



World Health
Organization

**GUIDELINES FOR THE MANAGEMENT OF SYMPTOMATIC
SEXUALLY TRANSMITTED INFECTIONS**



**WEB ANNEX F. SYSTEMATIC REVIEW FOR
SYNDROMIC MANAGEMENT OF THE
ANORECTAL SYNDROME**

JUNE 2021

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Guidelines for the management of symptomatic sexually transmitted infections: Web Annex F. Systematic review for syndromic management of the anorectal syndrome

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1. INTRODUCTION

Sexually transmitted infections (STIs), including human immunodeficiency virus (HIV), continue to present significant health, social, and economic problems in the developing world, leading to considerable morbidity, mortality, and stigma. In under-resourced settings, the lack of adequate laboratory infrastructure and/or high prohibitive costs of diagnostics means that in many settings, STI management relies on syndromic management rather than aetiological diagnosis and management. In these settings, the detection of asymptomatic STIs is largely non-existent. Therefore, synthesizing the latest evidence for the performance of syndromic STI case management would help the World Health Organization (WHO) in their guideline recommendations for syndromic STI management, last updated in 2003.[1]

To evaluate if there is still a role for syndromic STI management or whether STI diagnostics are critical for STI case management, we systematically reviewed the evidence for the performance of syndromic management of STIs. Specifically, we conducted reviews on the diagnostic accuracy and aetiologies of syndromic case management of genital ulcer, anorectal infection and lower abdominal pain. Our specific objectives were to review the flowcharts used for:

- people presenting with genital ulcer disease to detect herpes simplex virus (HSV) or syphilis or lymphogranuloma venereum (LGV) or chancroid, or if no flowcharts found, a minor review of test accuracy of different tests, or risk association/prevalence.
- people presenting with the anorectal syndrome to detect anal STIs or if no flowcharts found, a major review of test accuracy of different tests, or risk association/prevalence.
- people presenting with lower abdominal pain to detect pelvic inflammatory disease (PID) or vaginal or cervical infections, or if no flowcharts found, a major review of test accuracy of different tests, or risk association/prevalence.

2. METHODS

Study inclusion

- Clinical guidelines/algorithms
 - Flow charts for genital ulcer (for syphilis, HSV, LGV, chancroid), anorectal syndromes (for Ct/Ng/Mg/LGV/HSV/Tp/Donovanosis), lower abdominal pain (for PID, vaginal/cervical infections), and vaginal discharge
- Randomized controlled trials
- Observational studies
- Report on at least one of:
 - Comparing syndromic case management against laboratory-confirmed STIs
 - Risk factor analysis of signs/symptoms associated with STI diagnoses and other risk factors associated with STI syndromes

Study exclusion

- Contains no original data i.e. systematic reviews/Letter/editorials/Commentaries/Book chapters
 - But can use these to identify other relevant primary studies
- Qualitative research about outcomes
- Duplicated results from another study
- Laboratory studies about testing STI diagnostic performance
- Studies restricting study population, e.g. men with urethritis, women with cervicitis

Search method

Three separate searches were conducted: one for each of the syndromes under investigation. We included papers that focused on other aspects of syndromic management (i.e. acceptability, feasibility, equity, resources) in addition to the accuracy or sensitivity of the syndromic management approach. The search for each syndrome has been constructed as below.

- Concept 1: syndromic management
- Concept 2: syndrome under investigation
- Concept 3: diagnostic accuracy and sensitivity papers
- Results group 1: concept 1 AND concept 2 AND concept 3
- Results group 2: (concept 1 AND concept 2) NOT Results group 1

A draft search strategy was compiled in the OvidSP Medline database by an experienced information specialist. The search strategy included strings of terms, synonyms and controlled vocabulary terms (where available). As the syndromic management approach was not introduced until 1996, the search was limited to papers published in 1995 or after. No other limits were added. This search strategy was refined with the project team until the results retrieved reflected the scope of the project. The agreed OvidSP Medline search was adapted for each database to incorporate database-specific syntax and controlled vocabularies. Full details of the search strings used for each database can be found in the appendix. A

The following databases were searched on 12 and 13 September 2019.

