Web appendix: Supplementary material

Performance of alternative strategies for primary cervical cancer screening in sub-Saharan Africa: systematic review and meta-analysis of diagnostic test accuracy studies

Table of contents:

1. PICOS components

1.1. Research Question

Among the most studied alternative methods to cytology for cervical cancer screening (Visual inspection with Acetic Acid, Visual inspection with Lugol's Iodine and Human Papillomavirus testing), which tool performs better in the context of primary screening in sub-Saharan Africa ?

1.2. PICOS components

Population: women apparently healthy, previously unscreened, participating in a primary screening program in sub-Saharan Africa

Intervention (screening with index tests): each screening tool considered independently

I1 : Visual inspection with Acetic Acid

I2 : Visual inspection with Lugol's Iodine

I3 : Human Papillomavirus testing

Comparis*on* (reference standard) : either random biopsy without colposcopy, or colposcopy and colposcopy-directed biopsies, loop excision or endocervical curettage performed in all women of the study population ('Gold standard all' group, GSA) or in a proportion of women including all screen-positive women to the considered index text ('Gold standard partial' group, GSP)

Outcomes:

Outcome 1: absolute sensitivity and specificity in detecting CIN2+ for VIA, VILI and HPV testing

Outcome 2: relative sensitivity and specificity for CIN2+ detection of

- VIA versus VILI
- VIA versus HPV testing
- VILI versus HPV testing

Outcome 3: prevalence of CIN2+, positivity rate of VIA, VILI and HPV testing

Studies :

- Diagnostic test accuracy studies conducted in sub-Saharan Africa, where one of the index tests was performed using a cross-sectional design
- Diagnostic test accuracy studies conducted in sub-Saharan Africa, where two index tests were performed independently in women, using a cross-sectional design

- Randomized trial studies with either of the index texts in one arm, when both screening and reference tests were performed at enrollment

2. Literature review strings

2.1. In Medline (PubMed)

#1: Africa OR “Africa South of the Sahara” OR “sub-Saharan-Africa” OR “Low resource setting”

#2: Angola OR Benin OR Botswana OR “Burkina Faso” OR “Upper Volta” OR Burundi OR Urundi OR Cameroon OR Cameroons OR “Cape Verde” OR “Central African Republic” OR Chad OR Comoros OR “Comoro Islands” OR Comores OR Mayotte OR Congo OR “Cote d'Ivoire” OR “Ivory Coast” OR “Democratic Republic of the Congo” OR Zaire OR Djibouti OR “French Somaliland” OR Eritrea OR Ethiopia OR Gabon OR “Gabonese Republic” OR Gambia OR Ghana OR “Gold Coast” OR Guinea OR Kenya OR Lesotho OR Basutoland OR Liberia OR Madagascar OR “Malagasy Republic” OR Malawi OR Nyasaland OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR “Sao Tome” OR Seychelles OR Senegal OR “Sierra Leone” OR Somalia OR “South Africa” OR Sudan OR “South Sudan” OR Swaziland OR Tanzania OR Togo OR “Togolese Republic” OR Uganda OR Zambia OR Zimbabwe OR Rhodesia

#3: Cervical cancer OR cervical neoplasia OR cervical neoplasm OR cancer of the uterine cervix

#4: screening OR early detection

#5: (#1 OR #2) AND #3 AND #4

With the following Filters:

- Publication dates : from 01/01/1994 to 30/06/2014
- Species : Humans

2.2. In Embase

#1: low+resource+setting OR 'africa'/exp OR africa OR 'sub+saharan+africa'/exp OR sub+saharan+Africa

#2: angola OR benin OR botswana OR ‘burkina faso’ OR 'upper volta' OR burundi OR urundi OR cameroon OR cameroons OR 'cape verde' OR 'central african republic' OR chad OR comoros OR 'comoro islands' OR comores OR mayotte OR congo OR 'cote ivoire' OR 'ivory coast' OR 'democratic republic of the congo' OR zaire OR djibouti OR 'french somaliland' OR eritrea OR ethiopia OR gabon OR 'gabonese republic' OR gambia OR ghana OR 'gold coast' OR guinea OR kenya OR lesotho OR basutoland OR liberia OR madagascar OR 'malagasy republic' OR malawi OR nyasaland OR mali OR mauritania OR mauritius OR mozambique OR namibia OR niger OR nigeria OR rwanda OR 'sao tome' OR seychelles OR senegal OR 'sierra leone' OR somalia OR 'south africa' OR sudan OR 'south sudan' OR swaziland OR tanzania OR togo OR 'togolese republic' OR uganda OR zambia OR zimbabwe OR Rhodesia

#3: 'cervical+cancer'/exp OR cervical+cancer

#4: 'screening'/exp OR screening OR 'early detection of cancer'/exp OR 'early detection of cancer'

#5: (#1 OR #2) AND #2 AND #3

With the following Filters:

- Publication dates : from 01/01/1994 to 30/06/2014
- Map to preferred terminology
- Also search as free text
- Include sub-terms/derivatives

2.3. In Cochrane library

#1 : ‘cervical cancer’ or ‘cervical neoplasia’

#2 : Visual inspection with acetic acid

#3 : Visual inspection with Lugol’s Iodine

#4 : ‘Human papillomavirus’ or ‘Human papillomavirus testing’

#4 : ‘Low resource setting’ or ‘Africa’or ‘sub-saharan Africa’

With the following Filters:

