrates polymorphonuclear leukocytes with intracellular Gram-negative diplococci was considered diagnostic for infection with <i>N. gonorrhoeae</i> in patients.
• Exclusion criteria	Men with confirmed or suspected complicated or disseminated systemic gonococcal infection, such as epididymitis, prostatitis, genital ulcer disease, proctitis, arthritis or endocarditis, were not enrolled. Also, included the following: having a medical history of severe cardiopulmonary disorders, decompensated hepatic and renal insufficiency; allergy or prior adverse reaction to macrolides, cephalosporins, penicillins or fosfomycin; coinfections with additional sexually transmitted diseases including HIV, or concomitant infection requiring antibiotic treatment; current use of corticosteroid or immunosuppressive drugs; known significant immunosuppression; and clinically significant abdominal pain or diarrhoea.
• Patient & disease characteristics	The mean patient age was 28 years (range, 18–65 years) in the fosfomycin group and 29 years (range, 20–68 years) in the ceftriaxone group.
Interventions	
• Group 1 Ceftriaxone (250 mg) + azithromycin (1 g)	<p>Ceftriaxone 250 mg intramuscularly plus azithromycin 1 g orally provided simultaneously as a single dose.</p> <p>The drugs were administered under direct observation. After medication administration, patients were observed for at least 30 minutes in the outpatient clinic. Subjects enrolled onto the study were encouraged to report adverse events. All subjects were asked to return to undergo repeat clinical evaluation, bacterial smear and culture for the test of cure on days 7 and 14 after receipt of all the study medications.</p>
• Group 2 Fosfomycin trometamol (3 g)	<p>Three-doses of fosfomycin trometamol 3 g orally administered alone at days 1, 3 and 5.</p> <p>The drugs were administered under direct observation. After medication administration, patients were observed for at least 30 minutes in the outpatient clinic. Subjects enrolled onto the study were encouraged to report adverse events. All subjects were asked to return to undergo repeat clinical evaluation, bacterial smear and culture for the test of cure on days 7 and 14 after receipt of all the study medications.</p>



Results	
• Number cured (%) – clinical and microbiologic cure	Group 1: 61/64 (95.3%) vs Group 2: 60/62 (96.8%)
• Adverse events: nausea (%)	Group 1: 3/61 (4.9%) vs Group 2: 5/60 (8.3%)
• Adverse events: diarrhoea (%)	Group 1: 6/61 (9.8%) vs Group 2: 7/60 (11.7%)
• Adverse events: abdominal pain (%)	Group 1: 4/61 (6.6%) vs Group 2: 3/60 (5%)
• Adverse events: dyspepsia	Group 1: 3/61 (4.9%) vs Group 2: 5/60 (8.3%)
• Adverse events: fatigue	Group 1: 2/61 (3.3%) vs Group 2: 2/60 (3.3%)
• Compliance	Not reported.
• Microbial resistance	Not reported.
Limitations and other comments	
• Limitations	<p>Very high risk of bias due to performance bias, attrition bias and other bias related to method used for diagnosis. Culture was used to diagnose gonorrhoea in this study, previous review found that this test has a low sensitivity.</p> <p>Clinical cure was defined as a complete resolution of all signs and symptoms of uncomplicated gonococcal urethritis with no recurrence at the day 7 and 14 test-of-cure visits, while microbiologic cure was defined as consistently negative bacterial smears and cultures of urethral secretion or first-void urine specimens at the end of therapy.</p> <p>Study was conducted in China – prevalence and clinical practice may be different when compared to prevalence and clinical practice in Belgium.</p>
• Authors' conclusion	In summary, the results of this trial indicate that fosfomycin trometamol exhibits excellent efficacy for treatment of un-complicated gonococcal urethritis in men. Serious adverse effects are rare.



7.2.2. Pregnant women

7.2.2.1. Intervention studies

Table 19 – Evidence table of intervention studies for the treatment of gonorrhoea in pregnant women

Treatment of gonorrhoea in pregnancy. Cavenee 1993 ²³¹	
Methods	
• Design	RCT
• Source of funding and competing interest	Supported in part by grants from Roche Laboratories, The Upjohn Company and Wyeth-Ayerst Laboratories.
• Setting	Multicentre, urban setting in USA from January 1990 to March 1992. Patients referred to an obstetric complications clinic after presumptively positive gonorrhoea cultures.
• Sample size	Women enrolled and treated: N = 353 Excluded = n=101 Reasons for exclusions: negative pre-treatment cultures: n=86, lost to follow-up or had follow-up after 14 days=15 Patients evaluated: n=252 (71%) To determine sample sizes, the authors presumed an efficacy of 98% for ceftriaxone. A sample of 81 patients would be needed to have a 98% chance of detecting a difference of 20%, or a 71% chance of detecting a 10% difference between the ceftriaxone group and either the spectinomycin or amoxicillin with probenecid group.
• Duration and follow-up	Follow-up 14 days
• Statistical analysis	Performed using χ^2 or Fisher exact test (two-tailed) or Student t test where appropriate.
Patient characteristics	
• Eligibility criteria	Initial gonorrhoea cultures were obtained from all obstetric patients through a prenatal clinic system operated by the Dallas County Hospital District and Park Land Memorial Hospital. The cultures were examined by the Dallas county Health Department, which contacted patients with presumptively positive cultures and referred them to an Obstetric Complications Clinic. At the initial visit all untreated women were offered enrolment into the study. At the time of initial treatment, either sexual abstinence or non-lubricated condom use was strongly recommended.
• Exclusion criteria	Patients with penicillin allergy were excluded. Women were excluded from evaluation if they admitted unprotected coitus with untreated sexual partners. Patients who did not return for follow-up within 14 days of treatment were excluded.
• Patient & disease characteristics	Authors stated that there were no significant differences among the three treatment groups with respect to demographic variables.

Population enrolled/evaluated:

Group 1=114/84 vs Group 2: n=123/84 and Group 3: n=116/84

Population evaluated; N= 252

Mean age: 19.7 years

Mean gestational age at treatment: 22.2 weeks

Mean age:

Group 1: 19.6 vs Group 2: 19.7 vs Group 3: 20.1 years

Ethnicity:

Black: Group 1: 82% vs Group 2: 84% vs Group 3: 87%

White: Group 1: 6% vs Group 2: 5% vs Group 3: 6%

Hispanic: Group 1: 12% vs Group 2: 11% vs Group 3: 7%

Nulliparous: Group 1: 50% vs Group 2: 48% vs Group 3: 51%

Sites and type of pre-treatment infection:

Uncomplicated gonorrhea =330 mucosal sites from 252 women.

Endocervix: 245 women (97%)

Rectum: 68 women (27%)

Pharynx: 17 women (7%)

Interventions

- | | |
|-------------------------------|---|
| • Intervention group 1 | Ceftriaxone 250mg intramuscularly
Pretreatment visit: Patients had gonococcal cultures of the endocervix, pharynx and rectum taken
Patients scheduled for a follow up visit in 1 week for test of cure cultures.
At the first follow-up visit cultures of all pretreatment infection sites were obtained. |
| • Intervention group 2 | Amoxicillin 3 g orally given 30 minutes after probenecid 1 g orally.
Pretreatment visit: Patients had gonococcal cultures of the endocervix, pharynx and rectum taken
Patients scheduled for a follow up visit in 1 week for test of cure cultures.
At the first follow-up visit cultures of all pretreatment infection sites were obtained. |
| • Intervention group 3 | Spectinomycin 2 g intramuscularly |



	<p>Pretreatment visit: Patients had gonococcal cultures of the endocervix, pharynx and rectum taken</p> <p>Patients scheduled for a follow up visit in 1 week for test of cure cultures.</p> <p>At the first follow-up visit cultures of all pretreatment infection sites were obtained.</p>
Results	
<ul style="list-style-type: none"> Microbiological cure (from all infected sites) 	Group 1: 80/84 (95%) vs Group 2: 75/84 (89%) vs Group 3: 80/84 (95%)
<ul style="list-style-type: none"> Microbiological cure (from cervix, pharynx, rectum) 	<p>Cervix: Group 1: 78/82 (95%) vs Group 2: 75/82 (91%) vs Group 3: 78/81 (95%)</p> <p>Pharynx: Group 1: 6/6 (100%) vs Group 2: 4/5 (80%) vs Group 3: 5/6 (83%)</p> <p>Rectum: Group 1: 21/22 (95%) vs Group 2: 23/27 (85%) vs Group 3: 19/19 (100%)</p>
<ul style="list-style-type: none"> Adverse events 	<p>Group 1: No reported side effects in women other than discomfort at the injection site.</p> <p>Group 2: One woman reported vomiting several hours after treatment.</p> <p>Group 3: No reported side effects in women other than discomfort at the injection site.</p>
<ul style="list-style-type: none"> Incidence of major and minor congenital malformations in women (n=215, 79%) 	<p>Minor malformations:</p> <p>Group 1: 12/75 (16%) vs Group 2: 14/71 (20%) vs Group 3: 9/69 (13%)</p> <p>Type of minor malformations not provided.</p> <p>Major malformations:</p> <p>Group 1: 0/75 vs Group 2: 1/71 (1%) vs Group 3: 1/69 (1%)</p> <p>Type of major malformations:</p> <p>Group 2: unexplained symmetrical growth retardation with microcephaly.</p> <p>Group 3: exstrophy of the cloaca with pulmonary hypoplasia.</p>
<ul style="list-style-type: none"> Compliance 	Not reported.
<ul style="list-style-type: none"> Antimicrobial resistance 	Not reported.
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	<p>High risk of performance bias, detection bias, selection bias, reporting bias and attrition bias.</p> <p>Treatment 2 Amoxicillin not reported as penicillin group is no longer advised due to resistance.</p> <p>Cultures were used to diagnose gonorrhoea and the previous review found that this test had a low sensitivity. This could have resulted in missed cases of gonorrhoea and an overestimation of this outcome.</p>
<ul style="list-style-type: none"> Authors conclusion 	<p>The authors conclude that ceftriaxone and spectinomycin are safe and effective for the treatment of gonorrhoea in pregnancy.</p> <p>Amoxicillin with probenecid has lower efficacy and is not recommended for treatment of gonococcal infection in pregnancy.</p>

**A randomised trial that compared oral cefixime and intramuscular ceftriaxone for the treatment of gonorrhoea in pregnancy. Ramus 2001²³²****Methods**

• Design	RCT
• Source of funding and competing interest	Not reported.
• Setting	Multicentre, urban setting in USA. Patients referred to an obstetric complications clinic after presumptively positive gonorrhoea cultures.
• Sample size	Women enrolled and treated: N=161 Excluded: n=66 Reasons for exclusions: Negative pretreatment cultures: n=51; lost to follow-up or had follow-up after 14 days: n=15 Patients evaluated: n=95 A power calculation estimated 80 subjects in each group but the study discontinued enrolment early because of decreasing frequency of gonorrhoea in the patient population, with the determination that several more years would be necessary to achieve desired sample size.
• Duration and follow-up	Follow up: 14 days
• Statistical analysis	Statistical analysis by chi-square analysis.

Patient characteristics

• Eligibility criteria	Initial gonorrhoea cultures were obtained from all obstetric patients through a prenatal clinic system operated by the Dallas County Hospital District and Park Land Memorial Hospital. The cultures were examined by the Dallas county Health Department, which contacted patients with presumptively positive cultures and referred them to an obstetric complications clinic. At the initial visit all untreated women were offered enrolment into the study. At the time of initial treatment, either sexual abstinence or non-lubricated condom use was strongly recommended. Enrolment between April 1994 and October 1997.
• Exclusion criteria	Women with a known allergy to penicillin or any cephalosporin were excluded from the study. Patients that did not turn up for their follow-up visit within 14 days of treatment were excluded from evaluation in the study.
• Patient & disease characteristics	The study reports no statistical difference between the two treatment groups at baseline. Mean age=19.1 years Mean gestational age = 21.0 weeks

Age years (mean \pm SD):Group 1: 18.9 \pm 2.7 vs Group 2: 19.3 \pm 3.9Race:

Black: Group 1: 84% vs Group 2: 82%

Hispanic: Group 1: 16% vs Group 2: 10%

White: Group 1: 0% vs Group 2: 8%

Gestational age at treatment (week):Group 1: 21.3 \pm 8.1 vs Group 2: 20.8 \pm 9.7Sites of infection:

Endocervix: 86/95 (91%)

Rectum: 39/95 women (41%)

Pharynx: 11/95 women (12%)

Interventions

- **Intervention group 1** Ceftriaxone 125 mg intramuscularly
Patients submitted to gonococcal cultures of the endocervix, pharynx and anus on the day of treatment.
Patients scheduled for a follow up visit in 1 week for test of cure cultures.
- **Intervention group 2** Cefixime 400 mg orally
Patients submitted to gonococcal cultures of the endocervix, pharynx and anus on the day of treatment.
Patients scheduled for a follow up visit in 1 week for test of cure cultures.

Results

- **Number cured (%)** Overall: Group 1: 41/43 (95%) vs Group 2: 50/52 (96%)
RR: 0.99 (95% CI, 0.91 to 1.08)
- **Number cured (%) by site** Cervix: Group 1: 38/40 (95%) vs Group 2: 44/46 (96%)
Pharynx: Group 1: 5/5 (100%) vs Group 2: 6/6 (100%)
Anus: Group 1: 23/23 (100%) vs Group 2: 16/16 (100%)
Anogenital (defined as cervix and/or anal infections): Group 1: 40/42 (95%) vs Group 2: 50/52 (96%)
- **Adverse events** Pain at the injection site reported but no figures given.
- **Babies born with minor anomalies** Group 1: 10/60 (16.7%) vs Group 2: 7/62 (11.3%)



- Data available from 60/78 babies born in Group 1 and 62/81 in Group 2		RR: 1.48 (95% CI: 0.60 to 3.62) Group 1: Abnormalities including nevus=3, café au lait spots=3, hemangioma=2, clinodactyly=1, supernumerary nipple=2 Group 2: Abnormalities including nevus=2, cleft palate=1, skin tag=1, preauricular pit=1, polydactyly=1, absent right pectoral muscle=1.
• Adverse event-hyperbilirubinemia in infants		Group 1: 5/60 (8.3%) vs Group 2: 0/62 (0%)
• Compliance		Not reported.
• Antimicrobial resistance		Not reported.
Limitations and other comments		
• Limitations		High performance, selection bias, reporting bias and attrition bias. Cultures were used to diagnose gonorrhoea and the previous review found that this test had a low sensitivity. This could have resulted in missed cases of gonorrhoea and an overestimation of this outcome. The study reports minor abnormalities of infant but reports both groups as ceftriaxone. In this report we have assumed the later figures are those of group 2 as this is the order other results are reported.
• Authors conclusion		The authors concluded that both intramuscular ceftriaxone 125 mg and oral cefixime 400 mg appear to be effective for the treatment of gonococcal infection in pregnancy.

7.2.3. People with an allergy to cephalosporin

7.2.3.1. Intervention studies

No evidence was identified.



7.3. Diagnosis of syphilis

7.3.1. Screening strategies

7.3.1.1. Individual studies

Table 20 – Evidence table of diagnostic studies regarding the screening algorithms for syphilis

Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. Binnicker 2012. ²³³	
Methods	
• Design	Prospective cohort study
• Source of funding and competing interest	Study states that the authors have no conflicts of interest. Funding not reported.
• Setting	Single centre – laboratory, United States.
• Sample size	1000 sera samples
• Time interval between tests	Not reported.
• Statistical analysis	Number with reactive samples reported.
Patient characteristics	
• Eligibility criteria	Sera (one sample per patient) submitted for routine syphilis testing to their laboratory.
• Patient characteristics	Not reported.
• Prevalence of disease	Study population low prevalence.
Interventions	
• Intervention group 1	<p>Sera tested using reverse screening, which is the usual method at laboratory (n=1000):</p> <ul style="list-style-type: none"> - BioPlex 2200 syphilis IgG multiplex flow immunoassay (MFI), (Bio-Rad Laboratories, California). - Samples testing reactive by BioPlex assay were tested by rapid plasma regain (RPR), (Becton Dickinson, NJ). - If RPR gave a positive result, the titer of the serum sample was determined to an endpoint. - In addition, sera testing reactive by the BioPlex but non-reactive to RPR were also analysed by T. pallidum passive particle agglutination (TP-PA) (Fujirebio Diagnostics, Malvern, PA). - Definition of a positive screening examination: MFI+/RPR or TPPA+
• Intervention group 2	<p>Sera then tested using the traditional algorithm (n=1000):</p> <ul style="list-style-type: none"> - Screened by RPR with the performing technologist unaware of the results of reverse screening testing. - Titers of sera that were reactive by RPR were determined to an endpoint and subsequently tested by TP-PA.



- Definition of a positive screening examination: RPR+/TPPA+	
Results	
• Reactive samples	Group 1: 15/1000 (1.5%) vs Group 2: 4/1000 (0.4%)
• Medical records reviewed for discordant 11 patients reactive by reverse screening	<ul style="list-style-type: none"> - History of past, successfully treated syphilis and were not retreated based on this: n=3 - Reactive by BioPlex IgG assay and TP-PA but non-reactive by RPR. Patients examined as part of routine immigration or pre-transplant evaluation and had no history of syphilis or treatment. Both patients diagnosed with possible latent syphilis and were treated appropriately: n=2 - Reactive by BioPlex IgG assay but nonreactive by RPR and TP-PA result. Interpreted as a falsely reactive screening results based on alternative diagnosis and/or negative TP-PA result, and these patients were not treated for syphilis: n=6
• Adverse events	Not reported.
• User friendly aspects of tests	Not reported.
Limitations and other comments	
• Limitations	<p>Serious risk of bias due to high risk of bias for patient selection.</p> <p>No serious applicability/indirectness.</p>
• Authors conclusion	Reverse screening yields higher false-reactive rate than traditional testing does. The reverse syphilis screening algorithm detected two patients with possible latent syphilis that went undetected by RPR screening. Our findings support prior data suggesting that reverse screening may enhance the sensitivity for detection of early or late/latent disease.

The Laboratory Impact of Changing Syphilis Screening from the Rapid-Plasma Regain to a Treponemal Enzyme Immunoassay: a case-study from the Greater Toronto Area. Mishra 2011²³⁴

Methods

• Design	Retrospective time-series study.
• Source of funding and competing interest	Supported by the physician' Services Incorporated foundation grant number 06-31. Also supported by a Canadian Institutes for Health Research and Public Health Agency of Canada fellowship.
• Setting	Public Health Laboratory Toronto, Greater Toronto Area, Canada.
• Sample size	3,092,938 samples.
• Duration and follow-up	August 1, 1998 to July 31, 2008.
• Statistical analysis	Positive tests, testing patterns, patient characteristics associated with confirmed positive and RPR negative results during reverse algorithm period.

Patient characteristics



• Eligibility criteria	Laboratory data between August 1, 1998 and July 31, 2008 were collected on all serum samples submitted for syphilis screening from testing centres within the Greater Toronto Area.
• Exclusion criteria	Serum samples were excluded if they had been submitted via the Canadian blood Services as blood donor syphilis screening procedures are conducted under a separate protocol and samples are referred to the Public Health Laboratory Toronto (PHLT) only for confirmatory testing. Excluded repeat submissions on the basis of a prior confirmed positive result.
• Patient & disease characteristics	Demographic and limited clinical information were available for submissions between 1 August 2005 and 31 July 2008. Before 1 August 2005, demographic variables and clinical data were restricted to screen positive samples.
Interventions	
• Intervention group 1	Traditional screening: 1 st August 1998 - 31 July 2005 (n=2,055,913) <ul style="list-style-type: none"> - RPR reactive followed by confirmatory treponemal test - Screen positive defined as reactive RPR - Samples defined as confirmed positive in the case of a positive screening test if at least one of the treponemal tests used for confirmation (microhemagglutination assay T. pallidum; T. pallidum particle agglutination; fluorescent treponemal antibody absorption test) was positive.
• Intervention group 2	Reverse screening algorithm: 1 st August 2005 to 31 July 2008 (n=1,037,025). <ul style="list-style-type: none"> - Enzyme immunoassay screening (EIA) followed by RPR testing and an alternate treponemal confirmatory test. - Screen positive defined as a positive EIA or an indeterminate EIA on more than 1 of duplicate testing on the same sample. - Samples defined as confirmed positive in the case of a positive screening test if at least one of the treponemal tests used for confirmation (microhemagglutination assay T. pallidum; T. pallidum particle agglutination; fluorescent treponemal antibody absorption test) was positive.
Results	
• Samples screened positive	Group 1: 0.59% vs Group 2: 2.24%
• Samples confirmed positive	Group 1: 0.46% vs Group 2: 1.98% (Group 2: 69.6% of all confirmed positives were RPR negative).
• Proportion of confirmed positive tests during EIA screening that were RPR negative in patients with risk factors (in comparison to those that are RPR positive)	Risk factor (n=11 462) <ul style="list-style-type: none"> • None: 71.5% • MSM: 69.0% • Intravenous drug use (IDU): 69.9% • MSM and IDU: 68% • Antenatal: 71.7%
• Incidence rate ratio for confirmed positivity in the central, urban	Group 1: 1.69% (95% CI: 1.35-1.88) Group 2: 1.80% (95% CI: 1.67-1.91)



core of Toronto relative to surrounding suburban area	
• Prevalence	After reverse algorithm implementation, the monthly rate of confirmed positive results increased from 3.2 to 13.5 per 100 000 population.
• Adverse events	Not reported.
• User friendly aspects of tests	Not reported.
Limitations and other comments	
• Limitations	Very serious risk of bias due to high risk of patient selection and patient timing and flow. No serious applicability/indirectness.
• Authors conclusion	Reverse algorithm screening using EIA facilitates identification of probable latent syphilis and earlier serological detection of infectious syphilis. In the absence of a true gold standard, implementation of EIA screening warrants careful communication regarding serological interpretation.

7.3.2. Polymerase Chain Reaction (PCR) assay

7.3.2.1. Individual studies

Table 21 – Evidence table of diagnostic studies regarding the PCR assays for syphilis

Men and women

Development of a Real-Time PCR Assay to Detect <i>Treponema pallidum</i> in Clinical Specimens and Assessment of the Assay's Performance by Comparison with Serological Testing. Leslie 2007 ²³⁵	
Methods	
• Design	Prospective cohort study.
• Source of funding and competing interest	Not reported.
• Setting	Victorian Infectious Diseases Reference Laboratory (VIDRL), Melbourne, Australia. The VIDRL acts as a state reference laboratory for syphilis serology, confirming positive results from other laboratories. Specimens were referred to VIDRL between February 2004 and December 2005.
• Sample size	Total: 660 specimens from 598 patients tested. Number evaluated: Sub-set with adequate serological follow-up = 301 patients.



• Time interval between tests	Serology concurrently or subsequently referred to laboratory.
• Statistical analysis	Sensitivity and specificity reported.
Patient characteristics	
• Eligibility criteria	Specimens from patients undergoing investigation for infectious syphilis (primary or secondary) who had a concurrent or subsequent syphilis serology request. In many cases, results from prior serology testing were also available for comparison. Blood samples not accepted for testing. Only first specimen submitted from each patient was included.
• Patient characteristics	660 specimens from 598 patients: men/women=506/92; of which 125/506 men infected with HIV but none of the women. <u>Sample site for evaluated sub-set (TpPCR positive/total):</u> Total=45/301 Penile=26/102 Anorectal, perianal=8/80 Oropharyngeal, tongue, lip=6/39 Other superficial body site=1/15 Genital swab=2/13 Site not stated=2/11 Other deep site=0/0 Groin, scrotum, pubis, perineum=0/7 Urethral=0/20 Vulvovaginal, cervix=0/14 Cerebrospinal fluid=0/0
• Prevalence of disease	Study prevalence: 51/301 (16.9%)
Interventions	
• Index test	TpPCR: - TaqMan real-time PCR assay targeting the <i>polA</i> gene of <i>Treponema pallidum</i> (TpPCR). - To detect presence of pathogenic <i>Treponema pallidum</i> in swabs and biopsy specimens from genital and mucosal ulcers, placental specimens and cerebrospinal fluid. - Lesion swabs collected by attending doctor were transported to the laboratory in either bacterial or viral transport medium. - Blinding not reported.
• Reference standard	Serology:



- Including rapid plasma reagin (RPR), T Pallidum particle agglutination (TPPA), recombinant total antibody immunoassay (EIA) (rEIA), and whole cell lysate IgM EIA
- All tests performed according to manufacturer's instructions.
- All sera routinely tested using RPR, TPPA, and rEIA. Sera collected concurrently from patients with positive TpPCR results were also tested for IgM by EIA, as were sera from other patients, regardless of the PCR result guided by direct requests for the assay, clinical notes on the request suggesting the possibility of recent infection or exposure, or prior serology status.
- Sera considered showing evidence of recent infection if a concurrent serum specimen was positive or low positive by rEIA and TPPA and the IgM EIA was positive, regardless of the RPR result.
- Sera was considered not to show evidence of recent infection if all concurrent or subsequent rEIA, TPPA and IgM EIA results were negative or if serum tested within the last 12 months was positive by EIA/TPPA, indicating prior infection but a concurrent IgM EIA was negative and RPR remained negative or showed no increase in titer.
- Blinding not reported.

Results

- **Diagnostic accuracy of TpPCR compared with serology**
TP: 41
FP: 4 (all HIV negative; penile lesions)
FN: 10 (of which 6 were HIV infected; 9 genital lesion swabs and one mouth ulcer swab)
TN: 246
Sensitivity: 80.4%
Specificity: 98.4%
PPV: 91%*
NPV: 96%*
PLR: 50.25*
NLR: 0.20*
* Calculated by NGC

- **Adverse events** Not reported.

- **User friendly aspects of test** Not reported.

Limitations and other comments

- **Limitations**
Initial phase of study: specimens sent to VIDRL and retrospectively blind tested with TaqMan PCR assay; these specimens had been sent by the physician for microscopy and bacteria culture, Chlamydia PCR, gonorrhoeae PCR or herpes simplex virus PCR. During this phase of the study there were three results which were discussed with physicians and evidence of recent infection was confirmed by serology in all three cases. Once clinicians and laboratories became aware that a TpPCR assay was being trialled specimens were referred specifically for TpPCR.
Very serious risk of bias due to high risk of patient selection and patient flow and timing.
No serious applicability/indirectness.



- **Authors conclusion** The T. pallidum PCR will be a valuable addition to serology for the diagnosis of early syphilis and will be useful for the confirmation of other diagnostic methods such as histopathology in late and congenital syphilis.

7.3.3. Enzyme Immunoassay (EIA)

7.3.3.1. Individual studies

Table 22 – Evidence table of diagnostic studies regarding the Enzyme Immunoassay for syphilis

Serological diagnosis of syphilis: comparison of the Trep-Chek IgG enzyme immunoassay with other screening and confirmatory tests. Tsang 2007. ²³⁶	
Methods	
• Design	Prospective observational study.
• Source of funding and competing interest	Funding from the Office of Chief Scientists, Health Canada, for implementing ELISA with recombinant T. pallidum proteins.
• Setting	National Microbiology Laboratory, Canada.
• Sample size	604 serum specimens.
• Time interval between tests	Not reported.
• Statistical analysis	Sensitivity and specificity calculated.
Patient characteristics	
• Eligibility criteria	Serum specimens provided by local hospitals or provincial public health laboratories and submitted to the National Microbiology Laboratory for confirmation of local tests results or for further evaluation of serologic status. Specimens collected between 1 January 2003 and 31 August 2006. There was no prior selection of specimens and all specimens had been screened for syphilis with either conventional tests such as RPR or VDRL or some form of EIA test.
• Patient characteristics	None provided.
• Prevalence of disease	Study prevalence: 34/604 (5.6%)
Interventions	
• Index test(s)	EIA IgG: <ul style="list-style-type: none"> - Trep-Chek IgG treponemal enzyme immunoassay (EIA): - Followed by confirmatory testing - It is used for the qualitative detection of human IgG antibodies to T. pallidum. - Phoenix Biotech Corp, Toronto, Canada



	- Blinding not reported.
• Reference standard	<p>Consensus results derived from conventional screening and confirmatory tests:</p> <ul style="list-style-type: none"> - Conventional screening tests: Rapid plasma regain (RPR) and Venereal disease research laboratory (VDRL) and enzyme immunoassay (EIA) - Conventional as well as newer confirmatory tests used: Treponema pallidum particle agglutination (TP-PA), fluorescent treponemal antibody absorption (FTA-ABS). - Discordant test results also examined with INNO-LIA immunoassay. - Definition of a positive screening test: consensus results were derived from conventional serologic tests, both screening (RPR, VDRL or EIA) and confirmatory (FTA-ABS, INNO-LIA, or TPPA). - Sera was classified into the following categories: (1) syphilis-negative, negative for both screening and confirmatory tests, and the biological false positives that gave positive screening test results that could not be confirmed by any of the confirmatory tests; and (2) probably syphilis positives, which can be divided into probably past syphilis infection (negative by screening but positive by confirmatory tests); and probably active syphilis infection (positive by both screening and confirmatory tests). - Blinding not reported.

Results

• EIA IgG as screening tests followed by confirmatory test	<p>TP: 29 FP: 25 (7 equivocal) FN: 5 (1 equivocal) TN: 545 Sensitivity: 85.3% Specificity: 95.6% PPV: 53.7%* NPV: 99.1%* PLR: 19.45* NLR: 0.15* * Calculated using Review Manager</p>
• Adverse events	Not reported.
• User friendly aspects	Not reported.

Limitations and other comments

• Limitations	<p>Very serious risk of bias due to high risk of patient selection and patient flow and timing. No serious applicability/indirectness.</p>
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- **Authors conclusion** The authors do not recommend use of the Trep-Chek IgG EIA as a stand-alone test for either screening or confirmatory test for syphilis; they should be evaluated side-by-side with standard tests before they can be introduced as routine tests in the laboratory.

Evaluation of an IgM/IgG Sensitive Enzyme Immunoassay and the Utility of Index Values for the Screening of Syphilis Infection in a High-Risk Population. Wong 2011²³⁷

Methods

- **Design** Prospective cohort study.
- **Source of funding and competing interest** Trinity Biotech Inc and Phoenix Bio-tech for the provision of EIA kits in this study. One of authors is an employee of Trinity Biotech, the EIA evaluated in the study. Another is an employee of phoenix Biotech, whose assays were used in part of the evaluation of the EIA.
- **Setting** Single centre, San Francisco municipal Sexually Transmitted Disease clinic, US.
- **Sample size** 674 serum specimens that were tested by venereal disease research laboratory.
- **Time interval between tests** Specimens were transported at ambient temperature to the laboratory where serum was prepared and stored refrigerated for no more than 5 days before testing by VDRL or EIA. Time between tests was not reported.
- **Statistical analysis** True positive and true negative figures.

Patient characteristics

- **Eligibility criteria** De-identified remnant sera from clinical whole blood specimens collected from patients presenting the San Francisco municipal Sexually Transmitted Disease clinic.
- **Patient characteristics** The population at this clinic is 69.3% men who have sex with men and 16.6% of the tested population is HIV positive and 9.4% have a documented case of early syphilis.
De-identified serum so no study patient characteristics reported.
- **Prevalence of disease** 39.7% study prevalence.

Interventions

- **Index test(s)** EIA IgM/IgG
 - TrepSure EIA (Trinity Biotech, Jamestown, NY):
 - Index scores less than 0.8 are considered negative while those between 0.8 and 1.2 are considered "equivocal". Index scores greater than 1.2 are considered positive.
 - Blinding not reported.
- **Reference standard** Reference standard test:
 - VDRL screening with TPPA confirmation.
 - Positive test defined as samples that tested positive by TPPA confirmation test
 - Blinding not reported.



Results

<ul style="list-style-type: none"> Diagnostic accuracy of EIA IgM/IgG 	<p>TP: 298 FP: 5 FN: 6 TN: 364 Sensitivity: 98.0% (95.8-99.3)* Specificity: 98.6% (96.9-99.6)* PPV: 98.4% (96.2-99.5)* NPV: 98.4% (96.5-99.4)* PLR: 72.34* NLR: 0.020^a</p> <ul style="list-style-type: none"> Calculated by Cantor 2016 guideline²³⁸ <p>^a Calculated by NGC.</p> <p>Note: 1 specimen was reactive by VDRL and EIA but TPPA negative. Also positive by Western blot for IgM antibodies against T. pallidum antigens. This case has been removed from the analysis in Cantor 2016 guideline²³⁸ as unclear of outcome.</p>
<ul style="list-style-type: none"> Adverse events 	<p>Not reported.</p>
<ul style="list-style-type: none"> User friendly aspects – reported as time and work required to perform the tests 	<p>Time taken to assay 80 specimens: EIA IgM/IgG=120 minutes, but with incubation times (microbiologist free time) of both 60 and 30 minutes. VDLR =150 minutes approximately (to resolve both reactive and non-reactive specimens).</p> <p>EIA IgM/IgG specimens are pipetted only once into the assay plate wells, while for the VDRL, specimens found to be reactive must be diluted (3-5 dilutions per specimen, each requiring multiple pipetting steps) and subsequently reanalysed.</p>
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	<p>Very serious risk of bias due to high risk of patient selection and patient flow and timing. No serious applicability/indirectness.</p>
<ul style="list-style-type: none"> Authors conclusion 	<p>The EIA was slightly less sensitive but more specific than the VDRL test. The EIA IgM/IgG was far easier for laboratory staff to perform, making it amenable to the processing of many specimens at once.</p>



7.3.4. Rapid point of care (POC) tests for syphilis

7.3.4.1. Individual studies

Table 23 – Evidence table of diagnostic studies regarding POC tests for syphilis

Men and women

Novel Point-of-Care Test for Simultaneous Detection of Nontreponemal and Treponemal Antibodies in Patients with Syphilis. Castro 2010 ²³⁹	
Methods	
• Design	Diagnostic cohort study.
• Source of funding and competing interest	Georgia Department of Health Laboratories supplied serological specimens for the study.
• Setting	Georgia Public Health Laboratory in Atlanta, USA.
• Sample size	1601 banked sera.
• Time interval between tests	Not reported.
• Statistical analysis	Study reports reactivity for index test and reference standard and concordance between tests.
Patient characteristics	
• Eligibility criteria	Serum samples originally submitted to the laboratory for serological testing for syphilis were obtained for this study. All identifiers were removed prior to shipment to the CDC.
• Patient characteristics	De-identified serum with no patient characteristics.
• Prevalence of disease	834/1601 (52%) had a positive assay result with both reference standards (treponemal and non treponemal tests).
Interventions	
• Index test	Chembio DPP syp (non trep+trep) <ul style="list-style-type: none"> - The test lines include the treponemal line (T1) and synthetic nontreponemal antigen line (T2) and a control line (C). If antibodies to treponemal and nontreponemal antigens are present in the serum sample they will form visible red coloured lines within 15 minutes. - Confirmed reactivity was characterized by appearance of three red lines in the window of the device (T1, T2 and C). A visible T1 and C with no visible T2 was interpreted as probably due to an old or previously treated case of syphilis. A visible T2 and a C with no visible T1 were interpreted as a false-reactive nontreponemal test. A nonreactive result was demonstrated by the appearance of only one red control line (C). - Manufactured by Chembio Diagnostics Systems Inc, Medford, NY. - Blinding (investigator) to clinical information and/or to index test results not reported.



- **Reference standard** Rapid Plasma Reagin (RPR) and Treponema pallidum passive particle agglutination (TP-PA) assay:
 - RPR used as reference standard for non treponemal element of dual test
 - TP-PA used as reference standard for treponemal element of the dual test
 - Blinding (investigator) to clinical information and/or to index test results not reported.

Results

- **Diagnostic accuracy for chembio DPP sy (non trep+trep) – treponemal line using reference standard TP-PA using plasma**

TP: 972
 FP: 27
 FN: 35
 TN: 567
 *Sensitivity: 96.5% (95% CI: 95-98)
 *Specificity: 95.5% (95% CI: 93-97)
 *PPV: 97.3%
 *NPV: 94.2%
 *PLR: 21.24
 *NLR: 0.04
 * Calculated using Review Manager
Note: With the TP-PA assay, the reactive and non-reactive concordances of the POC test were 96.5% and 95.5%, respectively.
- **Diagnostic accuracy for chembio DPP sy (non trep+trep) – nontreponemal line using reference standard RPR using plasma**

TP: 739
 FP: 11
 FN: 95^a
 TN: 756
 *Sensitivity: 88.6% (95% CI: 86-91)
 *Specificity: 98.6% (95% CI: 97-99)
 *PPV: 98.5%
 *NPV: 88.8%
 *PLR: 61.78
 *NLR: 0.12
 * Calculated using Review Manager
Note: Of the 95 samples found non-reactive (FN) with the dual DPP test, 85 had an RPR titer of 1:1. With an RPR titer of $\geq 1:2$, the concordance with the POC tests was 98.4% and the concordance with the nonreactive RPR test was 98.6%.
- **Adverse events** Not reported.
- **User friendly aspects of tests** Not reported.



Limitations and other comments

- Limitations**
 Study also tested assay on a panel of 105 serum samples with known stages of syphilis and on serum samples from patients with different diseases other than syphilis.
 Very serious risk of bias due to high risk of patient selection and patient flow and timing.
 No serious applicability/indirectness.
- Authors conclusion**
 These results indicate that the dual test could be suited for the serological diagnosis of syphilis in primary health care clinics or resource-poor settings and therefore improve rates of treatment where patients may fail to return for their laboratory results.

Sensitivity and Specificity of Point-of-Care Rapid Combination Syphilis-HIV-HCV Tests. Hess 2014²⁴⁰

Methods

- Design**
 Prospective cohort study.
- Source of funding and competing interest**
 Support was provided by grant from the National Institute on Drug Abuse awarded to one of the authors; grant from the National Institute of Minority Health and Health Disparities funded part of two authors time; grant from the California HIV Research Program awarded to one of the authors
 POC rapid tests were provided at a reduced cost by Chembio Diagnostics Inc. Chembio also provided the training on their tests but had no involvement in study design, data collection, data analysis and interpretation, or writing of the manuscript. There was no other relevant declaration of interest.
- Setting**
 Center for Behavioural Research and Services in Long Beach, Southern California.
- Sample size**
 Screened for eligibility: N=2083.
 Excluded: Not eligible: n=859; not offered enrolment: n=142 (usually due to time restraints); declined enrollment: n=31 and not able to provide blood sample or missing RPR and TPPA results: n=103
 Total analysed: n=948.
 Note: This figure does not match crude numbers provided in diagnostic accuracy outcomes.
- Time interval between tests**
 At single visit.
- Statistical analysis**
 Sensitivity and specificity were calculated.