- Ovid SP Medline and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, 1946 to September 11, 2019
- OvidSP Embase, 1974 to 11 September 2019
- OvidSP Global Health, 1910 to week 35, 2019
- OvidSP Northern Light Life Sciences Conference Abstracts, 2010 to Week 34, 2019
- Ebsco CINAHL Plus, complete database
- Ebsco Africa-Wide Information, complete database
- Clarivate Analytics Web of Science Core Collection, consisting of the following databases:
 - Science Citation Index Expanded (SCI-EXPANDED), 1970 - present
 - Social Sciences Citation Index (SSCI), 1970 - present
 - Arts & Humanities Citation Index (A&HCI), 1975 - present
 - Conference Proceedings Citation Index - Science (CPCI-S), 1990 - present
 - Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH), 1990 - present
 - Emerging Sources Citation Index (ESCI), 2015 – present
- BIREME/PAHO/WHO Virtual Health Library LILACS, complete database

All citations identified by our searches were imported into EndNote X9 software. Duplicates were identified and removed using the method described on the LAS blog.¹

Data extraction

We followed the guidelines in the Cochrane Handbook 5.1.[2] Three groups of two independent reviewers screened the title and abstracts of unduplicated papers. Discrepancies in screening were resolved by a third reviewer (JO). Each team extracted relevant data from deduplicated full publications. Risk of bias assessment was conducted using the Joanna Briggs Institute Checklist for diagnostic studies.[3]

Statistical analysis

Diagnostic accuracy cannot be summarized by one measure as sensitivity and specificity are correlated. Therefore, we must choose hierarchical (multilevel) models that use a binomial data structure, i.e. we use a hierarchical logistic regression model in STATA 13.1. After pooling the studies, we report the sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratio. The inverse of the negative likelihood ratio (1/LR-) can be used to compare with the positive likelihood ratio to indicate whether the positive or negative test result has a greater impact on the odds of disease. Likelihood ratios assess the probability or likelihood that the test result obtained would be expected in a person with the condition, compared to the probability or likelihood that the same result would be seen in a person without the condition.

The positive likelihood ratio $LR+ = \frac{\text{sensitivity}}{(1-\text{specificity})} = \frac{TP}{(TP+FN)} \div \frac{FP}{(FP+TN)}$ expresses how many times more

likely people with the condition are to receive a positive test result compared to those who do not have the condition, while the negative likelihood ratio $LR- = \frac{(1-\text{sensitivity})}{\text{specificity}} = \frac{FN}{(TP+FN)} \div \frac{TN}{(FP+TN)}$

expresses how likely it is that people with the condition will receive a negative test result compared to those who do not have the condition.

Likelihood ratio	Approximate* change in probability ^[12]	Effect on posttest Probability of disease ^[13]
Values between 0 and 1 <i>decrease</i> the probability of disease (-LR)		
0.1	-45%	Large decrease
0.2	-30%	Moderate decrease
0.5	-15%	Slight decrease
1	-0%	None
Values greater 1 <i>increase</i> the probability of disease (+LR)		
1	+0%	None
2	+15%	Slight increase
5	+30%	Moderate increase
10	+45%	Large increase

[12] McGee, Steven (1 August 2002). "Simplifying likelihood ratios". *Journal of General Internal Medicine*. 17 (8): 647–650. doi:10.1046/j.1525-1497.2002.10750.x. ISSN 0884-8734. PMC 1495095. PMID 12213147.