- Cochrane reviews
- Other reviews

3. Excluded studies

List of studies excluded after reading of abstracts or methods of full texts

First Author, Year	Country	Screening Test (s)	Code exclusion
Untiet, 2014[1]	Cameroon	HPV	1
Dartell, 2014[2]	Tanzania	HPV, VIA	1
Ajenifuja, 2013[3]	Nigeria	VIA	1
Ugwu, 2013[4]	Nigeria	NS	2
Ogilvie, 2013[5]	Uganda	HPV	3
Firnhaber, 2013[6]	South Africa	HPV, VIA	4
Mwanahamuntu, 2013[7]	Zambia	VIA	4
De Vuyst, 2013	Kenya	HPV	4
Chigbu, 2013[9]	Nigeria	VIA	2
Busingye, 2012[10]	Uganda	VIA, VILI	2
Denny, 2012 [11]	South Africa	HPV, VIA, VILI	2
Moon, 2012[12]	Mozambique	NS	4
Horo, 2012[13]	Cote d'Ivoire	VIA	4
Mingo, 2012[14]	Botswana	NS	2
Audet, 2012[15]	Mozambique	VIA	2
Jemal, 2012[16]	NS	NS	2
Gage, 2012[17]	Nigeria	CareHPV	5
Ramogola-Masire, 2012[18]	Bostwana	VIA	4
Kahesa, 2012[19]	Tanzania	NS	2
Teguete, 2012[20]	Mali	VIA, VILI	6
Cronje, 2011[21]	NA	VIA, HPV	2
Awodele, 2011[22]	Nigeria	NS	2
Balandya, 2011[23]	Tanzania	VIA	4
Lewis, 2011[24]	Kenya	VILI	5
Saleh, 2011[25]	Tanzania	NS	2
Kuhn, 2010 [26]	South Africa	HPV	4
Hovland, 2010[27]	DRC	HPV	7
Were, 2010[28]	Kenya	VIA, VILI	2
Batra, 2010[29]	South Africa	Cytology	2
Peters, 2010[30]	Tanzania	NS	2
Denny, 2010[31]	South Africa	HPV, VIA	3
Koffi, 2010[32]	Central african Republic	cytology	2
Qureshi, 2010[33]	India	VIA, VILI	8
Hassan, 2009[34]	Sudan	Cytology	2
Hoque, 2009[35]	Botswana	NS	2
Akinwuntan, 2008[36]	Nigeria	VIA	4
Anorlu, 2008[37]	NA	NS	2
Kawonga, 2008[38]	South Africa	Cytology	2
Hoque, 2008[39]	South Africa	Cytology	2
Arbyn, 2008[40]	5 countries	VIA, VILI	2
Kamaté, 2008[41]	Mali	VIA, VILI	2

Roblyer, 2007[42]	Nigeria	NA	2
Akinola, 2007[43]	Nigeria	VIA	1
Anorlu, 2007[44]	Nigeria	NS	2
Kamal, 2007[45]	India	VIA, cytology	8
Cronje, 2007[46]	South Africa	Cytology	2
Sodhani, 2006[47]	India	VIA	8
Cronje, 2005[48]	NA	NS	2
Denny, 2005[49]	NA	NS	2
Denny, 2005[50]	NA	HPV	2
Doh, 2005[51]	Cameroon	VIA	1
Millogo, 2004[52]	Burkina Faso	VIA, VILI	9
El Shalakany, 2004[53]	Egypt	VIA	8
Bhatla, 2004[54]	India	VIA, VILI	8
Okewole, 2003[55]	Nigeria	NS	2
Petry, 2003[56]	Tanzania	HPV	2
Hawes, 2003[57]	Senegal	HPV	2
Claeys, 2003[58]	Nicaragua	VIA	8
Cronjé, 2003[59]	South Africa	VIA	6
Adanu, 2002[60]	Ghana	NS	2
Blumenthal, 2001[61]	Zimbabwe	VIA, HPV	10
Cronjé, 2001[62]	South Africa	VIA	6
Singh, 2001[63]	India	VIA	8
Cronje, 2000[64]	South Africa	VIA	1
Denny, 2000[65]	South Africa	VIA, HPV	10
Womack, 2000[66]	Zimbabwe	HPV	10
Chirenje, 1999[67]	Zimbabwe	VIA	1
Thistle, 1997[68]	Zimbabwe	cytology	2
Sitas, 1997[69]	South Africa	cytology	2
Megevand, 1996[70]	South Africa	Cytology	10
Nolting, 1995[71]	South Africa	VIA	2

HPV: human papillomavirus testing. NA: not applicable. NS: not specified. VIA: visual inspection with acetic acid. VILI: visual inspection with Lugol's Iodine.

Reasons for exclusion of studies

Code	Reason for exclusion	Number
1	Inappropriate gold standard or disease threshold	7
2	No accuracy study or no primary data (review, comment, letter)	35
3	Inappropriate design (including self-sampling for HPV testing)	2
4	HIV positive women	9
5	no primary screening (test used for triage)	2
6	Many screening tests performed not independently of each other	3
7	Symptomatic patients	1
8	Studies not conducted in sub-Saharan Africa	7
9	Screening performed by physicians	1
10	Double reporting	4

