World Health Organization

GUIDELINES FOR THE MANAGEMENT OF SYMPTOMATIC SEXUALLY TRANSMITTED INFECTIONS

WEB ANNEX B. UPDATED SYSTEMATIC REVIEW OF THE PERFORMANCE OF THE VAGINAL DISCHARGE SYNDROMIC MANAGEMENT IN TREATING VAGINAL AND CERVICAL INFECTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Design and layout by 400 Communications.

CONTENTS

1. METHODS

We performed an update of the systematic review for vaginal discharge by Zemouri 2016.

Electronic search and study selection

The original review searched various databases up to March 2015. We updated the search from January 2015 to September 2018 in OVID Medline and CENTRAL, and in EMBASE using the two strategies provided in Zemouri (2016).

Studies that evaluated the diagnostic accuracy and validation of vaginal discharge flowchart compared to any laboratory diagnostic test were included. Studies that did not distinguish between cervical infections [caused by *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT)] and vaginal infections [caused by *Trichomonas vaginalis* (TV) and *Bacterial vaginosis* (BV)] were not included in the final review. Studies that presented data on sensitivity, specificity, positive predictive values (PPV), negative predictive value (NPV) or that provided data from which these parameters could be calculated using two by two tables were included. We excluded studies published in languages other than English, French, Spanish and Dutch. Case reports and letter to editor were excluded. Two investigators (AMB and SD) assessed the studies for relevance, title, abstract, and content and applied the inclusion criteria to the full text articles. In case of disagreement between the reviewers, a discussion followed in order to reach consensus, otherwise the principal investigator (NS) was consulted.

Index tests

We followed Zemouri's categorisation of flowcharts (the index tests), as such:

- Flowchart 1 = history and risk assessment;
- Flowchart 2 = history, risk assessment and speculum examination;
- Flowchart 3 = history, risk assessment, speculum examination, and vaginal discharge samples for Gram staining and microscopy;
- Flowchart 4 = country adapted flowcharts or those not defined by the study method.

Statistical analysis

We conducted a meta-analysis by pooling of samples from all studies within different types of flowcharts. We calculated the pooled sensitivity and specificity for the different type of the flowcharts using the WINPEPI software (version 11.65, August 2016). If the study had presented the results separately for NG, CT, TV and BV, the study with the higher PPV was included in the meta-analyses so as not to over represent any study.

Risk of bias of included studies

We assessed the risk of bias of the different studies using the QUADAS-2 assessment tool. We graded as high, low or unclear the risk of bias for patient selection, index test, reference standard, flow and timing.

2. RESULTS

Study selection

The two detailed search strategies are below with hits:

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2018>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <2014 to September 20, 2018>

1. exp Vaginal Discharge/ (226)
2. vaginal discharge.ti,ab. (1040)
3. vaginal discharges.ti,ab. (40)
4. leukorrhea.mp. (134)
5. cervical discharge.mp. (28)
6. Cervix Uteri/ (3998)
7. cervical discharges.mp. (2)
8. vaginal.mp. (36974)
9. discharge.mp. (85265)
10. 8 and 9 (1957)
11. vagina.mp. (10943)
12. 9 and 11 (645)
13. cervix.mp. (15547)
14. 9 and 13 (297)
15. vaginal secretion.mp. (124)
16. Software Design/ (916)
17. flowcharts.mp. (110)
18. Flowchart.mp. (466)
19. algorithm.mp. (84700)
20. algorithms.mp. (94011)
21. flow charts.mp. (112)
22. flow chart.mp. (403)
23. clinical pathway.mp. (981)
24. clinical pathways.mp. (804)
25. risk assessment.mp. (97092)
26. syndromically.mp. (21)
27. syndromic.mp. (4848)
28. signs.mp. (97431)
29. symptoms.mp. (365438)
30. symptom.mp. (111199)
31. sign decision tree.mp. (0)
32. syndromic approach.mp. (82)
33. syndromic diagnosis.mp. (95)
34. syndromic management.mp. (123)
35. syndromic approaches.mp. (4)
36. (Software Design or flowcharts or Flowchart or algorithm or algorithms or flow charts or flow chart or clinical pathway or clinical pathways or risk assessment or syndromically or syndromic or signs or symptoms or symptom or sign decision tree or syndromic approach or syndromic diagnosis or syndromic management or syndromic approaches).mp. (717848)
37. discharges.mp. (9117)
38. 13 and 37 (7)
39. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 10 or 12 or 14 or 15 or 38 (6324)
40. 36 and 39 (1053)
41. limit 40 to yr="2015 -Current" (546)
42. remove duplicates from 41 (513)