Patient characteristics

- Eligibility criteria**
 At risk participants who were seeking HIV and sexually transmitted infection testing from a test centre were screened for eligibility from 26 March 2011 to 30 June 2013. In addition, clients who came in for testing were screened for eligibility. In addition, existing clients who were eligible and whose last visit was more than three months prior were sent letters inviting them to come in for the study. Eligible clients were 15 years of age and older, had not participated previously, and reported being in a behavioural risk group. Behavioural risk groups were defined as (1) injection drug users (IDU) with verified track marks, (2) women who reported at least two male partners



	in the last two years or engaging in anal intercourse, sex trading, or sex with a man who has sex with men, an IDU, or an HIV positive man, (3) MSM and men who have sex with men and women (MSMW) and (4) transgender individuals. Each participant provided a venous blood sample.
• Patient characteristics	<p>Total = 948</p> <p><u>Gender:</u> Male: 54.4%, Female: 44.2%; Transgender (male to female): 1.2%; Transgender (female to male): 0.2%</p> <p><u>Behavioural risk group:</u> Injection drug user: 22.2%; women at sexual risk: 38.5%; MSM/MSMW: 37.4%; Transgender: 1.4%</p> <p><u>Race/ethnicity:</u> Hispanic: 26.4%; White: 25.6%; Black: 35.1%; Asian: 2.1%; Hawaiian/pacific islander: 0.7%; Native American: 1.2%; more than 1 race reported: 8.0%</p>
• Prevalence of disease	<p>Pre study prevalence of RPR was 3.0% and TP-PA was 8.1%.</p> <p>Study prevalence of TPPA and RPR positive 23/948 (2.4%).</p>
Interventions	
• Index test 1	<p>Chembio DPP syp (non trep+trep)</p> <ul style="list-style-type: none"> - Dual Path Platform (DPP) Syphilis Screen and Confirm rapid test. - Manufactured by Chembio diagnostics Systems, Inc, Medford, NY. - Phlebotomist drew a venous blood sample. - Blinding (investigator) to clinical information and/or to index test results not reported.
• Index test 2	<p>Chembio DPP HIV-syp (trep)</p> <ul style="list-style-type: none"> - Manufactured by Chembio diagnostics Systems, Inc, Medford, NY. - Phlebotomist drew a venous blood sample - Original order of tests was HIV first and syphilis second; company switched order half way through to try to improve syphilis accuracy - Blinding (investigator) to clinical information and/or to index test results not reported.
• Index test 3	<p>Chembio DPP HIV-HCV-syp (trep):</p> <ul style="list-style-type: none"> - Manufactured by Chembio diagnostics Systems, Inc, Medford, NY. - Phlebotomist drew a venous blood sample. - Blinding (investigator) to clinical information and/or to index test results not reported.
• Reference standard	<p>Gold standard tests included:</p> <ul style="list-style-type: none"> - Comparison test for the treponemal antibody test was Treponema pallidum passive particle agglutination (TPPA) - Comparison for the non-treponemal test was rapid plasma reagin (RPR) - Tests HCV enzyme immunoassay (EIA) and HIV-1/2 EIA were used for HCV and HIV - Participants returned two weeks later for gold standard results. - Blinding (investigator) to clinical information and/or to index test results not reported.



Results

<ul style="list-style-type: none">Diagnostic accuracy of Chembio DPP syp (non trep+trep) – non-treponemal test compared to RPR (titer 1:1 or higher) reference standard	TP: 11 FP: 8 FN: 12 TN: 732 Sensitivity: 47.8% (95% CI: 26.8-69.4%) Specificity: 98.9% (95% CI: 97.9-99.5%) *PPV: 57.9% *NPV: 98.4% *PLR: 44.2391 *NLR: 0.5274 * Calculated by Review Manager Accuracy data calculated with other reference standards: TPPA + RPR and TPPA + RPR \geq 1:8 showing improved sensitivities of 57.9% and 90.0% respectively.
<ul style="list-style-type: none">Diagnostic accuracy of Chembio DPP syp (non trep+trep) – treponemal test compared to TP-PA reference standard	TP: 49 FP: 9 FN: 44 TN: 663 Sensitivity: 52.7% (95% CI: 42.1-63.1) Specificity: 98.7% (95% CI: 97.5-99.4) *PPV: 84.5% *NPV: 93.8% *PLR: 39.3405 *NLR: 0.4795 * Calculated by Review Manager Accuracy data calculated with other reference standards: TPPA + RPR and TPPA + RPR \geq 1:8 showing improved sensitivities of 79.0% and 90.0% respectively.
<ul style="list-style-type: none">Diagnostic accuracy of Chembio DPP syp (non trep+trep) – non treponemal and treponemal test compared to TPPA + RPR\geq1:8 reference standard	TP: 9 FP: 3 FN: 1 TN: 753 Sensitivity: 90.0% (95% CI: 55.5-99.8) Specificity: 99.6% (95% CI: 98.8-99.9)



	<p>*PPV: 75.0%</p> <p>*NPV: 99.9%</p> <p>*PLR: 226.8000</p> <p>*NLR: 0.1004</p> <p>* Calculated by Review Manager</p>
<ul style="list-style-type: none">• Diagnostic accuracy for Chembio DPP HIV-HCV-syp (trep)	<p>TP: 44</p> <p>FP: 5</p> <p>FN: 56</p> <p>TN: 776</p> <p>Sensitivity: 44.0% (95% CI: 34.8-54.3%)</p> <p>Specificity: 99.4% (95% CI: 98.5-99.8%)</p> <p>*PPV: 89.8%</p> <p>*NPV: 93.3%</p> <p>*PLR: 68.7280</p> <p>*NLR: 0.5636</p> <p>* Calculated by Review Manager</p>
<ul style="list-style-type: none">• Diagnostic accuracy for Chembio DPP HIV-syp (trep) Original order of tests was HIV first and syphilis second; company switched order half way through to try to improve syphilis accuracy	<p>Order 1: (HIV-Syphilis)</p> <p>TP: 13</p> <p>FP: 1</p> <p>FN: 15</p> <p>TN: 234</p> <p>Sensitivity: 46.4% (95% CI: 27.5-66.1%)</p> <p>Specificity: 99.6% (95% CI: 97.7-100%)</p> <p>*PPV: 92.9%</p> <p>*NPV: 94.0%</p> <p>*PLR: 109.1071</p> <p>*NLR: 0.5380</p> <p>Order 2: (Syphilis-HIV)</p> <p>TP: 37</p> <p>FP: 3</p> <p>FN: 41</p> <p>TN: 576</p>



	<p>Sensitivity: 47.4% (95% CI: 36.0-59.1%)</p> <p>Specificity: 99.5% (95% CI: 98.5-99.9%)</p> <p>*PPV: 92.5%</p> <p>*NPV: 93.4%</p> <p>*PLR: 91.5513</p> <p>*NLR: 0.5284</p> <p>* Calculated by Review Manager</p>
<ul style="list-style-type: none"> Concordance of the treponemal result between three POC tests 	Among participants who had data for all three tests and had a positive result on at least one for the three tests (n=55), 40 had a positive result on all three tests (73%).
<ul style="list-style-type: none"> Adverse events 	Not reported.
<ul style="list-style-type: none"> User friendly aspects of tests 	Not reported.
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	Serious risk of bias due to high risk in patient selection and patient flow and timing. No serious applicability/indirectness.
<ul style="list-style-type: none"> Authors conclusion 	The treponemal and non treponemal tests had low sensitivity which could be due to low prevalence of active syphilis in the sample population because the sensitivity improved when the gold standard was limited to those more likely to be active cases. Further evaluation required of new syphilis point of care tests before implementation into testing programs.

An evaluation of the SD Bioline HIV/syphilis duo test. Holden 2018²⁴¹

Methods

<ul style="list-style-type: none"> Design 	Diagnostic cohort study.
<ul style="list-style-type: none"> Source of funding and competing interest 	Grant from National Institutes of Health. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
<ul style="list-style-type: none"> Setting 	Single centre: Baltimore city Health Department (BCHD) sexually transmitted infection clinic.
<ul style="list-style-type: none"> Sample size 	394 achieved samples.
<ul style="list-style-type: none"> Time interval between tests 	Specimens collected between February and September 2009 and stored at -80 degrees Celsius. Rapid plasma reagin (RPR) testing performed at time of collection. Index testing took place in August 2014. Treponema pallidum particle agglutination (TPPA) testing took place in April 2015.



• Statistical analysis	Sensitivity and specificity were calculated using a traditional and reverse algorithm.
Patient characteristics	
• Eligibility criteria	Blood specimens collected from patients receiving routine care at BCHD. Blood was centrifuged to obtain serum and plasma aliquots and the serum tested on site by clinic personnel using RPR. Serum and plasma aliquots were transported to study laboratory and stored at -80 degrees Celsius.
• Patient characteristics	Not reported as patients de-identified.
• Prevalence of disease	Study prevalence reported: 3.3-8.4% depending on reference standard used.
Interventions	
• Index test(s)	<p>SD HIV-syp (trep)</p> <ul style="list-style-type: none"> - SD Bioline HIV/syphilis duo rapid test. - Rapid test that simultaneously detects antibodies to HIV and syphilis. - Manufactured by standard Diagnostics, Inc., Gyeonggi-do, South Korea. - Compact, qualitative, cartridge-based immunochromatographic assay, which uses finger-stick whole blood, plasma, or sera to detect antibodies to HIV-1/2 and T. Pallidum, and delivers results in 15-20 minutes. - Testing took place in April 2014 in study laboratory using serum and plasma aliquots. - Blinding (investigator) to clinical information and/or to index test results not reported.
• Reference standard	<p>RPR and TPPA testing:</p> <ul style="list-style-type: none"> - RPR testing took place at BCHD using Macro-Vue RPR Cards (Becton Dickinson BD Microbiology system, USA). 7 had insufficient volumes and were tested using the plasma aliquot. Testing from Feb – September 2009. - TPPA testing took place in study laboratory using serum or plasma and Serodia TPPA assay (Fujirebio, Tokyo, Japan). 384 were tested using serum and 10 were tested using plasma due to insufficient volumes of serum. Testing in April 2015. - Blinding (investigator) to clinical information and/or to index test result not reported. <p>Index test was also compared to traditional and reverse algorithms.</p> <ul style="list-style-type: none"> - For simulation of a traditional screening algorithm, the RPR test was used first and any patients with non-reactive RPR results were deemed negative for active infection and TPPA results excluded; otherwise the TPPA result was included in determining the patient's infection status and the patient deemed positive for syphilis if reactive. - For simulation of the reverse algorithm, the TPPA test was used first and any patients with non-reactive TPPA results were deemed negative for active infection and RPR results excluded. If the TPPA result was reactive, the patient's STI history was consulted, and on evidence of a previously treated infection, deemed negative for active infection; otherwise the patients were deemed positive for syphilis.
Results	
• Diagnostic accuracy of SD HIV-syp (trep) compared to RPR	<p>TP: 12</p> <p>FP: 12</p>



	FN: 2 TN: 368 Sensitivity: 85.7% (95% CI: 57.2-98.2) Specificity: 96.8% (95% CI: 94.4-98.4) PPV: 50.0% (95% CI: 29.1-70.9) NPV: 99.5% (95% CI: 98.1-99.9) *PLR: 27.1429 (95% CI: 95.2-98.7) *NLR: 0.1475 * Calculated by review manager
<ul style="list-style-type: none">• Diagnostic accuracy of SD HIV-syp (trep) compared to TPPA	TP: 23 FP: 1 FN: 10 TN: 360 Sensitivity: 69.7% (95% CI: 51.3-84.4) Specificity: 99.7% (95% CI: 98.5-100) PPV: 95.8% (95% CI: 78.9-99.9) NPV: 97.3% (95% CI: 95.2-98.7) *PLR: 251.6061 *NLR: 0.3039 * Calculated by review manager
<ul style="list-style-type: none">• Diagnostic accuracy of SD HIV-syp (trep) using traditional algorithm as reference standard	TP: 12 FP: 0 FN: 1 TN: 381 Sensitivity: 92.3% (95% CI: 64.0-99.8) Specificity: 100% (95% CI: 99.0-100) PPV: 100% (95% CI: 73.5-100) NPV: 99.7% (95% CI: 98.6-100) PLR: Not able to calculate *NLR: 0.0769 * Calculated by review manager
<ul style="list-style-type: none">• Diagnostic accuracy of SD HIV-syp (trep) using reverse	TP: 16 FP: 1



algorithm standard	as reference	FN: 6 TN: 371 Sensitivity: 72.9% (95% CI: 49.8-89.3) Specificity: 99.7% (95% CI: 98.5-100) PPV: 94.1% (95% CI: 71.3-99.9) NPV: 98.4% (95% CI: 96.6-99.4) *PLR: 270.5455 *NLR: 0.2735 * Calculated by review manager
False negatives and false positives		All apparent syphilis false negatives were from asymptomatic patients, four were from patients with a history of syphilis infection and none of the ten were non-reactive via RPR, with the tenth resulting in a 1:1 titer. One apparent false positive specimen was from an asymptomatic patient with no reported history of syphilis infection. Of 11 TPPA+/SD DUO+/RPR- specimens, four had no reported history of syphilis infection.
Adverse events		Not reported.
User friendly aspect of tests		Not reported.
Limitations and other comments		
Limitations		Very serious risk of bias due to high risk in patient selection and patient flow and timing. No serious applicability/indirectness. Samples were collected and first reference test performed. The samples were frozen and the index test performed 5 years later and the second reference test completed a year after that. Authors noted that seven specimens tested for syphilis by SD DUO using plasma aliquot, three yielded apparent false negative results. This suggests that 387/394 used plasma aliquots.
Authors conclusion		The HIV component of the SD DUO performed moderately well. However, results for the SD DUO syphilis component, when compared to TPPA, support the need for further testing and assessment.

Laboratory evaluation of the Chembio Dual Path Platform HIV-Syphilis Assay. Kalou. 2016²⁴²

Methods

Design	Prospective cohort study.
Source of funding and competing interest	Supported in part by the President's Emergency Plan for AIDS Relief (PEPFAR) through the CDC. Authors declared that they have no financial or personal relationship that may have inappropriately influenced them in writing this article. Chembio provided Chembio DPP HIV-Syphilis Assay test kits for evaluation and Dr Franko from the Georgia Public Health Laboratory supplied the serum samples.



• Setting	Georgia Public Health Laboratory in Atlanta, Georgia, US.
• Sample size	N=1006 serum samples Not included in the evaluation: N=16 (1.6%) specimens with incomplete/invalid predicate HIV and/or syphilis testing results. 990 serum samples evaluated.
• Time interval between tests	Not reported.
• Statistical analysis	Calculated sensitivity and specificity by comparing test with the HIV and syphilis reference testing algorithms.
Patient characteristics	
• Eligibility criteria	In 2013, 1006 serum were prospectively collected from the Georgia Public Health Laboratory. The specimens, normally discarded, were delinked from personal identifiers or any other demographic information and unique CDC identifiers were assigned. Specimens stored at -70 degrees Celsius until ready for testing. These sera were characterised and constituted the evaluation panel. The serum panel characterised for syphilis by TP-PA and then all TP-PA positive specimens were confirmed by TrepSure testing. All specimens with incomplete HIV and/or syphilis test results were excluded from the evaluation.
• Patient characteristics	No baseline characteristics provided as the specimens were delinked from personal identifiers or any other demographic information and unique CDC identifiers were assigned.
• Prevalence of disease	647/990 (65.4%) study prevalence. 299/990 (30.2%) had syphilis and 348/990 (35.2%) had syphilis and HIV.
Interventions	
• Index test(s)	Rapid diagnostic test (RDT) - Chembio Dual Path Platform (DPP) HIV-Syphilis Assay: <ul style="list-style-type: none">- Chembio, Medford, New York, US.- A single-use immunochromatographic rapid screening test for detection of specific antibodies against HIV types 1 and 2 and T. pallidum.- Two trained operators independently performed and interpreted the assay according to the manufacturer's instructions and test results recorded on separate sheets.- Any visible band in the positive region was considered as a positive result for HIV and/or syphilis, irrespective of the strength of the band.- Blinding (investigator) to clinical information and/or to index test results unclear.
• Reference standard	Treponema pallidum passive particle agglutination (TPPA) method and the TrepSure assay: <ul style="list-style-type: none">- The serum panel characterised for syphilis by TP-PA and then all TP-PA positive specimens were confirmed by TrepSure testing.- Blinding (investigator) to clinical information and/or to index test results unclear.
Results	
• Diagnostic accuracy Chembio DPP HIV-syp (trep) (n=990)	TP: 639 FP: 2



	FN: 8 TN: 341 Sensitivity: 98.8% (95% CI: 97.6%-99.5%) Specificity: 99.4% (95% CI: 97.9%-99.9%) *PPV: 99.7% *NPV: 97.7% *PLR: 169.4 *NLR: 0.012 * Calculated by Review Manager
• Inter-operator variability	There was high consistency in the interpretation of the DPP HIV-syphilis Assay results for both HIV (96%) and syphilis (91%) among three different technicians. Inter-lot and inter-operator variability were considered acceptable because both were less than 10%.
• Adverse events	Not reported.
• User friendly aspects of test	Authors report that test requires a pre-dilution step, use of second buffer and multiple steps, which may add some level of complexity for providers with limited laboratory expertise. The presence of three lines (one for control, a second for syphilis and a third for HIV) may cause misinterpretation of results by less trained individuals.
Limitations and other comments	
• Limitations	Very serious risk of bias due to high risk of bias in patient selection and patient flow and timing. No serious applicability/indirectness.
• Authors conclusion	The Chembio DPP HIV-Syphilis Assay had high sensitivity and specificity for detecting both HIV and treponemal antibodies. This assay could have a significant impact on the simultaneous screening of HIV and syphilis using a single test device for high-risk populations or pregnant women needing timely care and treatment.



MSM

Field evaluation of two point-of-care tests for syphilis among men who have sex with men, Verona, Italy. Zorzi 2017²⁴³

Methods

- **Design** Prospective cohort study.
- **Source of funding and competing interest** Partially based on data collected in the context of Sialon II project, co-funded under the second Programme of community action in the field of health (2008-2013).
The point-of-care tests were partially donated by the manufacturers or purchased with external funding, namely from the EU Public Health Programme, through which the Sialon II Respondent-Driven Sampling survey component has been funded. Manufacturers were not involved in any part of the study.
Competing interests: none declared.
- **Setting** Enrolled from Sialon II Respondent-Driven Sampling survey implemented in Verona, Italy.
Also enrolled from men having sex with men (MSM) attending the Infectious Diseases Unit of the Verona University Hospital screening facility from 2015 to 2016.
- **Sample size** 289 MSM enrolled.
SD Bioline Syphilis completed on 289 (100%) participants with blood and 227 (78.5%) with serum sample.
Chembio DPP reported 227 (99.3%) participants with blood sample and 205 (70.9%) with serum sample.
Sample size calculated at an expected prevalence of 10%. This sample size yield 30 subjects with treponemal positivity, which achieves 85% power to detect a change in sensitivity from 0.58 to 0.85 using a two-sided binomial test and a >99% power to detect a change in specificity from 0.58 to 0.85 using a binominal test.
- **Time interval between tests** Tests using blood were read immediately. Blood tubes sent to microbiology unit where they were centrifuged to obtain serum and to perform the lab-based syphilis serological tests. Specimens that could not be processed immediately were stored at 4 degrees and processed within 304 days.
- **Statistical analysis** Sensitivity, specificity, PPV and NPV for each rapid test were estimated comparing the point of care test results with the gold standard lab tests results. Figures were not provided for TP, TN, FN and FP.

Patient characteristics

- **Eligibility criteria** Asymptomatic MSM, potentially exposed to syphilis as a result of risky behaviours, were enrolled prospectively. Men or male-to female transgender, aged 18 years or over, who had sex with at least another man over the last 12 months and who provided witnessed written informed consent were included in this study. Participants could only be enrolled in the study once.
- **Patient characteristics** Mean age (range): 31.4 years (18-65 years).
Median age: 29 years (SD 9.2)
Number with previous syphilis diagnosis: 20/289 (6.8%)



- **Prevalence of disease** Study prevalence for treponemal testing with Chemiluminescent assay (CLIA) and T. pallidum passive particle agglutination (TPPA) = 35 (12.1%) and non treponemal testing using rapid plasma reagin (RPR) = 16 (5.5%) with reference standard tests. All RPR positive samples were also TPPA positive.

Interventions

- **Index test 1** SD Bioline Syphilis 3.0:
 - Manufactured by Standard diagnostics, South Korea.
 - Immunochromatographic assays: treponemal assay with detects antibodies of all isotypes (IgG, IgM, IgA) against Treponema pallidum.
 - Serum and finger prick blood sample tested.
 - Results read by naked eye by two independent readers who were blinded to each other results and their concordance assessed.
 - Results read after 20 minutes waiting.
- **Index test 2** Chembio DPP syp (non trep+trep)
 - DPP Syphilis Screen and Confirm assay:
 - Manufactured by Chembio Diagnostics Systems, USA.
 - Immunochromatographic assays: can simultaneously detect antibodies against treponemal and non-treponemal antigens.
 - Serum and finger prick blood sample tested.
 - Results read by naked eye by two independent readers who were blinded to each other results and their concordance assessed.
 - Results read after 20 minutes waiting.
- **Reference standard** Serology:
 - Chemiluminescent assay (CLIA) and T. pallidum passive particle agglutination (TPPA) tests were used in comparison with both the SD Bioline treponemal test and the treponemal component of the Chembio test.
 - The Chembio non –treponemal component was compared with a rapid plasma regain (RPR) non-treponemal test.
 - Serum and finger prick blood sample tested.
 - Titration for TPPA and RPR was recorded.

Results

- Diagnostic accuracy for SD HIV-syp (trep)**
- **treponemal reference standard TPPA using serum sample**
- By assessment of reader 1:
Sensitivity: 80.0% (95% CI: 63.1-91.6)
Specificity: 100.0% (95% CI: 98.6-100.0)
PPV: 100.0% (95% CI: 78.5-99.9)
NPV: 97.2% (95% CI: 94.6-98.4)
- By assessment of reader 2:
Sensitivity: 82.9% (95% CI: 66.4-93.4)
Specificity: 99.6% (95% CI: 97.8-100.0)



	PPV: 96.8% (95% CI: 81.0-99.5) NPV: 97.6% (95% CI: 95.1-98.8)
Diagnostic accuracy for SD HIV-syp (trep) – treponemal reference standard TPPA using blood sample	<u>By assessment of reader 1:</u> Sensitivity: 51.4% (95% CI: 34.0-68.6) Specificity: 100.0% (95% CI: 98.6-100.0) PPV: 100.0% (95% CI: 70.1-99.8) NPV: 93.4% (95% CI: 91.0-95.2) <u>By assessment of reader 2:</u> Sensitivity: 54.3% (95% CI: 36.6-71.2) Specificity: 100% (95% CI: 98.6-100.0) PPV: 100.0% (95% CI: 71.3-99.8) NPV: 93.8% (95% CI: 91.3-95.5)
Diagnostic accuracy for Chembio DPP syp (non trep+trep) – treponemal reference standard TPPA using serum sample	<u>By assessment of reader 1:</u> Sensitivity: 57.7% (95% CI: 36.9-76.6) Specificity: 99.5% (95% CI: 97.0-100.0) PPV: 93.9% (95% CI: 68.0-99.1) NPV: 94.2% (95% CI: 91.2-96.2) <u>By assessment of reader 2:</u> Sensitivity: 64.0% (95% CI: 42.5-82.0) Specificity: 99.4% (95% CI: 96.9-100.0) PPV: 94.4% (95% CI: 69.9-99.2) NPV: 95.0% (95% CI: 91.8-97.0)
Diagnostic accuracy for Chembio DPP syp (non trep+trep) – treponemal reference standard TPPA using blood sample	<u>By assessment of reader 1:</u> Sensitivity: 65.4% (95% CI: 44.3-82.8) Specificity: 99.5% (95% CI: 97.3-100.0) PPV: 95.1% (95% CI: 72.8-99.3) NPV: 95.2% (95% CI: 92.1-97.1) <u>By assessment of reader 2:</u> Sensitivity: 69.2% (95% CI: 48.2-85.7) Specificity: 99.5% (95% CI: 97.2-100.0) PPV: 95.2% (95% CI: 73.6-99.3) NPV: 95.7% (95% CI: 92.6-97.5)



Diagnostic accuracy for Chembio DPP syp (non trep+trep) – non-treponemal reference standard RPR using serum sample	<u>By assessment of reader 1:</u> Sensitivity: 63.6% (95% CI: 30.8-89.1) Specificity: 99.5% (95% CI:97.2-100.0) PPV: 86.8% (95% CI: 46.9-98.0) NPV: 98.1% (95% CI: 96.0-99.1) <u>By assessment of reader 2:</u> Sensitivity: 63.6% (95% CI:30.8-89.1) Specificity: 99.0% (95% CI:96.3-99.9) PPV: 76.3% (95% CI: 43.0-93.2) NPV: 98.1% (95% CI: 95.9-99.1)
Diagnostic accuracy for Chembio DPP syp (non trep+trep) – non-treponemal reference standard RPR using blood sample	<u>By assessment of reader 1:</u> Sensitivity: 63.6% (95% CI: 30.8-89.1) Specificity: 100% (95% CI:98.3-100.0) PPV: 100.0% (95% CI:46.6-99.6) NPV: 98.1% (95% CI:96.1-99.1) <u>By assessment of reader 2:</u> Sensitivity: 63.6% (95% CI: 30.8-89.1) Specificity: 99.5% (95% CI:97.4-100.0) PPV: 87.9% (95% CI:49.3-98.2) NPV: 98.1% (95% CI:96.0-99.1)
• Agreement between reader 1 and 2	High concordance % reported ranging from 98.96% to 99.56% for all tests and sample types. High Cohen's K range from 0.91 – 0.97 for all tests and sample types.
• Adverse events	Not reported.
• User friendly aspects of tests	Not reported.
Limitations and other comments	
• Limitations	Serious risk of bias due to high risk of patient flow and timing. No serious applicability/indirectness. Did not report crude data (TP, FP, TN, FN) needed to produce forest plots. Accuracy data included in the GRADE tables. Authors state that the treponemal reference standards were TPPA and CLIA but only TPPA used to determine diagnostic accuracy.
• Authors conclusion	Diagnostic performance of the syphilis POCTs was lower than expected; however, considering prevalence of syphilis among MSM, POCTs should be recommended to improve syphilis detection among MSM.



7.4. Treatment of syphilis

7.4.1. Research question 7 – What is the recommended treatment for uncomplicated syphilis in sexually active women and men including young people?

Table 24 – Evidence table of intervention studies for the treatment of syphilis

Single dose versus 3 doses of intramuscular Benzathine Penicillin for early syphilis in HIV: a randomised clinical trial. Andrade 2017 ²⁴⁴	
Methods	
• Design	Randomised controlled trial.
• Source of funding and competing interest	Funding from Baylor-University of Texas Houston Centre for AIDS research. No competing interests declared.
• Setting	Houston, Texas. Three clinical sites.
• Sample size	Sample size calculation based on alpha 0.05, beta 0.2, treatment success mean difference of 20% suggested 59 subjects in each group. 64 enrolled and randomised to the 2 groups: 35 to single treatment and 29 to triple treatment. At one year, 29 were analysed in the single treatment and 27 were analysed up in the triple treatment.
• Duration and follow-up	June 2009 to April 2013. Follow up was 12 months after initiation of therapy
• Statistical analysis	Simple inferential statistics, with 95% confidence intervals. Intention to treat and per-protocol analysis performed. Patients with missing data were assumed to have failed treatment in the intention to treat analysis.
Patient characteristics	
• Eligibility criteria	Aged ≥ 18 years; HIV infection; untreated early syphilis (primary, secondary or early latent).
• Exclusion criteria	History of penicillin allergy, diagnosis of late latent syphilis, antibiotic use with significant activity against Treponema Pallidum within the preceding 2 weeks
• Patient & disease characteristics	Baseline data given for single and triple respectively. No statistical difference reported between groups. Mean age: 35 years. <u>Male sex:</u> Group 1: 34/35 vs Group 2: 27/29 <u>Race/ethnicity:</u> African American: Group 1: 22/35 vs Group 2: 15/29 Hispanic: Group 1: 7/35 vs Group 2: 13/29



White: Group 1: 6/35 vs Group 2: 1/29
Men who have sex with men: Group 1: 28/35 vs Group 2: 24/29

Syphilis stage:

Primary: Group 1: 3/35 vs Group 2: 1/29
Secondary: Group 1: 23/35 vs Group 2: 16/29
Early latent: Group 1: 9/35 vs Group 2: 12/29
Previous history of syphilis: Group 1: 18/35 vs Group 2: 20/29

Median RPR titer Group 1: 1:128 vs Group 2: 1:128
CD4 count: Group 1: 381 vs Group 2: 397

Interventions

- **Intervention group 1:** Triple dose : Benzathine penicillin G (BPG), given as an intramuscular injection of 2.4 million units THREE TIMES over 3 weeks (total 7.2 million units)
- **Intervention group 2:** Single dose : BPG, given as an intramuscular injection of 2.4 million units ONCE (total 2.4 million units)

Results

- **Serological response – defined as treatment success: a 4-fold decrease in initial RPR titer within 12 months follow-up (Intention to treat analysis):** Treatment success – a 4-fold decrease in initial RPR titer within 12 months follow up (intention to treat analysis)
12 months
Group 2: standard 28/35 (risk=0.80); Group 1: Triple 27/29 (risk=0.93)
Risk difference: 0.13 (95% CI: -0.05 to 0.30), p=0.17
Per protocol analysis also reported which excluded patients lost to follow up and those who received extra doses of BPG in the standard therapy group.
- **Adverse events (including death or Jarisch-Herxheimer reactions):** None in either group.
No neurological symptoms during follow-up period.

Limitations and other comments

- **Limitations** Very serious risk of bias due to high risk of selection bias, performance bias and detection bias.
No serious applicability/indirectness.
- **Authors conclusion** When compared with a single dose of BPG, a 3-dose regimen did not improve syphilis serological outcomes. Our results support the Centers for Disease Control and Prevention recommendation of a single dose of BPG in HIV infected patients with early syphilis.
- **Remark formulated by KCE/NGC** The intention to treat analysis of treatment success is better in the triple dose strategy. This is what KCE/NGC have based their analysis and conclusion on. However, the study also reported a per-protocol analysis of 93% treatment success in standard and 100% in triple group. We assume the authors have used this information to conclude that there is no improvement with triple dose. The per-protocol



analysis was done excluding 5 patients lost to follow up and 1 patient that received an extra dose of BPG in single dose arm and 2 patients lost to follow up in the triple dose arm.

A multicenter Study Evaluating Ceftriaxone and Benzathine Penicillin G as Treatment Agents for Early Syphilis in Jiangsu, China. Cao 2017²⁴⁵

Methods

- **Design** Randomised controlled trial.
- **Source of funding and competing interest** Supported by Jiangsu Provincial Special Fund for Clinical Science and Technology from the Scientific and Technological office of Jiangsu Province.
All authors: no reported conflicts of interest.
- **Setting** Four hospitals in Jiangsu Province, China.
- **Sample size** Total randomized: N=301 (Enrolled 340 of which 39 excluded).
Total analyzed: n= 230

Excluded from analysis reasons: (n=71)
Lost to follow-up: n=60
Initial negative RPR titers: n=11
- **Duration and follow-up** Enrolled from November 2013 through November 2015. Follow-up for 12 months.
- **Statistical analysis** Available case analysis reported as patients with no follow-up information or initial negative RPR titers were not included in the analysis. Categorical variables differences measured using X² test.

Patient characteristics

- **Eligibility criteria** HIV-negative, non-pregnant adult patients with untreated early syphilis were enrolled in the study. Syphilis had been diagnosed for the first time in all patients.
- **Exclusion criteria** Patients who had a positive skin test reaction to the penicillin or ceftriaxone antigen or a history of penicillin or ceftriaxone allergy.
- **Patient & disease characteristics** Baseline data (n=230) given for ceftriaxone and BPG group respectively:
Male: 48/112, 59/118

Primary syphilis: 20/112, 25/118
Secondary syphilis: 72/112, 63/118
Early latent: 20/112, 30/118
RPR titer ≤1:8: 30/112, 28/118
RPR titer ≥1:16: 82/112, 90/118



Sexual partners in last 3 months ≤ 1 : 60/112, 62/118

Sexual partners in last 3 months ≥ 2 : 52/112, 56/118

Age 18-35 years: 58/112, 71/118

Age 36-54 years: 44/112, 42/118

Age 55-65 years: 10/112, 5/118

No significant differences reported for any of the above baseline characteristics.

Interventions

- **Intervention group 1:** Ceftriaxone given 1.0 g intravenously, once daily for 10 days
- **Intervention group 2:** Benzathine penicillin G (BPG) given as 2.4 million units intramuscularly, once weekly for two weeks.

Results

- **Serological response defined as a ≥ 4 -fold decline in the rapid plasma reagin (RPR) titer:**
 - 14 days (n=221):
Group 1: 22/108 (20.3%) vs Group 2: 18/113 (15.9%)
 - 3 months (n=225)
Group 1: 86/110 (78.2%) vs Group 2: 86/115 (74.8%)
 - 6 months (n=230)
Group 1: 101/112 (90.2%) vs Group 2: 92/118 (78.0%)
 - 9 months (n=230)
Group 1: 101/112 (90.2%) vs Group 2: 94/118 (79.7%)
 - 12 months (n=230)
Group 1: 103/112 (92.0%) vs Group 2: 96/118 (81.4%)
- **Serological response by syphilis stage**
 - 6 months (n=230)
Primary – Group 1: 19/20 (95%) vs Group 2: 24/25 (96%)
Secondary – Group 1: 69/72 (95.8%) vs Group 2: 48/63 (76.2%)
Early latent – Group 1: 13/20 (65%) vs Group 2: 20/30 (66.7%)
 - 12 months (n=230)
Primary – Group 1: 20/20 (100%) vs Group 2: 25/25 (100%)
Secondary – Group 1: 70/72 (97.2%) vs Group 2: 48/63 (76.2%)
Early latent – Group 1: 13/20 (65%) vs Group 2: 23/30 (76.7%)



• Non-cure defined as serofast at 12 months	Group 1: 6/112 vs Group 2: 9/118
• Adverse events (serious adverse events or adverse events related to study drugs)	Group 1: 0/112 vs Group 2: 0/118
• Clinical cure – skin lesions disappeared within a month	Group 1: 112/112 vs Group 2: 118/118
• Adverse events – probable Jarisch-Herxheimer	Group 1: 46/112 (41.1%) vs Group 2: 37/118 (31.4%)
Limitations and other comments	
• Limitations	Very serious risk of bias due to high risk of selection bias, performance bias and detection bias. No serious applicability/indirectness.
• Authors conclusion	Ceftriaxone regimen was non-inferior to the BPG regimen in non-pregnant, immunocompetent patients with early syphilis.

Early syphilis treatment in HIV-infected patients: single dose vs. three doses of benzathine penicillin G. Costa-Silva 2016²⁴⁶

Methods	
• Design	Retrospective cohort.
• Source of funding and competing interest	No funding. The authors have no conflicts of interest related to this article.
• Setting	Sexually Transmitted disease Clinic, Porto, Portugal.
• Sample size	91 patients treated but 31 excluded and 60 patients enrolled in the study; 17 single dose and 43 had triple dose. Reasons excluded: missing data (n=5), prozone phenomenon (n=6), treated with doxycycline (n=3), missing follow-up (n=17).
• Duration and follow-up	Treated between January 2000 and December 2014.
• Statistical analysis	Categorical variables were compared by Fisher's exact test or Chi-square test.
Patient characteristics	
• Eligibility criteria	All HIV-infected patients with early syphilis attending the STID clinic of a University hospital were enrolled.
• Exclusion criteria	Treatment other than BPG, missing follow-up testing within the 12-month period after treatment, patients with other stages of syphilis, primary syphilis with negative VDRL diagnosed by clinical signs and <i>Treponema pallidum</i> PCR positive and prozone phenomenon.



- **Patient & disease characteristics** Data reported for single dose and triple dose respectively:
Men: 94.1%, 93%
Age (years): 43 (24-69), 36 (20-70)

Sexual orientation:

MSM: 47.1%, 39.5%
Heterosexual: 47.1%, 55.8%
NA: 5.8%, 4.7%

Primary syphilis: 6/17, 6/43
Secondary syphilis: 7/17, 22/43
Early latent syphilis: 4/17, 15/43

Interventions

- **Intervention group 1:** Triple dose: Benzathine penicillin G (BPG) – three weekly doses
- **Intervention group 2:** Single dose: BPG

Results

- **Serological response** defined as a ≥ 4 -fold decline in Venereal Disease Research Laboratory (VDRL) titer within 12 months
3 months:
Group 1: 27/43 (62.8%) vs Group 2: 11/17 (64.7%)
6 months:
Group 1: 36/43 (83.7%) vs Group 2: 14/17 (82.3%)
12 months:
Group 1: 42/43 (97.6%) vs Group 2: 16/17 (94.1%)
P=0.42

Limitations and other comments

- **Limitations** Retrospective cohort study; small and unbalanced sample size.
No serious applicability/indirectness.
- **Authors conclusion** This study supports the current international treatment guidelines, recommending early syphilis treatment with a single dose of BPG in HIV patients.



A new enhanced antibiotic treatment for early and late syphilis. Drago 2016²⁴⁷

Methods

- **Design** Randomised controlled trial.
- **Source of funding and competing interest** No funding and no competing interests declared.
- **Setting** Likely to be Italy but unclear. Unclear number of sites, but likely to be a single site study.
- **Sample size** No sample size calculation carried out; 69 enrolled and randomised to the 2 groups: 38 to standard treatment and 31 to combined treatment. At one year, 38 were followed up in the standard treatment and 22 were followed up in the enhanced treatment.
- **Duration and follow-up** January 2010 to December 2013. Follow up was at least 12 months after initiation of therapy, and up to 5 years
- **Statistical analysis** Simple inferential statistics, with Fischer's test for pairwise treatment comparisons.