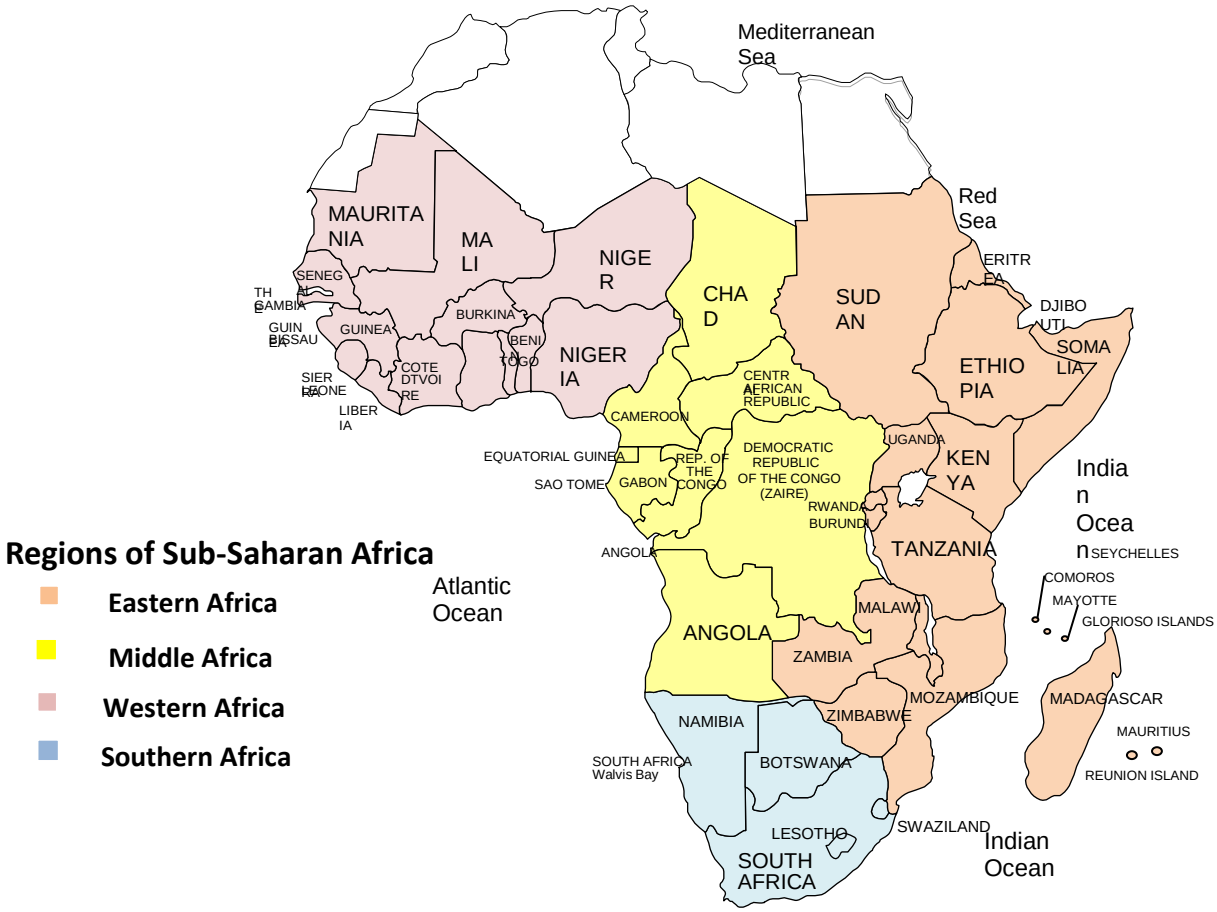
4. Items included in the systematic review of accuracy of alternative methods for cervical cancer screening in SSA according to the PRISMA guidelines[72]

Supplementary Table 1: Checklist of items included in the systematic review

n/topic	Checklist item
	Identifying the report as a systematic review, meta-analysis, or both.
CT	
summary	Providing a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings.
UCTION	
	Describing the rationale for the review in the context of what is already known.
s	Providing an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
OS	
criteria	Specifying study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
on sources	Describing all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
	Presenting full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
ction	Stating the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
ction	Describing method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
s	Listing and defining all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
as in studies	Describing methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level).
measures	Stating the principal summary measures (e.g., risk ratio, difference in means).
of results	Describing the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
as across	Specifying any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
l analyses	Describing methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.

n/topic	Checklist item
S	
ction	Giving numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
racteristics	For each study, presenting characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and providing the citations.
as within	Presenting data on risk of bias of each study and, if available, any outcome-level assessment.
of results	Presenting results of each meta-analysis done, including confidence intervals and measures of consistency.
as across	Presenting results of any assessment of risk of bias across studies.
l analysis	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression).
ION	
of evidence	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
s	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).
ns	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
G	
	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

5. Geographical areas in sub-Saharan Africa according to United Nations [73]



Supplementary figure 1: Countries in sub-Saharan Africa, by geographic region

Sub-Saharan Africa includes countries of Eastern Africa (Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mauritius, Mayotte, Mozambique, Uganda, Tanzania, Reunion, Rwanda, Seychelles, Somalia, South Sudan, Zambia, and Zimbabwe); Central or Middle Africa (Angola, Cameroon, Congo, Gabon, Equatorial Guinea, Central African Republic, Democratic Republic of Congo, Sao Tome and Principe, and Chad); Southern Africa (South Africa, Botswana, Lesotho, Namibia, and Swaziland) and Western Africa (Benin, Burkina Faso, Cape Verde, Ivory Coast, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Saint Helena, Senegal, Sierra Leone, and Togo). Sudan which belongs to Northern Africa is also part of sub-Saharan Africa. As part of this work, Sudan was linked to South Sudan (Eastern Africa), as the only study included in these two countries was conducted when they were still a single nation.