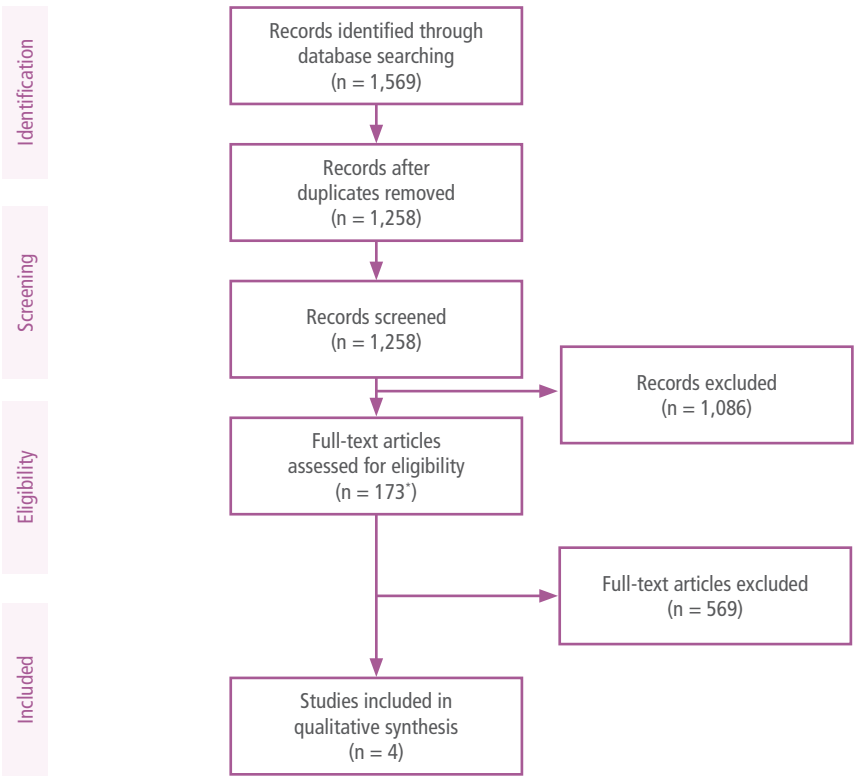
Database: Embase <1996 to 2018 September 20>