Patient characteristics

- **Eligibility criteria** No inclusion criteria given, apart from existence of syphilis (primary, secondary, early latent or late latent).
- **Exclusion criteria** No exclusion criteria given
- **Patient & disease characteristics** Baseline data given for standard and combined respectively.
Median age 31, 36 years; male participants 28/38, 24/31.
Stage of syphilis: Primary 15/38, 7/31; Secondary 12/38, 6/31; Early latent 8/38, 9/31; Late latent 3/38, 9/31.
HIV +ve 1/38, 5/31.
Median VDRL titer 1:64, 1:256.
Groups differed for HIV status, stage of syphilis and VDRL at baseline.

Interventions

- **Intervention group 1:** Combined therapy: Benzathine penicillin G (BPG), given as an intramuscular injection of 2.4 million units (one injection for primary, secondary and early latent, but 3 injections over 3 consecutive weeks for late latent).

PLUS

Intramuscular injection of ceftriaxone 1g/daily for 10 days followed by oral doxycycline 100mg/twice daily for 20 days.
- **Intervention group 2:** Standard therapy: BPG, given as an intramuscular injection of 2.4 million units (once for primary, secondary and early latent, but weekly for 3 consecutive weeks for late latent).



Results

- Serological response defined as a 3 to 4-fold decrease in initial VDRL titer within 6 months of therapy:**

3 months:
Group 1: 11/22 (50%) vs Group 2: 0/38 (0%)

6 months:
Group 1: 20/22 (91%) vs Group 2: 13/38 (34%)

12 months:
Group 1: 22/22 (100%) vs Group 2: 26/38 (68%)
- Serological response by stage of syphilis at 12 months:**

Group 1 (n=22): Primary syphilis=7/7; Secondary syphilis= 6/6, early latent syphilis= 8/8; late latent syphilis=1/1
Group 2 (n=38): Primary syphilis=14/15; Secondary syphilis= 12/12, early latent syphilis= 0/8; late latent syphilis=0/3
Study also reported serological response by syphilis stage at 3 and 6 months.
- Adverse events:**

Group 1: 0/22 vs Group 2: 0/38

Additional information:

 - In group 2; 1 patient (early latent syphilis) developed vertigo, headache and generalised tonic-clonic seizures 5 years after starting therapy with BPG and diagnosed as having neurosyphilis on the basis of neurological examination, laboratory investigations, brain magnetic resonance imaging and electroencephalogram.
 - Fever and/or acute exacerbation of a maculopapular skin rash within 24 hours of the initial BPG injection were observed in two patients (group not given), and these were defined as Jarisch-Herxheimer reactions and not an adverse event.

Limitations and other comments

- Limitations**

Very serious risk of bias due to high risk of selection bias, performance bias, detection bias and attrition bias.
No serious applicability/indirectness.
- Authors conclusion**

We suggest defining the treatment response to syphilis therapy both clinically and serologically. Our experience reveals that BPG alone is not always adequate in preventing late syphilis complications. By contrast, the combined regimen composed of BPG, ceftriaxone and doxycycline has proven to be more effective than the standard regimen, resulting in a more significant and faster cure rate. The combined regimen provides treponemicidal antibiotic levels in the CSF that prevent possible late complications, and it is suitable for administration in an outpatient context.



Doxycycline compared with Benzathine Penicillin for the Treatment of Early Syphilis. Ghanem 2006²⁴⁸

Methods

- **Design** Record-based retrospective case-control study.
- **Source of funding and competing interest** Financial support from National Institutes of Health.
All authors stated no potential conflicts of interests.
- **Setting** 2 Sexually transmitted disease clinics in Baltimore, Maryland, US.
- **Sample size** 1558 patients were treated for early syphilis and 87 received doxycycline; of which 34 met the inclusion criteria.
73 patients from a randomly selected group of 200 age-matched individuals treated with Benzathine penicillin G (BPG) met the inclusion criteria.
- **Duration and follow-up** October 1993 and June 2000.
Follow-up reported as a range up to 400 days.
- **Statistical analysis** Time to event statistical models used to construct Kaplan-Meier curves.
X² test used to compare independent proportions.

Patient characteristics

- **Eligibility criteria** Patients were adults (18 years or over) who received a diagnosis of early syphilis attending 2 public sexually transmitted disease clinics and treated.
Clinician-recorded diagnosis of primary, secondary or early latent syphilis with reactive serological test results at the time of diagnosis and at least 1 follow-up serological test titer (270-400 days after treatment).
Two to 3 patients treated with BPG chosen for each patient treated with doxycycline on the basis of year of birth to ensure an adequate eligible sample of BPG treated patients.
- **Exclusion criteria** Patients with primary syphilis whose serological test results were no nonreactive at the time of treatment were excluded, because this study focused on serological responses.
- **Patient & disease characteristics** There were no statistically significantly differences in demographic or clinical characteristics between the 2 groups, although a statistically trend of patients treated with doxycycline receiving a diagnosis of early latent disease and having a past history of syphilis was evident. Larger number of HIV positive patients in BPG group but authors note that the numbers in study are too small to find a difference.

Data reported for doxycycline and BPG respectively:
Female: 56%, 56%
Age, median (range): 34 (27-38), 34 (27-39)
HIV positive: 5.9%, 13.7%
Primary syphilis: 17.6%, 20.6%



	Secondary syphilis: 50.0%, 60.3% Early latent syphilis: 32.4%, 19.1%
Interventions	
• Intervention group 1:	Doxycycline, 100 mg orally, twice daily for 14 days.
• Intervention group 2:	Benzathine penicillin G (BPG), single dose of 2.4 million units intramuscularly.
Results	
• Serological response defined as failure with a 4-fold rise in RPR titers 30-400 days after treatment or the lack of a 4-fold drop in RPR titers 270-400 days after treatment with no evidence of reinfection on the basis of disease intervention specialists records.	Failure: Group 1: 0/34 vs Group 2: 4/73 (1 had previous history of syphilis and 2 had HIV) *failures were reverted to positive outcome of serological response: Group 1: 34/34 vs Group 2: 69/73
Limitations and other comments	
• Limitations	Retrospective cohort study with unbalanced numbers in each study arm. No serious applicability/indirectness bias.
• Authors conclusion	Doxycycline appears to be an effective agent for the treatment of early syphilis.
Randomised, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. Hook 2002²⁴⁹	
Methods	
• Design	Randomized controlled trial.
• Source of funding and competing interest	Supported by the centre for disease control and prevention through grants, and by donations of medication by Pfizer and Ortho-McNeil. Two authors received research grant support and honoraria from Pfizer.
• Setting	STD clinics in Birmingham, Alabama and New Orleans, Louisiana. Unclear number of clinics.
• Sample size	No sample size calculation carried out; 74 enrolled and randomized to the 3 groups: 21 to benzathine penicillin G, 21 to Azithromycin 2g and 32 to Azithromycin 4g.
• Duration and follow-up	October 1995 to December 1997. Follow-up was at 7 and 14 days, and then 1,3,6,9 and 12 months after initiation of therapy.
• Statistical analysis	Simple inferential statistics, with RRs and 95% CIs for pairwise treatment comparisons. No corrections for repeated pairwise testing.



Patient characteristics	
• Eligibility criteria	Aged ≥18 years; early (primary, secondary or early latent) syphilis: primary syphilis defined as positive dark-field microscopy for <i>Treponema Pallidum</i> on lesion exudate, secondary as dark-field-positive or clinically typical cutaneous eruption and RPG titer ≥1.8 with a reactive MHA-TP or FTA-ABS test, and early latent as RPG titer ≥1.8 with a reactive MHA-TP or FTA-ABS test with a history of primary/secondary syphilis in past year, definite exposure in past year, or negative serology in past year.
• Exclusion criteria	Pregnancy; breastfeeding; allergy to penicillin or macrolide antibiotics, history of IV drug abuse, use of drugs active against TP or use of an investigational drug in 30 days preceding enrolment; known or suspected STDs requiring TP treatment; advanced HIV infection; severe renal or hepatic disease; 'unreliability' or unwillingness to attend follow-up.
• Patient & disease characteristics	Data given for Penicillin, Azithromycin 2g and Azithromycin 4g respectively. Median age 29,33,28; male 57%, 62%, 50%; Primary 52%, 38%, 34%; Secondary 29%, 43%, 28%, Early latent 19%, 19%, 38% HIV +ve n=2, n=0, n=1
Interventions	
• Intervention group 1	Benzathine penicillin G (BPG), given as an intramuscular injection of 2.4 million units once in Birmingham or twice (7 days apart) in New Orleans. Thus, the dose was 4.8 million units in New Orleans, which was the standard dose there at the time of the study.
• Intervention group 2	Azithromycin, 2g, administered as a single oral dose
• Intervention group 3	Azithromycin, 4g: 2 x 2g doses administered 6-8 days apart
Results	
• Serological response (defined as ≥ 2-dilution decrease in RPR titer) ≥ 4-fold decrease in RPR titer:	3 months: BPG 12/14, Azithromycin 2g 15/17, Azithromycin 4g 20/28 6 months: BPG 10/12, Azithromycin 2g 16/17, Azithromycin 4g 20/26 9 months: BPG 9/9, Azithromycin 2g 14/14, Azithromycin 4g 19/24 12 months: BPG 10/10, Azithromycin 2g 14/14, Azithromycin 4g 19/22
• Improvement of lesions 1 week after therapy:	'All patients with clinical manifestations of syphilis such as chancres, rashes or condylomata lata demonstrated clear improvement of lesions at the first follow-up visit, 1 week after therapy. No participant experienced the onset of new or recurrent syphilitic lesions or rashes after therapy'. Unfortunately the denominator (those with visible lesions at baseline) is not reported, so risks for each group not possible to present.
• Adverse events:	Jarisch-Herxheimer: Penicillin 5/21, Azithromycin 2g/4g 9/53 Vomiting: Penicillin 0/21, Azithromycin 2g/4g 1/52 Nausea: Penicillin 1/21, Azithromycin 2g/4g 7/52 Diarrhoea: Penicillin 0/21, Azithromycin 2g/4g 5/52 Overall GI side effects for penicillin v azithromycin: RR: 0.21 (95% CIs: 0.03 to 1.50) Overall GI side effects for azithromycin v penicillin: RR: 4.75 (95% CIs: 0.67 to 33.7)
Limitations and other comments	
• Limitations	Very serious risk of bias due to high risk of selection bias, performance bias and attrition bias.



	No serious applicability/indirectness.
• Authors conclusion	In this pilot study the response to treatment of early syphilis with azithromycin, 2g, given by mouth as either a single dose or two doses 1 week apart, appeared similar to response rates with recommended doses of benzathine penicillin G. If its efficacy is verified by further study, azithromycin may be the first new agent effective for single-dose treatment of syphilis in > 30 years.

A Phase III Equivalence Trial of Azithromycin versus Benzathine Penicillin for Treatment of Early Syphilis. Hook 2010²⁵⁰

Methods

• Design	Randomized controlled trial.
• Source of funding and competing interest	Financial support from National Institute of Allergy and Infectious Diseases. Potential conflicts of interest: none reported.
• Setting	Multicentre: 5 clinical sites in North America and 3 clinical sites in Madagascar.
• Sample size	<p>Screened subjects: N=7112 Enrolled subjects: N=568, randomised 238 azithromycin vs 285 benzathine G (was 569 but 1 randomized but not treated).</p> <p>Enrolled into intent-to-treat cohort: N=517 (255 azithromycin vs 262 benzathine G). Intent-to-treat cohort analysed: N=469 subjects (232 azithromycin vs 237 benzathine G); excluded n=99 Per-protocol cohort: N=450 (218 azithromycin vs 232 benzathine G); excluded n=118</p> <p>Intent-to-treat cohort: all subjects who met the eligibility criteria. The per-protocol analysis includes all subjects who did not have protocol status change during the period when the primary endpoint data collected.</p> <p>When a participant had a status change, the patient was recommended to be retreated with the penicillin therapy. Reasons for status change included participants who did not tolerate treatment, subjects who did not complete at least 6months of follow-up, subjects who took intercurrent antibiotics, became pregnant, subjects deemed to be reinfected with syphilis and subjects who were found to have HIV infection while participating in the trial.</p>
• Duration and follow-up	Participants screened from 1 June 2000 through 31 March 2007. Follow-up at 7 days, 14 days, 30 days, 3 months and 6 months.
• Statistical analysis	Analyses performed for the intent-to-treat cohort, as well as a subset referred as the per protocol cohort.



Patient characteristics	
<ul style="list-style-type: none">Eligibility criteria	People between 18-55 years of age, had early syphilis (primary, secondary, or early latent), had reactive rapid plasma regain and fluorescent treponemal antibody absorption test results, were not pregnant, had serological tests results negative for HIV infection and had not taken antibiotics effective against <i>Treponema pallidum</i> within the 30 days preceding enrolment, and had no known allergies to penicillin or macrolide antibiotics.
<ul style="list-style-type: none">Exclusion criteria	Exclusion from intent-to-treat cohort: missing data.
<ul style="list-style-type: none">Patient & disease characteristics	<p>Data given for azithromycin and penicillin respectively:</p> <p>Male: 55% vs 66%</p> <p>Mean age: 27 years vs 27 years</p> <p><u>Race/ethnicity:</u></p> <p>African American: 16% vs 16%</p> <p>White: 2% vs 2%</p> <p>Malagasy: 82% vs 81%</p> <p>Other: 1% vs 1%</p> <p><u>Syphilis stage:</u></p> <p>Primary: 25% vs 28%</p> <p>Secondary: 46% vs 46%</p> <p>Early latent: 29% vs 26%</p>
Interventions	
<ul style="list-style-type: none">Intervention group 1	Azithromycin, 2.0 g administered orally as a single dose (four 500 mg tablets orally). Observed for 30 minutes.
<ul style="list-style-type: none">Intervention group 2	Benzathine Penicillin G, 2.4 million units intramuscularly (received as 2 deep intramuscular injections of 1.2 million units). Observed for 30 minutes.
Results	
<ul style="list-style-type: none">Serological response	<p>described as serological cure and defined as a decrease in RPR titer at the time of the 6-month follow-up visit of ≥ 2 dilutions (4-fold) when compared with the initial RPR titer</p> <p>3 months: Group 1: 177/238 (74.4%) vs Group 2: 187/247 (75.7%)</p> <p>6 months: Group 1: 180/232 (77.6%) vs Group 2: 186/237 (78.5%)</p>



(intention to treat analysis)	* Per protocol analysis also reported.
<ul style="list-style-type: none"> Non serious adverse events (includes gastrointestinal, central nervous system, cutaneous, administration related) 	<p><u>Overall:</u> Group 1: 174/283 (61.5%) vs Group 2: 132/285 (46.3%)</p> <ul style="list-style-type: none"> Gastrointestinal (including nausea, gastrointestinal discomfort and diarrhoea): Group 1: 69/283 (24.4%) vs Group 2: 21/285 (7.4%) Central nervous system: Group 1: 19/283 (6.7%) vs Group 2: 7/285 (2.5%) Cutaneous: Group 1: 4/283 (1.4%) vs Group 2: 12/285 (4.2%) Administration related: Group 1: 14/283 (4.9%) vs Group 2: 28/285 (9.8%)
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	Very serious risk of bias due to high risk of selection bias, performance bias, detection bias and attrition bias. No serious applicability/indirectness bias.
<ul style="list-style-type: none"> Authors conclusion 	The efficacy of azithromycin at a dosage of 2.0 g administered orally was equivalent to that of benzathine penicillin G for the treatment of early syphilis in periods without HIV infection.

Therapeutic effect of ceftriaxone and penicillin G procaine in patients with early-stage syphilis. Liu 2017²⁵¹

Methods

<ul style="list-style-type: none"> Design 	Randomized controlled trial.
<ul style="list-style-type: none"> Source of funding and competing interest 	Funding not reported. Disclosure of conflict of interest – None.
<ul style="list-style-type: none"> Setting 	Hospital, China.
<ul style="list-style-type: none"> Sample size 	60 patients enrolled.
<ul style="list-style-type: none"> Duration and follow-up 	Patients treated between May 2014 and May 2015. Follow up for 12 months.
<ul style="list-style-type: none"> Statistical analysis 	Mean \pm SD, and means of two groups compared by t-test. The count data of two groups compared by Chi-square test.

Patient characteristics

<ul style="list-style-type: none"> Eligibility criteria 	Patients with early stage syphilis who were receiving treatment at the hospital were enrolled. Inclusion criteria: conformed to diagnostic criteria for early syphilis, negative for HIV, signed informed consent with good compliance, not having received medication.
<ul style="list-style-type: none"> Exclusion criteria 	Combined with low immunity; diagnosed as tumours; concurrent with severe diseases of liver, heart and kidney; women during lactation or pregnancy.



<ul style="list-style-type: none"> Patient & disease characteristics 	<p>Males: Group 1: 16/30, Group 2: 14/30</p> <p>Age average (range): Group 1: 35.4±9.5 years (22-67 years), Group 2: 34.6±9.4 years (23-68)</p> <p>Primary syphilis: Group 1: 12/30, Group 2: 14/30</p> <p>Secondary syphilis: Group 1: 13/30, Group 2: 12/30</p> <p>Early latent syphilis: Group 1: 5/30, Group 2: 4/30</p> <p>Age, sex and stage of syphilis were not significantly different.</p>
Interventions	
<ul style="list-style-type: none"> Intervention group 1: 	Ceftriaxone, intravenous infusion of 1.0 g ceftriaxone once daily for ten days.
<ul style="list-style-type: none"> Intervention group 2: 	Penicillin G procaine; intramuscular injection of 800,000 units penicillin G procaine once daily for 15 days
Results	
<ul style="list-style-type: none"> Clinical cure defined as subsidence of skin lesions after 1 week 	Group 1: 27/30 (90.00%) vs Group 2: 20/30 (67.67%)
<ul style="list-style-type: none"> Serological response defined as comparison of negative conversion rate in Tolidine red unheated serum test (TRUST) 	<p>12 months:</p> <p>Group 1: 30/30 (100.00%) vs Group 2: 28/30 (93.33%)</p>
<ul style="list-style-type: none"> Non cure - incidence of seroresistance defined as after the manifestations had disappeared for 6 months, serum positive for unheated serum reagin test 	Group 1: 5/30 (16.67%) vs Group 2: 7/30 (23.33%)
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	<p>Very serious risk of bias due to high risk of selection bias, performance bias and detection bias.</p> <p>No serious applicability/indirectness bias.</p>
<ul style="list-style-type: none"> Authors conclusion 	Our study demonstrated a comparable clinical efficacy of ceftriaxone and penicillin G procaine for early –stage syphilis.



Single-Dose Azithromycin versus Penicillin G Benzathine for the Treatment of Early Syphilis. Riedner 2005¹⁹⁹

Methods

- **Design** Randomized controlled trial.
- **Source of funding and competing interest** Research Training Fellowship from the Wellcome Trust, UK, and a grant from the European commission. Pfizer donated 250 doses of azithromycin but had no other involvement in the study.
- **Setting** Mbeya, Tanzania.
- **Sample size** Power calculation that 133 participants required in each group to have a statistical power of 80% and assuming at least 30% of participants lost to follow-up.
628 recruited on site, 300 were retrospectively found to be ineligible on basis of serological results; resulting in 328 subjects recruited (n=65 female bar workers; n=149 attendees of a sexually transmitted infection clinic, and n=114 traditional brew-sellers).
- **Duration and follow-up** Study conducted between September 2000 and September 2003.
Follow-up every 3 months for up to nine months until they were cured.
- **Statistical analysis** Percentages cured provided with 95% CI. Data on participants who were lost to follow-up before being cured where censored on the date of the last follow-up visit. Differences between groups in the cure rates were assessed with the use of an approximate z-test after complementary log-log transformation.

Patient characteristics

- **Eligibility criteria** People with confirmed early symptomatic syphilis (primary or secondary) or high-titer latent syphilis were recruited through screening of high risk populations in Mbeya Region, Tanzania, including a cohort of female bar workers, patients with sexually transmitted infections attending four public clinics, and traditional-brew sellers participating in a screening and treatment intervention for sexually transmitted infections. As part of intervention activities for sexually transmitted infections, persons from these three groups were examined for clinical and serologic signs of syphilis.
People with presumptive primary or secondary syphilis and those with reactive rapid plasma reagin (RPR) test at the time of screening were eligible. Additional eligibility criteria included an age of at least 18 years and residence in Mbeya.
- **Exclusion criteria** Pregnancy, known allergy to penicillin or macrolide antibiotics, use of antibiotics active against syphilis during the preceding six months for symptomatic cases or during the preceding two years for asymptomatic cases, and concurrent illnesses requiring treatment with antibiotics effective against syphilis.
- **Patient & disease characteristics** Total subjects 328 (Penicillin G benzathine group N=165 vs Azithromycin group N=163)
Average age was 27.0 years (range 15-60)
Authors state that groups were generally similar with regard to sociodemographic, behavioural and biological characteristics (no statistical analysis)

Data for penicillin G benzathine and azithromycin respectively;
Female: 124/165, 111/163



Age 15-24 years: 77/165, 69/163

Age 25+: 88/165, 94/163

Number of sexual partners in past 3 months:

≤1: 121/165, 110/163

≥2: 40/165, 50/163

HIV seropositive: 87/165, 84/163

Primary syphilis: 14/165, 11/163

Latent syphilis: 151/165, 152/163

RPR titer at treatment ≤1:32: 110/165, 107/163

RPR titer at treatment ≥1:64: 55/165, 56/163

Under 18 years = 12

Interventions

- **Intervention group 1:** Azithromycin 2g orally.
- **Intervention group 2:** Penicillin G Benzathine 2.4 MU intramuscularly.

Results

- **Serological response** defined as a decrease in the RPR titer by at least two dilutions before or at the nine-month follow-up examination, with the titer at the time of treatment used as the baseline. For primary and secondary syphilis, complete resolution or improvement of lesions within one or two weeks after treatment was also required.
 - 3 months:
Group 1: 92/155 (59.4%) vs Group 2: 91/153 (59.5%)
 - 6 months:
Group 1: 129/151 (85.5%) vs Group 2: 122/150 (81.5%)
 - 9 months:
Group 1: 145/149 (97.7%) (95% CI: 94.0 to 99.4%) vs Group 2: 141/148 (95.0%)

* Paper only presents percentages but crude figures above taken from Cochrane review Bai 2012²⁵²



- Serological response at 9 months by syphilis stage**

Primary syphilis;
Group 1: 100% vs Group 2: 100%

Latent syphilis:
Group 1: 97.5% (95% CI: 93.5-99.3) vs Group 2: 94.5% (95% CI: 89.6 to 97.6%)

- Adverse events/for azithromycin**

Only reported for azithromycin group:
Nausea: 12/140
Stomach pain: 6/140
Diarrhoea: 1/140
Vomiting: 1/140

Limitations and other comments

- Limitations**

Serious risk of bias due to high risk of performance bias.
No serious applicability/indirectness bias.
- Authors conclusion**

Single dose oral azithromycin is effective in treating syphilis and may be particularly useful in developing countries in which the use of penicillin G benzathine injections is problematic.

A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. Rolfs 1997²⁵³

Methods

- Design**

Randomized double blind controlled trial.
- Source of funding and competing interest**

Merck Sharp & Dohme Research Laboratories supplied probenecid and probenecid placebo tablets, and SmithKline Beecham Pharmaceuticals supplied amoxicillin and amoxicillin placebo capsules. No other conflicts or funding reported.
- Setting**

Eight study centres, though country is unclear (likely to be USA). Healthcare setting: unclear; urban/rural/mixed: unclear.
- Sample size**

A sample size calculation (alpha 0.05, beta 0.20, doubling or tripling of failure rate) suggested 1200 patients. This was not only powered to detect differences between treatments but also between HIV and non-HIV participants.
541 patients enrolled, with 265 randomized to combined therapy and 276 to standard therapy. At 12 months follow up there were only 142 in combined therapy and 137 in standard therapy.
- Duration and follow-up**

Patients enrolled between Jan 1991 and June 1994. Follow up was up to 12 months.
52% follow-up reported at 12 months.
- Statistical analysis**

Cox proportional hazards methods were used to estimate the hazard of symptom resolution across treatment groups adjusting for confounders such as HIV status. Linear models were used for other outcomes, adjusting for confounders. Overall, a highly sophisticated and appropriate analysis was used.



Patient characteristics	
• Eligibility criteria	Consenting patients with untreated primary, secondary, or early latent syphilis.
• Exclusion criteria	Pregnant; under 18 years of age; unable to receive penicillin; if they had received antibiotics effective against T. Pallidum within the preceding two weeks; and if such therapy was required at enrolment in addition to treatment for syphilis.
• Patient & disease characteristics	<p>HIV positive: Standard therapy: 42/276 vs combined therapy: 59/265</p> <p>Baseline characteristics are reported for HIV +ve compared to HIV -ve patients in the paper. Therefore, it was not possible to give characteristics for each treatment group.</p> <p>In general, participants were aged around 30 years; were predominantly male (84% male if HIV+ and 68% male if HIV-); had completed 12 years of education; 139 had primary syphilis, 253 had secondary syphilis and 149 had early latent syphilis. 100 had a previous history of syphilis.</p> <p>Authors report that patients in the two treatment groups were similar with regard to age, race, education, stage of syphilis, reported sexual behaviors, history of syphilis and frequency of lumbar puncture at the initial visit, but the patients assigned to combined therapy were more commonly infected with HIV.</p>
Interventions	
• Intervention group 1	Combined therapy 2.4 million units of intramuscular penicillin G benzathine given as a single injection PLUS 2 g of amoxicillin and 500 mg of probenecid, taken orally three times a day for 10 days
• Intervention group 2	Standard therapy: 2.4 million units of intramuscular penicillin G benzathine given as a single injection PLUS placebo tablets (identical to the amoxicillin and probenecid tablets taken in the combined group) taken orally three times a day for 10 days.
Results	
• Serological response - treatment failure (defined as present when the RPR titer did not decrease by 2 or more dilutions or the test results did not become non-reactive after treatment):	<p>Serologically defined treatment failure at 3 months Combined: 46/185 (25%) Standard therapy: 40/175 (23%)</p> <p>Serologically defined treatment failure at 6 months (% given in paper but numbers calculated and presented here) Combined: 29/169 (17%) Standard therapy: 28/157 (18%)</p>



The above 6 month raw data were also adjusted (for age, sex, stage of syphilis, history of syphilis, HIV status, initial RPR titer, study site, compliance and incidental antibiotic use) in a multivariate logistic regression, giving an adjusted OR of 1.1 (95% CI 0.6 to 2.2) for standard vs combined treatment. Thus for combined versus standard it is the reciprocal: 0.91 (0.45 to 1.67)

Serologically defined treatment failure at 9 months (% given in paper but numbers calculated and presented here)

Combined: 24/148 (16%)

Standard therapy: 28/153 (18%)

Serologically defined treatment failure at 12 months (% given in paper but crude numbers calculated and presented here)

Combined: 20/142 (14%)

Standard therapy: 21/137 (15%)

Authors also report treatment failure by stage of syphilis and by HIV status.

- **Time to chancre healing:** Non-significant difference between treatment groups (no data shown).
- **Time to resolution: of skin rashes:** Non-significant difference between treatment groups (no data shown).
- **Adverse events:** Not generally reported per treatment group (but reported for HIV+ vs HIV- participants).

Diarrhoea: Combined = 45/265 (17%) versus standard therapy = 28/276 (10%), p=0.04
*Only percentages reported in paper but crude figures calculated for analysis.
- **Compliance:** Authors stated that 'the patients receiving the combined treatment did not differ from those receiving the standard treatment with regard to compliance with medication'.

Limitations and other comments

- **Limitations** Serious risk of bias due to high risk of attrition bias.
No serious applicability/indirectness bias.
- **Authors conclusion** After treatment for primary or secondary syphilis, the HIV-infected patients responded less well serologically than the patients without HIV infection, but clinically defined failure was uncommon in both groups. Combined treatment with amoxicillin and probenecid did not improve the outcomes. The current recommendations for treating early syphilis appear to be adequate for most patients, whether or not they have HIV infection.



Serological response to treatment of syphilis with doxycycline compared with penicillin in HIV-infected individuals. Salado-Rasmussen 2016²⁵⁴

Methods

- **Design** Retrospective observational study
- **Source of funding and competing interest** Funding not stated.
The authors declare no conflicts of interest.
- **Setting** 2 Departments of Infectious Diseases and 1 sexually transmitted disease clinic at University Hospitals in Copenhagen.
- **Sample size** 221 cases of syphilis diagnosed were identified from the records of the 3 clinics between May 2004 and October 2009. 172 cases in HIV infected individuals. In total, 202 were treated with doxycycline or intramuscular benzathine penicillin G. Of these, 12 cases were evaluated at 12 months (78 with doxycycline and 48 with penicillin).
- **Duration and follow-up** Treatment duration differed according to intervention and syphilis stage (see intervention group for details). Follow up was at 3, 6, 9 and 12 months following therapy.
- **Statistical analysis** Where appropriate the Chi squared for Fisher's exact test were used to compare independent proportions. For comparison of continuous variables the t-test and the Mann-Whitney test were used for normal distributed and non-normal distributed variables respectively. The Kruskal-Wallis test was used for comparison of titers between different syphilis stages. Odds ratios were computed by logistic regression.

Patient characteristics

- **Eligibility criteria** HIV-infected individual's ≥18 years of age diagnosed with syphilis between 1 May 2004 and 31 October 2009. An individual could contribute more than one episode, provided that treatment and appropriate treatment response was documented in the patient files.
- **Exclusion criteria** Patients who received intravenous antibiotics, who were diagnosed with neurosyphilis or who lacked information on therapy.
- **Patient & disease characteristics** Reported as doxycycline (n=127) and benzathine penicillin G (n=75) respectively [n (%)]:

Age, years, median (range): 40 (20-83), 39 (24-61)

Female: 1 (1), 1(1)
Male: 126 (99), 74 (99)
MSM: 121 (96), 70 (95)

Syphilis stage:
 - Primary: 12 (9), 8 (11)
 - Secondary: 75 (59), 42 (56)
 - Early latent: 18 (14), 10 (13)
 - Late latent: 21 (17), 13 (17)
 - Relapse: 1 (1), 0 (0)



- Unknown: 0 (0), 2 (3)

No statistically significant differences between treatment groups were observed, except for CD4 cell count ≤ 200 cells/ μ l, which was less common and proportion on cART, which was higher for the doxycycline treated group.

Interventions

- **Intervention group 1** Doxycycline, 100mg orally twice daily for 14 days for early syphilis, i.e. primary, secondary and early latent stages, and for 30 days for late latent syphilis.
- **Intervention group 2:** Penicillin, a single dose of intramuscular 2.4 million units of benzathine penicillin G (BPG) for early syphilis and 3 doses each at 1-week intervals for late latent syphilis.
At the beginning of the study period 15 patients were treated with intramuscular procaine penicillin (1 dose of 600,000 units once daily for 10 days) these cases were grouped with the BPG treated cases.

Results

- **Serological response rate** defined as 4-fold or greater decline in RPR titers
(Failure rate also reported by study as the reverse of these results – not reported here)
 - 3 months
Group 1: 20/89 (22%) vs 12/58 (21%)
 - 6 months
Group 1: 37/74 (50%) vs 28/45 (62%)
 - 9 months
Group 1: 52/68 (76%) vs 31/39 (79%)
 - 12 months
Group 1: 66/78 (85%) vs 40/48 (83%)

No statistically significant differences were observed between treatment groups at any time-point (all $p > 0.05$).

Limitations and other comments

- **Limitations** Retrospective cohort study. Groups unbalanced at baseline for possible confounding factors.
Does not appear to have taken confounders into account, likely only a univariate analysis.
No serious applicability/indirectness bias.
- **Authors conclusion** Our study supports the use of doxycycline as an efficient treatment option for syphilis when treating an HIV-infected population with close follow-up.



Could lengthening minocycline therapy better treat early syphilis? Shao 2016²⁵⁵

Methods

- **Design** Retrospective cohort study.
- **Source of funding and competing interest** None reported.
- **Setting** Tianjin Medical University General Hospital sexually transmitted disease (STD) outpatient clinic, China.
- **Sample size** 875 cases of which 137 were primary syphilis, 193 were secondary syphilis cases, 4 were late syphilis cases, 3 were congenital syphilis cases, and 538 were latent syphilis cases.
397 received recommended treatments (478 excluded due to lost to follow-up or not received recommended regimen N=478)
Minocycline: N=330 (further 174 excluded due to intolerance or other reasons after treatment).

Minocycline 2 weeks: n=77, Minocycline 4 weeks: n=79, Benzathine penicillin G (BPG) N=40, Other treatments N=27.
- **Duration and follow-up** Duration from January 2011 and December 2013 with at least a 2 year follow-up.
- **Statistical analysis** Pearson chi-square test was used to compare differences in categorical variables.
Significance differences tested for various baseline factors between the two minocycline doses.

Patient characteristics

- **Eligibility criteria** Syphilis patients who visited the STD clinic with :
 - a first time diagnosis of early syphilis (primary, secondary or early latent stages)
 - at least 2 serological titers within 24 months, with 1 titer at or around the date of treatment, that is, baseline titer
 - must have had regular follow-ups at 3, 6, 9, 12, 18 and 24 months posttreatment
 - must have received a recommended regimen based on the national Sexually Transmitted Infections (STI) Guidelines even if the syphilis patients were coinfectd with other STDs.
- **Exclusion criteria** HIV or pregnant, did not have follow-up data or had a total follow-up period of less than 2 years, did not receive a recommended regimen based on the national STI Guidelines.
- **Patient & disease characteristics** Data reported for Minocycline 2 weeks, Minocycline 4-weeks and BPG respectively:

Male: 46.75%, 44.30%, 55%
Primary syphilis: 19.48%, 17.72%, 57.50%
Secondary syphilis: 80.52%, 82.28%, 42.50%



Statistical differences not provided for baseline data.

Interventions

- **Intervention group 1** Minocycline 2 weeks: 100 mg orally, twice daily, for 14 days
- **Intervention group 2:** Minocycline 4 weeks: 100 mg orally, twice daily, for 28 days
- **Intervention group 3:** BPG: single intramuscular dose of 2.4 million units

Results

- **Serological response** described as serological cure rate and defined as patients whose RPR titers became nonreactive after the disappearance of clinical manifestations of syphilis
 - 1 year follow-up:
Group 1: N=50/77 (64.93%) vs Group 2: N=52/79 (65.82%) vs Group 3: NR
 - 2 years follow-up:
Group 1: N=56/77 (72.73%) vs Group 2: N=69/79 (87.34%) vs Group 3: 31/40 (77.50%)
 - Primary syphilis 2 year follow-up:
Group 1: N=11/15 (73.33%) vs Group 2: N=10/14 (71.43%) vs Group 3: NR
 - Secondary syphilis 2 year follow-up:
Group 1: N=45/62 (72.58%) vs Group 2: N=59/65 (90.77%) vs Group 3: NR

Limitations and other comments

- **Limitations** Retrospective cohort study with unbalanced numbers in each study arm.
No serious applicability/indirectness bias.
- **Authors conclusion** Minocycline appears to be an effective agent for treating early syphilis, especially when applied as a 4-week, lengthened therapy.



Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. Smith 2004²⁵⁶

Methods

- **Design** Randomised controlled trial
- **Source of funding and competing interest** Source of funding or conflicts not reported.
- **Setting** One centre, Texas, USA. Healthcare setting: Clinic
- **Sample size** Sample size calculation not reported. 31 randomised to the two treatment groups: 16 to penicillin and 15 to ceftriaxone. 6 dropped out of the penicillin group and 1 from the ceftriaxone group, but reasons are not given.
- **Duration and follow-up** Enrollment dates not given. Follow up at 3, 6, 9 and 12 months and beyond as required by primary care provider.
- **Statistical analysis** T test, Wilcoxon rank sum test and chi square test comparisons across treatment groups

Patient characteristics

- **Eligibility criteria** Patients with asymptomatic syphilis based on an RPR titer $\geq 1:4$, a reactive MHA-TP and the absence of symptoms or signs suggestive of syphilis in any stage. Gave consent for lumbar puncture which is required to distinguish latent syphilis from asymptomatic neurosyphilis.
- **Exclusion criteria** Unclear as only reasons for actual exclusions are reported: recent therapy which was active against syphilis, cryptococcal meningitis.
- **Patient & disease characteristics** All patients HIV+ve. Nearly all the patients were prescribed HIV therapy with a single nucleoside analogue as prior to antiretroviral therapy.
Baseline RPR titer was (median) 1:32 in the penicillin group and 1:128 in the ceftriaxone group. Mean age was 35.4 years in penicillin group and 34.5 years in the ceftriaxone group. 81% male in penicillin group and 93% male in the ceftriaxone group.
The ceftriaxone group had a lower mean CD4 cell count (194 vs 354), higher cerebrospinal fluid protein (51 vs 37) and higher frequency of reactive Venereal Disease Research Laboratory test in the CSF (4 vs 0) at baseline compared to the penicillin group.

Interventions

- **Intervention group 1:** Procaine penicillin 2.4 million units intramuscularly (IM) **once a day** with probenecid 500 mg by mouth four times daily for 15 days.
- **Intervention group 2:** Ceftriaxone 1g IM daily for 15 days.

Results

- **Serological response** defined as > 4 -fold decline in RPR titer at median 32 months follow up for penicillin group and 18 months follow up for ceftriaxone group Penicillin 7/10 versus Ceftriaxone 10/14
- **Serological response** defined as > 4 -fold decline in RPR without subsequent Penicillin 5/10 vs Ceftriaxone 9/14



relapse (responders) at median 32 months follow up for penicillin group and 18 months follow up for ceftriaxone group

- **Treatment failure** Penicillin 0/10 vs Ceftriaxone 2/14

Defined as ≥ 4 -fold rise in RPR, persistent titer $\geq 1:64$, or clinical progression to disease at median 32 months follow up for penicillin group and 18 months follow up for ceftriaxone group

- **Adverse events:** Penicillin 0/10 vs Ceftriaxone 0/14

Limitations and other comments

- **Limitations** Very serious risk of bias due to high risk of selection bias, performance bias, detection bias and attrition bias. No serious applicability/indirectness bias.
- **Authors conclusion** Intensive treatment with procaine penicillin plus probenecid or ceftriaxone was associated with a high failure rate. Similar serological response rates occurred in patients with and without CSF abnormalities. No patient in either treatment group developed neurological or clinical symptoms of active syphilis during this study. Nevertheless, it is clear that the treatment response in HIV-infected patients differs from that in immunocompetent hosts, and prolonged, close monitoring, is warranted.