Supplementary Table 2: Assessment of methodological validity of selected studies

Studies	Screening test(s)	Risk of bias													Applicability concerns		
		Patient Selection		Index test		Reference test			Flow and timing						Patient Selection	Index test	Reference test
		P1	P2	T1	T2	R1	R2	R3	F1	F2	F3	F4	F5	F6			
Megevand, 1996[74]	VIA	Y	U	Y	Y	N	U	N	Y	N	N	N	N	N	L	H	L
Univ. Zimbabwe, 1999[75]	VIA	U	U	Y	Y	N	Y	N	Y	Y	N	Y	y	y	L	L	L
Womack, 2000[76]	HPV test	U	U	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	L	L	L
Wright, 2000[77]	HPV test	U	U	Y	Y	N	Y	Y	N	N	Y	N	N	N	L	L	L
Kuhn, 2000[78]	HPV test	U	U	Y	U	N	U	Y	U	N	Y	N	N	N	L	L	L
Denny, 2000[79]	VIA	U	U	Y	Y	N	U	N	Y	N	N	Y	N	N	L	H	L
Denny, 2002[80]	VIA	U	U	Y	Y	N	U	N	N	N	N	Y	N	Y	L	H	L
Sankaranarayan, 2004[81]	VIA/VILI	Y	U	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	L	L	L
De Vuyst, 2005[82]	VIA/HPV test	Y	U	Y	Y	N	Y	N/Y*	Y	Y	N/Y*	N	N	N	H	L	H
Sangwa-Lugoma, 2006[83]	VIA/VILI	Y	U	Y	Y	N	Y	N	Y	Y	N	N	N	Y	L	L	L
Muwonge, 2010[84]	VIA/VILI	U	U	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	L	L	L
Ngoma, 2010[85]	VIA/VILI	Y	U	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	L	U	L
Ibrahim, 2012[86]	VIA	U	U	Y	Y	N	U	N	Y	N	N	U	N	N	L	H	L
Mahmud, 2012[87]	HPV test	Y	U	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	L	L	L
Jeronimo, 2014[88]	VIA/HPV test	U	U	Y	Y	N	U	N/Y*	Y	N	N/Y*	Y	N	N	L	U	L

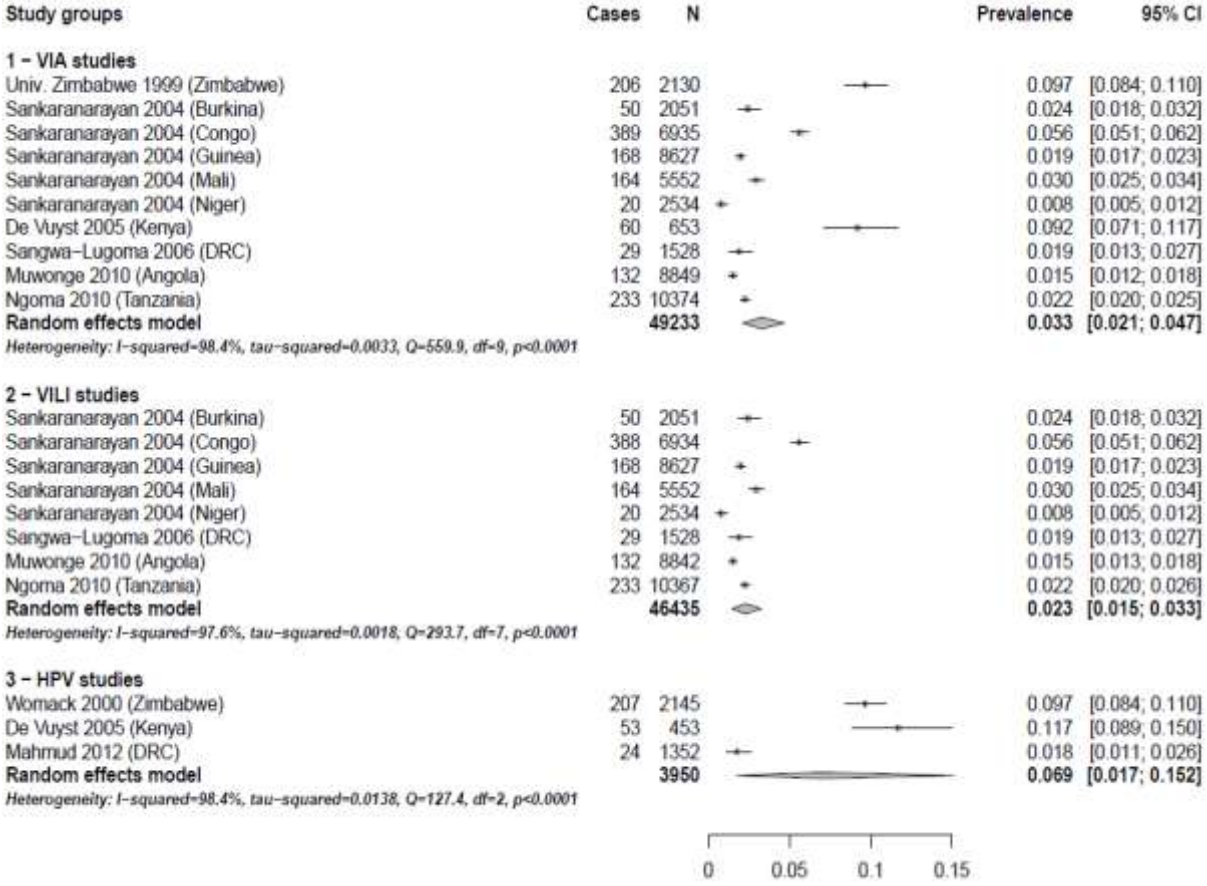
QUADAS items[89]: P1=acceptable enrolment method, P2=inappropriate exclusions avoided, T1=pre-specified test cut-off or criteria for a positive result, T2=results of the index test are masked towards the reference test, R1=imperfect gold standard bias avoided, R2=results of the reference test are masked towards the index test, R3=incorporation bias avoided, F1=acceptable delay between index test and reference test, F2=partial verification avoided, F3=differential verification avoided, F4=withdrawals explained, F5=uninterpretable results reported for index test, F6=uninterpretable results reported for reference test. Each quality item is judged with the following: Y=fulfilled, U=unclear and N=not fulfilled for risk of bias and L=low risk, U=unclear risk and H=high risk for concerns of applicability. * N for VIA and Y for HPV test. HPV test: Human Papillomavirus testing, VIA: visual inspection with acetic acid, VILI: visual inspection with Lugol's Iodine.

