WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention

Use of human papillomavirus (HPV) DNA genotyping

Web Annex A.
Evidence summaries

World Health Organization

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Contents

This document is Web Annex A for *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention: use of human papillomavirus (HPV)*. Available at: https://iris.who.int/handle/10665/385575

The additional web annex for this guideline is:
Web Annex B. Evidence-to-decision tables. Available at: https://doi.org/10.2471/B09737

1. Evidence summary 1. Assessment of the genotype-specific cumulative incidence of cervical pre-cancer and cancer.

Arbyn M, Egemen D, Rousta P and Wentzensen N

1.1 Background

Human papillomavirus (HPV)-based screening is more effective at reducing the burden of cervical cancer than screening using cytology or direct visual inspection with acetic acid (VIA) of the cervix. The use of HPV assays typically generates a higher number of screen-positive results compared to microscopic inspection for cytological lesions, generating a considerable therapeutic burden in screen-and-treat strategies where all HPV-positive women are referred for treatment.

Triage of carcinogenic HPV (cHPV)-positive women identifies those at highest risk of prevalent or incipient pre-cancer or cancer and consequently reduces the number of women to be referred immediately. This is achieved at the expense of a drop in sensitivity, which should be as small as possible. The challenge of a triage strategy is to reach a risk of pre-cancer (of degree cervical intraepithelial neoplasia [CIN]3 or worse [CIN3+]) among triage-positive women (positive predicted value [=PPV]) that should exceed a defined decision threshold. Moreover, the risk of CIN3+ among triage-negative women should be lower than an agreed level of low risk where experts and stakeholders agree that it is safe to return women to routine screening.

It is highly recommended to define guidelines for management of cHPV-positive women according the underlying CIN3+ risk, as CIN3+ is a more reliable and definitive end-point than CIN2+.

In previous meta-analyses performed for the 2021 World Health Organization (WHO) guidelines for cervical cancer screening[1], diverse triage tests or combinations of tests were evaluated. Extended genotyping was included in the meta-analyses but was hampered by the fact that all authors of eligible studies used different hierarchical ranking of HPV types, with ordering frequently based on the local prevalence of the considered genotype in CIN2+ or CIN3+. Consequently, pooling of accuracy estimates over groups of HPV types often was not possible.

At the first Guideline Development Group (GDG) meeting (WHO Living Recommendations for Screening and Treatment to Prevent Cervical Cancer, 6–7 December 2022) the assessment of performance of extended HPV genotyping in the triage of HPV-positive women was proposed as a priority for future review work.

1.2 Definition of extended HPV genotyping

In the literature assessing HPV genotyping capacity of cHPV assays, the following terminology is generally accepted:

- Limited genotyping: An HPV assay that identifies the most carcinogenic types (HPV16, HPV18 and may include HPV45) and reports the remaining carcinogenic types (typically the other 10 cHPV types and often one or two additional HPV types);
- Full genotyping: An HPV assay that identifies all 12 cHPV types separately and may additionally individually identify other HPV types;
- Extended genotyping: An HPV assay that provides more detailed results than limited genotyping by separately identifying types HPV16, HPV18 and may include HPV45, and

[1] WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/342365).

further pooling the other 10 cHPV types into two or three groups. Some assays may also individually identify other cHPV types than HPV16, HPV18 and HPV45 and one or two other HPV types.

1.3 Aim

The aim was to establish the evidence on test performance of extended genotyping among women who test positive on an HPV screening test, with the purpose of developing evidence-based guidelines on its use in the triage of HPV-positive women.

To address the problem described above, two main approaches were suggested to assess the triage performance of HPV genotyping:

- to rank HPV types according to a universal ranking system and to request aggregated data from authors of studies that assessed the cross-sectional and/or longitudinal risk of CIN3+ or cervical cancer;
- to request aggregated data from database owners with large population-based files containing records of baseline HPV genotyping status, with or without cytology, linked to pathology databases with clinical outcome data, including the occurrence of CIN3+ or cancer, allowing the computation of cumulative risks over time.