1. exp vagina discharge/ (6641)
2. fluor vaginalis.mp. (29)
3. genital fluor.mp. (1)
4. vagina fluid.mp. (4)
5. vagina fluor.mp. (0)
6. vaginal discharge.mp. (3111)
7. vaginal fluid.mp. (965)
8. vaginal fluor.mp. (5)
9. leukorrhea.mp. (697)
10. exp leukorrhea/ (661)
11. fluor albus.mp. (4)
12. cervical discharges.mp. (2)
13. vaginal.mp. (108743)
14. discharge.mp. (264824)
15. 13 and 14 (8193)
16. vagina.mp. (65309)
17. 14 and 16 (8017)
18. cervix.mp. (111422)
19. 14 and 18 (2082)
20. discharges.mp. (28343)
21. 18 and 20 (53)
22. vaginal secretion.mp. (740)
23. exp uterine cervix/ (13159)
24. secretion.mp. (319639)
25. discharge.mp. (264824)
26. discharges.mp. (28343)
27. secretions.mp. (22068)
28. 24 or 25 or 26 or 27 (609769)
29. 23 and 28 (1038)
30. exp algorithm/ (247451)
31. flowcharts.mp. (353)
32. Flowchart.mp. (1243)
33. algorithm.mp. (308870)
34. algorithms.mp. (89527)
35. flow charts.mp. (414)
36. flow chart.mp. (1378)
37. clinical pathway.mp. (8931)
38. clinical pathways.mp. (2579)
39. risk assessment.mp. (469668)
40. syndromically.mp. (50)
41. syndromic.mp. (12598)
42. signs.ti,ab. (289594)
43. symptoms.mp. (968757)
44. symptom.mp. (428354)
45. sign.ti,ab. (83781)
46. decision tree.mp. (12424)
47. decision trees.mp. (1932)
48. syndromic approach.mp. (258)
49. syndromic diagnosis.mp. (343)
50. syndromic management.mp. (368)
51. syndromic approaches.mp. (12)
52. (algorithm or flowcharts or Flowchart or algorithm or algorithms or flow charts or flow chart or clinical pathway or clinical pathways or risk assessment or syndromically or syndromic or signs or symptoms or symptom or sign or decision tree or decision trees or syndromic approach or syndromic diagnosis or syndromic management or syndromic approaches).mp. (2208740)
53. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 17 or 19 or 21 or 22 or 29 (13368)
54. 52 and 53 (3697)
55. limit 54 to yr="2015 -Current" (1056)

In total, we found 1,569 citations (duplicates included). After removal of 311 duplicates, there were 1,258 citations for title and abstract screening. After excluding 1,086 studies that were not relevant, we obtained and screened 173 full text articles. We included four studies in the updated review (Bannaheke 2016, Barry 2018, Molaei 2018, Vallely 2017). See PRISMA diagram below.

Therefore, in addition to the 16 studies from the previous review, the updated systematic review now includes 20 studies.

PRISMA Flow Diagram



*Screening the record 'Anonymous (2017). "IDSOG Abstracts 2017." American Journal of Obstetrics and Gynecology. Conference: 44th Annual Scientific Meeting Infectious Disease Society for Obstetrics and Gynecology, IDSOG 217(6)' identified 2 articles requiring assessment for eligibility.

Study characteristics

The four newly identified studies included 2,240 participants. The previous review included 16 studies with 10,538 participants. An overview of the study characteristics of the 20 studies are presented in the next table.

Study characteristics of all included studies

Study	Country	Design	N	Prevalence (%)	Setting	Population	Flowchart	Reference test
Banneheke 2016	Sri Lanka	Cross-sectional	100	TV: 6.0	STI clinics, well woman clinics, gynecology clinics, institutional health clinics	General population women (15-45 years)	WHO syndromic algorithm flowchart 1 + clinical and speculum examination; WHO flowchart 1 + clinical and speculum examination + Trichomonas immunochromatographic test (ICT)	TV: culture
Barry 2018	Senegal	Cross-sectional	276	NG: 1.1 CT: 4.7 NG/CT: 5.4 BV (GV): 39.5 TV: 2.5 BV/TV: 40.2	Hospitals, primary health facilities	General population women (18-49 years)	WHO syndromic algorithm (symptoms, history, risk assessment, bimanual and speculum examination	NG/CT: NAAT BV: Nugent scoring TV: wet mount microscopy
Clark 2009	Peru	Cross-sectional	320	NG: 2.8 CT: 14.1	General health clinic	General population women	WHO 1	NG/CT: NAAT
Cornier 2010	Bulgaria	Cross-sectional	424	NG: 0.7 CT: 9.2 TV: 2.9 Either CT/NG: 9.5	Sexual health clinic	Non pregnant women	WHO 1,2,3, MSF 1	NG/CT: NAAT BV/TV: Microscopy
Das 2011	India	Cross-sectional	417	NG: 14.1 CT: 17.1 TV: 31.1 BV: 71 Either NG/CT: 26.1	STI clinic for sex workers	Sex workers	WHO1,2 NACO 3	NG/CT: NAAT TV: PCR BV: Nugent's criteria
Desai 2003	India	Cross-sectional	118	NG: 15.3 CT: 8.5 TV: 14.4	Red light district	Sex workers	NACO 2	NG: Culture and Gram staining CT: Pace 2 CT assay. TV: Wet mount