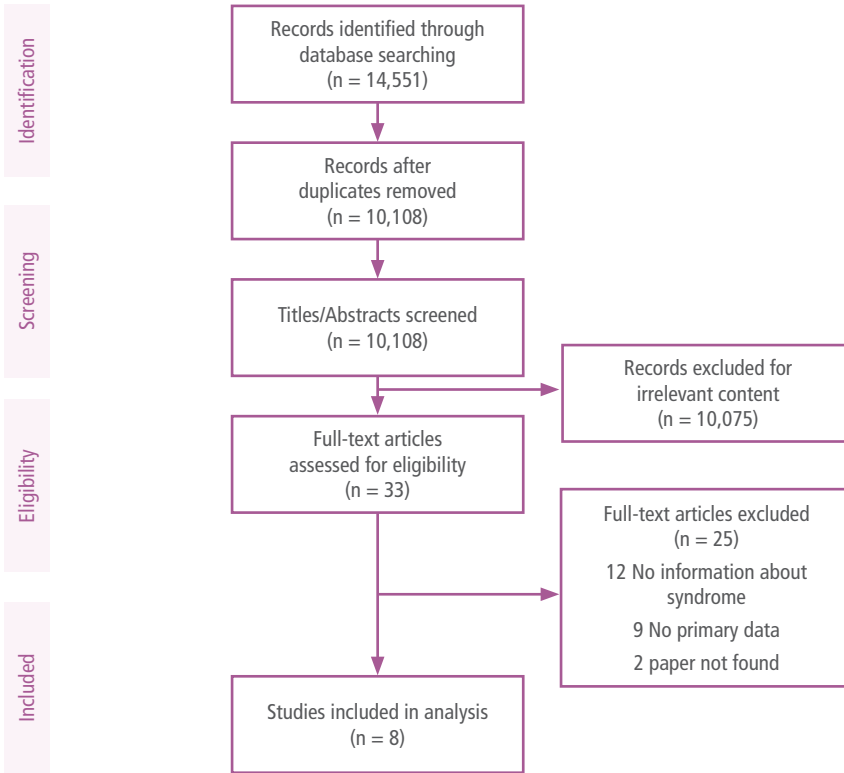
[13] Henderson, Mark C.; Tierney, Lawrence M.; Smetana, Gerald W. (2012). *The Patient History (2nd ed.)*. McGraw-Hill. p. 30. ISBN 978-0-07-162494-7.

To graphically display the trade-off between sensitivity and specificity, we present the summary receiver operating characteristic (SROC) curve from the hierarchical summary receiver operating characteristic (HROC) model^[4] and prediction region (i.e. for the forecast of the true sensitivity and specificity in a future study). We also plot the summary operating point and its confidence region. Forest plots for showing within-study estimates and confidence intervals for sensitivity and specificity separately.

In the meta-analyses below, we have only included papers where we could calculate the numbers of true positive, false positives, true negatives and false negatives. For the other papers without this data, we have summarized their results qualitatively (i.e. without pooling).