1.4 Objective

The objective was to determine the risk of CIN3+ over time associated with cHPV genotypes hierarchically ranked according to the WHO target product profiles (TPPs).

1.5 Steps and methods

The following steps were followed:

- Establish consensus on a ranking principle.
- Identify studies that contain data on the risk of CIN3+ associated with presence or absence of cHPV genotypes.
- Develop Excel sheets for use in data requests.
- Request aggregated data sets.
- Compile data sets.
- Assess study quality.
- Develop a statistical analysis plan.
- Cross-tabulate study-specific findings.
- Conduct pooled analyses of cumulative risks of CIN3+ associated with ranked groups of cHPV types according to the WHO TPPs for HPV screening tests[2] by follow-up time.

1.5.1 *Structure of the data sets requested from targeted authors*

A template data-set worksheet was submitted to the relevant authors of published papers with the request to complete it (see Table 1). Optionally, data sets could be stratified by baseline cytology and repeated for multiple years of follow-up.

[2] Target product profiles for human papillomavirus screening tests to detect cervical precancer and cancer. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/379099).

Table 1 Data collection worksheet template

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z
1	author	year	study	country	test	N	types	h_label	cyt_0	via_0	fu_time	av_futime	hiv	art	cd4	load_hiv	n_hpv	n_hpv_his	n_c2p	n_c3p	n_aisp	n_sqce	n_adca	n_adsqce	n_ca	
2							-1	absence any HPV																		
3							0	absence of hrHPV																		
4							1	hrHPV																		
5							16	HPV16																		
6							18	HPV18																		
7							45	HPV45																		
8							33	HPV33																		
9							58	HPV58																		
10							31	HPV31																		
11							52	HPV52																		
12							35	HPV35																		
13							59	HPV59																		
14							39	HPV39																		
15							68	HPV68																		
16							51	HPV51																		
17							56	HPV56																		
18							66	HPV66																		
19							1618	HPV1618																		
20							1845	HPV1845																		
21							11	oth11 hrHPV but not H16/18																		
22							12	oth12 hrHPV but not H16/18																		
23							101	iarcC																		
24							102	iarcD																		
25							103	danA																		
26							201	danB																		
27							202	sweA																		
28							211	sweB																		
29							212	sweC																		
30							220	onc16																		
31							221	onc18																		
32							222	onc45																		
33							223	onc3358																		
34							224	onc31																		
35							225	onc52																		
36							226	onc353969																		
37							227	onc595666																		
38							230	ali16																		
39							231	ali18																		
40							232	ali45																		
41							233	ali31335258																		
42							234	alioth																		
43							240	xp16																		
44							241	xp1845																		
45							242	xp31335258																		
46							243	xp5159																		
47							244	xpoth																		
48							250	sfireA																		
49							251	sfireB																		
50							252	sfireC																		
51							253	sfireD																		

1.5.2 *Statistical analysis*

The following outcomes were computed from the received data sets:

- Study-specific cumulative risk (=longitudinal PPV), n_lesion/N positive (number of lesions per number positive), for a given cHPV type or cHPV type group, including CIN2+, CIN3+ and cervical cancer lesions.
- Study-specific relative risks or cumulative risk ratios comparing type-specific cumulative risks with a comparator group. The comparator groups included women with atypical squamous cells of undetermined significance (ASCUS+) or worse cytology and women who were HPV-negative at baseline if the data include a second screening round.
- Risks and risk ratios will be presented ranked (according to the International Agency for Research on Cancer (IARC) and WHO TPPs tables 1 and 2). A life table was used to compute risks over time when data owners were able to provide longitudinal data over multiple screening rounds.
- Triage test positivity rate (only when all cHPV-positive samples were genotyped).
- The number of referrals needed to detect one case of targeted lesions (CIN3+, CIN2+ or cancer), =1/PPV.
- Addition of risks and risk ratios directly derivable from the literature and included in a comprehensive meta-analysis conducted by Sciensano.
- For cross-sectional data, sensitivity and specificity of triage by extended genotyping groups could be computed.
- Meta-analytical pooling of risks and relative risks.