Study	Country	Design	N	Prevalence (%)	Setting	Population	Flowchart	Reference test
Francis 2014	United Republic of Tanzania	Cross-sectional	966	NG: 4 CT: 12 TV: 19	Women working in bars, hotels.	HIV negative women	WHO 2	NG/CT: PCR TV: culture BV: Nugent's criteria
Garcia 2004	Peru	Cross-sectional	754	NG: 1.2 CT:6.8	Mothers Club	General population	Peruvian Algorithm 1	NG/CT: PCR
Kisa 2009	Turkey	Cross-sectional	300	TV: 14	Maternal health clinic	Married women	WHO 2	TV: Wet mount
Lima 2013	Brazil	Cross-sectional	104	TV: 3.8 BV: 27.9	ANC	Pregnant women	WHO 1	TV: wet mount BV: Amsel criteria.
Moherdaui 2005	Honduras	Cross-sectional	933	NG/CT: 5.9 TV: 6.8 BV: 27.4	General health clinic	General population	WHO 1,2,3	NG: Gram CT: immuno-florence TV: microscopy
Molaei 2018	Iran (Islamic Republic of)	Prospective	100	BV (GV): 14.0 TV: 10.0	Hospital gynaecological outpatient department	General population married women (18-49 years)	History; History + bimanual and speculum examination (clinical diagnosis)	BV: Amsel criteria + Nugent score TV: wet mount microscopy
Msuya 2009	United Republic of Tanzania	Cross-sectional	2645	TV: 5 BV: 20.9 Either: 23.9	ANC	Pregnant women	Tanzanian STI case management 2	TV: Wet mount BV: Amsel Nugent.
Onyekownu 2011	Nigeria	Cross-sectional	195	NG/CT: 12.8 BV/ TV: 57.4	STI Clinic	General population	Nigeria National Algorithm (2b)	NG: Culture CT: Elisa TV: wet mount BV: Nugents criteria
Rassjo 2006	Uganda	Cross-sectional	199	NG: 9 CT: 4.5	Youth health clinic	Adolescents	National Algorithm 2	NG/CT/TV: PCR

Study	Country	Design	N	Prevalence (%)	Setting	Population	Flowchart	Reference test
Romoren 2007	Botswana	Cross sectional	703	NG: 3 CT: 8 TV: 18.8 BV: 38.1	ANC	Pregnant women	WHO 2	NG/CT: LCR TV: wet-mount BV: Nugent's criteria
Smith Fawzi 2006	Haiti	Case- Control	944	NG: 1.7 CT: 6.2 Either: 7.4	Women's health clinic	General population	WHO 1, 2, 3, Haiti National Algorithm 1	NG/CT: Gen Probe PACE 2
Tann 2006	Uganda	Cross-sectional	250	TV: 17.3 BV: 47.7	ANC	Pregnant women	Nigeria National Algorithm 2	TV: inoculation culture media kit & wet mount BV: Nugent's criteria.
Tolosa 2012	Colombia	Cross-sectional	1266	NG: 1.2 CT: 9 TV: 0.9 BV: 39	General health clinic	General population	WHO 1	NG/CT : PCR TV: wet mount BV: Nugent's criteria
Vallely 2017	Papua New Guinea	Cross-sectional	1,764	NG: 12.5 CT: 16.9 TV: 18.0	Antenatal clinics, well woman clinics, sexual health clinics	General population women (18-59 years)	WHO history + risk factors (antenatal clinic); WHO history + risk factors + genital examination (well woman and sexual health clinics)	NG/CT: real time PCR TV: real time PCR

Vaginal discharge flowcharts

One study (Barry 2018) validated one type of vaginal discharge flowchart for both cervical and vaginal infections. The other three studies validated two types of flowcharts each: Banneheke2016 for vaginal infection (TV only), Molaei 2018 assessed for vaginal infection, and Vallely 2017 for both cervical and vaginal (TV only) infections.