3. RESULTS

3.1 PRISMA flow chart for anorectal syndromes



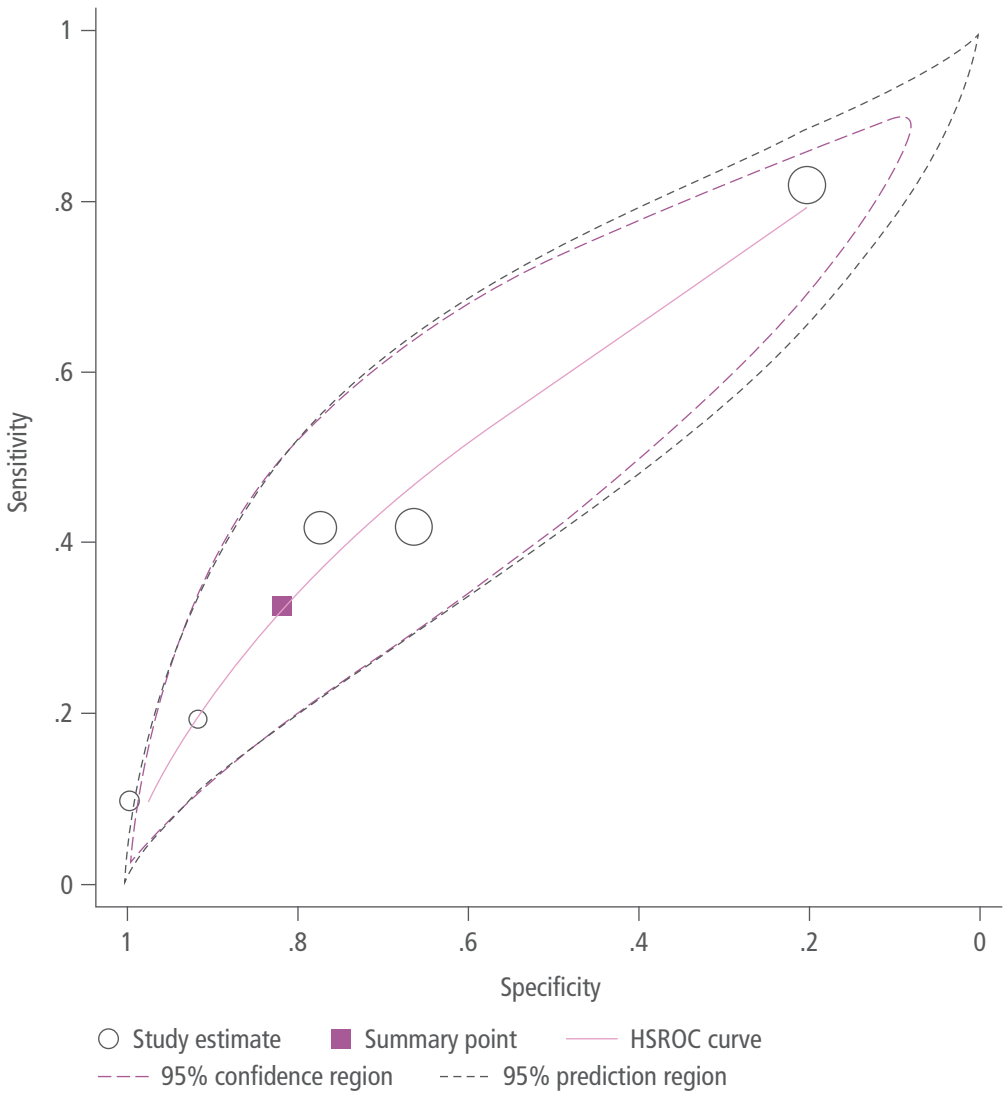
3.2 Anorectal syndrome

- Country income level
 - 1/8 (13%) High income
 - 3/8 (38%) Upper Middle
 - 4/8 (50%) Lower Middle
- Study population recruited from (may not add up to 100% because of multiple recruitment sites)
 - 5/8 (63%) Sexual health clinics
 - 1/8 (13%) Community setting (incl. bar, discos, CBOs)
 - 3/18 (38%) Unclear
- Year of study
 - 2/8 (25%) 2009 and before
 - 3/8 (38%) 2010-2014
 - 1/8 (13%) 2015 and after
 - 2/8 (25%) unclear

For detection of any STIs (chlamydia, gonorrhoea), four studies provided five estimates for pooling.[5-8] The pooled sensitivity for detecting chlamydia/gonorrhoea using a syndromic management approach is 32.4% (95% CI: 11.4-64.0), and pooled specificity is 81.7% (95% CI: 43.1-96.3). The diagnostic odds ratio is 2.13 (95% CI: 1.17-3.89). The positive likelihood ratio is 1.77 (95% CI: 0.94-3.31), and negative likelihood ratio is 0.83 (95% CI: 0.72-0.95). The inverse negative likelihood ratio is 1.21 (95% CI: 1.05-1.39).