6. **Forest plot of the prevalence of CIN2+ and positivity rate of screening tests**

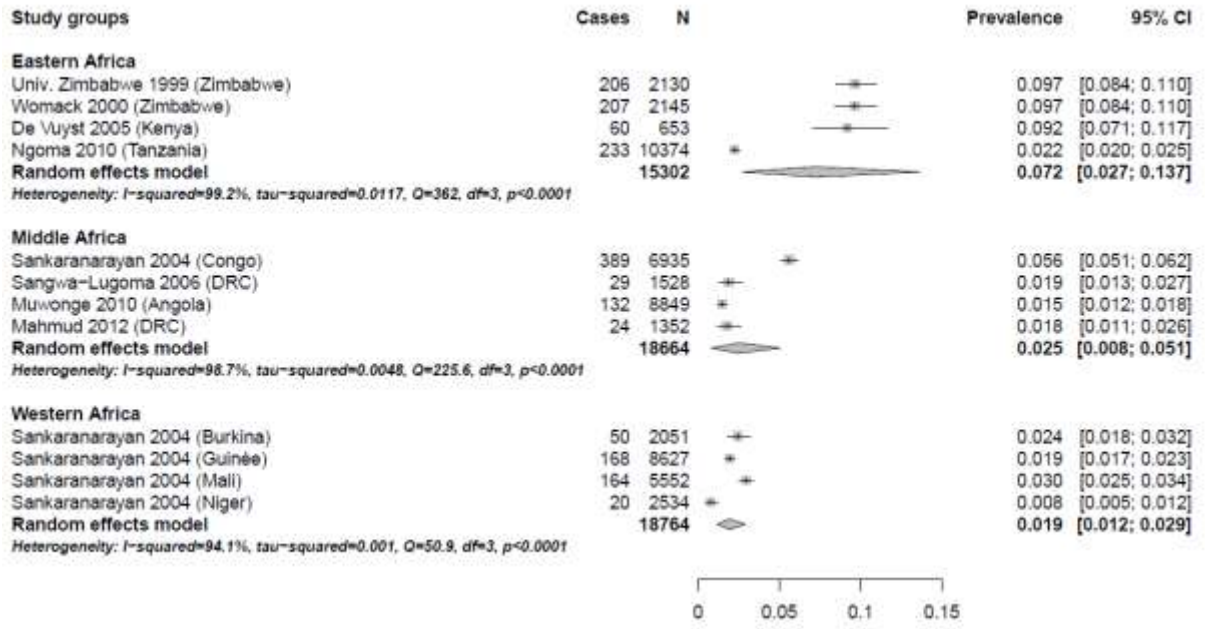
6.1. In the GSA Group

Supplementary figure 2a: Prevalence of disease (CIN2+) in the GSA group, by screening test

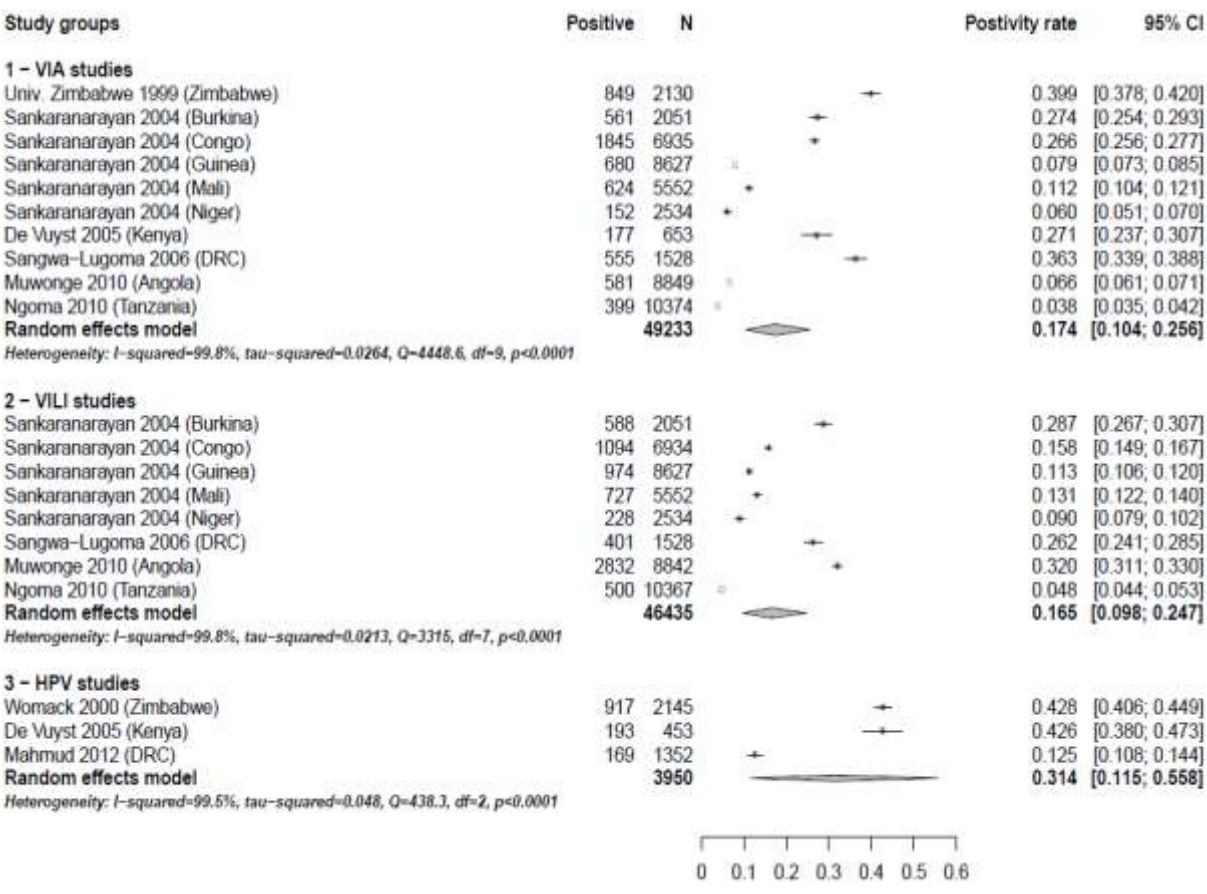
GSA: gold standard (colposcopy followed by colposcopy directed biopsies) performed in all women of the study population. CIN2+: cervical intraepithelial neoplasia grade 2 or worse. N: number of patients. VIA: visual inspection with acetic acid. VILI: visual inspection with Lugol's iodine. HPV: Human papillomavirus.