Comparison of Serological Response to Doxycycline versus Benzathine Penicillin G in the Treatment of Early Syphilis in HIV-Infected Patients: A Multi-Center Observational Study. Tsai 2014²⁵⁷

Methods

- **Design** Multicentre retrospective cohort study.
- **Source of funding and competing interest** Supported by a grant from the Centers for Disease Control, Taiwan. Authors declared that there are no competing interests.
- **Setting** 9 hospitals designated for HIV care around Taiwan, where inpatient or outpatient HIV care, including combination antiretroviral therapy, treatments of HIV-related opportunistic illnesses, and monitoring of plasma HIV RNA load and CD4 counts are reimbursed by the government.
- **Sample size** Enrolled 123 patients who had doxycycline and 271 patients that had benzathine penicillin G (BPG). 32 lost to follow up from doxycycline group at 12 months.



• Duration and follow-up	Data collected from 2007 and 2013. Follow-up reported at 6 and 12 months.
• Statistical analysis	Last observed carried forward principle was used to deal with missing values of RPR titers. Categorical variables were compared using χ^2 or Fisher's exact test. Multiple logistic regression used to identify factors associated with serological response.
Patient characteristics	
• Eligibility criteria	HIV-infected men aged 20 years or higher, who presented with early syphilis and received a 14-day treatment course of doxycycline or a single dose of benzathine penicillin.
• Exclusion criteria	If antibiotics were concurrently given that were treatment options for syphilis when early syphilis was diagnosed, or if those antibiotics were used for treatment of diseases other than syphilis during the 6 months of follow-up after treatment. Patients with RPR titers of less than 4 were not included because of concerns about increased risk of biological false-positive syphilis serologies (RPR titers of 1:1 or 1:2). Neurosyphilis such as CNS dysfunction, stroke, auditory and ophthalmic abnormalities or tertiary syphilis were also excluded.
• Patient & disease characteristics	Data for patients in doxycycline and BPG groups respectively. Age, median (range years): 32 (20-59), 31.4 (20-71) MSM: 114 (92.7%), 260 (95.9%) Primary syphilis: 11(8.9%), 24 (9.3%) Secondary syphilis: 51 (41.5%), 167 (65.4%) Early latent: 61 (49.6%), 80 (25.3%) All baseline characteristics similar except for patients with secondary and early latent syphilis.
Interventions	
• Intervention group 1:	Doxycycline: 100 mg twice daily for 14 days
• Intervention group 2:	Benzathine penicillin: single dose of 2.4 MU
Results	
• Serological response defined as a decline of RPR titer by 4-fold or greater from baseline value	6 months: Group 1: 78/123 (63.4%) vs Group 2: 196/271 (72.3%), $p=0.075$ 12 months: Group 1: 60/91 (65.9%) vs Group 2: 185/271 (68.3%), $p=0.681$ *Only percentages given in the paper and NGC calculated crude numbers.
Limitations and other comments	



• Limitations	Retrospective cohort study with unbalanced numbers in each study arm. No serious applicability/indirectness bias.
• Authors conclusion	The serological response rates to a 14-day course of doxycycline and a single dose of benzathine penicillin were similar in HIV infected patients with early syphilis at 6 and 12 months of follow-up. Patients with secondary syphilis were more likely to achieve serological response than those with other stages.

Primary Syphilis: Serological Treatment Response to Doxycycline/Tetracycline versus Benzathine Penicillin. Wong 2008²⁵⁸

Methods

• Design	Retrospective cohort study.
• Source of funding and competing interest	Funding from Alberta Health and Wellness and from the Public Health Agency of Canada.
• Setting	Alberta, Canada.
• Sample size	863 primary syphilis cases reported; 445 with available outcome data were included in final study sample. Benzathine penicillin G N=420 and Doxycycline/tetracycline N=25.
• Duration and follow-up	Subjects from 1980 to 2001.
• Statistical analysis	Median time to successful response was estimate and factors associated with treatment success were identified by unadjusted logistic regression.

Patient characteristics

• Eligibility criteria	All first time primary syphilis patients who had at least 2 serological titers within 12 months (1 titer at or around the date of treatment [baseline titer] and at least 1 follow-up post-treatment test). Subjects included if treated with penicillin or doxycycline or tetracycline.
• Exclusion criteria	Excluded if patient known to be HIV infected, baseline serology showed a nonreactive rapid plasma regain test, follow-up was inadequate to determine serological outcome of treatment (minimum of 6 months if serological response did not happen sooner); or T. pallidum enzyme immunoassay was used instead of rapid plasma regain test. Records from patients whose HIV status was undocumented were not excluded.
• Patient & disease characteristics	Data reported for Benzathine penicillin G and doxycycline or tetracycline respectively. Median [IQR] age: 27.8 [15.2], 29.8 [15.1] Male: 73.8%, 64.0% Caucasian 53.2%, 47.4% Aboriginal: 33.2%, 36.8% Black: 3.3%, 10.5%



Asian/South Asian:10.3%, 5.3%

Heterosexual: 84.3%, 70.8%

Homosexual/bisexual: 15.7%, 29.2%

There was a similar distribution of patient characteristics in each treatment group.

Interventions

- **Intervention group 1** Doxycycline, 100mg twice a day for 14-days **OR** oral tetracycline, 500 mg 4 times a day for 14 days.
- **Intervention group 2** Benzathine penicillin G, 2.4 million units intramuscularly as single dose.

Results

- **Serological response** defined as a minimum 4-fold decrease in baseline rapid plasma reagin test antibody titer within 6 months, or ≥ 8 -fold decrease within 12 months, or ≥ 16 -fold decrease by 24 months. Group 1: 25/25 (100%) vs Group 2: 409/420 (97.4%)

Limitations and other comments

- **Limitations** Retrospective cohort study with unbalanced numbers in each study arm.
No serious applicability/indirectness bias.
- **Authors conclusion** Doxycycline/tetracycline had a similarly high serological treatment success rate when compared with penicillin in the treatment of primary syphilis.

Comparison of Doxycycline and Benzathine Penicillin G for the treatment of Early Syphilis. Xiao 2017²⁵⁹

Methods

- **Design** Record based retrospective study.
- **Source of funding and competing interest** Supported by the Natural Science Foundation of Shandong Province.
- **Setting** STD clinic in Shandong, China.
- **Sample size** 747 primary syphilis cases reported during study period.
601 included in final study sample (doxycycline: n=105 and benzathine penicillin G (BPG): n=496)



	<p>If follow-up was inadequate to determine the serological outcome of treatment, the patients would then be excluded.</p> <p>Patients with primary syphilis whose serological test results were non-reactive at the time of treatment were excluded, because this study focused on serological responses.</p>
<ul style="list-style-type: none">• Duration and follow-up	<p>Study period from 1st January 2008 to 31 December 2014.</p> <p>All patients followed-up for at least 12 months.</p>
<ul style="list-style-type: none">• Statistical analysis	<p>Pearson's chi-squared or Fisher's exact test were used to compare the categorical variables.</p>
Patient characteristics	
<ul style="list-style-type: none">• Eligibility criteria	<p>Participants were aged from 16 to 70 years with early syphilis (in the primary, secondary or early latent stages) diagnosed at a STD clinic.</p> <p>All subjects were HIV negative and without other bacterial infections.</p>
<ul style="list-style-type: none">• Exclusion criteria	<p>If follow-up was inadequate to determine the serological outcome of treatment, the patients would then be excluded.</p> <p>Patients with primary syphilis whose serological test results were non-reactive at the time of treatment were excluded, because this study focused on serological responses.</p>
<ul style="list-style-type: none">• Patient & disease characteristics	<p>Data given for doxycycline and BPG respectively:</p> <p>Age median years (IQR): 31 (25-41), 30 (24-40)</p> <p>Male: 42/105, 244/496; of which 8 identified themselves as being MSM.</p> <p>Primary syphilis: 19/105, 99/496</p> <p>Secondary syphilis: 58/105, 252/496</p> <p>Early latent: 28/105, 145/496</p> <p>Co-infection with other STDs: 13/105, 90/496</p> <p>None of baseline data provided had significant differences (including ethnicity and RPR titer).</p>
Interventions	
<ul style="list-style-type: none">• Intervention group 1:	<p>Doxycycline 100 mg orally twice daily for 14 days.</p> <p>Only patients who were allergic to penicillin or refused intramuscular BPG were given this intervention.</p>
<ul style="list-style-type: none">• Intervention group 2:	<p>BPG 2.4 MU single-dose.</p>
Results	
<ul style="list-style-type: none">• Serological response defined as a decline of RPR titer by 4-fold or greater from the baseline value at 6 or 12	<p>12 months:</p> <p>Group 1: 97/105 (92.38%) vs 477/496 (96.17%)</p>



months of doxycycline or BPG treatment if initial RPR titer was 1:8 or higher. If RPR titer was 1:4, 1:2, or 1:1 at baseline for primary syphilis or secondary syphilis, successful treatment was considered to be when the lesions disappeared and RPR turned to be negative after treatment.

Limitations and other comments

- **Limitations** Unbalanced intervention groups and only patients that were allergic to penicillin or refused intramuscular BPG were given doxycycline. Retrospective cohort study with unbalanced numbers in each study arm. No serious applicability/indirectness bias.
- **Authors conclusion** The results of the study demonstrate that doxycycline still appears to be an effective agent for the treatment of syphilis.

One dose versus three weekly doses of benzathine penicillin G for patient co-infected with HIV and early syphilis: A multicentre, prospective observational study. Yang 2014²⁶⁰

Methods

- **Design** Prospective observational study
- **Source of funding and competing interest** Supported by the Centres for Disease Control, Taiwan. The authors declared that there were no competing interests.
- **Setting** Multicentre, 8 hospitals designated for HIV care, Taiwan.
- **Sample size** 1128 patients with syphilis screened for inclusion, 2007-2012. 555 were excluded for the following reasons; 408 late latent syphilis, 22 low rapid plasma reagin (RPR) titer, 41 received another antibiotic, 57 lost to follow-up on the second day after treatment. 537 patients were subsequently enrolled: 295 to 1 dose, 278 to 3 doses.
- **Duration and follow-up** Patients received either 1 or 3 doses of benzathine penicillin G (BPG) depending on the assessment of the treating physicians. Follow-up of RPR titers was every 3 to 6 months. Each patient was followed up at least twice. The final study follow up was at 12 months.
- **Statistical analysis** An ITT analysis with last observation carried forward was adopted to deal with missing data. Categorical variables were compared by Fisher's exact test or Chi-square test. Non-categorical variables were compared by Mann-Whitney U test. Factors with a P value ≤ 0.2 or biological significance were included in the multivariate analysis. Binary logistic regression analysis was used to determine the factors associated with serological responses at 12 months.



Patient characteristics	
<ul style="list-style-type: none">Eligibility criteria	HIV infected patients who were 20 years or older, had early syphilis (i.e. primary, secondary or early latent), and had reactive rapid plasma reagin titers of 1:4 or greater and a reactive result of <i>Treponema pallidum</i> particle agglutination (TPPA) test (titer $\geq 1:320$).
<ul style="list-style-type: none">Exclusion criteria	Patients with a prior history of syphilis who received treatment within 12 months before enrolment. Patients who were pregnant, received antibiotics such as penicillin, ceftriaxone, doxycycline, or macrolides for syphilis or other infections within the preceding 12 months or during follow-up, were lost to follow-up immediately after treatment, had a history of penicillin allergy, or were receiving immunosuppressants, immunomodulators, or chemotherapy.
<ul style="list-style-type: none">Patient & disease characteristics	<p>Most patients were MSM. There were no statistically significant differences between the two groups of patients in terms of age, sex, gender, the stage of syphilis, RPR titer, prior history of syphilis, CD4 count, plasma HIV RNA load, and receipt of cART. More than half (57.8%) of the patients had secondary syphilis at enrollment, 64% had baseline CD4 cell counts of more than 350 cells/μl, and 35.4% had a prior history of syphilis.</p> <p>Data given for 1 dose (n=295) and 3 doses (n=278) respectively:</p> <p>Age, mean (SD) years: 32.8 (7.9), 33.5 (7.8)</p> <p>Risk for HIV transmission, n (%)</p> <ul style="list-style-type: none">MSM: 284 (96.3), 255 (91.7)Heterosexuals: 8 (2.7), 15 (5.4)Others: 3 (1.0), 8 (2.9) <p>Syphilis stage, n (%)</p> <ul style="list-style-type: none">Primary: 28 (9.5), 23 (8.3)Secondary: 173 (58.6), 158 (56.8)Early latent: 94 (31.9), 97 (34.9)
Interventions	
<ul style="list-style-type: none">Intervention group 1:	1 dose BPG (2.4 MU, 1179 IU/mg) intramuscularly
<ul style="list-style-type: none">Intervention group 2:	3 weekly doses BPG (2.4 MU, 1179 IU/mg) intramuscularly
Results	
<ul style="list-style-type: none">Serological response rate defined as 4-fold or greater decline in RPR titers at 12th month follow-up	<p>Overall: Group 1 (1 dose): 198/295 vs 208/278</p> <p>Syphilis stage:</p> <ul style="list-style-type: none">Primary; Group 1: 24/36 vs 46/74Secondary; Group 1: 119/165 vs 99/116



visit when compared with baseline titers.	<ul style="list-style-type: none"> Early latent; Group 1: 52/85 vs 61/85
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	No details on gender provided. Prospective cohort study. No serious applicability/indirectness bias.
<ul style="list-style-type: none"> Authors conclusion 	We failed to demonstrate the non-inferiority of 1 dose of BPG to 3 weekly doses of BPG for treatment of early syphilis in HIV-infected patients. A substantial rate of treatment failure due to reinfection in both groups suggests that counselling for risk behaviour modification should be integral component of management of HIV infected patients with early syphilis.

Comparison of serological responses to single-dose azithromycin (2g) versus benzathine penicillin G in the treatment of early syphilis in HIV-infected patients in an area of low prevalence of macrolide-resistant *Treponema pallidum* infection. Yang 2016

Methods

<ul style="list-style-type: none"> Design 	Prospective cohort study
<ul style="list-style-type: none"> Source of funding and competing interest 	Supported by grants from the Centers for Disease Control, Taiwan. No competing interests.
<ul style="list-style-type: none"> Setting 	Multicentre – 5 hospitals designated for HIV care in Taiwan.
<ul style="list-style-type: none"> Sample size 	Among the 238 HIV-infected patients receiving azithromycin treatment for early syphilis, 85 patients had <i>T. pallidum</i> (that did not harbour macrolide resistance mutations) and 1 patient was excluded because of infection with <i>T. pallidum</i> harbouring macrolide resistance mutation (A2058G); 162 HIV-infected patients with early syphilis were treated with benzathine penicillin G (BPG).
<ul style="list-style-type: none"> Duration and follow-up 	Single dose of drug, all patients followed-up at 3, 6 and 12 months after treatment.
<ul style="list-style-type: none"> Statistical analysis 	Categorical variables were compared using Chi ² or Fischer's exact test whereas non-categorical variables were compared using Student's t-test or Mann-Whitney U-test. Multiple logistic regression method was used to identify factors associated with serological response at 6 months of treatment.

Patient characteristics

<ul style="list-style-type: none"> Eligibility criteria 	HIV infected patients aged 20 years or over who presented with early syphilis and received single-dose benzathine penicillin G (2.4 MU) between Jan 2007 to April 2014. Patients receiving azithromycin who had completed follow-up for 12 months between 2012 and 2014 were included in the study using the same inclusion criteria.
<ul style="list-style-type: none"> Exclusion criteria 	Concurrent antibiotic use (if they were treatment options for syphilis such as ceftriaxone or doxycycline) when early syphilis was diagnosed, or if those antibiotics were used for treatment of diseases other than syphilis during the 12 months of follow-up after azithromycin or BPG treatment was administered. Patients with rapid plasma regain (RPR) titers of <1.4 were not included because of concerns about increased



	risk of biological false positive serology of syphilis (RPR titer of 1:1 or 1:2). Patients with symptomatic neurosyphilis or tertiary syphilis were also excluded.
<ul style="list-style-type: none"> Patient & disease characteristics 	<p>All except one patient in the penicillin group and two patients in the azithromycin group were MSM. Compared with the patients in the penicillin group, patients in the azithromycin group had a lower percentage of secondary syphilis (35.5% versus 50.6%, $P=0.003$), CD4 count $<200\text{cells/mm}^3$ (78.5% versus 66.1%, $P=0.01$), PVL <400 copies/mL (73.4% versus 54.9%, $P<0.001$), prior syphilis (67.9% versus 35.2%, $P<0.001$), taking cART (82.3% versus 69.1%, $P=0.003$) and lower mean \log_{10} PVL (2.22 ± 1.41 versus 2.98 ± 1.54 copies/mL, $P<0.001$).</p> <p>Data given for BPG and azithromycin respectively: Age, mean (SD), years: 32.0 (7.6), 33.1 (7.6)</p> <p>Sexual preference, n (%)</p> <ul style="list-style-type: none"> MSM: 161 (99.4), 235 (99.2) Non-MSM: 1 (0.6), 2 (0.8) <p>Syphilis stage, n (%)</p> <ul style="list-style-type: none"> Primary: 13 (8.0), 33 (13.9) Secondary: 82 (50.6), 84 (35.4) Early latent: 67 (41.4), 120 (50.6) <p>Prior history of syphilis, n (%): 57 (35.2), 161 (67.9)</p>
Interventions	
<ul style="list-style-type: none"> Intervention group 1: 	Single-dose BPG, 2.4 MU (n=162)
<ul style="list-style-type: none"> Intervention group 2: 	Single-dose azithromycin, 2g (n=237)
Results	
<ul style="list-style-type: none"> Serological response rate <p>Defined as a decline of an RPR titer by ≥ 4-fold from the baseline value at 12 months of azithromycin or BPG treatment.</p>	<p>Group 1: 61.1% (n=99*) Group 2: 56.5% (n=134*)</p> <p>*Only percentages given in the paper and NGC calculated crude numbers.</p>
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	<p>Retrospective study. Unbalanced numbers in each arm. Baseline characteristics differ at baseline for a number of factors.</p> <p>No serious applicability/indirectness.</p>



-
- **Authors conclusion** Our study suggests that, in the settings of a low prevalence of macrolide-resistant *T. pallidum*, azithromycin had a similar serological response rate to that of benzathine penicillin G in HIV-infected MSM. The major adverse effects of azithromycin are gastrointestinal symptoms and lassitude/somnolence in those individuals concurrently taking cART.
-

7.4.2. Research question 8 – What is the recommended treatment for uncomplicated syphilis in case of allergy to penicillin?

No evidence was identified for people with an allergy to penicillin. Comparisons with treatments other than penicillin are included in section 4.1.1 above.



8. FOREST PLOTS

8.1. *N. Gonorrhoea* and *C. trachomatis*: diagnosis

The following forest plots show the sensitivity and specificity with 95% Confidence Intervals for the respective studies by gender, sample type and assay.

Figure 20 – Men: NAATs and culture tests using rectal samples for detecting *N. gonorrhoea*

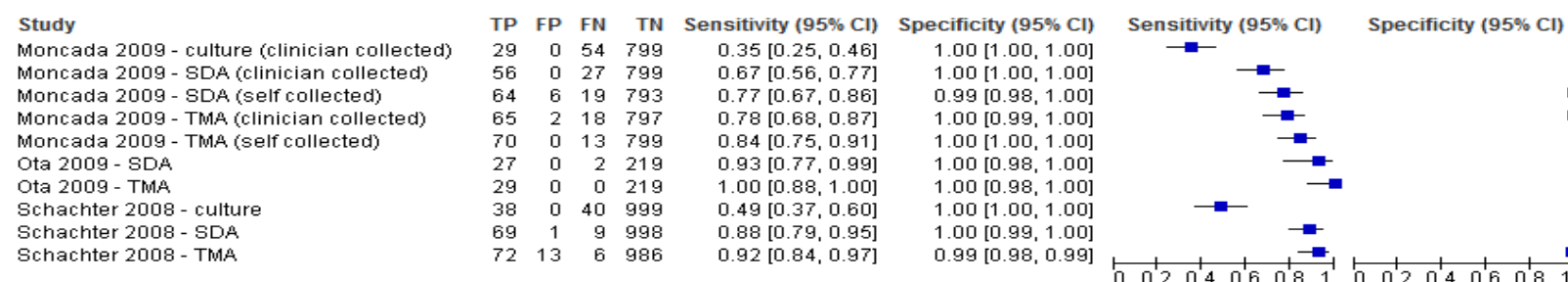


Figure 21 – Men: NAATs and culture tests using rectal samples for detecting *C. trachomatis*

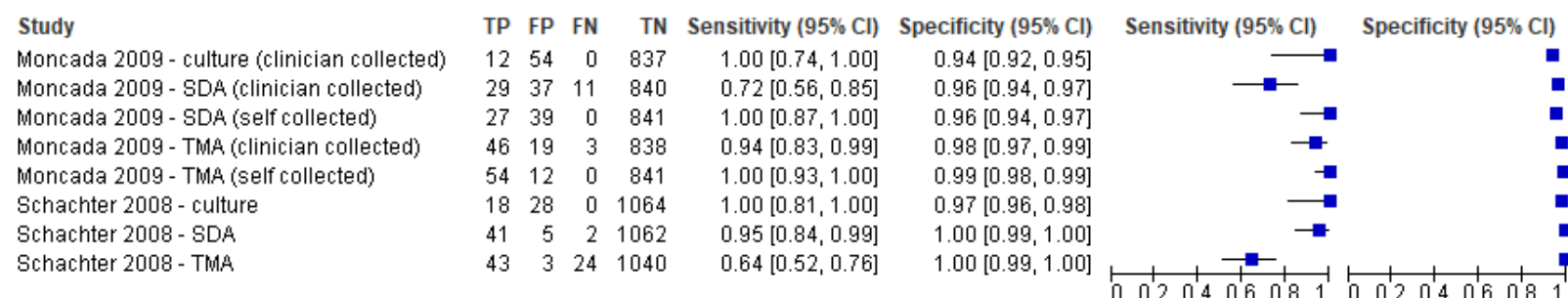
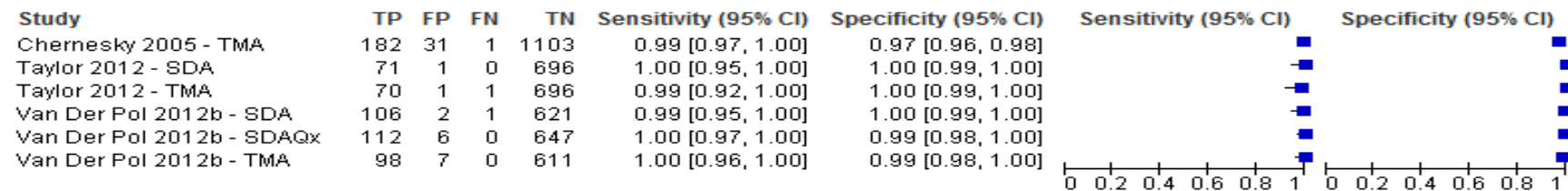


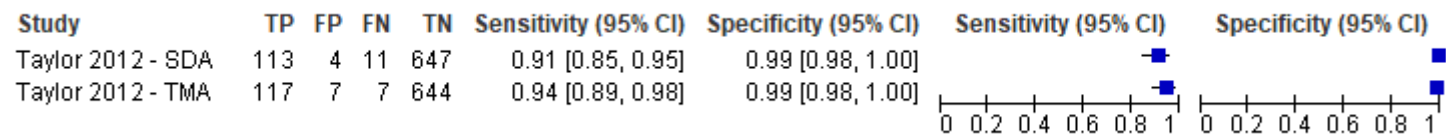


Figure 22 – Men: NAATs using urethral samples for detecting *N. gonorrhoea*



Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

Figure 23 – Men: NAATs using urethral samples for detecting *C. trachomatis*



Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

Figure 24 – Men: NAATs using pharynx samples for detecting *N. gonorrhoea*

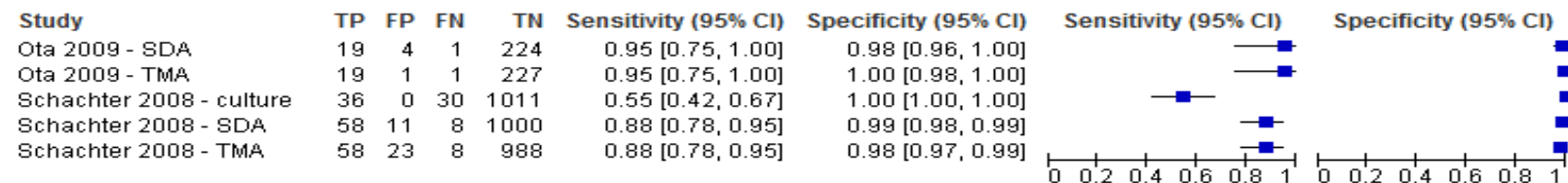
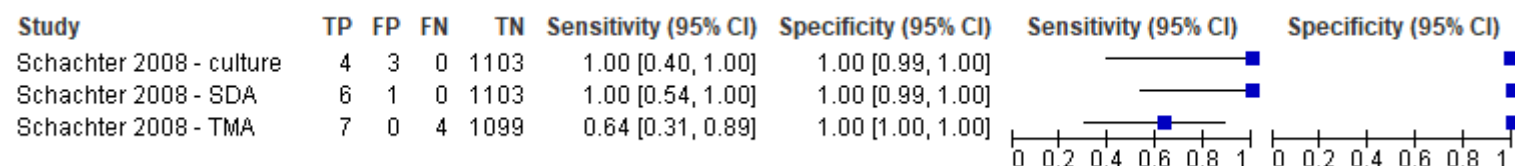
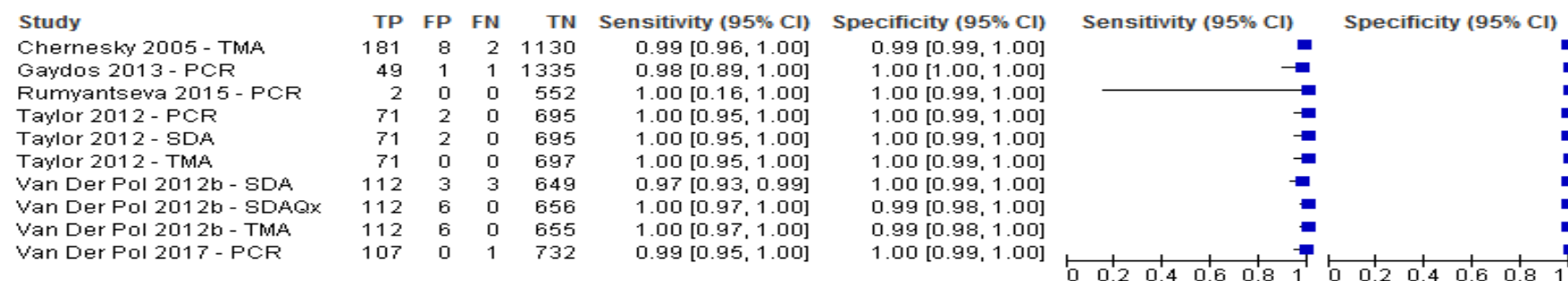
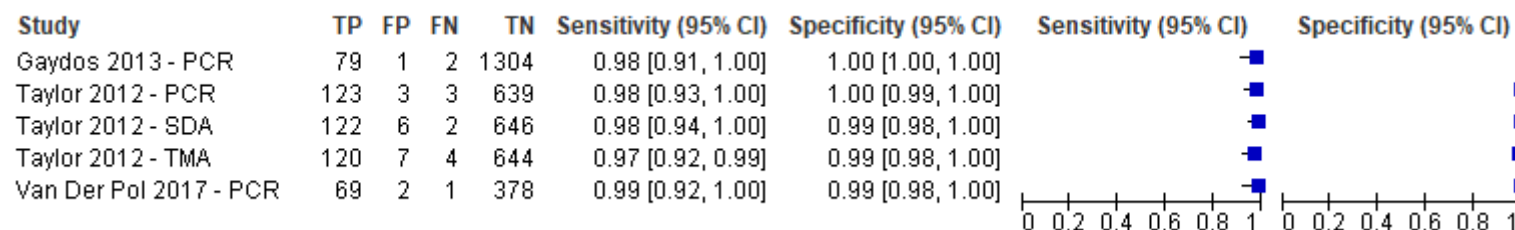


Figure 25 – Men: NAATs using pharynx samples for detecting *C. trachomatis*Figure 26 – Men: NAATs using first catch urine samples for detecting *N. Gonorrhoea*

Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

Figure 27 – Men: NAATs using first catch urine samples for detecting *C. trachomatis*



Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

Figure 28 – Men and women: NAATs and culture tests using rectal samples for detecting *N. gonorrhoea*

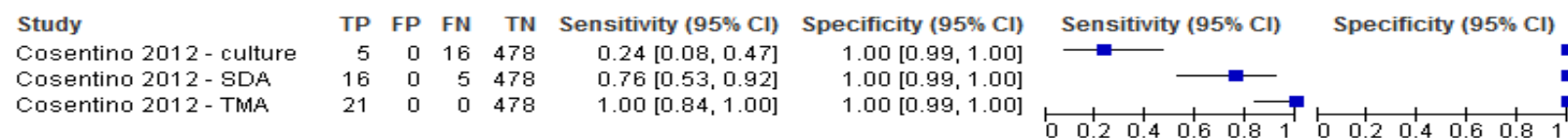


Figure 29 – Men and women: NAATs and culture tests using rectal samples for detecting *C. trachomatis*

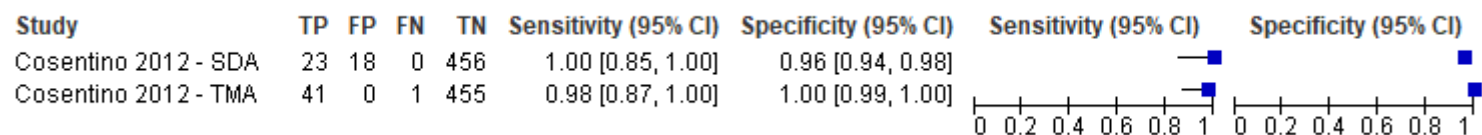


Figure 30 – Women: NAAT using vulvovaginal samples (self-taken) for detecting *N. gonorrhoea*

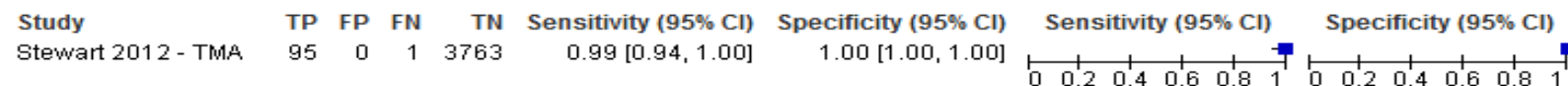
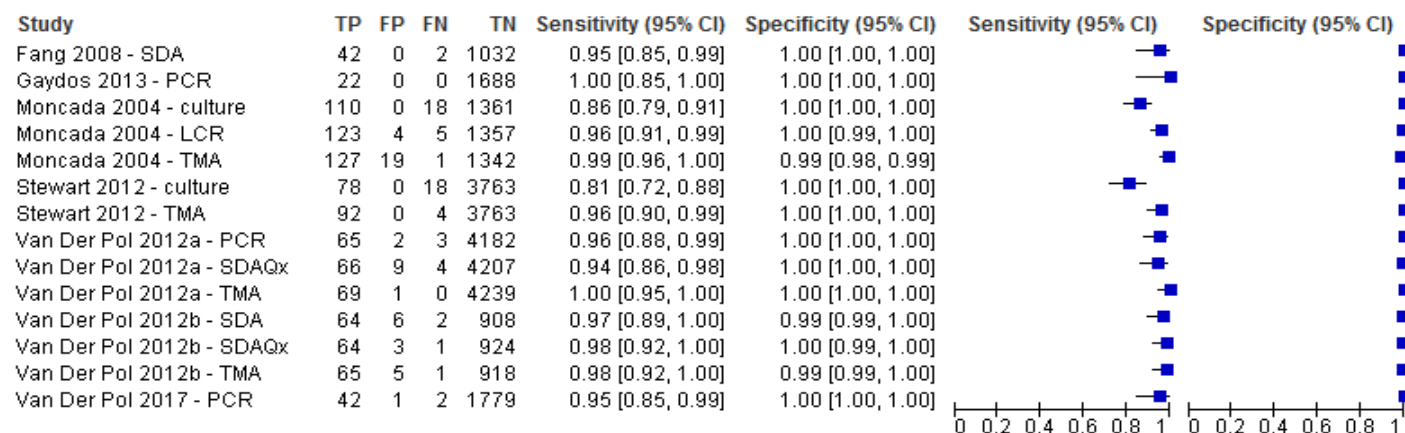


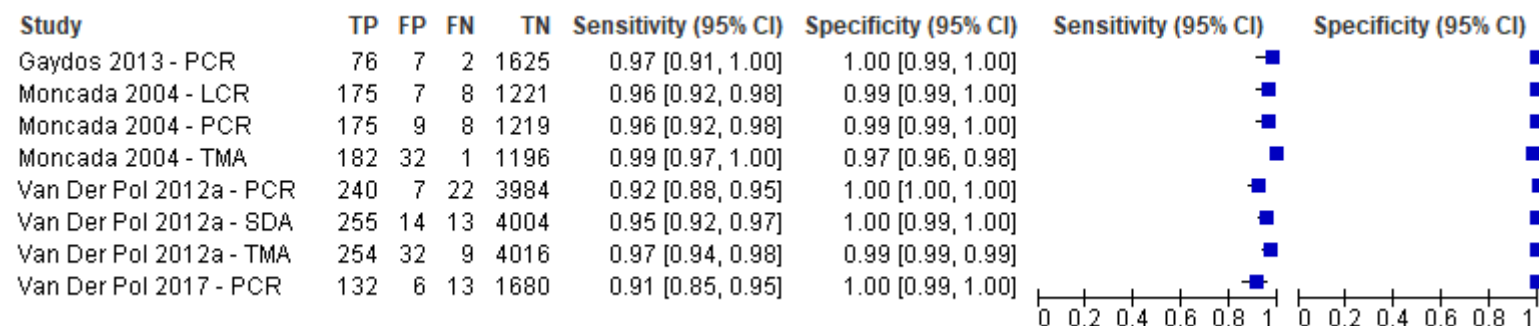


Figure 31 – Women: NAATs and culture using endocervical samples for detecting *N. gonorrhoea*

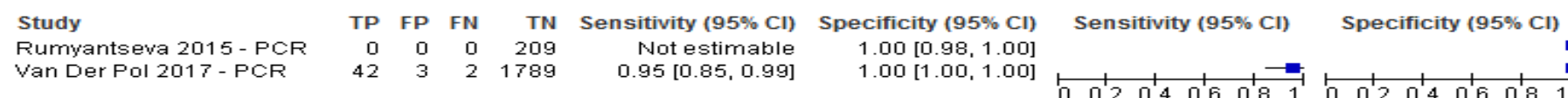


Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

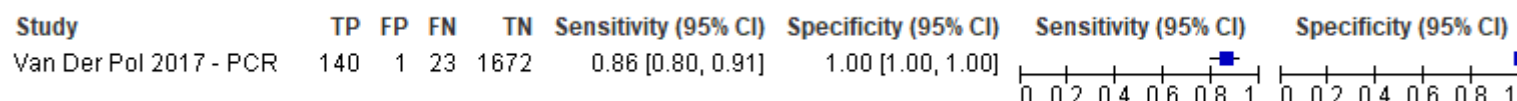
Figure 32 – Women: NAATs and culture using endocervical samples for detecting *C. trachomatis*



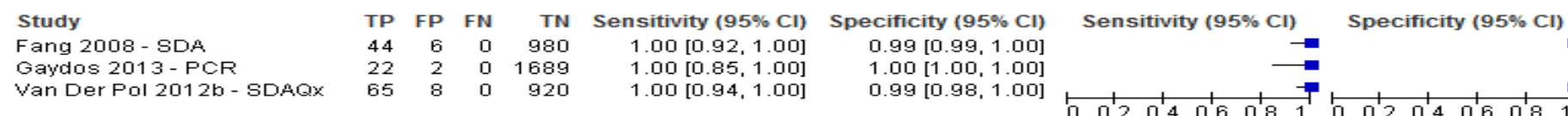
Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

**Figure 33 – Women: NAATs using vaginal samples (clinician collected) for detecting *N. gonorrhoea***

Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile. Schachter 2005 did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

Figure 34 – Women: NAATs using vaginal samples for detecting *C. trachomatis*

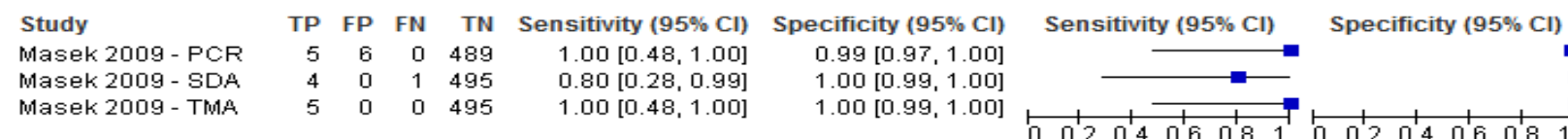
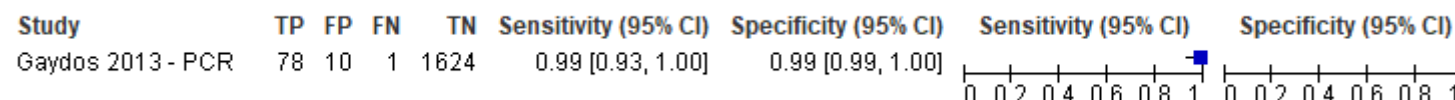
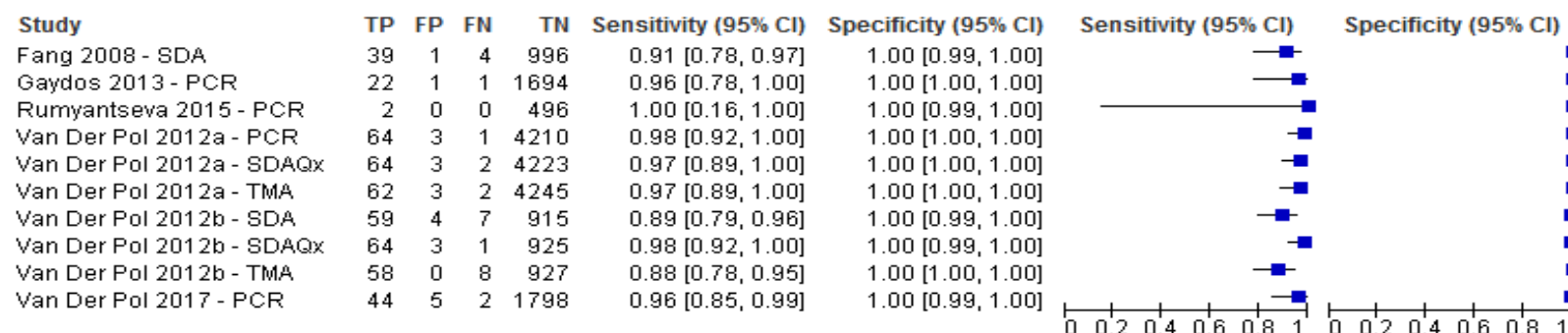
Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

Figure 35 – Women: NAATs using self-collected vaginal samples for detecting *N. gonorrhoea*

Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile. Schachter 2005 did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

Figure 36 – Women: NAATs using self-collected vaginal samples for detecting *C. trachomatis*

Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

Figure 37 – Women: NAATs using vaginal self-collected and posted samples for detecting *N. gonorrhoea*Figure 38 – Women: NAATs using vaginal self-collected and posted samples for detecting *C. trachomatis*Figure 39 – Women: NAATs using first catch urine samples for detecting *N. gonorrhoea*

Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.