For a cohort of 1000 individuals:

Prevalence	Sensitivity	Specificity	PPV	NPV	Number of cases	Missed cases	False Positive (Overtreated)
0.05	0.324	0.817	0.085	0.958	50	34	174
0.1	0.324	0.817	0.164	0.916	100	68	165
0.15	0.324	0.817	0.238	0.873	150	101	156
0.2	0.324	0.817	0.307	0.829	200	135	146
0.25	0.324	0.817	0.371	0.784	250	169	137
0.3	0.324	0.817	0.431	0.738	300	203	128
0.35	0.324	0.817	0.488	0.692	350	237	119
0.4	0.324	0.817	0.541	0.644	400	270	110
0.45	0.324	0.817	0.592	0.596	450	304	101
0.5	0.324	0.817	0.639	0.547	500	338	92
0.55	0.324	0.817	0.684	0.497	550	372	82
0.6	0.324	0.817	0.726	0.446	600	406	73
0.65	0.324	0.817	0.767	0.394	650	439	64
0.7	0.324	0.817	0.805	0.341	700	473	55
0.75	0.324	0.817	0.842	0.287	750	507	46
0.8	0.324	0.817	0.876	0.232	800	541	37
0.85	0.324	0.817	0.909	0.176	850	575	27
0.9	0.324	0.817	0.941	0.118	900	608	18
0.95	0.324	0.817	0.971	0.060	950	642	9
1	0.324	0.817	1.000	0.000	1000	676	0



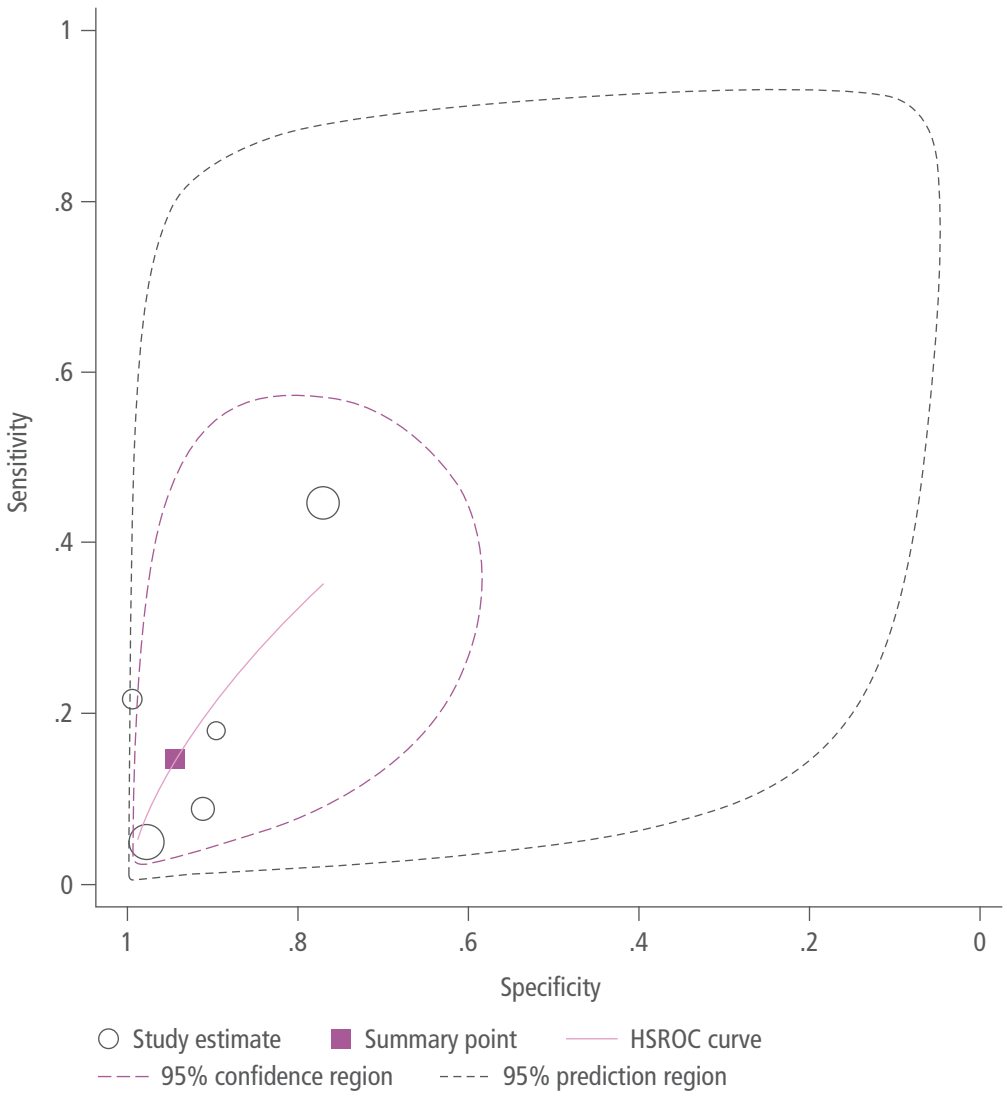
Detection of any STI for the anorectal syndrome

Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Pathogens / Test	True positive	False negative	False positive	True negative
Mugundu[5]	2008-2009	India	Lower middle	868	Sexual health clinic	100% MSM	Receptive anal sex +/- anal discharge + subsequent proctoscopy +/- smear findings	Ct/Ng NAAT - Roche Amplicor	53	74	250	491
Mugundu[5]	2008-2009	India	Lower middle	868	Sexual health clinic	100% MSM	Adding "risk assessment" to above		104	23	592	149
Quilter[8]	Unclear	Kenya	Lower middle	698	Community settings	99% MSM	Anal symptoms + "risk assessment" (Model derived risk score)	Ct/Ng NAAT - Abbott Realtime	15	21	151	511
Rebe[6]	2012	South Africa	Upper middle	200	Sexual health clinic	100% MSM	Symptoms only	Ct/Ng, Aptima Combo 2	9	38	13	140
Sanders[7]	2011-2012	Kenya	Lower middle	244	Unclear	100% MSM	Symptoms + "risk assessment"	Ct/Ng Aptima Combo 2	3	28	1	212

For detection of anal gonorrhoea, five studies provided five estimates for pooling.[6-10] The pooled sensitivity for detecting gonorrhoea using a syndromic management approach is 14.2% (95% CI: 6.1-29.7), and pooled specificity is 94.4% (95% CI: 84.8-98.1). The diagnostic odds ratio is 2.82 (95% CI: 1.08-7.40). The positive likelihood ratio is 2.56 (95% CI: 1.05-6.23), and the negative likelihood ratio is 0.91 (95% CI: 0.81-1.01). The inverse negative likelihood ratio is 1.10 (95% CI: 0.99-1.23).

For a cohort of 1000 individuals:

Prevalence	Sensitivity	Specificity	PPV	NPV	Number of cases	Missed cases	False Positive (Overtreated)
0.05	0.142	0.944	0.118	0.954	50	43	53
0.1	0.142	0.944	0.220	0.908	100	86	50
0.15	0.142	0.944	0.309	0.862	150	129	48
0.2	0.142	0.944	0.388	0.815	200	172	45
0.25	0.142	0.944	0.458	0.767	250	215	42
0.3	0.142	0.944	0.521	0.720	300	257	39
0.35	0.142	0.944	0.577	0.671	350	300	36
0.4	0.142	0.944	0.628	0.623	400	343	34
0.45	0.142	0.944	0.675	0.574	450	386	31
0.5	0.142	0.944	0.717	0.524	500	429	28
0.55	0.142	0.944	0.756	0.474	550	472	25
0.6	0.142	0.944	0.792	0.423	600	515	22
0.65	0.142	0.944	0.825	0.372	650	558	20
0.7	0.142	0.944	0.855	0.320	700	601	17
0.75	0.142	0.944	0.884	0.268	750	644	14
0.8	0.142	0.944	0.910	0.216	800	686	11
0.85	0.142	0.944	0.935	0.163	850	729	8
0.9	0.142	0.944	0.958	0.109	900	772	6
0.95	0.142	0.944	0.980	0.055	950	815	3
1	0.142	0.944	1.000	0.000	1000	858	0