Supplementary figure 2b: Prevalence of disease (CIN2+) in the GSA group, by geographic region
GSA: gold standard (colposcopy followed by colposcopy directed biopsies) performed in all women of the study population. CIN2+: cervical intraepithelial neoplasia grade 2 or worse. N: number of patients. VIA: visual inspection with acetic acid. VILI: visual inspection with Lugol's iodine. HPV: Human papillomavirus.

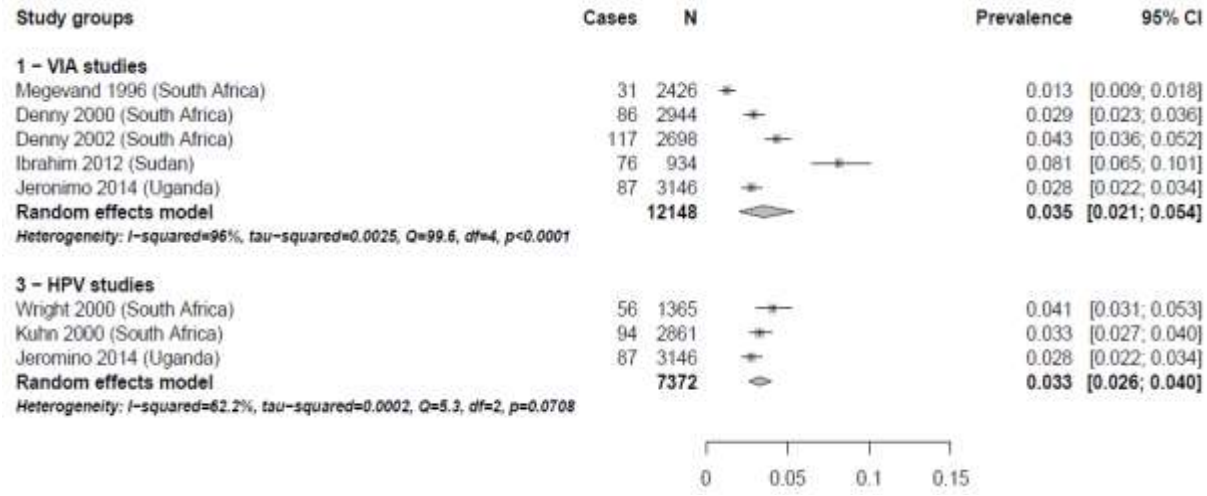


Supplementary figure 3: Positivity rate of VIA, VILI and HPV testing in the GSA group
GSA: gold standard (colposcopy followed by colposcopy directed biopsies) performed in all women of the study population. CIN2+: cervical intraepithelial neoplasia grade 2 or worse. N: overall number of patients. VIA: visual inspection with acetic acid. VILI: visual inspection with Lugol's iodine. HPV: Human papillomavirus.

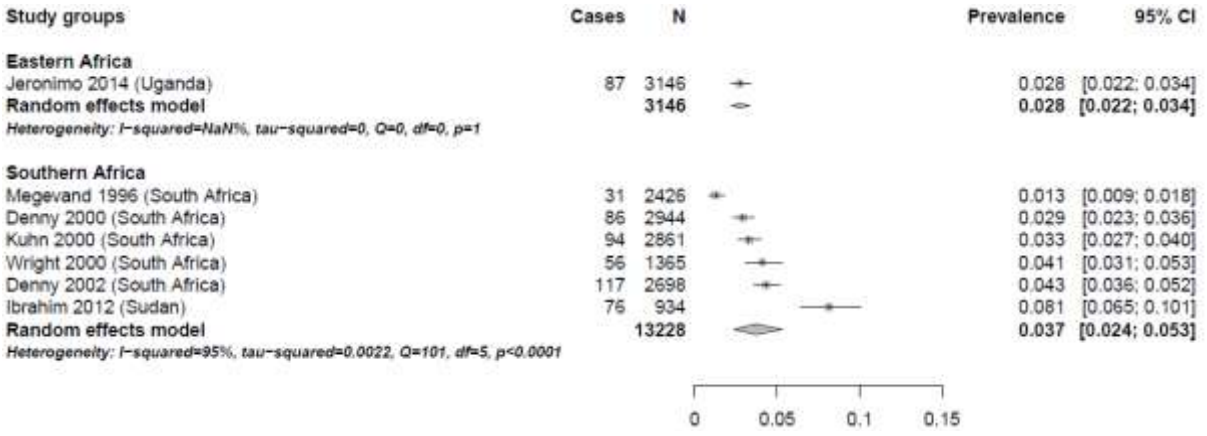


6.2. In the GSP group

Supplementary figure 4a: Prevalence of disease (CIN2+) in the GSP group, by screening test
GSP: gold standard (colposcopy followed by directed biopsies) performed in screen positive women and only a portion of screen negative women. CIN2+: cervical intraepithelial neoplasia grade 2 or worse. N: overall number of patients. VIA: visual inspection with acetic acid. HPV: Human papillomavirus.