Figure 40 – Women: NAATs using first catch urine samples for detecting *C. trachomatis*

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Gaydos 2013 - PCR	80	3	2	1633	0.98 [0.91, 1.00]	1.00 [0.99, 1.00]	■	■
Van Der Pol 2012a - PCR	251	10	21	3997	0.92 [0.88, 0.95]	1.00 [1.00, 1.00]	■	■
Van Der Pol 2012a - SDA	253	9	14	4015	0.95 [0.91, 0.97]	1.00 [1.00, 1.00]	■	■
Van Der Pol 2012a - TMA	250	19	11	4029	0.96 [0.93, 0.98]	1.00 [0.99, 1.00]	■	■
Van Der Pol 2017 - PCR	130	12	8	1699	0.94 [0.89, 0.97]	0.99 [0.99, 1.00]	■	■



Note. Gaydos (2010) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

8.2. N. Gonorrhoea: treatment

8.2.1. Sexually active women and men including young people

8.2.1.1. Gentamicin + azithromycin vs gemifloxacin + azithromycin

Figure 41 – Number cured: Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people

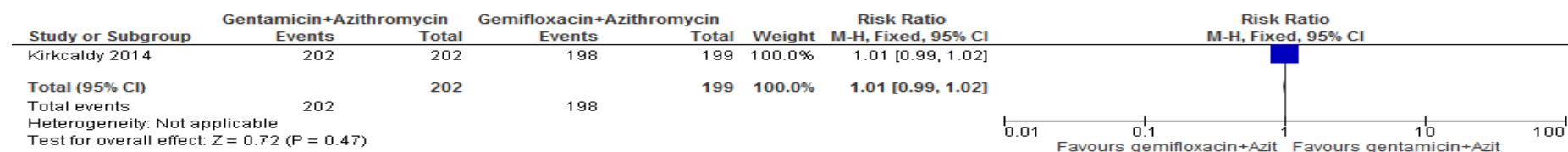


Figure 42 – Number cured (additional rectal infections): Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people

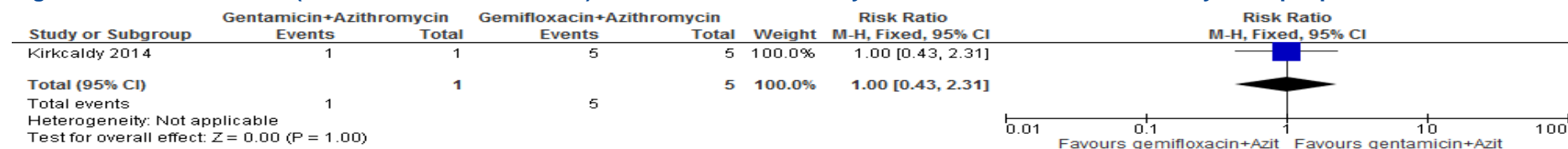




Figure 43 – Number cured (additional pharyngeal infections): Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people

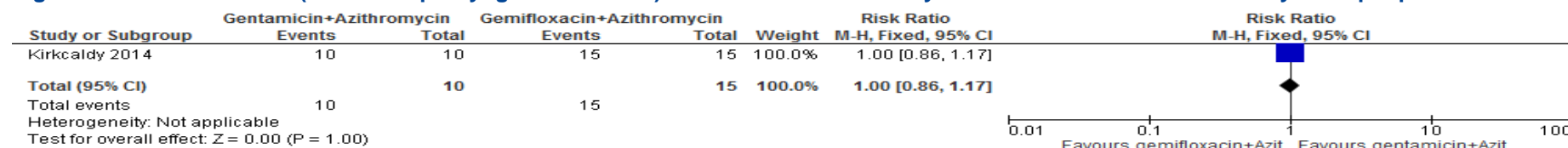


Figure 44 – Adverse event – Nausea: Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people with severe cephalosporin allergy

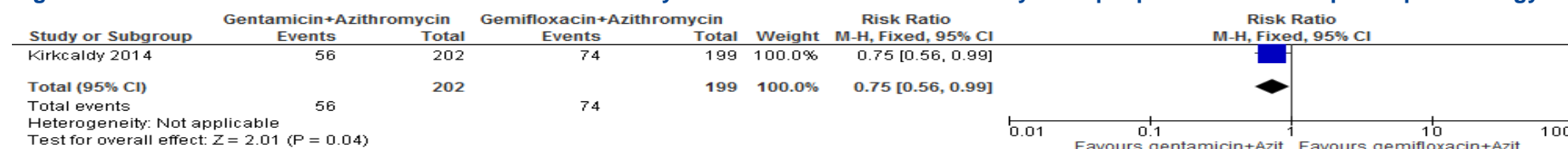


Figure 45 – Adverse event – Vomiting: Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people with severe cephalosporin allergy

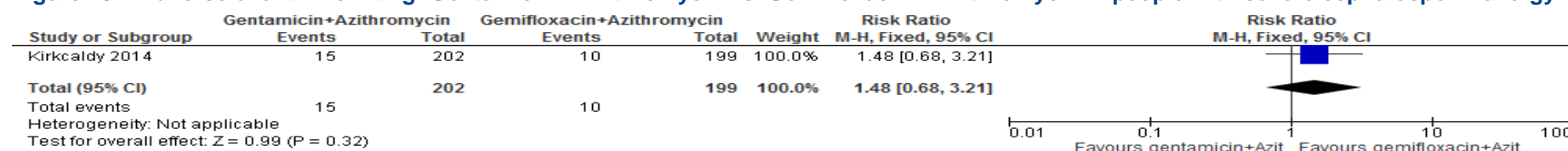
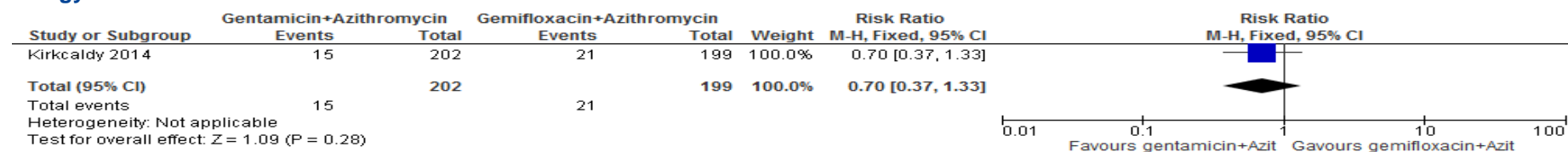


Figure 46 – Adverse event – Abdominal pain: Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people with severe cephalosporin allergy



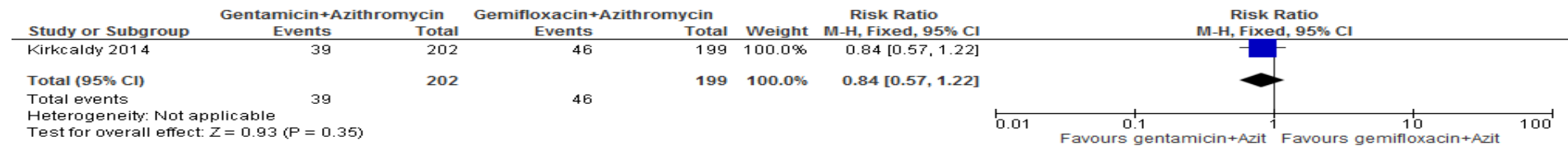
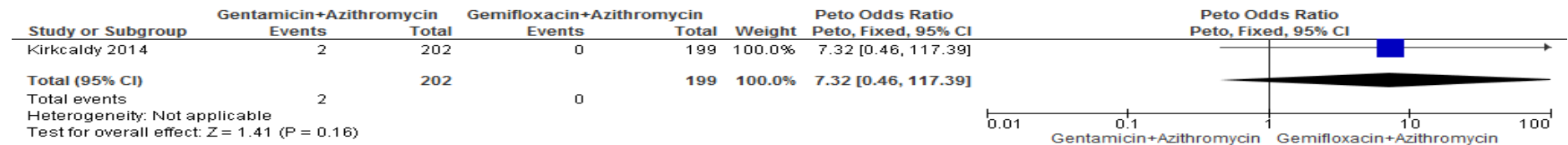
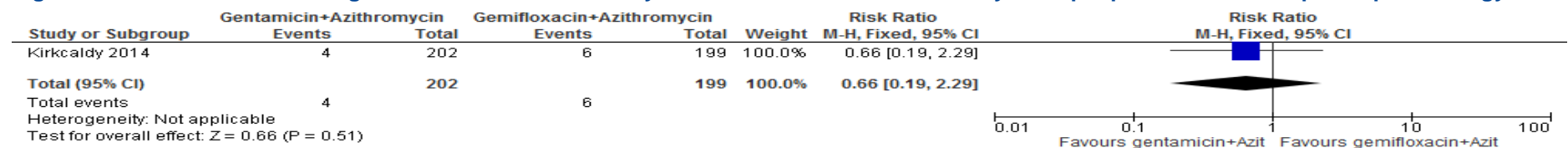
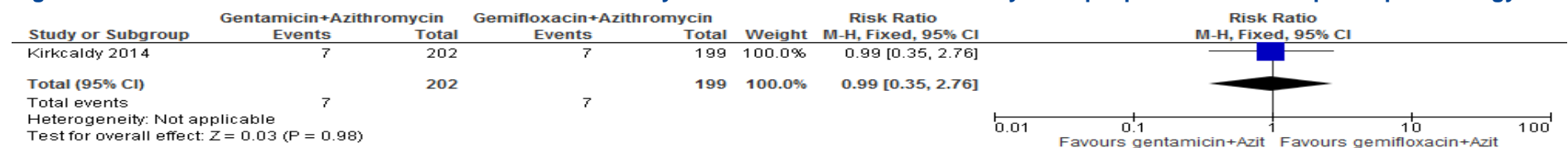
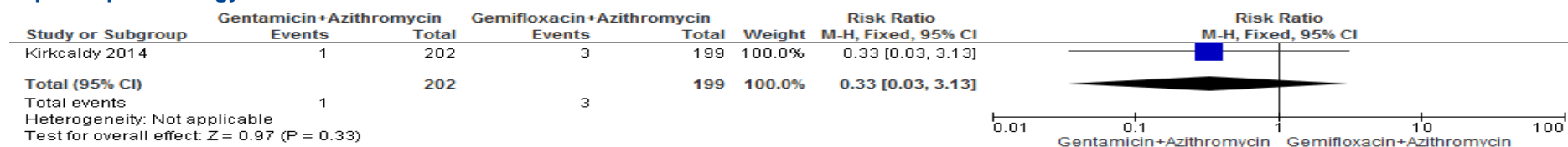
**Figure 47 – Adverse event – Diarrhoea: Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people with severe cephalosporin allergy****Figure 48 – Adverse event – Injection site pain: Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people with severe cephalosporin allergy****Figure 49 – Adverse event - Fatigue: Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people with severe cephalosporin allergy****Figure 50 – Adverse event - Dizziness: Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people with severe cephalosporin allergy**



Figure 51 – Adverse event – Tendon disorder/tendonitis: Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin in people with severe cephalosporin allergy



8.2.1.2. Ceftriaxone + azithromycin vs fosfomycin trometamol in men

Figure 52 – Number cured: Ceftriaxone + azithromycin vs. fosfomycin trometamol in men

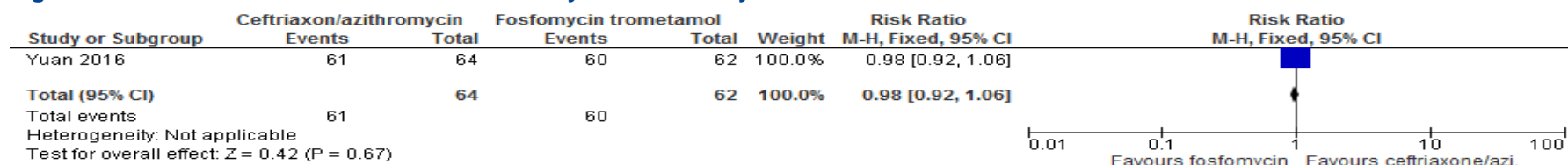


Figure 53 – Adverse event: Nausea - Ceftriaxone + azithromycin vs. fosfomycin trometamol in men

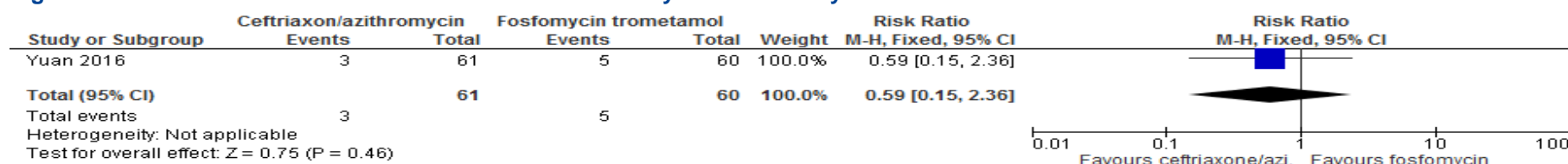


Figure 54 – Adverse event: Diarrhoea: Ceftriaxone + azithromycin vs. fosfomycin trometamol in men

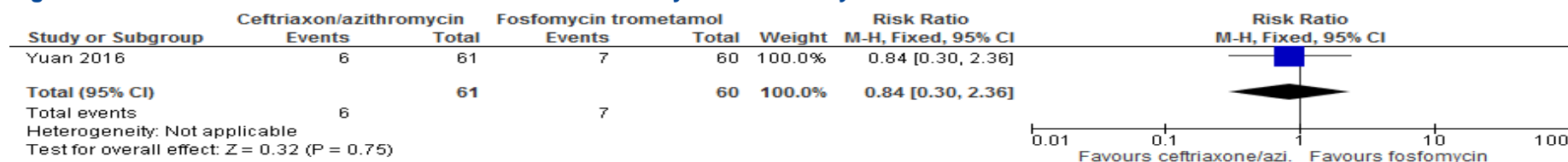




Figure 55 – Adverse event: Abdominal pain or discomfort: Ceftriaxone + azithromycin vs. fosfomycin trometamol in men

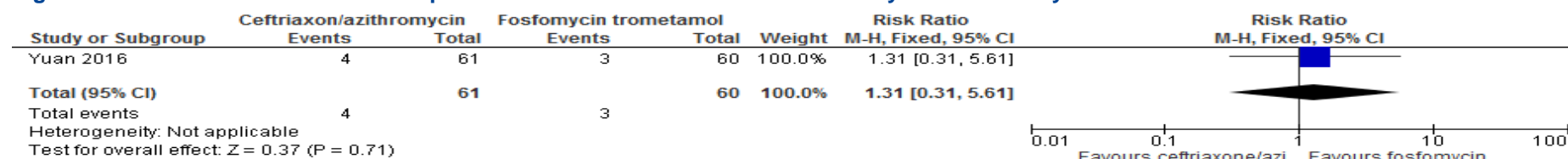


Figure 56 – Adverse event: Fatigue: Ceftriaxone + azithromycin vs. fosfomycin trometamol in men

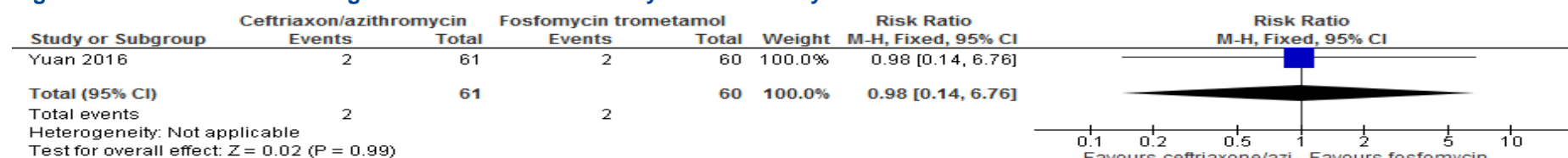
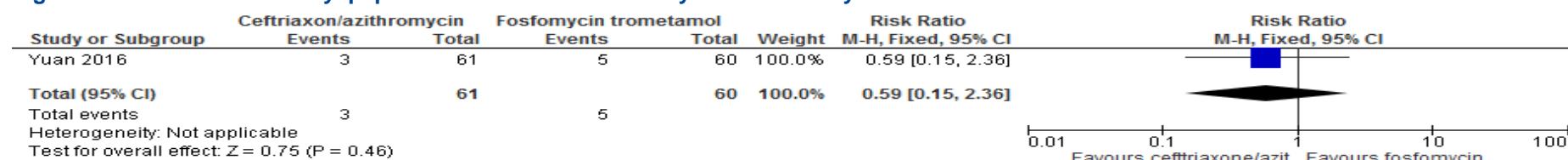
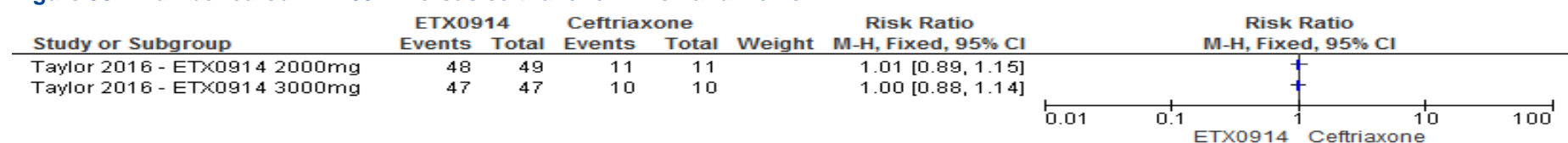


Figure 57 – Adverse event: Dyspepsia: Ceftriaxone + azithromycin vs. fosfomycin trometamol in men



8.2.1.3. ETX0914 2000mg versus ceftriaxone

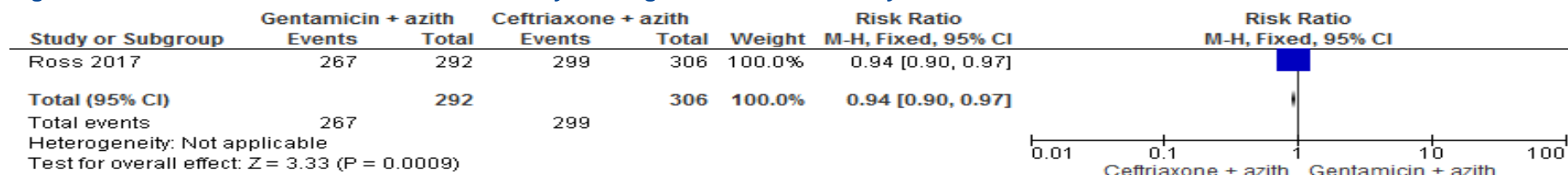
Figure 58 – Number cured: ETX0914 versus ceftriaxone in men and women





8.2.1.4. Ceftriaxone + azithromycin vs gentamicin + azithromycin

Figure 59 – Number cured: Ceftriaxone + azithromycin vs. gentamicin + azithromycin



8.2.2. Pregnant women

8.2.2.1. Ceftriaxone vs cefixime

Figure 60 – Number cured (overall): Ceftriaxone vs. Cefixime in pregnant women



Figure 61 – Number cured (cervix): Ceftriaxone vs. Cefixime in pregnant women





Figure 62 – Number cured (pharynx): Ceftriaxone vs. Cefixime in pregnant women



Figure 63 – Number cured (anus): Ceftriaxone vs. Cefixime in pregnant women

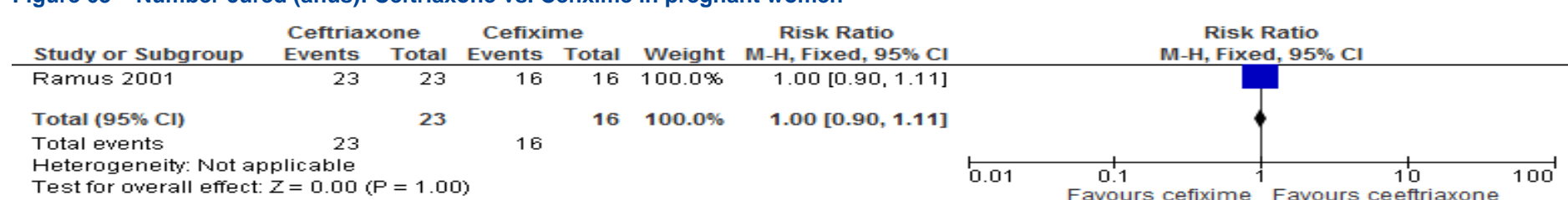
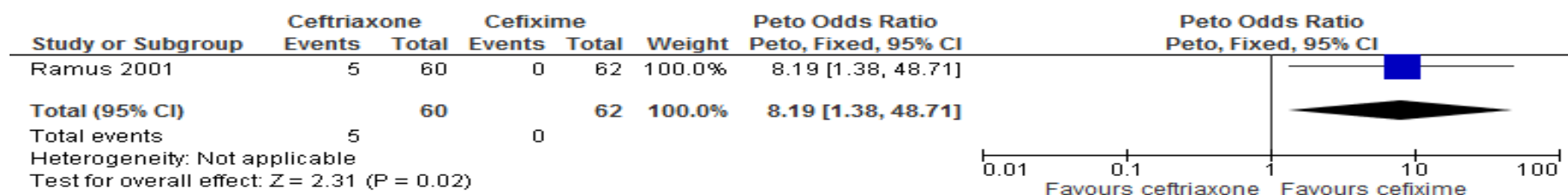


Figure 64 – Babies minor abnormalities: Ceftriaxone vs. Cefixime in pregnant women





Figure 65 – Hyperbilirubinemia in infants: Ceftriaxone vs. Cefixime in pregnant women



8.2.2.2. Ceftriaxone vs spectinomycin

Figure 66 – Number cured: Ceftriaxone vs. Spectinomycin in pregnant women

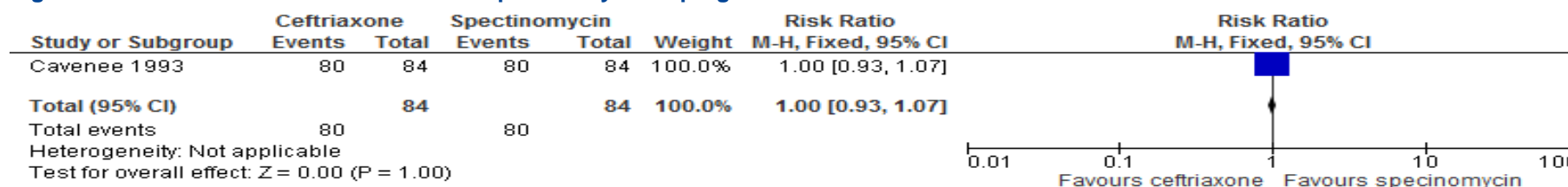


Figure 67 – Minor malformations: Ceftriaxone vs. Spectinomycin in pregnant women

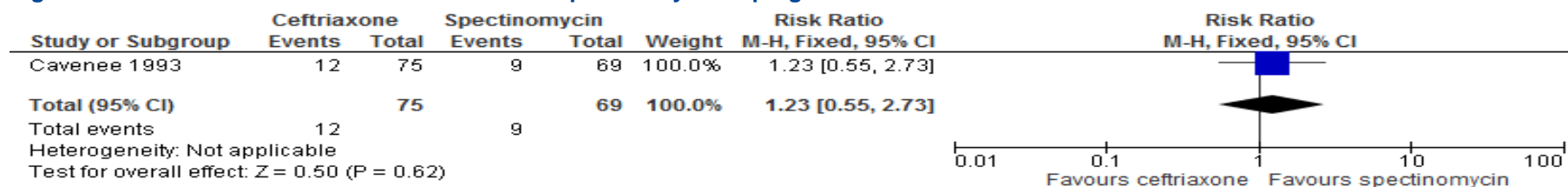




Figure 68 – Major malformations: Ceftriaxone vs. Spectinomycin in pregnant women

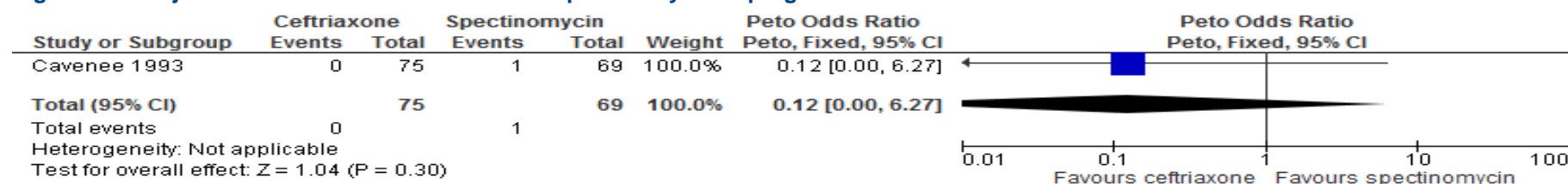


Figure 69 – Number cured (cervix): Ceftriaxone vs. Spectinomycin in pregnant women



Figure 70 – Number cured - pharynx: Ceftriaxone vs. Spectinomycin in pregnant women

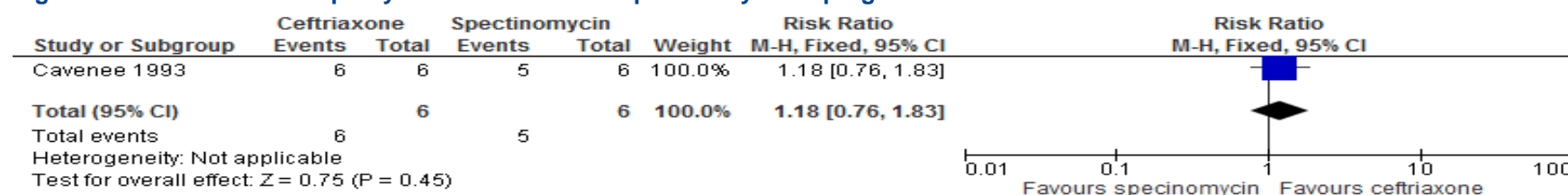
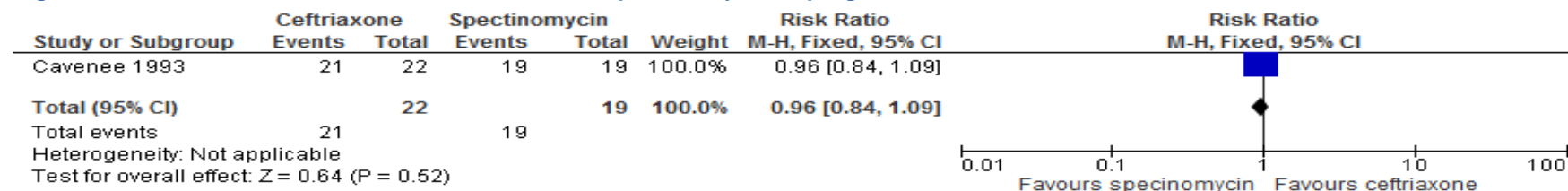




Figure 71 – Number cured - rectum: Ceftriaxone vs. Spectinomycin in pregnant women



8.2.3. People with severe cephalosporin allergy

No evidence identified.

8.3. Syphilis: diagnosis

Figure 72 – Women and men: TpPCR vs. serology for detecting syphilis

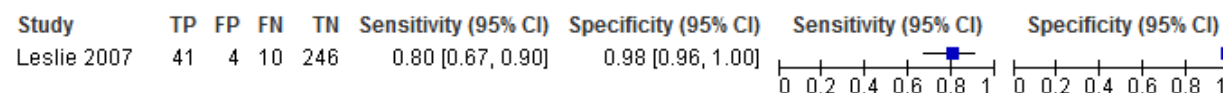


Figure 73 – Women and men: EIA IgG vs. serology for detecting syphilis

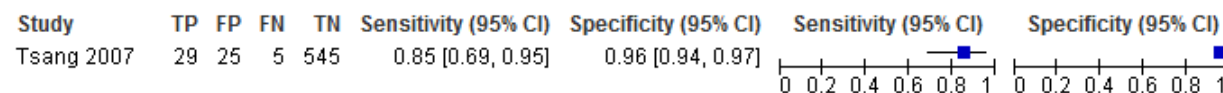
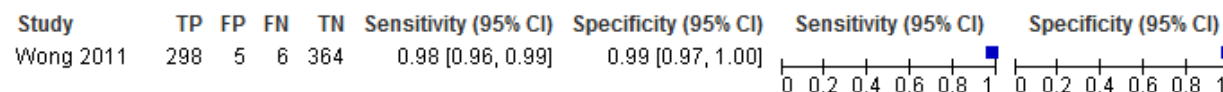
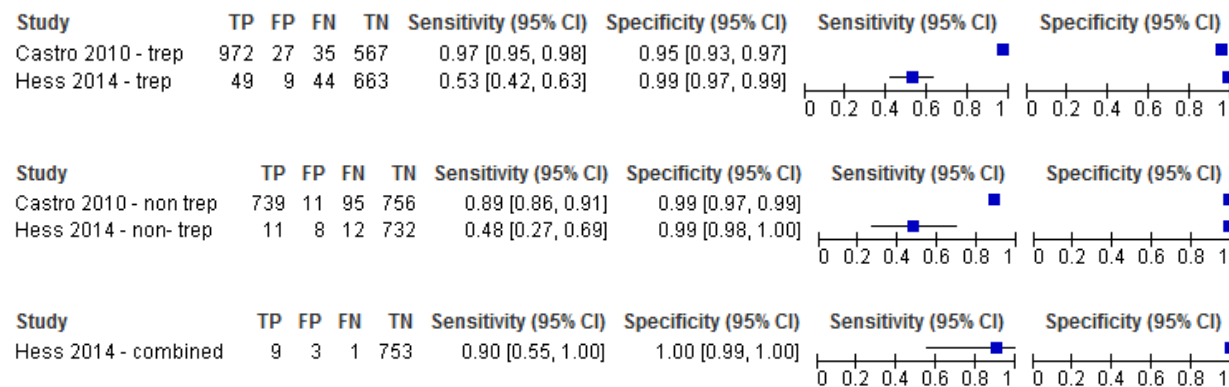
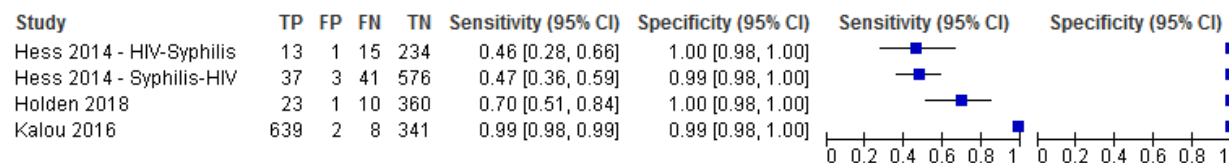
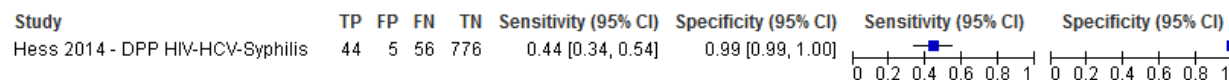


Figure 74 – Women and men: EIA IgM/IgG vs. serology for detecting syphilis



**Figure 75 – Women and men: Chembio DPP syp (non trep + trep) vs. serology for detecting syphilis**

Note: Hess (2014) combined reports the treponemal and non treponemal compared to a reference standard of TPPA + RPR $\geq 1:8$

Figure 76 – Women and men: HIV-syp (trep) vs serology for detecting syphilis**Figure 77 – Women and men: HIV-HCV-syphilis vs serology for detecting syphilis****Figure 78 – Men: Chembio DPP syp (non trep + trep) vs serology for detecting syphilis**

Note. Zorzi (2017) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.

Figure 79 – Men: SD syphilis 3.0 assay vs serology for detecting syphilis

Note. Zorzi (2017) did not report crude data (TP, FP, TN, FN); no forest plot could be displayed for this study. Results were however reported in the GRADE profile.