Detection of anal gonorrhoea for the anorectal syndrome

Study	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How is a positive case defined	Pathogens / Test	True positive	False negative	False positive	True negative
Caracas[9]	2015-16	Brazil	Upper middle	345	Unclear	100% Transwomen	Symptoms only	Not reported	4	43	26	272
Passaro[10]	2012-14	Peru	Upper middle	787	Unclear	100% MSM	Symptoms only	NAAT	3	62	16	706
Quilter[11]	Unclear	Kenya	Lower middle	698	Community settings	99% MSM	Anal symptoms + "risk assessment" (Model derived risk score)		12	15	154	517
Rebel[6]	2012	South Africa	Upper middle	200	Sexual health clinic	100% MSM	Symptoms only		3	14	19	164
Sanders[7]	2011-12	Kenya	Lower middle	19	Unclear	100% MSM	Symptoms + "risk assessment"		4	3	11	1

There were no estimates found for evaluating the accuracy of syndromic management for herpes or syphilis. One study among MSM from sexual health clinics in the Netherlands provided an estimate for the sensitivity of syndromic management to detect LGV: 4.6% (95% CI: 1.3-11.4).[12]

Studies with relevant information for evaluating anorectal syndrome

- Caracas C, Jalil EM, Garcia ACF, Nazer SC, De Oliveira LP, Veloso V, et al. High chlamydia and gonorrhea prevalences and low performance of syndromic management among Brazilian transwomen. *AIDS Research and Human Retroviruses*. 2018;34 (Supplement 1):240.
- Mugundu PR, Narayanan P, Das A, Morineau G. Assessing syndromic management algorithms for the diagnosis of rectal chlamydia and gonorrhoeae among MSM clinic attendees from two cities in India. *Sexually Transmitted Infections*. 2013;89(SUPPL. 1).
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3.3 Risk of Bias using QUADAS-2

Study	Patient selection	Index Test	Reference standard	Flow and Timing
Mugundu[5]	Low	Low	Low	Low
Quilter[8]	Low	Low	Low	Low
Rebe[6]	Low	Low	Low	Low
Sanders[7]	Low	Low	Low	Low
Caracas[9]	Low	Low	Unclear	Low
Passaro[10]	Low	Low	Low	Low

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3. Joanna Briggs Institute Reviewer's Manual. Diagnostic test accuracy systematic reviews. Appendix 9.1 Critical appraisal checklist [Available from: <https://wiki.joannabriggs.org/display/MANUAL/Appendix+9.1+Critical+appraisal+checklist>].
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5. APPENDIX A - SEARCH RESULTS

5.1 Anorectal syndromes

The search retrieved a total of 14,551 results. 4443 (31%) were identified as duplicates. The number of results pre-and post-deduplication is listed in the table below.

Database name	Diagnostic accuracy: Total number of results	Diagnostic accuracy: Number of results once duplicates removed	Other papers: Total number of results	Other papers: Number of results once duplicates removed
Ovid SP Medline and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily	1910	1904	1032	1030
OvidSP Embase	4750	3584	2550	2009
OvidSP Global Health	1155	475	413	223
OvidSP Northern Light Life Sciences Conference Abstracts	62	31	78	39
Ebsco CINAHL Plus	532	106	476	202
Ebsco Africa-Wide Information	237	13	49	8
Clarivate Analytics Web of Science Core Collection	896	220	332	99
BIREME/PAHO/WHO Virtual Health Library LILACS	47	44	32	31
Total	9589	6377	4962	3731

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