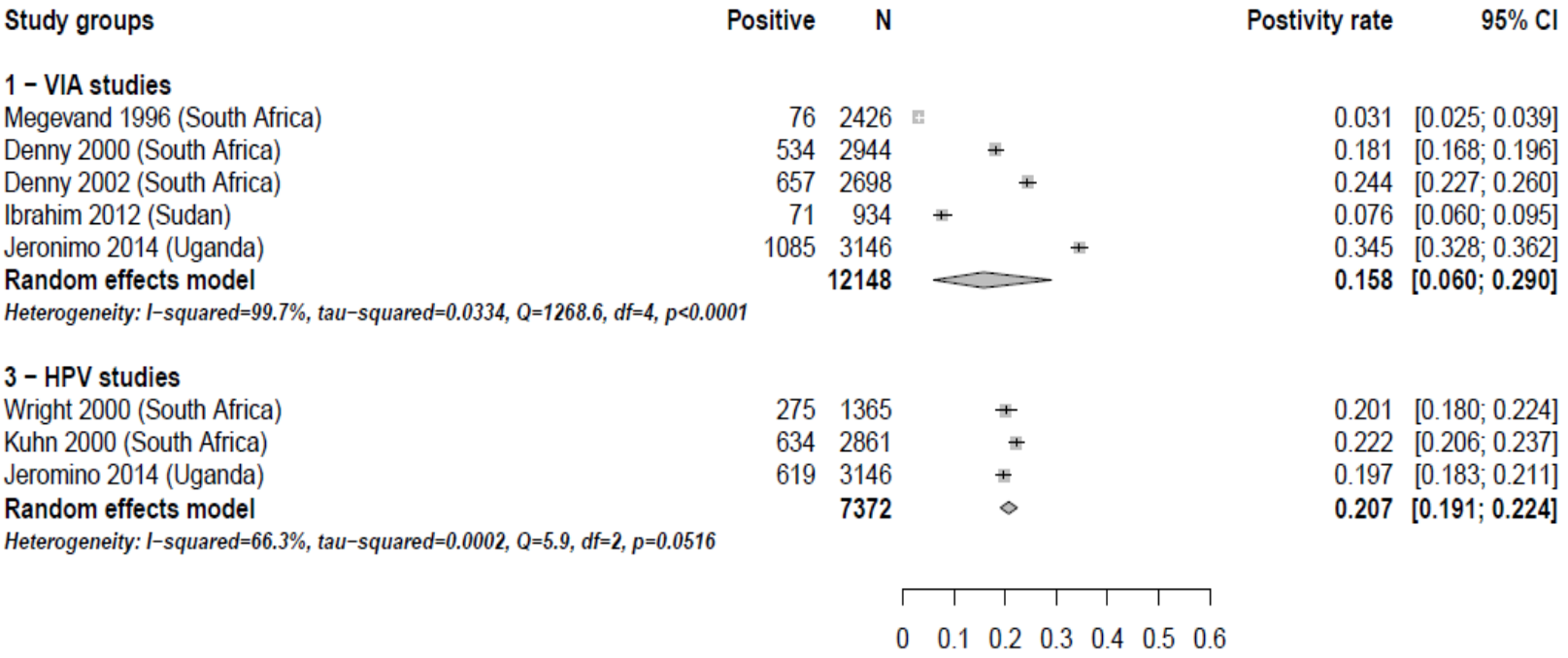


Supplementary figure 4b: Prevalence of disease (CIN2+) in the GSP group, by geographic region
GSP: gold standard (colposcopy followed by directed biopsies) performed in screen positive women and only a portion of screen negative women. CIN2+: cervical intraepithelial neoplasia grade 2 or worse. N: overall number of patients. VIA: visual inspection with acetic acid. HPV: Human papillomavirus.



Supplementary figure 5: Positivity rate of VIA, VILI and HPV testing in the GSP group