8.4. Syphilis: treatment

8.4.1. Treatment of syphilis in women and men including young people

8.4.1.1. Azithromycin vs BPG

Randomised controlled trials

Figure 80 – Serological response – 4 fold decrease in RPR titer at 3 months

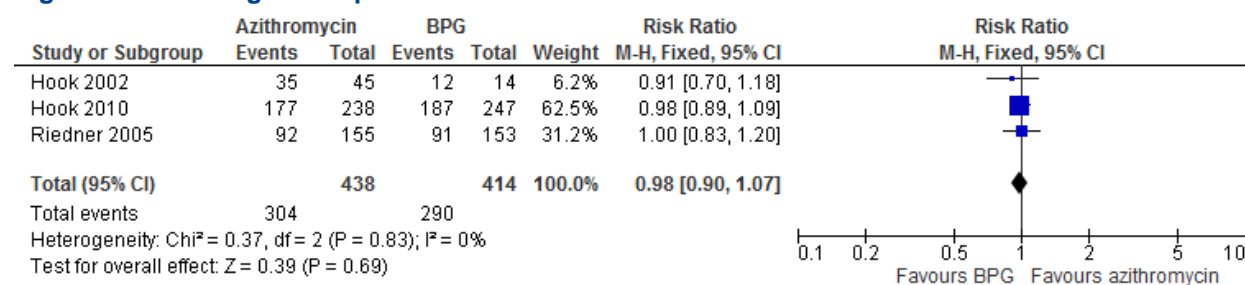


Figure 81 – Serological response – 4 fold decrease in RPR titer at 6 months



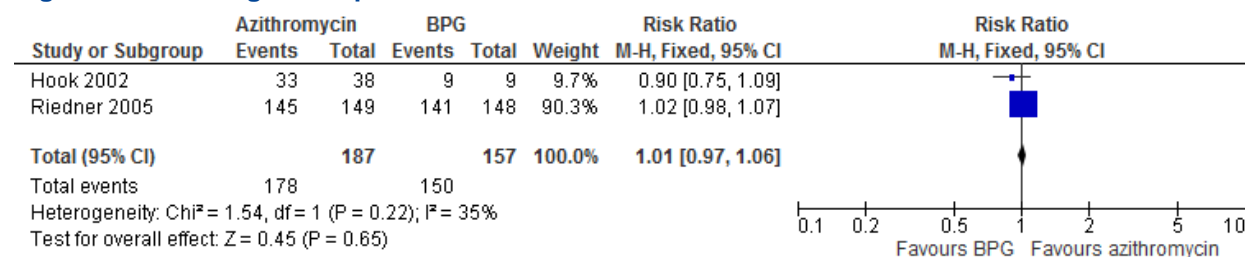
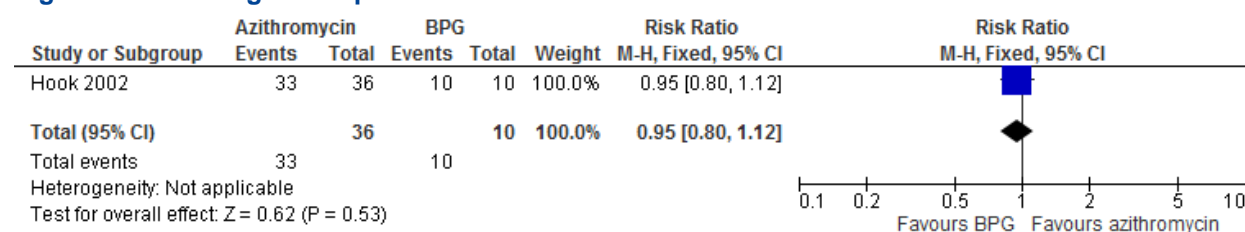
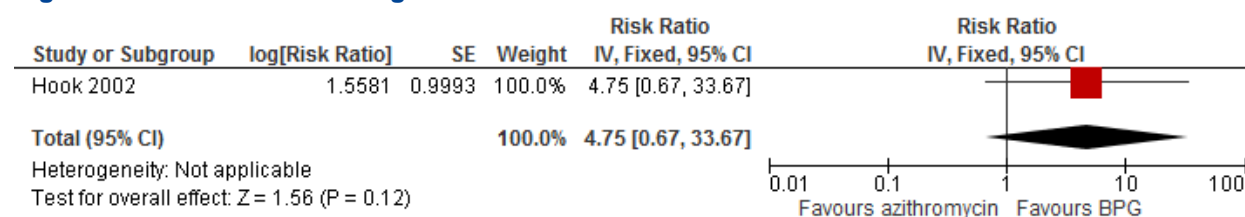

Figure 82 – Serological response – 4 fold decrease in RPR titer at 9 months

Figure 83 – Serological response – 4 fold decrease in RPR titer at 12 months

Figure 84 – Adverse events – general GI effects




Figure 85 – Adverse events – gastrointestinal events

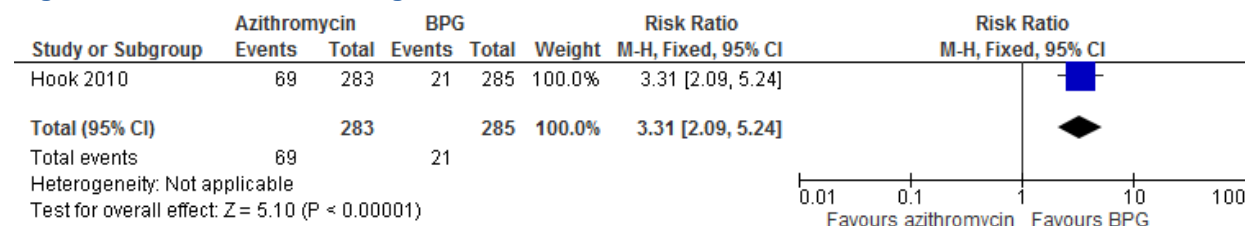


Figure 86 – Adverse events – nausea

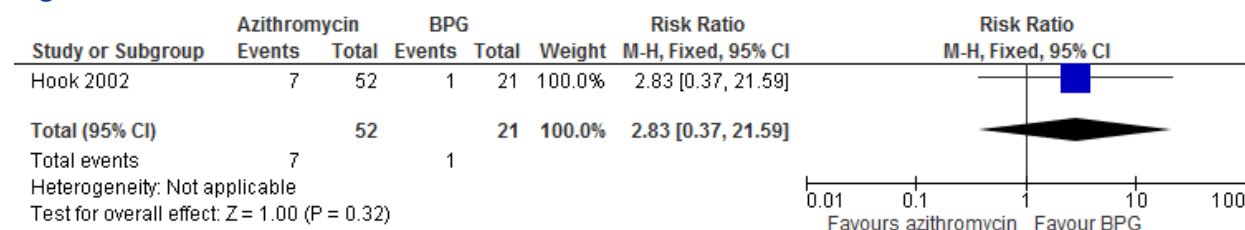


Figure 87 – Adverse events – diarrhoea

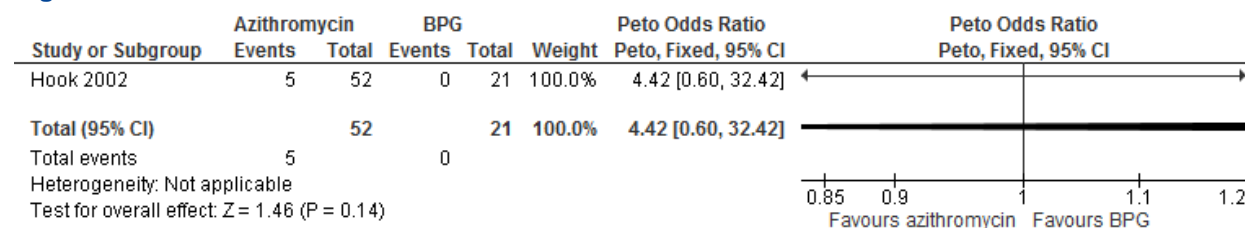
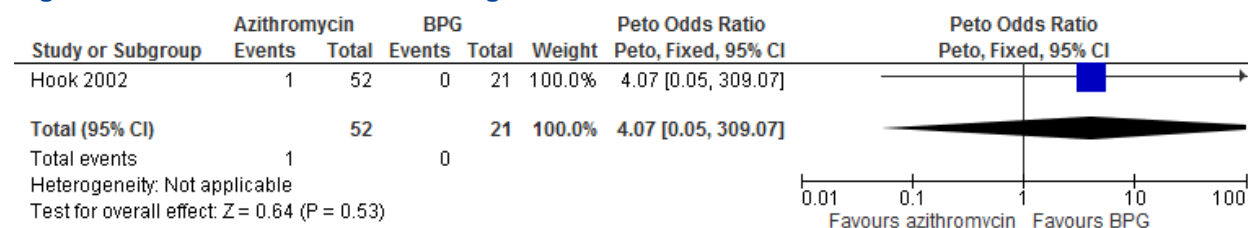
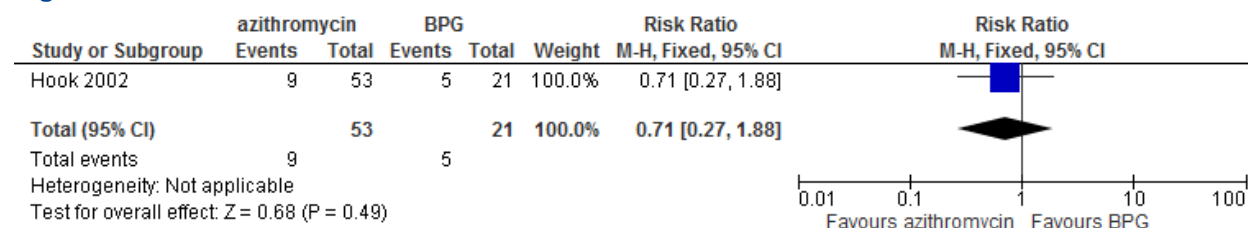
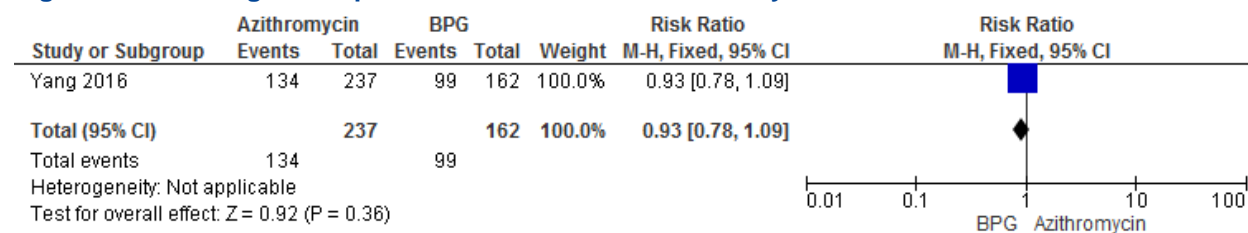


Figure 88 – Adverse events – vomiting

Figure 89 – Adverse events – Jarisch-Herxheimer


Observational trials

Figure 90 – Serological response – decline of an RPR titer by 4 fold from baseline at 12 months




8.4.1.2. Azithromycin 2g vs azithromycin 4g

Randomised controlled trials

Figure 91 – Serological response – 4 fold decrease in RPR titer at 3 months

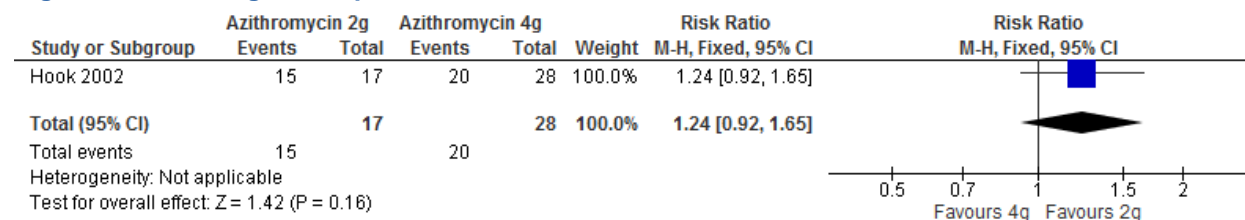


Figure 92 – Serological response – 4 fold decrease in RPR titer at 6 months

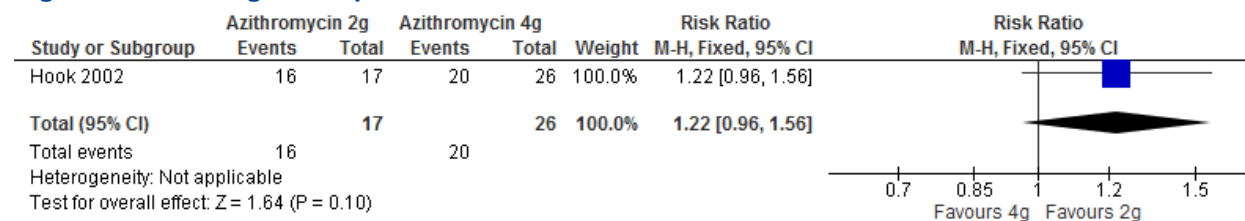


Figure 93 – Serological response – 4 fold decrease in RPR titer at 9 months

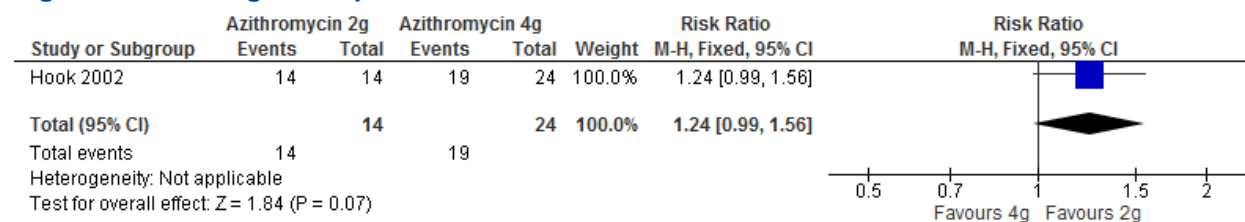
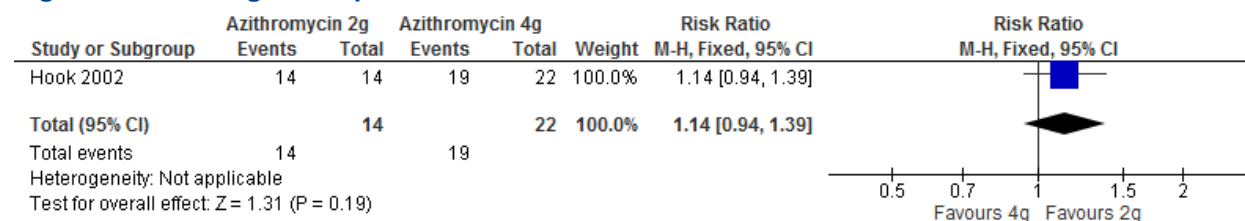




Figure 94 – Serological response – 4 fold decrease in RPR titer at 12 months



8.4.1.3. BPG and ceftriaxone/doxycycline vs BPG

Randomised controlled trials

Figure 95 – Serological response – 3 to 4 fold decrease in VDRL titer at 3 months

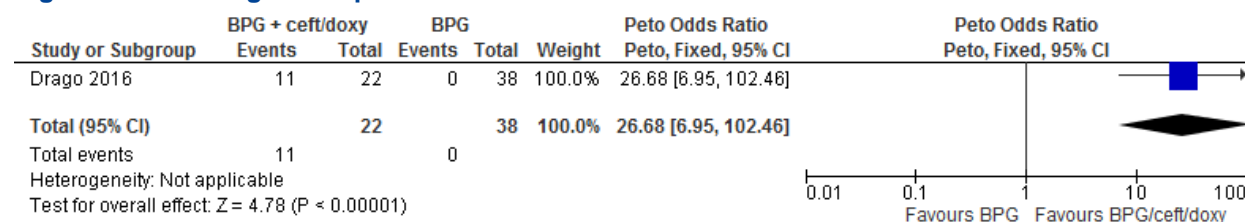
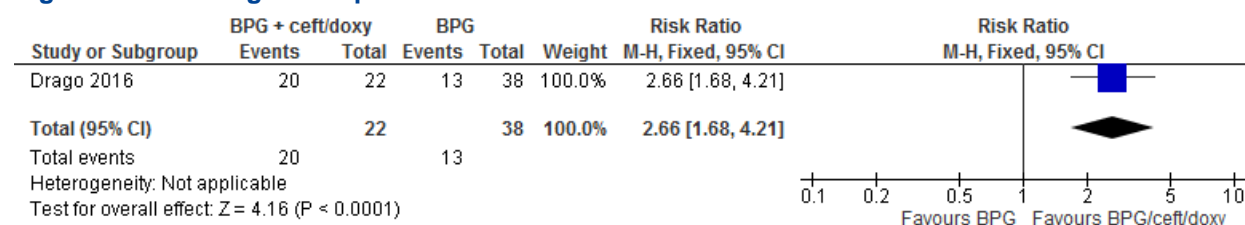
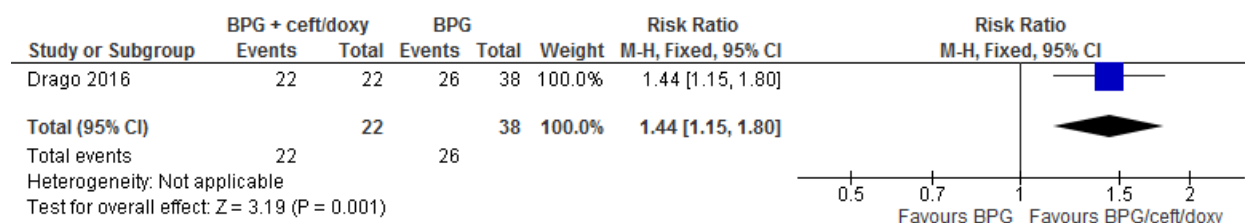
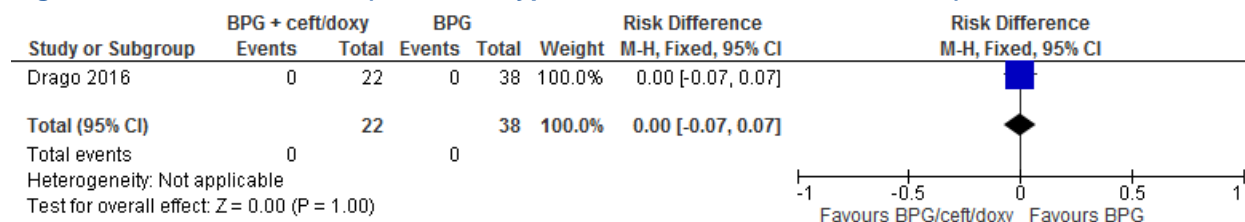


Figure 96 – Serological response – 3 to 4 fold decrease in VDRL titer



**Figure 97 – Serological response – 3 to 4 fold decrease in VDRL titer at 12 months****Figure 98 – Adverse events (related to syphilis but not Jarisch-Herxheimer)**

8.4.1.4. BPG (triple dose) vs BPG (single dose)

Randomised controlled trials

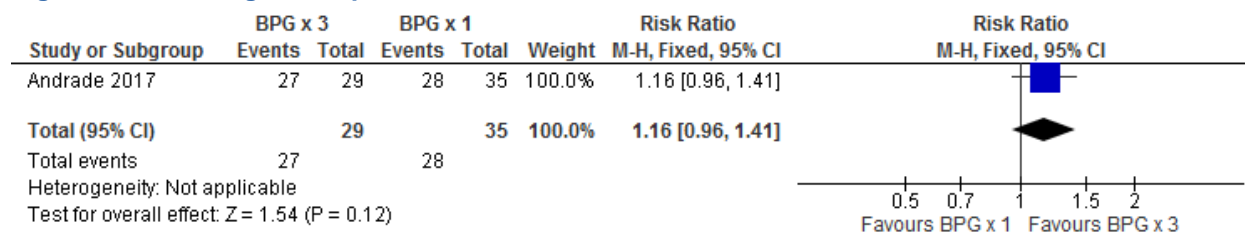
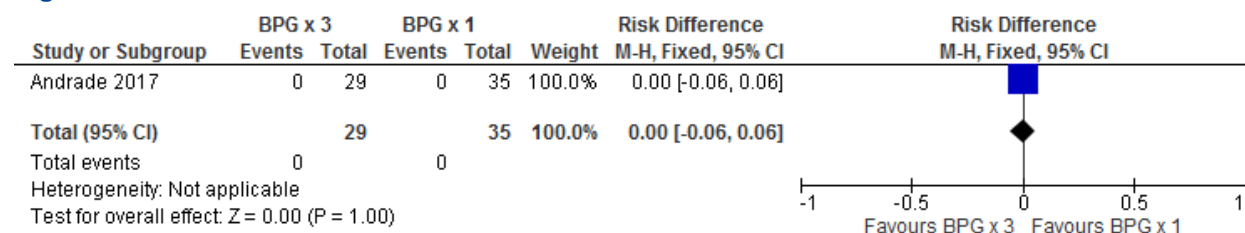
Figure 99 – Serological response – defined as treatment success – 4 fold decrease in initial RPR titer at 12 months


Figure 100 – Adverse events


8.4.1.5. BPG (triple dose) vs BPG (single dose)

Observational studies

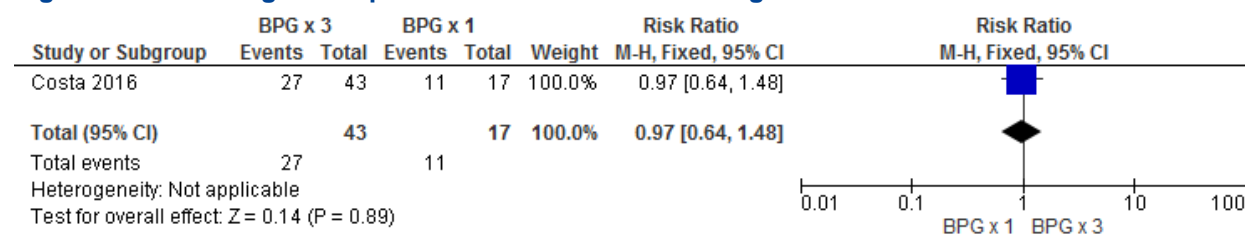
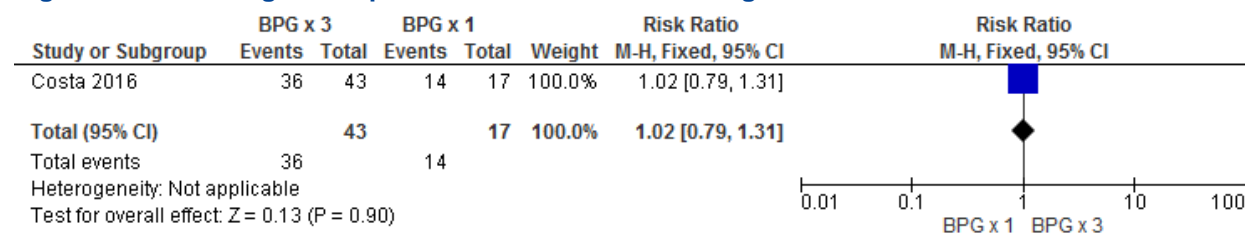
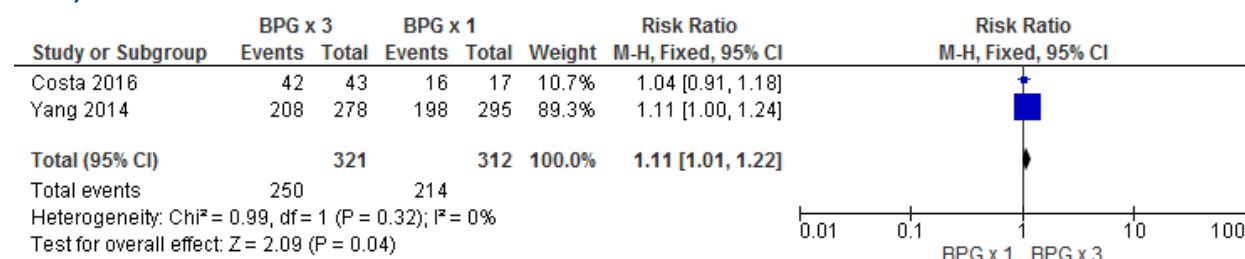
Figure 101 – Serological response at 3 months – 4-fold or greater decline in VDRL titer

Figure 102 – Serological response at 6 months – 4-fold or greater decline in VDRL titer




Figure 103 – Serological response at 12 months – 4-fold or greater decline in RPR titer (Yang 2014) or 4-fold or greater decline in VDRL titer (Costa 2016)



8.4.1.6. BPG and amoxicillin/probenecid vs PBG

Randomised controlled trials

Figure 104 – Treatment failure - < 4 fold decrease in RPR titer or test results non-reactive, at 3 months

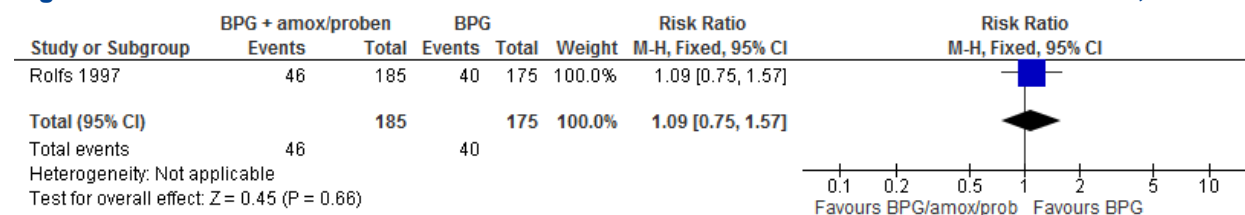


Figure 105 – Treatment failure - < 4 fold decrease in RPR titer or test results non-reactive, at 6 months





Figure 106 – Treatment failure - < 4 fold decrease in RPR titer or test results non-reactive, at 6 months (adjusted)

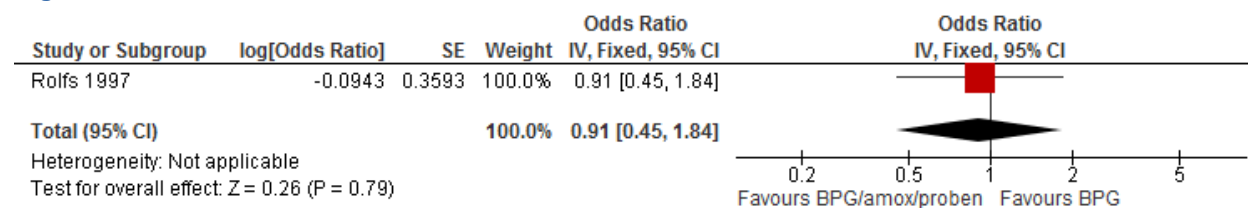
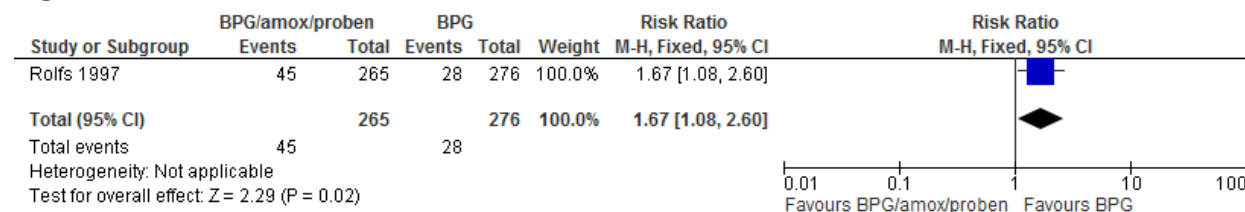


Figure 107 – Treatment failure - < 4 fold decrease in RPR titer or test results non-reactive, at 9 months



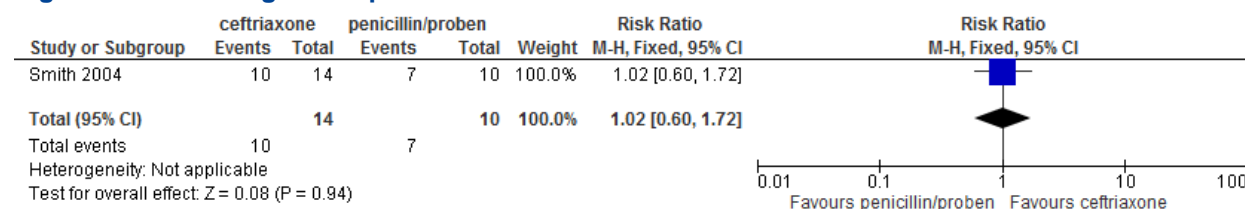
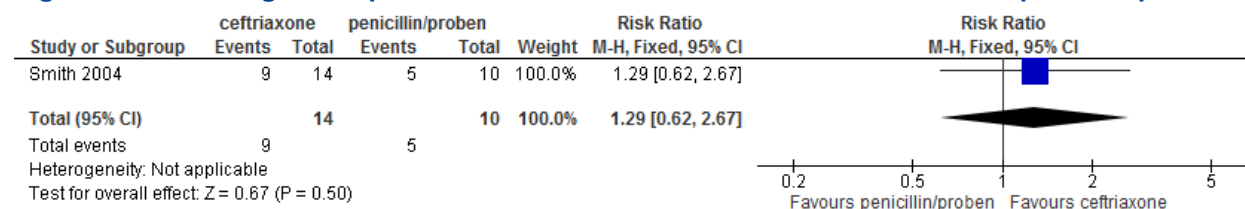
Figure 108 – Treatment failure - < 4 fold decrease in RPR titer or test results non-reactive, at 12 months

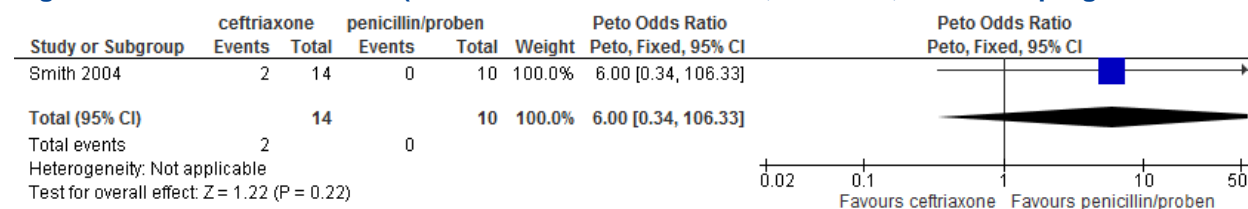
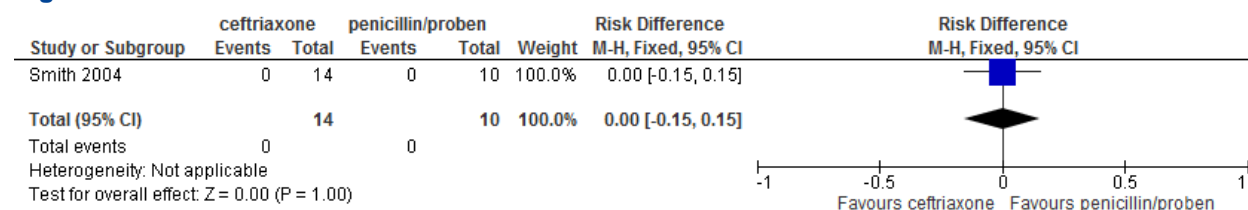


**Figure 109 – Adverse events – diarrhoea**

8.4.1.7. Ceftriaxone vs procaine penicillin/probenecid

Randomised controlled trials

Figure 110 – Serological response – 4 fold decrease in RPR titer**Figure 111 – Serological response – 4 fold decrease in RPR titer without subsequent relapse**

**Figure 112 – Treatment failure (>4 fold increase in RPR titer, titer 1:64, or clinical progression to disease)****Figure 113 – Adverse events**

8.4.1.8. Ceftriaxone vs BPG

Randomised controlled trials

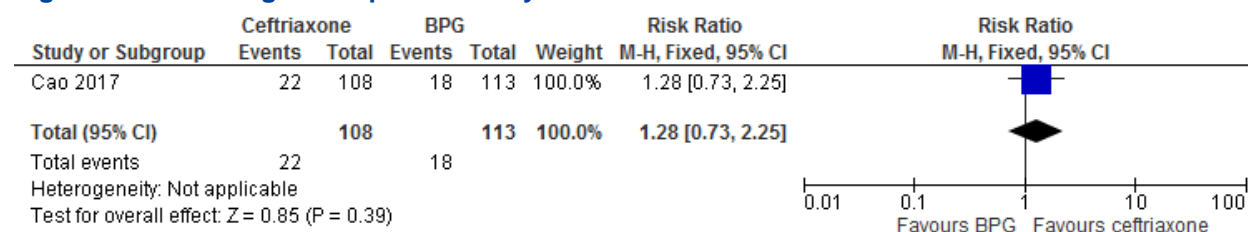
Figure 114 – Serological response 14 days– 4 fold decrease in RPR titer



Figure 115 – Serological response 3 months – 4 fold decrease in RPR titer

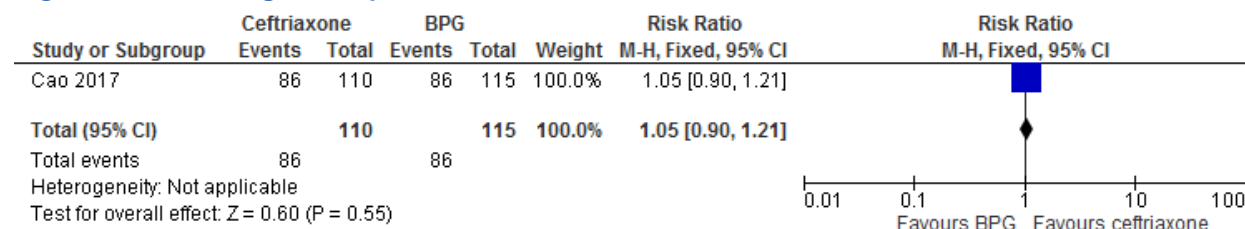


Figure 116 – Serological response 6 months – 4 fold decrease in RPR titer

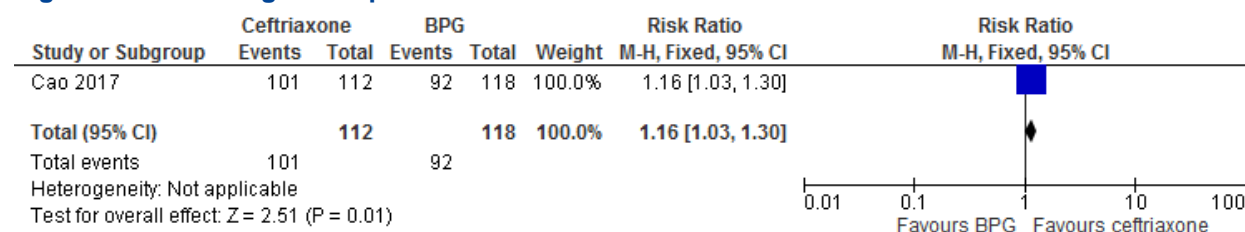


Figure 117 – Serological response 9 months – 4 fold decrease in RPR titer

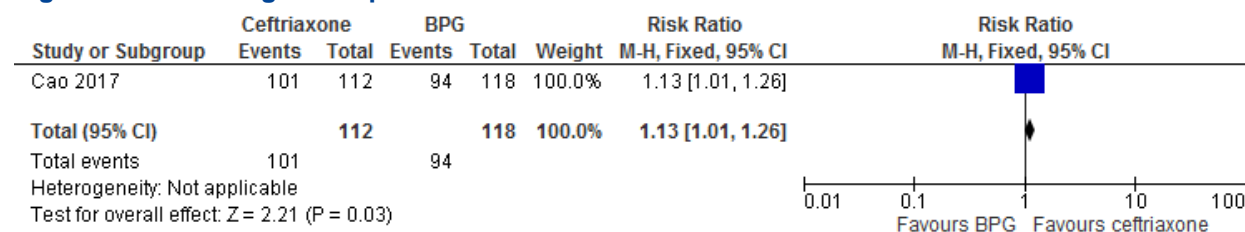




Figure 118 – Serological response 12 months– 4 fold decrease in RPR titer

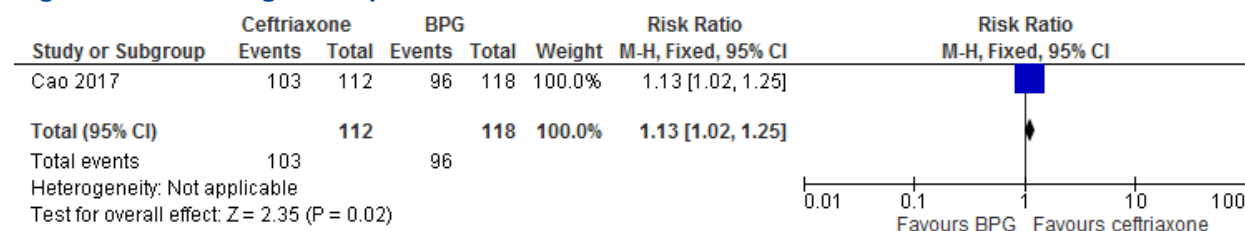


Figure 119 – Adverse events (serious adverse events or adverse events related to study drugs)

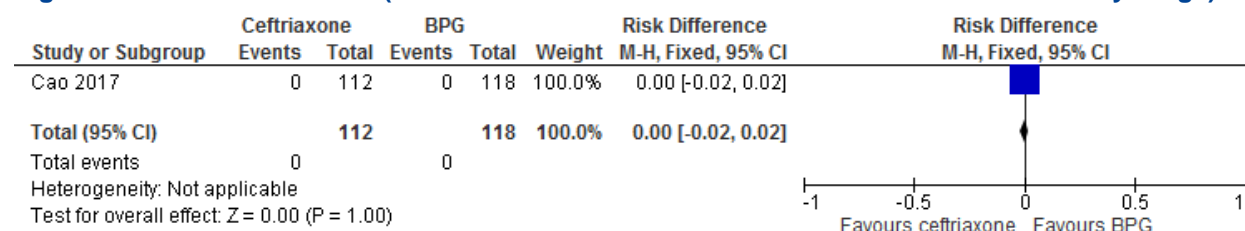


Figure 120 – Adverse events – probable Jarisch-Herxheimer

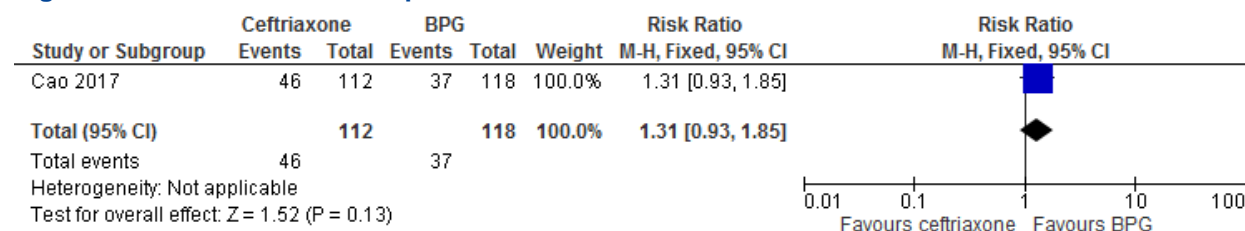




Figure 121 – Non cure – serofast at 12 months

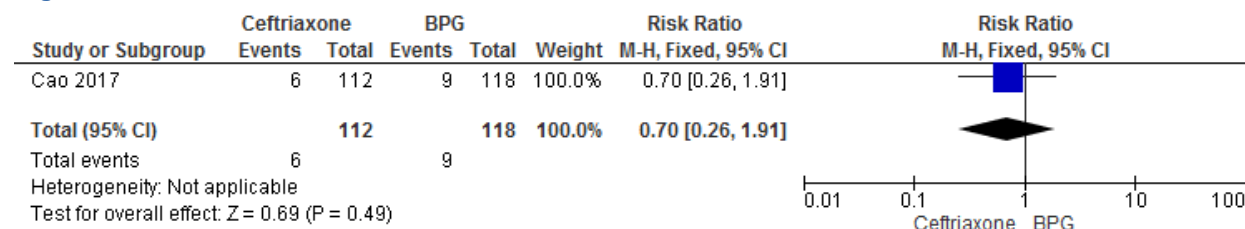
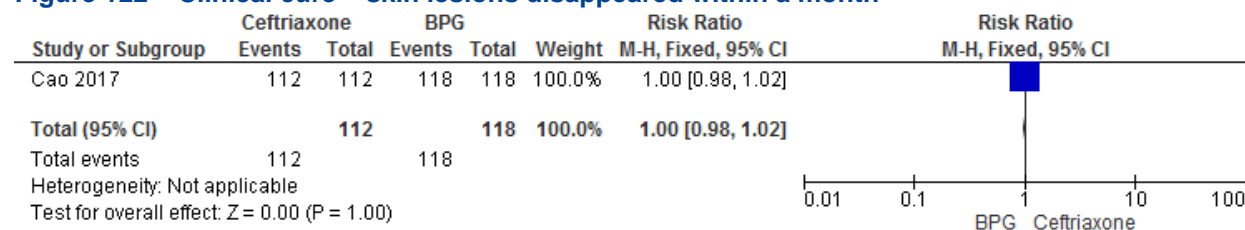


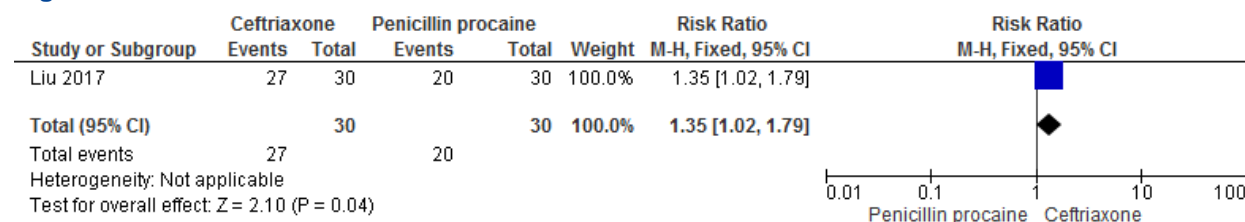
Figure 122 – Clinical cure – skin lesions disappeared within a month

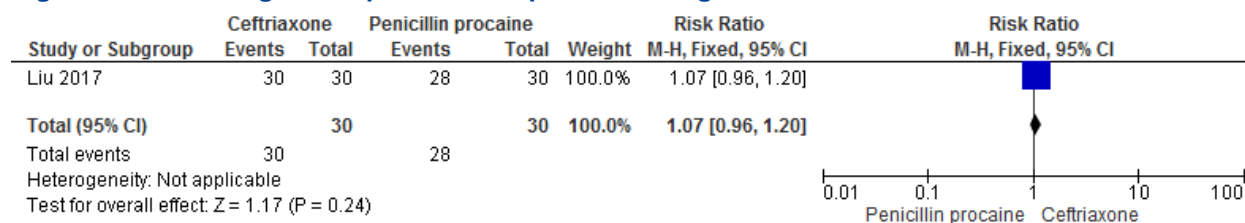
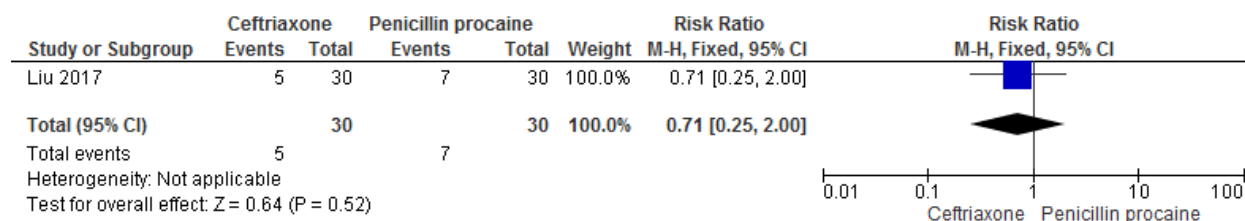