Cervical infections

Diagnostic performance of different vaginal discharge flowcharts for treating NG and/or CT

Study	Compared with Gold Standard	Flowchart	NG Prev (%)	CT Prev (%)	Sensitivity (%)	Specificity (%)
Flowchart 1						
Clark 2009	YES	1	2.8	14.1	(25/52) 48.1	(119/268) 44.4
Cornier 2010	YES	1	9.5		(25/40) 62.5	(230/383) 60
Das 2011	YES	1	26.1		(74/109) 67.9	(114/308) 37
Moherdaui 2005	NO	1	4		(6/37) 16.2	(842/896) 94
Smith Fawzi 2002	YES	1	7.4		(24/69) 34.8	(553/870) 63.6
Tolosa 2012	YES	1	1.2	9	(14/127) 11	(1030/1133) 90.9
Vallely 2017	Yes	1	14.2	-	(16/109) 14.7	(516/656) 78.7
Vallely 2017	Yes	1	-	22.9	(37/175) 21.1	(471/590) 79.8
Flowchart 2						
Barry 2018	Yes	2	1.1	-	(2/3) 66.7	(148/273) 54.2
Barry 2018	Yes	2	-	4.7	(6/13) 46.2	(142/263) 54.0
Barry 2018	Yes	2	5.4		(7/15) 46.7	(141/261) 54.0
Cornier 2010	YES	2	9.5		(37/40) 92.5	(107/383) 27.9
Das 2011	YES	2	26.1		(91/109) 83.5	(66/308) 21.4
Francis 2014	YES	2	4	N/A	(12/92) 13	(2015/2185) 92.2
Francis 2014	YES	2	N/A	12	(20/183) 10.9	(1934/2096) 92.3
Francis 2014	YES	2	11.33		(32/258) 12.4	(1869/2019) 92.6
Moherdaui 2005	NO	2	4		(19/40) 48.7	(505/953) 53
Romoren 2007	YES	2	3	8	(2/11) 16.7	(79/93) 85
Rassjo 2006	YES	2	11.5		(14/23) 60.9	(68/176) 38.6
Smith Fawzi 2002	YES	2	7.4		(27/69) 39.1	(510/870) 58.6
Vallely 2017	Yes	2	11.1	-	(79/112) 70.5	(263/887) 29.7
Vallely 2017	Yes	2	-	12.4	(94/124) 75.8	(266/875) 30.4

Study	Compared with Gold Standard	Flowchart	NG Prev (%)	CT Prev (%)	Sensitivity (%)	Specificity (%)
Flowchart 3						
Cornier 2010	YES	3	9.5		(39/40) 97.5	(50/383) 13.1
Moherdaui 2005	NO	3	4		(21/37) 56.8	(537/895) 60
Smith Fawzi 2002	YES	3	7.4		(48/70) 68.6	(271/874) 31
Flowchart 4						
Cornier 2010	YES	MSF 1b	9.5		(34/40) 85	(150/383) 39.2
Das 2010	YES	Flow chart 2 + gram stain	26.1		(93/109) 85.3	(58/308) 18.8
Desai 2003	NO	NACO 2b	N/A	8.5	(7/10) 70	(54/108) 50
Desai 2003	NO	NACO 4 2b	10.2	N/A	(7/12) 58.3	(52/106) 49.1
Desai 2003	NO	NACO 4 2b	20.3		(13/24) 54.2	(46/94) 48.9
Garcia 2004	YES	Peru algo	1.2	N/A	(3/9) 33.3	(579/743) 77.9
Garcia 2004	YES	Peru algo	N/A	6.8	(17/51) 33.3	(573/701) 73.9
Garcia 2004	YES	Peru algo	7.45		(20/60) 33.3	(545/692) 78.8
Onyekownu 2011	NO	NNA 2b	12.8		(5/25) 20	(156/170) 91.8
Rassjo 2006	YES	1b risk score	11.5		(6/23) 26.1	(119/176) 67.6
Smith Fawzi 2002	YES	MSPP 1b	7.4		(66/68) 97.1	(131/856) 15.3