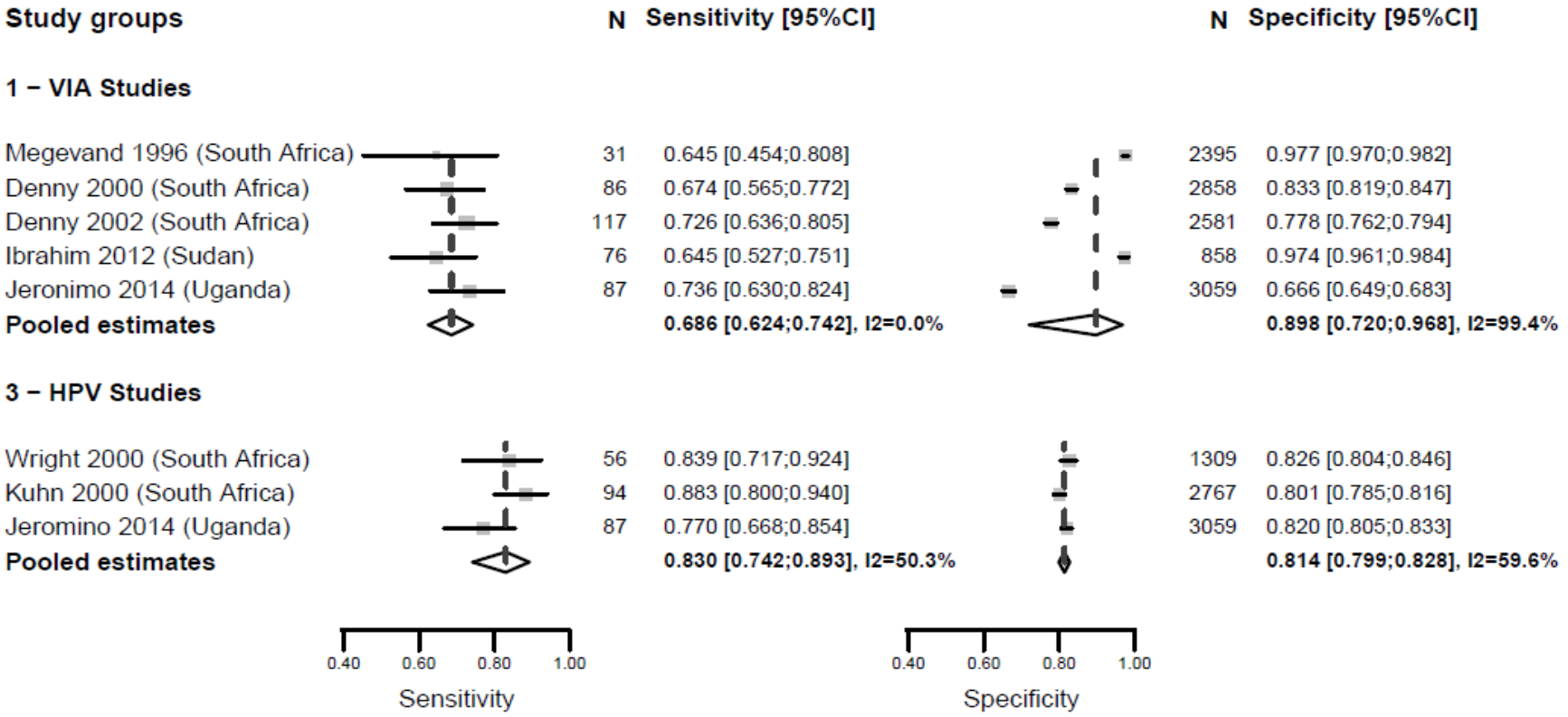
GSP: gold standard (colposcopy followed by colposcopy directed biopsies) performed in screen positive women and only a portion of screen negative women. CIN2+: cervical intraepithelial neoplasia grade 2 or worse. N: overall number of patients. VIA: visual inspection with acetic acid. HPV: Human papillomavirus.



7. Forest plots of absolute sensitivity and specificity for CIN2+ detection of VIA and HPV testing in the GSP group

Supplementary figure 6: Absolute sensitivity and specificity to detect CIN2+ in the GSP group, by screening test

Heterogeneity analysis across studies provided the following Cochran's Q p-values: in VIA studies, p=0.62 and p<0.0001 for sensitivity and specificity, respectively; and in HPV studies, p=0.13 and p=0.08 for sensitivity and specificity, respectively. GSP: gold standard (colposcopy followed by directed biopsies) performed in screen positive women and only a portion of screen negative women. CIN2+: cervical intraepithelial neoplasia grade 2 or worse. N: overall number of patients. VIA: visual inspection with acetic acid. HPV: Human papillomavirus.



8. Pooled positive predictive value (PPV) and negative predictive value (NPV) of VIA, VILI and HPV testing in sub-Saharan Africa, by geographic region

Supplementary table 3: Estimated predictive values of screening tests to detect CIN2+ in sub-Saharan Africa, by geographic region

		Positive predictive Value (95% CI)			Negative predictive Value (95% CI)		
Geographical Area	**Pooled prevalence**	**VIA**	**VILI**	**HPV testing**	**VIA**	**VILI**	**HPV testing**
Western Africa	2.0%	11.7% (6.5 to 20.8)	13.1% (7.8 to 21.7)	6.4% (3.4 to 13.6)	99.6% (99.4 to 99.7)	99.9% (99.7 to 99.9)	99.7% (99.2 to 99.9)
Middle Africa	2.5%	14.3% (8.0 to 24.8)	15.9% (9.6 to 25.8)	8.0% (4.2 to 16.5)	99.5% (99.2 to 99.6)	99.9% (99.7 to 99.9)	99.6% (99.0 to 99.8)
Southern Africa	3.7%	20.0% (11.5 to 33.1)	22.1% (13.8 to 34.3)	11.5% (6.2 to 22.9)	99.2% (98.9 to 99.5)	99.8% (99.5 to 99.9)	99.4% (98.5 to 99.8)
Eastern Africa	6.2%	30.1% (18.3 to 46.0)	32.8% (21.6 to 47.3)	18.2% (10.2 to 33.8)	98.7% (98.1 to 99.1)	99.6% (99.2 to 99.8)	99.0% (97.5 to 99.6)

We included all selected studies in this analysis, as the prevalence of disease was not different between the GSA and GSP groups, by screening test. VIA: visual inspection with acetic acid. VILI: visual inspection with Lugol's iodine. HPV: Human papillomavirus. CIN2+: cervical intraepithelial neoplasia grade 2 or worse. CI: confidence interval.

References

1. Untiet S, Vassilakos P, McCarey C, et al. HPV self-sampling as primary screening test in sub-Saharan Africa: Implication for a triaging strategy. *Int J Cancer* 2014; **135**(8): 1911–7.
2. Dartell M, Rasch V, Iftner T, et al. Performance of visual inspection with acetic acid and human papillomavirus testing for detection of high-grade cervical lesions in HIV positive and HIV negative Tanzanian women. *Int J Cancer* 2014; **135**(4): 896–904.
3. Ajenifuja K, Gage J, Adepiti A, et al. A population-based study of visual inspection with acetic acid (VIA) for cervical screening in rural Nigeria. *Int J Gynecol Cancer* 2013; **23**(3): 507–12.
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