8.4.1.9. Ceftriaxone vs penicillin G procaine

Randomised controlled trials

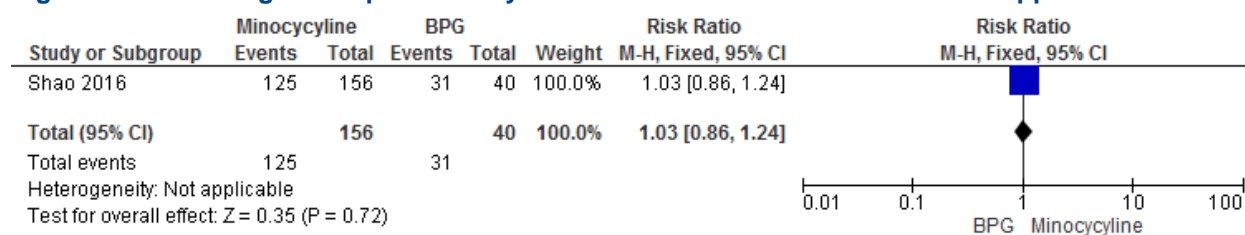
Figure 123 – Clinical cure – subsidence of skin lesions after one week



**Figure 124 – Serological response – comparison of negative conversion rate in toluidine red unheated serum test****Figure 125 – Non cure – incidence of seroresistance**

8.4.1.10.PBG vs minocycline (2 week and 4 week doses combined)

Observational trials

Figure 126 – Serological response at 2 years – RPR titers nonreactive after disappearance of clinical manifestations of syphilis



8.4.1.11. Minocycline 2 weeks vs minocycline extended 4 week dose

Observational trials

Figure 127 – Serological response at 1 year – RPR titers nonreactive after disappearance of clinical manifestations of syphilis

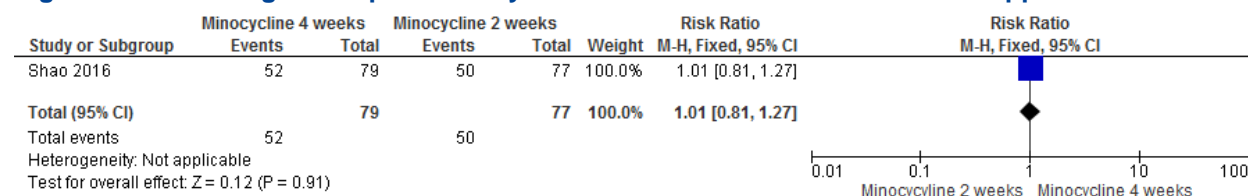
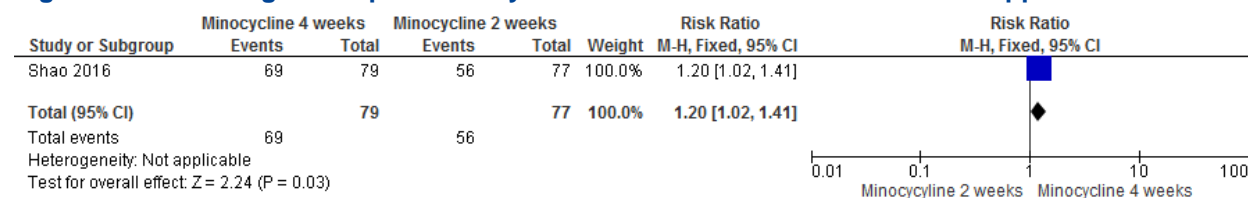


Figure 128 – Serological response at 2 year – RPR titers nonreactive after disappearance of clinical manifestations of syphilis



8.4.1.12. Doxycycline vs BPG

Observational trials

Figure 129 – Serological response at 3 months – 4-fold or greater decline in RPR titers

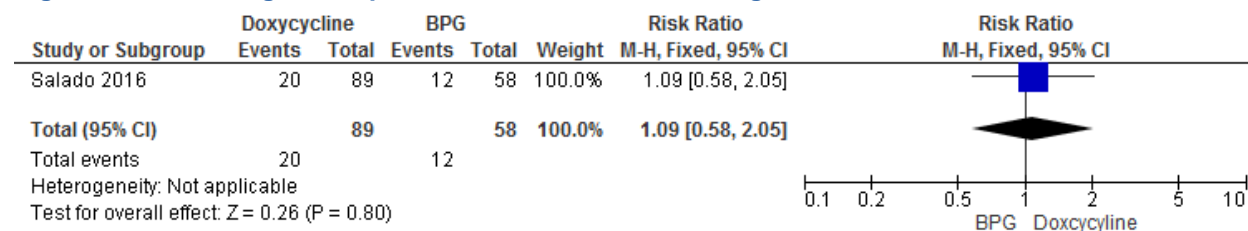
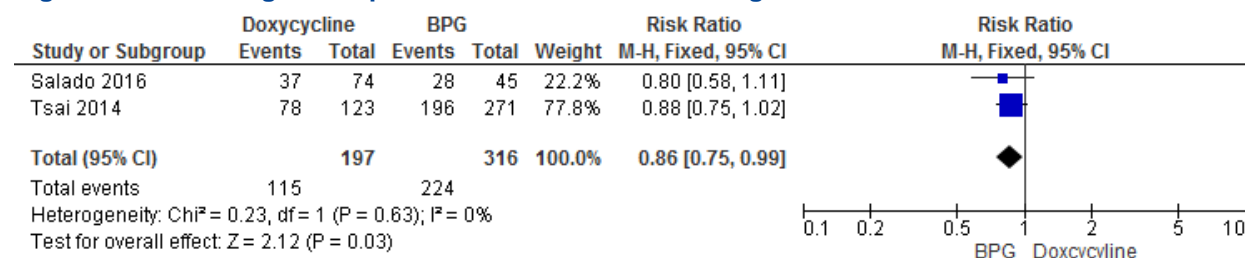
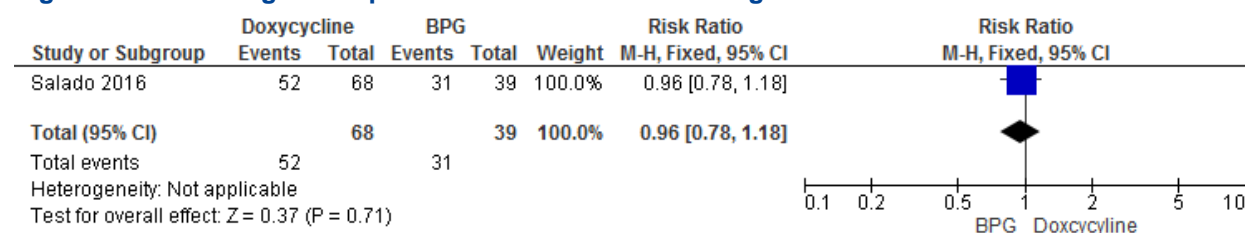
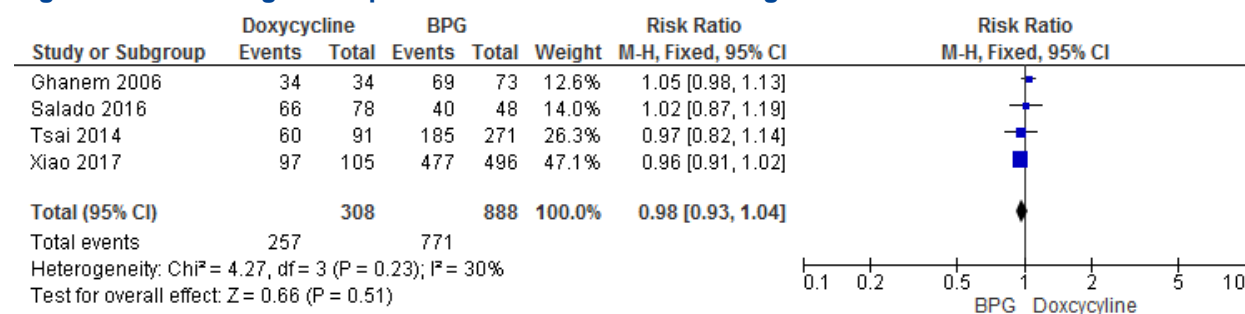



Figure 130 – Serological response at 6 months – 4-fold or greater decline in RPR titers

Figure 131 – Serological response at 9 months – 4-fold or greater decline in RPR titers

Figure 132 – Serological response at 12 months – 4-fold or greater decline in RPR titers


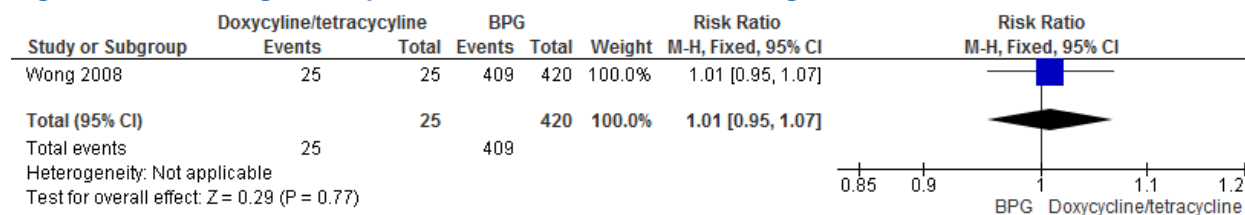
Note. Ghanem (2006) reported serological failure defined as a 4 fold rise in RPR titers 30-400 days after treatment or the lack of a 4-fold drop of RPR titers 270-400 days after treatment with no evidence of reinfection on basis of disease intervention specialist records. NGC have reversed this outcome for consistency in reported outcomes.



8.4.1.13. Doxycycline/tetracycline vs BPG

Observational trials

Figure 133 – Serological response at 6-24 months – 4-fold or greater decline in RPR titers



Note. Wong (2008) reported serological treatment success defined as a decrease in the baseline rapid plasma regain test titer since treatment initiation of at least 4-fold by 6 months, or at least an 8-fold decrease within 12 months or at least a 16-fold decrease within 24 months.

8.5. Research question 8: Treatment of syphilis in adults in case of allergy to penicillin

No evidence identified.



9. SUMMARY OF FINDINGS TABLES AND GRADE PROFILES

9.1. Neisseria gonorrhea: diagnosis

Table 25 – Grade table for diagnosis of gonorrhoea by gender, sample site and assay

Study characteristics			Quality Assessment					Summary of findings Range %(95% CI)		Quality
No. of studies	Design	No.	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (%)	Specificity (%)	
NAAT tests										
Men – rectal samples – SDA (prevalence: 9.4%, 11.7% and 11.7%)										
3	Diagnostic cohort studies	2240	Serious risk of bias ²	Serious inconsistency ³	No serious indirectness	Serious imprecision ⁴	None	67 (56 to 77) to 93 (77 to 99)	99 (98 to 100) to 100 (95% CI 100 to 100)	VERY LOW
Men – rectal samples – TMA (prevalence: 9.4%, 11.7% and 11.7%)										
3	Diagnostic cohort studies	2240	Serious risk of bias ²	Serious inconsistency ³	No serious indirectness	Serious imprecision ⁴	None	78 (68 to 87) to 100 (88 to 100)	99 (98 to 99) to 100 (95% CI 100 to 100)	VERY LOW
Men – urethral samples - SDA (prevalence: 9.2% and 14.5%)										
2	Diagnostic cohort studies	2536	Very serious risk of bias ¹	No serious inconsistency	No serious indirectness	No serious imprecision	None	99 (95 to 100) to 100 (97 to 100)	99 (98 to 100) to 100 (99 to 100)	LOW
Men – urethral samples – TMA (prevalence: 9.2%, 13.9%, 14.5% and 16.7%)										
4	Diagnostic cohort studies	5676	Serious risk of bias ²	Serious inconsistency ³	No serious indirectness	No serious imprecision	None	81.8 (48.2 to 97.7) to 100 (96 to 100)	97 (96 to 98) to 100 (99 to 100)	LOW
Men – urethral samples – PCR (prevalence: 16.7%)										
1	Diagnostic cohort study	1818	No serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	None	Symptomatic: 99.2 (97.0 to 99.9) Asymptomatic: 81.8 (48.2 to 99.7)	Symptomatic: 99.3 (98.3 to 99.8) Asymptomatic: 99.8 (99.1 to 100)	HIGH



Study characteristics			Quality Assessment					Summary of findings Range %(95% CI)		Quality
No. of studies	Design	No.	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (%)	Specificity (%)	
1	Diagnostic cohort study	497	No serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	None	100 (84 to 100)	100 (99-100)	HIGH
Women – vulvovaginal samples (self-taken) – TMA (prevalence: 2.5%)										
1	Diagnostic cohort study	3859	No serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	None	99 (94-100)	100 (100-100)	HIGH
Women – endocervical samples – SDA (prevalence: 1.6%, 3.8%, 6.5% and 11.7%)										
4	Diagnostic cohort studies	8440	Serious risk of bias ²	Serious inconsistency ³	No serious indirectness	No serious imprecision	None	87.5 (71.0 to 96.5) to 98 (92 to 100)	98.9 (97.8 to 99.6) to 100 (100 to 100)	LOW
Women – endocervical samples – TMA (prevalence: 1.6%, 2.5%, 3.8%, 6.5% and 8.7%)										
5	Diagnostic cohort studies	13446	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	90.6 (75.0 to 98.0) to 100 (95 to 100)	99 (98 to 99) to 100 (100 to 100)	HIGH
Women – endocervical samples – PCR (prevalence: 1.3%, 1.6%, 2.4% and 3.8%)										
4	Diagnostic cohort studies	11605	No serious risk of bias	Serious inconsistency ³	No serious indirectness	No serious imprecision	None	87.1 (70.2-96.4) to 100 (85 to 100)	99.7 (99.0-100) to 100 (100 to 100)	MODERATE
Women – endocervical samples – LCR (prevalence: 8.7%)										
1	Diagnostic cohort studies	1489	Serious risk of bias ²	Not applicable	No serious indirectness	No serious imprecision	None	96 (91 to 99)	100 (99 to 100)	MODERATE
Women – clinician collected vaginal samples – PCR (prevalence: 2.4% and 3.8%)										
2	Diagnostic cohort studies	4180	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	95 (85 to 99) – 97 (83-100)	99 (99-100) to 100 (100-100)	HIGH
Women – clinician collected vaginal samples – TMA (prevalence: 3.8% and 5.4%)										
2	Diagnostic cohort studies	3478	Serious risk of bias ²	No serious inconsistency	No serious indirectness	No serious imprecision	None	93.8 (79.2 to 99.2) – 96.2 (CI not reported)	99.3 (98.4 to 99.8) to: 99.7 (98.9 to 100.0)	MODERATE



Study characteristics			Quality Assessment					Summary of findings Range %(95% CI)		Quality
No. of studies	Design	No.	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (%)	Specificity (%)	
Women – self-collected vaginal samples – SDA (prevalence: 6.5% and 11.7%)										
2	Diagnostic cohort studies	2110	Very serious risk of bias ¹	No serious inconsistency	No serious indirectness	No serious imprecision	None	100 (92 to 100) to 100 (94-100)	99 (98-100) to 99 (99 to 100)	LOW
Women – self-collected vaginal samples – PCR (prevalence: 1.3% and 3.8%)										
2	Diagnostic cohort studies	5123	Serious risk of bias ²	No serious inconsistency	No serious indirectness	No serious imprecision	None	95.7 (78.1 to 99.9) to 100 (85 to 100)	99.7 (98.9 to 100.0) to 100 (100 to 100)	MODERATE
Women – self-collected vaginal samples – TMA (prevalence: 3.8%)										
1	Diagnostic cohort studies	1464	Very serious risk of bias ¹	Not applicable	No serious indirectness	No serious imprecision	None	TMA Combo: 98.7 TMA NG: 96.1 (CI not reported)	TMA Combo: 99.6 TMA NG: 96.3 (CI not reported)	LOW
Women – vaginal self-collected – postal – SDA (prevalence: 1%)										
1	Diagnostic cohort study	500	Very serious risk of bias ¹	Not applicable	No serious indirectness	Very serious imprecision ⁴	None	80 (28 to 99)	100 (99 to 100)	VERY LOW
Women – vaginal self-collected – postal - PCR (prevalence: 1%)										
1	Diagnostic cohort study	500	Very serious risk of bias ¹	Not applicable	No serious indirectness	Very serious imprecision ⁴	None	100 (48 to 100)	99 (97 to 100)	VERY LOW
Women – vaginal self-collected – postal - TMA (prevalence: 1%)										
1	Diagnostic cohort study	500	Very serious risk of bias ¹	Not applicable	No serious indirectness	Very serious imprecision ⁴	None	100 (48 to 100)	100 (99 to 100)	VERY LOW
Women – first catch urine samples – SDA (prevalence: 1.6, 3.8%, 6.5% and 11.7%)										
4	Diagnostic cohort studies	8440	Serious risk of bias ²	Serious inconsistency ³	No serious indirectness	Serious imprecision ⁴	None	76.7 (57.7 to 90.1) to 98 (92 to 100)	95.6 (93.7 to 97.0) to 100 (100 to 100)	VERY LOW



Women – first catch urine samples – PCR (prevalence: 0.3%, 1.3%, 1.6%, 2.5% and 3.8%)										
5	Diagnostic cohort studies	11540	No serious risk of bias	Serious inconsistency ³	No serious indirectness	No serious imprecision	None	87.0 (66.4 to 97.2) to 100 (16 to 100)	99.6 (98.7 to 99.9) to 100 (100 to 100)	MODERATE
Women – first catch urine samples – TMA (prevalence 1.6%, 2.5% and 3.8%)										
3	Diagnostic cohort studies	8098	No serious risk of bias	Serious inconsistency ³	No serious indirectness	No serious imprecision	None	82.6 (61.2 to 95.0) to 97 (89 to 100)	99.4 (98.5 to 99.8) to 100 (100 to 100)	MODERATE
Culture test										
Men – rectal samples (prevalence: 9.4% and 11.7%)										
2	Diagnostic cohort studies	1992	Very serious risk of bias ¹	No serious inconsistency	No serious indirectness	No serious imprecision	None	35 (25 to 46) to 49 (37 to 60)	100 (100 to 100)	LOW
Men – pharynx samples (prevalence: 11.7%)										
1	Diagnostic cohort study	1110	Very serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ⁴	None	55 (42 to 67)	100 (100 to 100)	VERY LOW
Men and women – rectal samples (prevalence: 4.2%)										
1	Diagnostic cohort study	497	No serious risk of bias	Not applicable	No serious indirectness	Serious imprecision ⁴	None	24 (8 to 47)	100 (99 to 100)	MODERATE
Women – endocervical samples (prevalence: 2.5% and 8.7%)										
2	Diagnostic cohort studies	5348	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	81 (72 to 88) to 86 (79 to 91)	100 (100 to 100) to 100 (100 to 100)	HIGH

¹ Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

² Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias.

³ Inconsistency was assessed by inspection of the sensitivity (considered to be the primary measure for this review) using the point estimate of individual studies on the forest plots. The evidence was downgraded by 1 increment if the individual study comparisons varied across 2 areas [(for example, 50–90% and 90–100%)] and by 2 increments if the individual study comparisons varied across 3 areas [(for example, 0–50%, 50–90% and 90–100%)].

⁴ Imprecision was based on the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. As a general rule a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.



9.2. Chlamydia trachomatis (only for TMA Aptima Combo test): diagnosis

Table 26 – Grade table for diagnosis of chlamydia by gender, sample type and assay

Study characteristics			Quality Assessment					Summary of findings Range %(95% CI)		Quality
No. of studies	Design	No.	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (%)	Specificity (%)	
Men – rectal samples – TMA										
2	Diagnostic cohort studies	2017	Serious risk of bias ²	Serious inconsistency ³	No serious indirectness	Serious imprecision ⁴	None	64 (52 to 76) to 100 (93 to 100)	99 (97 to 99) to 100 (95% CI 99 to 100)	VERY LOW
Men – urethral samples – TMA										
2	Diagnostic cohort studies	4607	Serious risk of bias ²	No serious inconsistency	No serious indirectness	No serious imprecision	None	94 (89 to 98) <u>Symptomatic:</u> 98.4% (95.3-99.7) <u>Asymptomatic:</u> 91.2% (83.4-96.1)	99 (98 to 100) <u>Symptomatic:</u> 98.5% (97.2-99.3) <u>Asymptomatic:</u> 99.1% (98.0-99.7)	MODERATE
Men – pharynx samples – TMA										
1	Diagnostic cohort studies	1110	Very serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ⁴	None	64 (31 to 89)	100 (100 to 100)	VERY LOW
Men – first catch urine – TMA										
2	Diagnostic cohort studies	4607	Serious risk of bias ²	No serious inconsistency	No serious indirectness	No serious imprecision	None	97 (92 to 99) <u>Symptomatic:</u> 99.5% (97.0-100.0) <u>Asymptomatic:</u> 98.9% (94.0-100.0)	99 (98 to 100) <u>Symptomatic:</u> 99.4% (98.4-99.8) <u>Asymptomatic:</u> 99.5% (98.5-99.9)	MODERATE



Women – endocervical samples – TMA										
2	Diagnostic cohort studies	5722	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	97 (94 to 98) to 99 (97 to 100) <u>Symptomatic:</u> 91.4% (83.0-96.5) <u>Asymptomatic:</u> 78.7% (64.3-89.3)	97 (96 to 98) to 99 (99 to 99) <u>Symptomatic:</u> 99.4% (98.5-99.8) <u>Asymptomatic:</u> 98.6% (97.4-99.4)	HIGH
Women – first catch urine samples – TMA										
1	Diagnostic cohort studies	4311	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	96 (93 to 98) <u>Symptomatic:</u> 93.8% (86.2-98.0) <u>Asymptomatic:</u> 93.5% (82.1-98.6)	100 (99 to 100) <u>Symptomatic:</u> 99.4% (98.5-99.8) <u>Asymptomatic:</u> 99.2% (98.2-99.8)	MODERATE
Women – self-collected vaginal sample – TMA										
1	Diagnostic cohort studies	1000	Very serious risk of bias	Not applicable	No serious indirectness	No serious imprecision	None	100.0% (96.1-100)	100.0% (99.6-100)	LOW



9.3. Neisseria gonorrhea: treatment

9.3.1. Treatment of gonorrhea in sexually active women and men

Table 27 – Clinical evidence profile: Gentamicin + Azithromycin vs. Gemifloxacin + Azithromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gentamicin/azithromycin	Gemifloxacin/azithromycin	Relative (95% CI)	Absolute		
Number cured – total urogenital (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	202/202 (100%)	99.5%	RR 1.01 (0.99 to 1.02)	10 more per 1000 (from 10 fewer to 20 more)	⊕⊕⊕⊕ LOW	CRITICAL
Cure - rectal infections (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	1/1 (100%)	100%	RR 1 (0.43 to 2.31)	0 fewer per 1000 (from 570 fewer to 1000 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Cure - pharyngeal infections (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/10 (100%)	100%	RR 1 (0.86 to 1.17)	0 fewer per 1000 (from 140 fewer to 170 more)	⊕⊕⊕⊕ LOW	CRITICAL
Nausea (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	56/202 (27.7%)	37.2%	RR 0.75 (0.56 to 0.99)	93 fewer per 1000 (from 4 fewer to 164 fewer)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Vomiting (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	15/202 (7.4%)	5%	RR 1.48 (0.68 to 3.21)	24 more per 1000 (from 16	⊕⊕⊕⊕ VERY LOW	CRITICAL



										fewer to 111 more)		
Abdominal pain (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	15/202 (7.4%)	10.6%	RR 0.7 (0.37 to 1.33)	32 fewer per 1000 (from 67 fewer to 35 more)	⊕○○○ VERY LOW	CRITICAL
Diarrhoea (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	39/202 (19.3%)	23.1%	RR 0.84 (0.57 to 1.22)	37 fewer per 1000 (from 99 fewer to 51 more)	⊕○○○ VERY LOW	CRITICAL
Injection site pain (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	None	2/202 (0.99%)	0%	OR 7.32 (0.46 to 117.39)	9.9 more per 1000 (from 6.8 more to 26.6 more) ³	⊕○○○ VERY LOW	CRITICAL
Fatigue (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	4/202 (2%)	3%	RR 0.66 (0.19 to 2.29)	10 fewer per 1000 (from 24 fewer to 39 more)	⊕○○○ VERY LOW	IMPORTANT
Dizziness (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	7/202 (3.5%)	3.5%	RR 0.99 (0.35 to 2.76)	0 fewer per 1000 (from 23 fewer to 62 more)	⊕○○○ VERY LOW	IMPORTANT
Tendon disorder/tendonitis (follow-up 10-17 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	1/202 (0.5%)	1.5%	RR 0.33 (0.03 to 3.13)	10 fewer per 1000 (from 15 fewer to 32 more)	⊕○○○ VERY LOW	IMPORTANT

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

³ Zero events in one arm so absolute effect calculated from risk difference.



Table 28 – Clinical evidence profile: Ceftriaxone + Azithromycin vs Fosfomycin trometamol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone + azithromycin	Fosfomycin	Relative (95% CI)	Absolute		
Number cured (clinical and microbiologic cure) (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/64 (95.3%)	96.8%	RR 0.98 (0.92 to 1.06)	19 fewer per 1000 (from 77 fewer to 58 more)	⊕⊕⊕⊕ LOW	CRITICAL
Nausea (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	3/61 (4.9%)	8.3%	RR 0.59 (0.15 to 2.36)	34 fewer per 1000 (from 71 fewer to 113 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Diarrhoea (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	6/61 (9.8%)	11.7%	RR 0.84 (0.3 to 2.36)	19 fewer per 1000 (from 82 fewer to 159 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Abdominal pain (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	4/61 (6.6%)	5%	RR 1.31 (0.31 to 5.61)	15 more per 1000 (from 34 fewer to 231 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Fatigue (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	2/61 (3.3%)	3.3%	RR 0.98 (0.14 to 6.76)	1 fewer per 1000 (from 29 fewer to 192 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Dyspepsia (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	3/61 (4.9%)	8.3%	RR 0.59 (0.15 to 2.36)	34 fewer per 1000 (from 71 fewer to 113 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs


Table 29 – Clinical evidence profile: Gentamicin + azithromycin vs ceftriaxone + azithromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gentamicin + azith	Ceftriaxone + azith	Relative (95% CI)	Absolute		
Microbiological cure (follow-up 14 days; assessed with: NAAT)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	267/292 (91.4%)	97.7%	RR 0.94 (0.9 to 0.97)	59 fewer per 1000 (from 29 fewer to 98 fewer)	⊕⊕⊕⊕ LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 30 – Clinical evidence profile: ETX914 v ceftriaxone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETX0914 versus ceftriaxone	Ceftriaxone	Relative (95% CI)	Absolute		
ETX0914 2000mg - Microbiological cure (follow-up 7 days; assessed with: Culture)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	48/49 (98%)	100%	RR 1.01 (0.89 to 1.15)	10 more per 1000 (from 110 fewer to 150 more)	⊕⊕⊕⊕ LOW	CRITICAL
ETX0914 3000mg - Microbiological cure (follow-up 7 days; assessed with: Culture)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/47 (100%)	100%	RR 1.00 (0.88 to 1.14)	Not calculated	⊕⊕⊕⊕ LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias



9.3.2. Treatment for pregnant women

Table 31 – Clinical evidence profile: Ceftriaxone vs Cefixime in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Cefixime	Relative (95% CI)	Absolute		
Number cured - overall (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/43 (95.3%)	96.2%	RR 0.99 (0.91 to 1.08)	10 fewer per 1000 (from 87 fewer to 77 more)	⊕⊕⊕⊕ LOW	CRITICAL
Babies minor abnormalities (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	10/60 (16.7%)	11.3%	RR 1.48 (0.6 to 3.62)	54 more per 1000 (from 45 fewer to 296 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
hyperbilirubinemia in infants (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴ imprecision	none	5/60 (8.3%)	0%	OR 8.19 (1.38 to 48.71)	80 more per 1000 (from 10 more to 160 more) ³	⊕⊕⊕⊕ VERY LOW	CRITICAL
Number cured - cervix (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/40 (95%)	95.7%	RR 0.99 (0.9 to 1.09)	10 fewer per 1000 (from 96 fewer to 86 more)	⊕⊕⊕⊕ LOW	CRITICAL
Number cured - pharynx (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	5/5 (100%)	100%	RR 1 (0.73 to 1.37)	0 fewer per 1000 (from 270 fewer to 370 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Number cured - anus (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/23 (100%)	100%	RR 1 (0.9 to 1.11)	0 fewer per 1000 (from 100 fewer to 110 more)	⊕⊕⊕⊕ LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. ² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

³ Zero events in one arm so absolute effect calculated from risk difference.

⁴ Downgraded for imprecision due to not meeting the required optimal information size.


Table 32 – Clinical evidence profile: Ceftriaxone vs Spectinomycin in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Spectinomycin	Relative (95% CI)	Absolute		
Number cured (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	80/84 (95.2%)	95.2%	RR 1 (0.93 to 1.07)	0 fewer per 1000 (from 67 fewer to 67 more)	⊕⊕⊕⊕ LOW	CRITICAL
Minor malformations												
1	randomised trials	very serious ²	no serious inconsistency	no serious indirectness	very serious ²	none	12/75 (16%)	13%	RR 1.23 (0.55 to 2.73)	30 more per 1000 (from 58 fewer to 225 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Major malformations												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	0/75 (0%)	1.5%	OR 0.12 (0 to 6.27)	10 fewer per 1000 (from 50 fewer to 20 more) ³	⊕⊕⊕⊕ VERY LOW	CRITICAL
Number cured - cervix (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	78/82 (95.1%)	96.3%	RR 0.99 (0.93 to 1.05)	10 fewer per 1000 (from 67 fewer to 48 more)	⊕⊕⊕⊕ LOW	CRITICAL
Number cured - pharynx (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	6/6 (100%)	83.3%	RR 1.18 (0.76 to 1.83)	150 more per 1000 (from 200 fewer to 691 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Number cured - rectum (follow-up 14 days)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/22 (95.5%)	100%	RR 0.96 (0.84 to 1.09)	40 fewer per 1000 (from 160 fewer to 90 more)	⊕⊕⊕⊕ LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

³ Zero events in one arm so absolute effect calculated from risk difference

9.3.3. Treatment for people with severe cephalosporin allergy

No evidence was identified.

9.4. Syphilis: diagnosis

Table 33 – Grade table for diagnosis of syphilis by test and gender

Study characteristics			Quality Assessment					Summary of findings Range %(95% CI)		Quality
No. of studies	Design	No.	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (%)	Specificity (%)	
PCR tests										
Women and men – TpPCR using swabs and biopsies (prevalence 16.9%)										
1	Diagnostic cohort studies	301	Very serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ³	None	80 (67 to 90)	98 (96 to 100)	VERY LOW
EIA tests										
Women and men - EIA IgG using serum samples (prevalence 5.6%)										
1	Diagnostic cohort studies	604	Very serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ³	None	85 (69 to 95)	96 (94 to 97)	VERY LOW
Women and men - EIA IgM/IgG using serum samples (prevalence 39.7%)										
1	Diagnostic cohort studies	674	Very serious risk of bias ¹	Not applicable	No serious indirectness	No serious imprecision	None	98 (96 to 99)	99 (97 to 100)	LOW
Chembio DPP syp (non trep + trep) tests										
Women and men - treponemal test with TP-PA as reference standard using serum samples (prevalence 52%)										
1	Diagnostic cohort studies	1601	Very serious risk of bias ¹	Not applicable	No serious indirectness	No serious imprecision	None	97 (95 to 98)	95 (93 to 97)	LOW
Women and men - treponemal test with TP-PA as reference standard using blood samples (prevalence 2.4%)										
1	Diagnostic cohort studies	765	Very serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ³	None	53 (42 to 63)	99 (97 to 99)	VERY LOW
Women and men - non treponemal test with RPR as reference standard using serum samples (prevalence 52%)										



1	Diagnostic cohort studies	1601	Very serious risk of bias ¹	Not applicable	No serious indirectness	No serious imprecision	None	89 (86 to 91)	99 (97 to 99)	LOW
Women and men - non treponemal test with RPR as reference standard using blood samples (prevalence 2.4%)										
1	Diagnostic cohort studies	763	Very serious risk of bias ¹	Not applicable	No serious indirectness	Very serious imprecision ³	None	48 (27 to 69)	99 (98 to 100)	VERY LOW
Women and men - combined treponemal and non treponemal using blood samples (prevalence 2.4%)										
1	Diagnostic cohort studies	766	Very serious risk of bias ¹	Not applicable	No serious indirectness	Very serious imprecision ³	None	90 (55 to 100)	100 (99 to 100)	VERY LOW
Point of Care – dual and triple tests										
Women and men - SD HIV-syp (trep) – using serum and plasma samples (prevalence 8.4%)										
1	Diagnostic cohort studies	394	Very serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ³	None	70 (51 to 84)	100 (98 to 100)	VERY LOW
Women and men - Chembio DPP HIV-syp (trep) – using blood samples (prevalence 2.4%)										
1	Diagnostic cohort studies	920	Very serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ³	None	Order 1: 46 (28 to 66) Order 2: 47 (36 to 59)	Order 1: 100 (98 to 100) Order 2: 99 (98 to 100)	VERY LOW
Women and men - Chembio DPP HIV-syp (trep) – using serum samples (prevalence 65.4%)										
1	Diagnostic cohort studies	990	Very serious risk of bias ¹	Not applicable	No serious indirectness	No serious imprecision	None	99 (98 to 99)	99 (98 to 100)	LOW
Women and men - Chembio DPP HIV-HCV-syp (trep) using blood samples (prevalence 2.4%)										
1	Diagnostic cohort studies	881	Very serious risk of bias ¹	Not applicable	No serious indirectness	No serious imprecision	None	44 (34 to 54)	99 (99 to 100)	LOW



Chembio DPP syp (non trep + trep) tests										
Men – treponemal test with TP-PA as reference standard using blood sample (prevalence 12.1%)										
1	Diagnostic cohort studies	227	Serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ³	None	Reader 1: 65 (44 to 83) Reader 2: 69 (48 to 86)	Reader 1: 100 (97 to 100) Reader 2: 100 (97 to 100)	LOW
Men – treponemal test with TP-PA as reference standard using serum samples (prevalence 12.1%)										
1	Diagnostic cohort studies	205	Serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ³	None	Reader 1: 58 (37 to 77) Reader 2: 64 (43 to 82)	Reader 1: 100 (97 to 100) Reader 2: 99 (97 to 100)	LOW
Men – non treponemal test with RPR as reference standard using blood samples (prevalence 5.5%)										
1	Diagnostic cohort studies	227	Serious risk of bias ¹	Not applicable	No serious indirectness	Very serious imprecision ³	None	Reader 1: 64 (31 to 89) Reader 2: 64 (31 to 89)	Reader 1: 100 (98 to 100) Reader 2: 100 (97 to 100)	VERY LOW
Men – non treponemal test with RPR as reference standard using serum samples (prevalence 5.5%)										
1	Diagnostic cohort studies	205	Serious risk of bias ¹	Not applicable	No serious indirectness	Very serious imprecision ³	None	Reader 1: 64 (31 to 89) Reader 2: 64 (31 to 89)	Reader 1: 100 (97 to 100) Reader 2: 99 (96 to 100)	VERY LOW
Point of care – treponemal test										
Men – SD Syphilis 3.0 assay using blood sample (prevalence 12.1%)										
1	Diagnostic cohort studies	289	Serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ³	None	Reader 1: 51 (34 to 69) Reader 2: 54 (37 to 71)	Reader 1: 100 (99 to 100) Reader 2: 100 (99 to 100)	LOW



Men – SD Syphilis 3.0 assay using serum sample (prevalence 12.1%)										
1	Diagnostic cohort studies	227	Serious risk of bias ¹	Not applicable	No serious indirectness	Serious imprecision ³	None	Reader 1: 80 (63 to 92) Reader 2: 83 (66 to 93)	Reader 1: 100 (99 to 100) Reader 2: 100 (98 to 100)	LOW

¹ Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 1 increments if the majority of studies were rated at high risk of bias. The evidence was downgraded by 2 increment if the majority of studies were rated at very high risk of bias.

² Inconsistency was assessed by inspection of the sensitivity (considered to be the primary measure for this review) using the point estimate of individual studies on the forest plots. The evidence was downgraded by 1 increment if the individual study comparisons varied across 2 areas [(for example, 50–90% and 90–100%)] and by 2 increments if the individual study comparison varied across 3 areas [(for example, 0–50%, 50–90% and 90–100%)].

³ Imprecision was based on the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. As a general rule a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

Table 34 – Grade table for diagnosis of syphilis by screening tests and strategy

Study characteristics			Quality Assessment					Summary of findings Positive samples (%)		Quality
No. of studies	Design	No.	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reverse algorithm	Traditional algorithm	
Reverse versus traditional algorithm - women and men										
Reactive samples										
1	Diagnostic cohort study	1000	Serious risk of bias ¹	Not applicable	No serious indirectness	Not applicable	None	15/1000 1.50%	4/1000 0.40%	MODERATE
Samples confirmed positive										
1	Time-series	3,092,938	Very serious risk of bias ¹	Not applicable	No serious indirectness	Not applicable	None	20,533/1,037,025 1.98%	9457/2,055,913 0.46%	LOW

¹ Risk of bias was assessed using the QUADAS-2 checklist. If there was one criterion with a high risk of bias the study was considered to have a serious risk of bias. If there were two or more criteria with a high risk of bias the study was considered to have a very serious risk of bias. The evidence was downgraded by 1 increments if the majority of studies were rated at high risk of bias. The evidence was downgraded by 2 increment if the majority of studies were rated at very high risk of bias.