Pooled diagnostic validity of vaginal discharge flowcharts to diagnose cervical infection

Flowchart	N. studies	Sensitivity	Specificity
1	**7**	**27.9 (24.7 – 31.1)**	**57.0 (56.1 - 58.0)**
2	**9**	**44.9 (42.2 - 47.7)**	**74.2 (73.3 - 75.1)**
3	3	90.1 (85.8 – 94.4)	35.3 (33.4 – 37.1)
4	7	83.92 (80.9 – 87.0)	45.3 (43.9 – 47.9)

Flowchart 1= history and risk assessment; Flowchart 2= history, risk assessment and speculum examination; Flowchart 3= history, risk assessment, speculum examination, and vaginal discharge samples for Gram staining and microscopy; Flowchart 4= country adapted flowcharts or other combinations of screening

Vaginal infections

Diagnostic performance of different vaginal discharge flowcharts for treating BV and/or TV

Study	Compared with Gold Standard	Flowchart	NG Prev (%)	CT Prev (%)	Sensitivity (%)	Specificity (%)
Flowchart 1						
Das 2014	YES	1	71	31.1	(188/308) 61	(39/94) 41.9
Garcia 2004	NO	1	48.9		(96/369) 26	(308/385) 80
Kisa 2009	NO	1	27.8	16.7	(110/120) 91.7	(125/180) 69.4
Lima 2013	YES	1	27.9	N/A	(29/29) 100	(48/75) 64
Lima 2013	NO	1	N/A	3.8	(2/4) 50	(46/100) 46
Lima 2013	NO	1	31.7		(31/33) 93.9	(46/71) 64.8
Molaei 2018	Yes	1	14.0	-	(5/14) 35.7	(81/86) 94.2
Molaei 2018	No	1	-	10.0	(5/10) 50.0	(81/90) 90.0
Romoren 2007	YES	1	38.1	-	(50/268) 18.7	(365/435) 83.9
Romoren 2007	NO	1	-	18.8	(28/132) 21.2	(480/571) 84.1
Romoren 2007	NO	1	51		(69/359) 19.2	(296/344) 86
Tann 2006	NO	1	47.7	-	(58/116) 50	(68/127) 53.5
Tann 2006	YES	1	-	17.1	(28/42) 66.7	(113/203) 55.7
Tolosa 2012	NO	1	48.2		(497/608) 81.7	(221/652) 33.9
Vallely 2017	Yes	1	-	22.4	(33/171) 19.3	(471/594) 79.3
Flowchart 2						
Banneheke 2016	Yes	2	-	6.0	(0/6) 0	(76/94) 80.9
Barry 2018	Yes	2	39.5	-	(75/109) 68.8	(15/167) 9.0
Barry 2018	No	2	-	2.5	(6/7) 85.7	(48/269) 17.8
Barry 2018	No	2	40.2		(77/111) 69.4	(15/165) 9.1
Cornier 2010	NO	2	35.7		(150/150) 100	(3/270) 1.1
Garcia 2004	YES	2	30.6	-	(110/229) 48	(189/519) 36.4
Garcia 2004	NO	2	-	16.5	(74/124) 59.7	(405/627) 64.6
Garcia 2004	NO	2	48.9		(179/369) 48.5	(268/385) 69.6
Francis 2014	YES	2	45.8	-	(150/1819) 8.2	(2010/2149) 93.5
Francis 2014	NO	2	-	19	(43/365) 11.8	(1840/1914) 96.1
Francis 2014	NO	2	48.4		(89/1142) 7.8	(1126/1219) 92.4
Moherdaui 2005	NO	2	27.4	6.8	(146/318) 45.9	(381/615) 62
Molaei 2018	Yes	2	14.0	-	(7/14) 50.0	(86/86) 100
Molaei 2018	No	2	-	10.0	(6/10) 60	(87/90) 96.7
Valley 2017	Yes	2	-	14.6	(110/146) 75.3	(260/853) 30.5