9.5. Syphilis: treatment

Table 35 – Clinical evidence profile: Azithromycin versus BPG for men and women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin	BPG	Relative (95% CI)	Absolute		
Serological response - 4 fold decrease in RPR titer at 3 months												
3	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	304/438 (69.4%)	85.7%	RR 0.98 (0.9 to 1.07)	17 fewer per 1000 (from 86 fewer to 60 more)	⊕⊕⊕⊕ LOW	CRITICAL
Serological response - 4 fold decrease in RPR titer at 6 months												
3	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	345/426 (81%)	83.3%	RR 1.01 (0.95 to 1.08)	8 more per 1000 (from 42 fewer to 67 more)	⊕⊕⊕⊕ LOW	CRITICAL
Serological response - 4 fold decrease in RPR titer at 9 months												
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	178/187 (95.2%)	100%	RR 1.01 (0.97 to 1.06)	10 more per 1000 (from 30 fewer to 60 more)	⊕⊕⊕⊕ LOW	CRITICAL
Serological response - 4 fold decrease in RPR titer at 12 months												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/36 (91.7%)	100%	RR 0.95 (0.8 to 1.12)	50 fewer per 1000 (from 200 fewer to 120 more)	⊕⊕⊕⊕ LOW	CRITICAL
Adverse events - general GI effects												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	Generic inverse variance analysis so pooled data unavailable	Generic inverse variance analysis so pooled data unavailable	RR 4.75 (0.67 to 33.67)	-	⊕⊕⊕⊕ VERY LOW	CRITICAL
Adverse events - nausea												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	7/52 (13.5%)	4.8%	RR 2.83 (0.37 to 21.59)	88 more per 1000 (from 30 fewer to 988 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL



Adverse events - diarrhoea												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	5/52 (9.6%)	0%	Peto OR 4.42 (0.6 to 32.42)	100 more (from 10 fewer to 200 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events - vomiting												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	1/52 (1.9%)	0%	Peto OR 4.07 (0.05 to 309.07)	20 more per 1000 (from 60 fewer to 100 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events - Jarisch-Herxheimer												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	9/53 (17.0%)	23.8%	RR 0.71 (0.27 to 1.88)	69 fewer per 1000 (from 174 fewer to 209 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events - gastrointestinal												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	69/283 (24.4%)	0%	RR 3.31 (2.09 to 5.24)	171 more per 1000 (from 81 more to 314 more)	⊕○○○ VERY LOW	CRITICAL
Serological response at 12 months												
1	observational studies	Serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	134/237 (56.5%)	61.1%	RR 0.93 (0.78 to 1.09)	43 fewer per 1000 (from 134 fewer to 55 more)	⊕○○○ VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

³ Downgraded for imprecision due to not meeting the required optimal information size.



Table 36 – Clinical evidence profile: Azithromycin 2g vs Azithromycin 4g for men and women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin 2g	Azithromycin 4g	Relative (95% CI)	Absolute		
Serological response – 4 fold decrease in RPR titer at 3 months												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	15/17 (88.2%)	20/28 (71.4%)	RR 1.24 (0.92 to 1.65)	171 more per 1000 (from 57 fewer to 464 more)	⊕○○○ VERY LOW	CRITICAL
Serological response – 4 fold decrease in RPR titer at 6 months												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	16/17 (94.1%)	20/26 (76.9%)	RR 1.22 (0.96 to 1.56)	169 more per 1000 (from 31 fewer to 431 more)	⊕○○○ VERY LOW	CRITICAL
Serological response – 4 fold decrease in RPR titer at 9 months												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	14/14 (100%)	19/24 (79.2%)	RR 1.24 (0.99 to 1.56)	190 more per 1000 (from 8 fewer to 443 more)	⊕○○○ VERY LOW	CRITICAL
Serological response – 4 fold decrease in RPR titer at 12 months												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	14/14 (100%)	19/22 (86.4%)	RR 1.14 (0.94 to 1.39)	121 more per 1000 (from 52 fewer to 337 more)	⊕○○○ VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.


Table 37 – Clinical evidence profile: BPG + ceftriaxone/doxycycline versus BPG for men and women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BPG + ceftriaxone/doxycycline	BPG	Relative (95% CI)	Absolute		
Serological response – 3 to 4 fold decrease in VDRL titer at 3 months												
1	randomised trials	very serious ¹	no inconsistency	serious indirectness	serious ⁴	None	11/22 (50%)	0/38 (0%)	Peto OR 26.68 (6.95 to 102.46)	500 more per 1000 (from 290 more to 710 more)	⊕000 VERY LOW	CRITICAL
Serological response – 3 to 4 fold decrease in VDRL titer at 6 months												
1	randomised trials	very serious ¹	no inconsistency	serious indirectness	serious ⁴	None	20/22 (90.9%)	13/38 (34.2%)	RR 2.66 (1.68 to 4.21)	568 more per 1000 (from 233 more to 1000 more)	⊕000 VERY LOW	CRITICAL
Serological response – 3 to 4 fold decrease in VDRL titer at 12 months												
1	randomised trials	very serious ¹	no inconsistency	serious indirectness	serious ²	None	22/22 (100%)	26/38 (68.4%)	RR 1.44 (1.15 to 1.8)	301 more per 1000 (from 103 more to 547 more)	⊕000 VERY LOW	CRITICAL
Adverse events												
1	randomised trials	very serious ¹	no inconsistency	serious indirectness	Very serious ³	None	0/22 (0%)	0/38 (0%)	RD: 0.00 (-0.07 to 0.07)	0 more per 1000 (from 70 fewer to 70 more)	⊕000 VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

³ Downgraded by 2 increments as sample size was less than 70 in single studies with zero events in both arms.

⁴ Downgraded for imprecision due to not meeting the required optimal information size.



Table 38 – Clinical evidence profile: BPG x 3 versus BPG x 1 for men and women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BPG x 3	BPG x 1	Relative (95% CI)	Absolute		
Serological response - treatment success - 4 fold decrease in initial RPR titer at 12 months												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	27/29 (93.1%)	28/35 (80%)	RR 1.16 (0.96 to 1.41)	128 more per 1000 (from 32 fewer to 328 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious imprecision ³	none	0/29 (0%)	0/35 (0%)	RD 0.00 (-0.06 to 0.06)	0 more per 1000 (from 60 fewer to 60 more)	⊕○○○ VERY LOW	CRITICAL
Serological response at 3 months – 4-fold or greater decline in VDRL titer												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	27/43 (62.8%)	64.7%	RR 0.97 (0.64 to 1.48)	19 fewer per 1000 (from 233 fewer to 311 more)	⊕○○○ VERY LOW	CRITICAL
Serological response at 6 months – 4-fold or greater decline in VDRL titer												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious ²	none	36/43 (83.7%)	82.4%	RR 1.02 (0.79 to 1.31)	16 more per 1000 (from 173 fewer to 255 more)	⊕○○○ VERY LOW	CRITICAL
Serological response at 12 months – 4-fold or greater decline in VDRL titer or – 4-fold or greater decline in RPR titer												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	250/321 (77.9%)	80.6%	RR 1.11 (1.01 to 1.22)	89 more per 1000 (from 8 more to 177 more)	⊕⊕○○ LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

³ Downgraded by 2 increments as sample size was less than 70 in single studies with zero events in both arms.



Table 39 – Clinical evidence profile: BPG + amoxy/probenecid versus BPG for men and women

Quality assessment							No of patients			Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BPG + amoxy/probenecid		BPG	Relative (95% CI)	Absolute		
Treatment failure - < 4 fold decrease in RPR titer or test results did not become non-reactive at 3 months													
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	None	46/185 (24.9%)		40/175 (22.9%)	RR 1.09 (0.75 to 1.57)	21 more per 1000 (from 57 fewer to 130 more)	⊕○○○ VERY LOW	CRITICAL
Treatment failure - < 4 fold decrease in RPR titer or test results did not become non-reactive at 6 months													
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	None	29/169 (17.2%)		28/157 (17.8%)	RR 0.96 (0.6 to 1.54)	7 fewer per 1000 (from 71 fewer to 96 more)	⊕○○○ VERY LOW	CRITICAL
Treatment failure - < 4 fold decrease in RPR titer or test results did not become non-reactive at 6 months (adjusted for confounders)													
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	None	Generic inverse variance analysis so pooled data unavailable		Generic inverse variance analysis so pooled data unavailable	RR 0.91 (0.45 to 1.84)	-	⊕○○○ VERY LOW	CRITICAL
Treatment failure - < 4 fold decrease in RPR titer or test results did not become non-reactive at 9 months													
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	None	24/148 (16.2%)		28/153 (18.3%)	RR 0.89 (0.54 to 1.46)	20 fewer per 1000 (from 84 fewer to 84 more)	⊕○○○ VERY LOW	CRITICAL
Treatment failure - < 4 fold decrease in RPR titer or test results did not become non-reactive at 12 months													
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	None	20/142 (14.1%)	21/137 (15.3%)	RR 0.92 (0.52 to 1.62)	12 fewer per 1000 (from 74 fewer to 95 more)		⊕○○○ VERY LOW	CRITICAL
Adverse events - diarrhoea													
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	45/265 (17%)	28/276 (10.1%)	RR 1.67 (1.08 to 2.6)	68 more per 1000 (from 8 more to 162 more)		⊕⊕○○ LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

³ Based on estimate of the likely standard deviation of the baseline measure, utilising the SE and sample size, and using default MIDs half a standard deviation from the null.



Table 40 – Clinical evidence profile: Ceftriaxone vs. procaine penicillin/probenecid for men and women

Quality assessment							No of patients			Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone)	Penicillin procaine/probenecid	Relative (95% CI)	Absolute			
Serological response – 4 fold decrease in RPR titer (18 months for ceftriaxone and 32 months for PP)													
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	10/14 (71.4%)	7/10 (70%)	RR 1.02 (0.6 to 1.72)	14 more per 1000 (from 280 fewer to 504 more)	⊕000 VERY LOW	CRITICAL	
Serological response – 4 fold decrease in RPR titer without subsequent relapse (18 months for ceftriaxone and 32 months for PP)													
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	9/14 (64.3%)	5/10 (50%)	RR 1.29 (0.62 to 2.67)	145 more per 1000 (from 190 fewer to 835 more)	⊕000 VERY LOW	CRITICAL	
Serofast – persistent RPR titer after treatment (18 months for ceftriaxone and 32 months for PP)													
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	2/14 (14.3%)	3/10 (30%)	RR 0.48 (0.1 to 2.35)	156 fewer per 1000 (from 270 fewer to 405 more)	⊕000 VERY LOW	CRITICAL	
Treatment failure (>4 fold increase in RPR titer, titer 1:64, or clinical progression to disease) (18 months for ceftriaxone and 32 months for PP)													
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	2/14 (14.3%)	0/10 (0%)	Peto OR 6 (0.34 to 106.33)	140 more per 1000 (from 80 fewer to 370 more)	⊕000 VERY LOW	CRITICAL	
Adverse events													
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	0/14 (0%)	0/10 (0%)	RD: 0.00 (-0.15 to 0.15)	0 more per 1000 (from 150 fewer to 150 more)	⊕000 VERY LOW	CRITICAL	

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

³ Downgraded for imprecision due to not meeting the required optimal information size.

⁴ Downgraded by 2 increments as sample size was less than 70 in single studies with zero events in both arms.


Table 41 – Clinical evidence profile: Ceftriaxone vs. BPG for men and women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	BPG	Relative (95% CI)	Absolute		
Serological response 14 days – 4 fold decrease in RPR titer												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	22/108 (20.4%)	15.9%	RR 1.28 (0.73 to 2.25)	45 more per 1000 (from 43 fewer to 199 more)	⊕○○○ VERY LOW	CRITICAL
Serological response 3 months – 4 fold decrease in RPR titer												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	86/110 (78.2%)	74.8%	RR 1.05 (0.9 to 1.21)	37 more per 1000 (from 75 fewer to 157 more)	⊕⊕○○ LOW	CRITICAL
Serological response 6 months – 4 fold decrease in RPR titer												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	101/112 (90.2%)	78%	RR 1.16 (1.03 to 1.3)	125 more per 1000 (from 23 more to 234 more)	⊕○○○ VERY LOW	CRITICAL
Serological response 9 months – 4 fold decrease in RPR titer												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	101/112 (90.2%)	79.7%	RR 1.13 (1.01 to 1.26)	104 more per 1000 (from 8 more to 207 more)	⊕○○○ VERY LOW	CRITICAL
Serological response 12 months – 4 fold decrease in RPR titer												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	103/112 (92%)	81.4%	RR 1.13 (1.02 to 1.25)	106 more per 1000 (from 16 more to 204 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events (serious adverse events or adverse events related to study drugs)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	0/112 (0%)	0%	RD 0.00 (-0.02-0.02)	0 more per 1000 (from 20 fewer to 20 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events – Jarisch-Herxheimer												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	46/112 (41.1%)	31.4%	RR 1.31 (0.93 to 1.85)	97 more per 1000 (from 22 fewer to 267 more)	⊕○○○ VERY LOW	CRITICAL



Non-cure – serofast at 12 months												
1	randomised trials	very serious ¹	no inconsistency	serious indirectness	Very serious ²	none	6/112 (5.4%)	7.6%	RR 0.7 (0.26 to 1.91)	23 fewer per 1000 (from 56 fewer to 69 more)	⊕○○○ VERY LOW	CRITICAL
Clinical cure – skin lesions disappeared within a month												
1	randomised trials	very serious ¹	no inconsistency	serious indirectness	no serious imprecision	none	112/112 (100%)	100%	RR 1 (0.98 to 1.02)	0 fewer per 1000 (from 20 fewer to 20 more)	⊕⊕○○ LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

³ Downgraded by 1 increment as sample size between 70-350 in single study with zero events in both arms.

Table 42 – Clinical evidence profile: Ceftriaxone vs. penicillin procaine for men and women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	penicillin procaine	Relative (95% CI)	Absolute		
Clinical cure – subsidence of skin lesions after one week												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	27/30 (90%)	66.7%	RR 1.35 (1.02 to 1.79)	233 more per 1000 (from 13 more to 527 more)	⊕○○○ VERY LOW	CRITICAL
Serological response – comparison of negative conversion rate in toluidine red unheated serum test												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision ²	none	30/30 (100%)	93.3%	RR 1.07 (0.96 to 1.2)	65 more per 1000 (from 37 fewer to 187 more)	⊕⊕○○ LOW	CRITICAL
Non cure – incidence of sero resistance												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	5/30 (16.7%)	23.3%	RR 0.71 (0.25 to 2)	68 fewer per 1000 (from 175 fewer to 233 more)	⊕○○○ VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.


Table 43 – Clinical evidence profile: BPG vs minocycline 2 weeks and extended 4 weeks combined for men and women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BPG	Minocycline	Relative (95% CI)	Absolute		
Serological response at 2 years – RPR titers nonreactive after disappearance of clinical manifestations of syphilis												
1	observational studies	serious ¹	no inconsistency	no indirectness	no imprecision	none	125/156 (80.1%)	77.5%	RR 1.03 (0.86 to 1.24)	23 more per 1000 (from 108 fewer to 186 more)	⊕○○○ VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 44 – Clinical evidence profile: Minocycline 2 weeks vs minocycline extended 4 weeks for men and women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 2 weeks	Minocycline 4 weeks	Relative (95% CI)	Absolute		
Serological response at 1 year - RPR titers nonreactive after disappearance of clinical manifestations of syphilis												
1	observational studies	serious ¹	no inconsistency	serious no indirectness	serious ²	none	52/79 (65.8%)	64.9%	RR 1.01 (0.81 to 1.27)	6 more per 1000 (from 123 fewer to 175 more)	⊕○○○ VERY LOW	CRITICAL
Serological response at 2 years - RPR titers nonreactive after disappearance of clinical manifestations of syphilis												
1	observational studies	serious ¹	no inconsistency	serious no indirectness	serious ²	none	69/79 (87.3%)	72.7%	RR 1.2 (1.02 to 1.41)	145 more per 1000 (from 15 more to 298 more)	⊕○○○ VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.



Table 45 – Clinical evidence profile: Doxycycline vs BPG for men and women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	BPG	Relative (95% CI)	Absolute		
Serological response at 3 months – 4-fold or greater decline in RPR titers												
1	observational studies	serious ¹	no inconsistency	no serious indirectness	very serious ²	none	20/89 (22.5%)	20.7%	RR 1.09 (0.58 to 2.05)	19 more per 1000 (from 87 fewer to 217 more)	⊕○○○ VERY LOW	CRITICAL
Serological response at 6 months – 4-fold or greater decline in RPR titers												
2	observational studies	serious ¹	no inconsistency	no serious indirectness	Serious ²	none	115/197 (58.4%)	67.3%	RR 0.86 (0.75 to 0.99)	94 fewer per 1000 (from 7 fewer to 168 fewer)	⊕○○○ VERY LOW	CRITICAL
Serological response at 9 months – 4-fold or greater decline in RPR titers												
1	observational studies	serious ¹	no inconsistency	no serious indirectness	no serious imprecision	none	52/68 (76.5%)	79.5%	RR 0.96 (0.78 to 1.18)	32 fewer per 1000 (from 175 fewer to 143 more)	⊕○○○ VERY LOW	CRITICAL
Serological response at 12 months – 4-fold or greater decline in RPR titers (except Ghanem which was a serological failure that was reversed for this outcome)												
4	observational studies	serious ¹	no inconsistency	no serious indirectness	no serious imprecision	none	257/308 (83.4%)	88.9%	RR 0.98 (0.93 to 1.04)	18 fewer per 1000 (from 62 fewer to 36 more)	⊕○○○ VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.


Table 46 – Clinical evidence profile: Doxycycline/tetracycline vs BPG for men and women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BPG	Doxycycline/tetracycline (obs)	Relative (95% CI)	Absolute		
Serological response												
1	observational studies	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/25 (100%)	97.4%	RR 1.01 (0.95 to 1.07)	10 more per 1000 (from 49 fewer to 68 more)	⊕○○○ VERY LOW	CRITICAL



10. NEISSERIA GONORRHOEA RESISTANCE: BELGIAN DATA

Table 47 – Minimum inhibitory concentrations for 597 gonorrhoea isolates 2016 Belgium by the CLSI

Sensitivity isolates		Sensitive		MIC*		Intermediate sensitive		MIC*		Resistant		MIC*	
Antibiotic	N	%	mg/L	N	%	mg/L	N	%	mg/L	N	%	mg/L	
Ceftriaxone	597	100.0	≤ 0.25	-	-	-	-	-	-	-	-	-	-
Cefixime	596 ^a	99.8	≤ 0.25	-	-	-	-	-	-	-	-	-	-
Azithromycine	549	92.0	S & I ≤ 0.5	-	-	-	48	8.0	≥ 1.0				
Spectinomycine	597	100.0	≤ 32	0	0.0	64	0	0.0	≥ 128				
Penicilline	69	11.6	≤ 0.06	369	61.8	0.125 - 1.0	159	26.6	≥ 2.0				
Ciprofloxacin	323	54.1	≤ 0.06	5	0.8	0.125 - 0.5	269	45.1	≥ 1.0				
Tetracycline	150	25.2	≤ 0.25	248	41.5	0.5 - 1.0	199	33.3	≥ 2.0				

From Vanden Berghe et al. 2018. *MIC: Minimum inhibitory concentration. ^a one isolate decreased susceptibility

Table 48 – Number of multiresistant isolates out of 597 samples for Belgium 2016 by CLSI*

Resistant isolates; N=254	%	Penicilline	Tetracycline	Azithromycine	Ciprofloxacin
3	1.3	X	X	X	X
5	2.2	X	X	X	
57	24.7	X	X		X
6	2.6	X		X	X
15	6.5	X	X		
0	0.0	X		X	
64	27.7	X			X
11	4.8		X	X	X
54	23.4		X		X
8	3.5		X	X	
8	3.5			X	X

From Vanden Berghe et al. 2018.²⁶¹ *ceftriaxone, cefixime and spectinomycin are not listed as no resistance was detected. X=resistance detected.


Table 49 – Number of multiresistant isolates out of 597 samples for Belgium 2016 by EUCAST*

Number of resistant isolates; N=254	%	Penicilline	Tetracycline	Azithromycine	Ciprofloxacin	Cefixime
69	27.2	X			X	
54	21.3		X		X	
53	20.9	X	X		X	
21	8.3				X	X
15	5.9	X	X			
8	3.1		X	X	X	
8	3.1		X	X		
6	2.4			X	X	X
5	2.0	X	X	X		
4	1.6	X	X		X	X
4	1.6	X		X	X	X
2	0.8	X		X	X	
2	0.8			X	X	
2	0.8	X	X	X	X	
1	0.4	X	X	X	X	X

From Vanden Berghe et al. 2018.²⁶¹ *ceftriaxone and spectinomycin are not listed as no resistance was detected. X=resistance detected.



11. 6 STEPS FOR TESTING STIS IN A SEXUAL HEALTH CONSULTATION

11.1. STEP 1: Starting a conversation about sexual health testing

Offering opportunistic STI testing makes a conversation about sexual health easier for the patient and the carer. The STI testing can be offered at the following occasions:

Examples of occasions	Examples of opening statements
Young people	"STIs are very common among young people and they may not even know they have an STI. We encourage all sexually active young people to get tested regularly for STIs. Would you like a sexual health check-up today?"
Pregnant women	"It is recommended that every pregnant woman should be tested for HIV and syphilis infection. This is an important opportunity to have a sexual health check."
Sexual health questions including reproductive health consultation	"While you're here for contraception advice/cervical screening it's a good time to talk about other areas of sexual health, like having a sexual health check-up..."
Travel consultation	"Some people take risks when they travel overseas and that includes having unprotected sex. If you like, we could do a sexual health check-up before you go and when you return."
Hepatitis B vaccination	"Have you had a hepatitis B vaccination? It protects against an infection that can be sexually transmitted. Do you want to talk about this today?"
Partner has an STI	"I am sorry to hear your partner has a sexually transmitted infection. I suggest we test you today as well and perform a sexual health check-up; would that be something you would like done?"
MSM any occasion	"Did you know that STIs are very common among men who have sex with men? We encourage all sexually active MSM to get tested regularly for STIs. Would you like a sexual health check-up today?"
Patient asking for a check-up	"You are interested in a blood test to check up on your health. Are you also thinking of STI tests? Is it OK if I we talk about that?"
When the media talks about STIs	"Have you noticed the campaign on TV on STIs? Maybe you had some questions in that context that we can talk about today?"
End of a couple relationship (e.g. divorced)	"When starting a new relationship it is recommended to be tested for STIs before having sexual contact without condom. Is this something you would like to talk about?"

Online Links: 6 STEPS FOR TESTING STIs as part of A SEXUAL HEALTH CONSULTATION

- Hepatitis B and hepatitis C information: <https://www.sciensano.be/en/health-topics/hepatitis-a-b-c-d-and-e#what-are-the-different-types-of-hepatitis->



- 'Onder 4 ogen' Sensoa Vlaanderen: <https://www.sensoa.be/praten-over-seksuele-gezondheid-de-huisartsenpraktijk>
- <https://www.sensoa.be/praten-over-hiv-de-huisartsenpraktijk>

11.2. STEP 2 : Sexual history questions for readiness, needs and risk assessment

Examples of **open questions** about sexual behaviour to identify patient readiness and needs

Is it ok to talk about having a sexual health check-up today?

How do you feel about having an STI test done today?

Would you be willing to have some STI tests done today?

Most people find it difficult to talk about sex, contrary to what people think it is not easy to ask questions and find the right answers. Is that something you experience?

Young people often have questions about their body and sex, do you have them and would you like to talk about this?

Condoms are not that easy to use routinely; what are your experiences with them?

Most people struggle to continue to have protected sex when the relation is no longer new; is this something you recognise?

Ask **closed** questions to **identify potential risk** and which tests to do

"You agreed to have STI tests performed (today); I would like to ask some questions about your sexual activity in order to decide what tests to do:"

When did you last have sex?

Was it with a woman, a man, or both?

When you had sex, was it vaginal, oral or anal sex?

Did you use condoms? What did you use as protection?

When did you last have sex with a different person(s)?

Did you use condoms with all of them?

Do you sometimes use drugs or other products to have better sex?

Information for the patient:

- <https://depistage.be/> (French)
- <https://www.sidasos.be/> (French)
- <https://www.sensoa.be/> (Dutch)



11.3. STEP 3: STI testing overview

Recommendations from the KCE and chlamydia STI guideline

Who is the patient?*	What infection?
1. Young people	Standard tests <ul style="list-style-type: none">• Chlamydia (whenever positive and anal sex, test for LGV)• Gonorrhoea Unknown immune status Hep B: add Hep B Sexual contact with patient from 4 to 7: add HIV, Syphilis, Hep C
2. Heterosexuals	Standard tests <ul style="list-style-type: none">• Chlamydia (whenever positive and anal sex, test for LGV)• Gonorrhoea Unknown immune status Hep B: add Hep B Sexual contact with patient from 4 to 7: add HIV, Syphilis, Hep C
3. Pregnant women	Standard tests for all pregnant women <ul style="list-style-type: none">• Syphilis• HIV Unknown immune status Hep B: Hep B Pregnant women <25 years and older pregnant women at increased risk (new or multiple sex partners, previous or coexisting STI, sex partner who has a STI, exchanging sex for money or drugs): add Chlamydia, gonorrhoea
4. Persons with a migration background, mobile populations and travellers	Standard tests <ul style="list-style-type: none">• Chlamydia (whenever positive and anal sex, test for LGV)• Gonorrhoea• Syphilis Unknown immune status Hep B: add Hep B Persons from Sub-Saharan origin or HIV status unknown: add HIV Persons from endemic region for hepatitis C: add Hep C
5. MSM	Standard tests <ul style="list-style-type: none">• Chlamydia (whenever positive and anal sex, test for LGV)• Gonorrhoea• Syphilis



	<ul style="list-style-type: none"> • HIV <p>Unknown immune status: add Hep B, Hep A</p> <p>HIV positive, on PrEP, or performing traumatic sexual practices: add Hep C</p>
6. Sexual activity for money	<p>Standard tests</p> <ul style="list-style-type: none"> • Chlamydia (whenever positive and anal sex, test for LGV) • Gonorrhoea • Syphilis • HIV <p>Unknown immune status: add Hep B</p> <p>HIV positive, on PrEP, snorting drugs, or performing traumatic sexual practices: add Hep C</p>
7. Drug use with sharing of drug instruments	<p>Standard tests</p> <ul style="list-style-type: none"> • Chlamydia (whenever positive and anal sex, test for LGV) • Gonorrhoea • Syphilis • HIV • Hepatitis C • Unknown immune status: Hep B

*definitions at the end of the document

- Links for information on STIs: <https://www.partneralert.be/N/soas> <https://www.sciensano.be/nl/gezondheidsonderwerpen/seksueel-overdraagbare-aandoening-soa>
- Sharing of drug instruments: The prevention message here is not to share" drug instruments, Kresina said. "Any time you have bodily fluids being transferred, you have a risk of transmission of hepatitis C." The full study, "Hepatitis C Virus Infection Among Noninjecting Drug Users in New York City," is published in the July issue of Journal of Medical Virology (2003;70(3):387-390).
- <https://www.cdc.gov/std/stats16/Gonorrhea.htm>
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4672879/>
- <https://ecdc.europa.eu/en/publications-data/public-health-guidance-brief-hiv-hepatitis-b-and-c-testing-eueea>



11.4. STEP 4: How to test

Infection	Specimen collection site	Test
Chlamydia (and LGV)	Woman: vaginal swab [§] (first option) or first-void urine (second option) IF oral sex: throat swab [€] IF anal sex: anorectal swab [§] Men: First stream urine anytime IF oral sex: throat swab [€] IF anal sex: anorectal swab [§] <i>§self-collected or by clinician €clinician collected</i>	NAAT (always use synthetic swabs) May be negative in the first 2 weeks after risk contact A positive anorectal chlamydia should be tested for LGV by genotyping in all men; in women only when presenting with proctitis symptoms.
Gonorrhoea	Woman: vaginal swab ^μ (first option) OR first-void urine IF oral sex: throat swab [€] IF anal sex: anorectal swab [§] Women with high sexual risk behaviour: all three sites Men: First stream urine anytime IF oral sex: throat swab [€] IF anal sex: anorectal swab [§] MSM: all three sites <i>§self-collected or by clinician €clinician collected μself-collected</i>	NAAT (always use synthetic swabs) May be negative in the first 2 weeks after risk contact Do NOT use culture testing for diagnosis (except for symptomatic male gonorrhoea). Take a sample for culture in case of a positive NAAT before treatment (for surveillance of resistance) is started.
Syphilis	Blood IF ulcer: swab (NAAT analysis only performed at the National Reference Centre – Sexually Transmitted Infections (NRC-STI))	Syphilis serology; repeat serology at 6 weeks after risk contact in case of a negative result NAAT (always use a synthetic swab)
HIV	Blood	HIV Ab/Ag; Repeat serology at 6 weeks after risk contact in case of a negative results
Hepatitis A	Blood	Anti-HAV Ig-total
Hepatitis B	Blood	Infected? HBsAg and when positive add HBeAg, anti-HBe, IgM- anti-HBc, and anti-HBs (distinguish acute from chronic infection) Vaccination status? Anti-HBs
Hepatitis C	Blood	HCV Ab RNA analysis after + HCV Ab test



11.5. STEP 5: Treatment overview - Test of cure - Follow up

Give general advice whenever an infection is detected:

- Patient should be advised to abstain from sexual contact for 7 days after they and their partners have completed treatment and their symptoms have resolved.
- All persons who receive a diagnosis of an STI should be tested for other STIs, including Chlamydia, Gonorrhoea, Syphilis and HIV

Infection	Treatment	Test of cure and follow up
Chlamydia (and LGV)	<p>Men and non-pregnant women</p> <ul style="list-style-type: none">• Urogenital, oropharyngeal: doxycycline 100mg orally twice daily for 7 days OR Azithromycin 1g orally• Anorectal: doxycycline 100mg orally twice daily for 7 days<ul style="list-style-type: none">○ Except in HIV positive men with unknown LGV status: doxycycline 100mg orally twice daily for 21 days• Anorectal LGV: doxycycline 100mg orally twice daily for 21 days <p>Pregnant women and breastfeeding</p> <ul style="list-style-type: none">• Urogenital, oropharyngeal, anorectal: Azithromycin 1g orally <p>Person with allergy to Penicillin</p> <ul style="list-style-type: none">• doxycycline as described above for the specific indications	<p>Optionally, unless</p> <ul style="list-style-type: none">• rectal infection• treatment with other than recommended• poor compliance• persistence of symptoms• pregnant women <p>Performed 4 weeks after treatment.</p>
Gonorrhoea	<p>Men and non-pregnant women</p> <ul style="list-style-type: none">• Dual therapy of single doses of Ceftriaxone 500mg IM AND Azithromycin 2g orally <p>Pregnant women</p> <ul style="list-style-type: none">• single therapy of Ceftriaxone 500mg IM <p>Person with allergy to Penicillin</p> <ul style="list-style-type: none">• Referral	<p>Optionally, unless</p> <ul style="list-style-type: none">• suspicion of treatment failure• pharyngeal infection• alternative regimen is used• pregnant women• after travelling to Southeast and East Asia <p>Performed 4 weeks after treatment.</p>
Combined Gonorrhoea and Chlamydia infection	<p>Men and non-pregnant women</p> <ul style="list-style-type: none">• Urogenital, oropharyngeal: Dual therapy of single doses of Ceftriaxone 500mg IM and Azithromycin 2g orally• Anorectal: Dual therapy of single doses of Ceftriaxone 500mg IM AND doxycycline 100mg orally twice daily for 7 days<ul style="list-style-type: none">○ Except in HIV positive men with unknown LGV status: Ceftriaxone 500mg IM AND doxycycline 100mg orally twice daily for 21 days	<p>Standard for gonorrhoea and</p> <p>Optionally for chlamydia, unless</p> <ul style="list-style-type: none">• rectal infection• treatment with other than recommended• poor compliance• persistence of symptoms



	<ul style="list-style-type: none"> With anorectal LGV: Dual therapy of single dose ceftriaxone 500 mg IM AND doxycycline 100 mg orally twice daily for 21 days. <p>Pregnant women</p> <ul style="list-style-type: none"> Ceftriaxone 500mg IM AND Azithromycin 1g orally <p>Person with allergy to Penicillin: Referral</p>	<ul style="list-style-type: none"> pregnant women <p>Performed 4 weeks after treatment.</p>
Syphilis	<p>Early Syphilis</p> <ul style="list-style-type: none"> First choice: BPG 2.4 million units IM Second choice: Doxycycline 100mg orally twice daily for 14 days Third choice: ceftriaxone 1g IM daily for 10 days <p>Late Syphilis</p> <ul style="list-style-type: none"> First choice: BPG 2.4 million units IM once weekly for 3 weeks (day 1, day 8 and day 15) Second choice: Doxycycline 100mg orally twice daily for 28 days <p>Pregnant women: referral</p> <p>Person with allergy to Penicillin:</p> <ul style="list-style-type: none"> alternative therapies (such as doxycycline) + referral needed 	<p>Patient with positive serology: Clinical and serological (non-trep RPR) follow-up indicated for</p> <ul style="list-style-type: none"> Early syphilis: at 3 and 6 months Late syphilis: at 3, 6 and 12 months <p>Referral is indicated when RPR titres do not decrease four-fold within 6 months from day 1 of treatment for early syphilis, or 12 months from day 1 of treatment for late syphilis</p> <p>Negative results in suspected infected patient:</p> <ul style="list-style-type: none"> Symptomatic patient with ulcer: treat and repeat serologic tests at 6 weeks after ulcer appearance. Optionally, serologic tests at 2 weeks after ulcer appearance Asymptomatic patients after isolated high risk episode: repeat serologic test at 6 weeks. Optionally at 12 weeks after treatment according to lab procedures
HIV	Referral	
Hepatitis A, B, C	<p>Hepatitis A and/or B: vaccination</p> <p>Referral for acute infection whenever abnormal liver tests. Hepatitis C and chronic infections: referral</p>	



11.6. STEP 6: Partner management and contact

IDENTIFICATION OF PARTNERS	CONTACTING OF PARTNERS	Notification
<p>Discuss and identify the sexual partners of your patient. Opening statements:</p> <p><i>"It is important your partner(s) get treated so you don't get infected again".</i></p> <p><i>"Most people with an STI don't know they have it because they have no symptoms, but can pass it on to other partners or have long-term problems"</i></p> <p><i>"Think back to when and where you had sex recently or any special events"</i></p> <p><i>"From our discussion, there are a few people who need to be informed. How would it be best to contact them?"</i></p> <p>Identify the last 1 to 5 partners OR if too many those in the last month.</p>	<p>Patient informs the partner(s)</p> <ul style="list-style-type: none"> • Patient provides Information on the STI to the partner and advises the partner to be tested: www.zanzu.be • Letter given by the patient to the partner: <ul style="list-style-type: none"> • Domus Medica: new letter soon online • Explanation about the STI allesoverseks.be • Need for the partner to come / go for a sexual health consultation • https://www.zorg-en-gezondheid.be/sites/default/files/atoms/files/2016%20Brief%20Partnerverwittiging%20voor%20SOA%20juli%202016%20%28002%29.docx Online partner notification: partneralert.be • Follow-up consultation needed with patient to check that all went well 	<p>Brussels: Phone: 0478 77 77 08 (24h/24 and 7d/7); Mail: notif-hyg@ccc.brussels; https://www.wiv-isp.be/matra/bru/connexion.aspx</p> <p>Flanders: Phone: on https://www.zorg-en-gezondheid.be/contact-infectieziektebestrijding-en-vaccinatie. For urgent cases or outside of office hours, the phone number is 02 512 93 89; Mail: infectieziekten@zorg-en-gezondheid.be; https://www.zorg-en-gezondheid.be/een-meldingsplichtige-infectieziekte-aangeven</p> <p>Wallonia: Phone: 071 205 105; Mail: surveillance.sante@aviq.be; https://www.wiv-isp.be/matra/CF/connexion.aspx</p>
<p>Timeframes for lookback periods to consider (but only as in indication)</p> <p>Chlamydia and LGV, gonorrhoea: 3 weeks to 1 month</p> <p>Syphilis and HIV: 12 months</p> <p>Hepatitis A: 2 months</p> <p>Hepatitis B and C: 6 months</p>	<p>Practitioner informs the partner(s)</p> <ul style="list-style-type: none"> • When anonymity is required <ul style="list-style-type: none"> • a letter can be posted to the partner by the GP • Online partner notification: partneralert.be • Referral to specialist agency: <ul style="list-style-type: none"> • Elisa Centre Brussels • Help Centre Antwerp • S-clinic Brussels 	<p>List of notifiable diseases: While chlamydia, gonorrhoea and syphilis have to be notified in Brussels and Flanders, only congenital syphilis needs to be notified in Wallonia.</p>



Definitions for groups at risk in STEP 3

- **Young people and adolescents:** Aged up to 29 years (no minimum age), with (or planning) unprotected oral, anal or vaginal intercourse and with two or more serial monogamous relationships.
- **Heterosexuals:** In a non-exclusively monogamous relationship, with unprotected oral, anal or vaginal intercourse and unknown STI status of partner(s). Relationships at risk include: concurrent partners, multiple partners over a short time period, partner from a risk group (sex worker, MSM, mobile population, IV drug use), **or** partners in an anonymous setting, new partners with unknown STI status.
- **Pregnant women:** any time of pregnancy in all pregnant women.
- **Persons with a migration background, mobile populations and travellers:** Patient or sex partner originates or travels to and from countries that are mostly affected by STIs (see links and maps for high STI prevalence countries).
- **Men who have sex with men (MSM):** All MSM with unprotected oral, or anal sex and unknown STI status of partner(s). Relationships and behaviours at high risk include: unprotected oral or anal sex with concurrent partners, multiple partners over a short time period, partner from another risk group (sex worker, mobile population, IV drug use), **or** with partners in an anonymous setting; taking Pre-exposure prophylaxis (PrEP), a recent HIV diagnosis, **or** an STI diagnosis in the past or taking Post Exposure Prophylaxis (PEP) in the past.
- **People who engage in sexual relationships for money (including Sex worker, escort, sugar baby...):** This category include men and women who engage in the exchange of sexual activity for income, employment, goods (i.e. food, drugs), services, or housing. Young people, mostly students or single mums, do not consider themselves as sex workers but should be considered when having high risk sexual behaviours.
- **Drug users sharing drug instruments (syringes and needles for injection, straw or rolled bill for snorting):** Sexually active people who injected or snorted drugs in the last 12 months. The life styles of people who inject or snorted drugs may involve unprotected sexual contact.



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