Study	Compared with Gold Standard	Flowchart	NG Prev (%)	CT Prev (%)	Sensitivity (%)	Specificity (%)
Flowchart 3						
Cornier 2010	NO	3	35.7		(141/150) 94	(197/270) 73
Moherdaui 2005	NO	3	27.4	6.8	(286/318) 89.8	(615/615) 100
Flowchart 4						
Banneheke 2016	Yes	WHO 2 + ICT	-	6.0	(0/6) 0	(93/94) 98.9
Cornier 2010	NO	MSF 1b	35.7		(132/150) 88	(254/270) 94.1
Desai 2003	NO	NACO 2b	N/A	14.4	(15/17) 88.2	(55/101) 54.5
Msuya 2009	NO	TNA 2b	N/A	5	(37/129) 28.7	(2076/2525) 81.5
Msuya 2009	NO	TNA 2b	20.08	N/A	(136/533) 25.5	(1771/2121) 83.5
Msuya 2009	NO	TNA 2b	23.9		(160/611) 26.2	(1717/2043) 84
Onyekownu 2011	NO(tv) YES (bv)	NNA 2b	57.4		(98/112) 87.5	(5/83) 6

Pooled diagnostic validity of vaginal discharge flowcharts to diagnose vaginal infections (BV/TV)

Flowchart	N. studies	Sensitivity	Specificity
1	**9**	**56.2 (54.5 - 57.9)**	**71.0 (69.4 - 72.6)**
2	**8**	**74.8 (74.0 - 75.6)**	**53.2 (52.5 - 54.0)**
3	2	91.7 (89.2- 94.2)	100 (99.9– 100)
4	**5**	**53.1 (50.5 - 55.6)**	**85.8 (84.7 - 86.9)**

Flowchart 1= history and risk assessment; Flowchart 2= history, risk assessment and speculum examination; Flowchart 3= history, risk assessment, speculum examination, and vaginal discharge samples for Gram staining and microscopy; Flowchart 4= country adapted flowcharts or other combinations of screening

Risk of Bias

Study	Patient Selection	Index Test	Reference Standard		Flow and Timing
Banneheke 2016	Low	Low	Low		Low
Barry 2018	Low	Low	Low	High*	High
Clark 2009	Unclear	Low	Low		Low
Cornier 2010	Low	Low	Low		High
Das 2011	Low	Low	Low		Low
Desai 2003	High	High	High		Low
Francis 2014	Low	High	Low		Low
Garcia 2004	High	Low	Low		Low
Kisa 2009	High	Low	High		Low
Lima 2013	High	Low	High		Low
Moherdaui 2005	Low	Low	High		Low
Molaei 2018	High	Low	Low	High*	Low
Msuya 2009	Low	Low	High		Low
Onyekownu 2011	Low	Low	High		Low
Rassjo 2006	High	Low	Low		Low
Romoren 2007	Low	Low	Low		Low
Smith Fawzi 2006	Low	Unclear	Low		Unclear
Tann 2006	Low	Low	High		Low
Tolosa 2009	High	Low	Low		Unclear
Vallely 2017	Low	Low	Low		Low

*reference standard is low risk of bias for NG, CT and/or BV, but high risk of bias for TV

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