As an extension, we considered application of METAsurv methodology, where published or requested cumulative incidence plots (smoothed curves or stairway Kaplan-Meier format) are scanned, digitized and submitted to survival analysis. The statistical analysis produces absolute cumulative incidences estimates and hazard ratios. See examples in Figs. 1 and 2. Tables 2, 3 and 4 detail carcinogenic HPV types.

Fig. 1 Cumulative incidence of CIN3+ by infection with a given HPV type at baseline

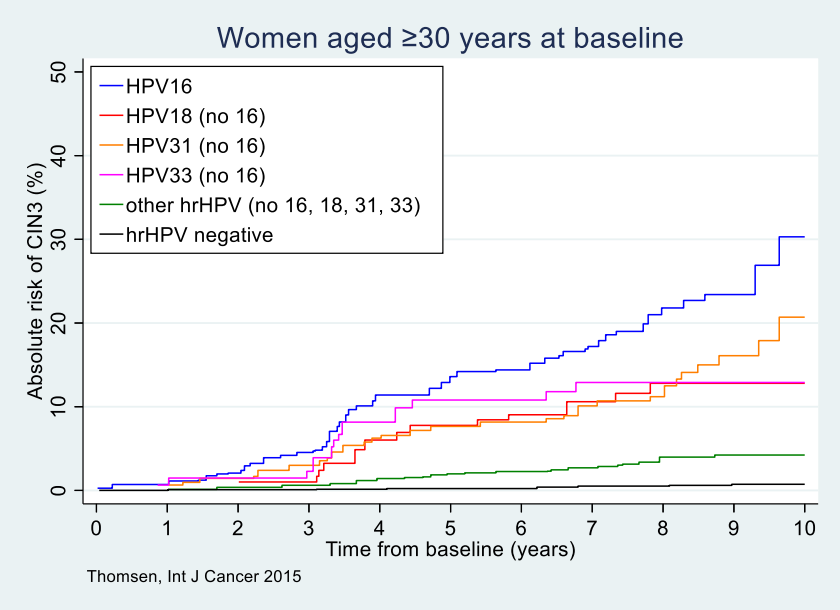
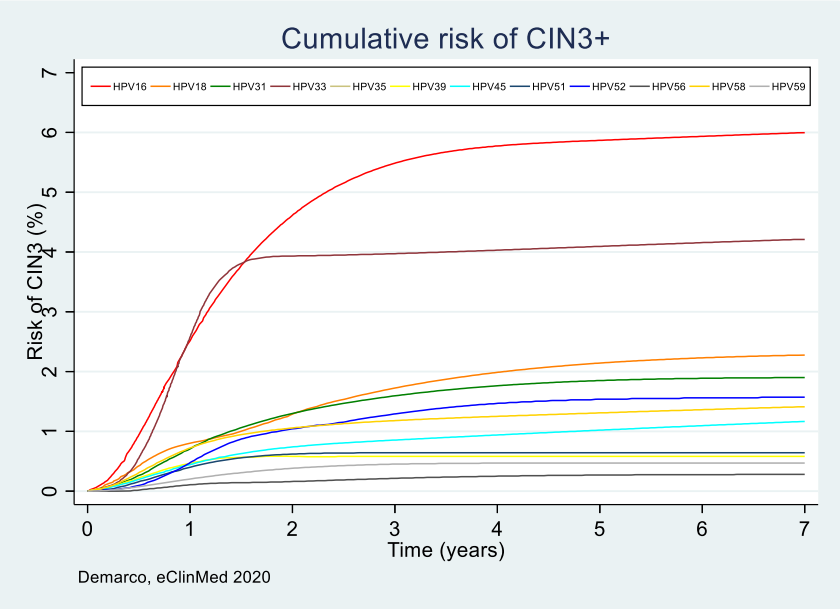


Fig. 2 Cumulative incidence of CIN3+ by infection with a given HPV type at baseline



Curves are scanned, digitized and translated into a data set using DigitzeIt.
Source: adapted from Demarco, 2020[3].

[3] Demarco M, Hyun N, Carter-Pokras O, Raine-Bennett TR, Cheung L, Chen X et al. A study of type-specific HPV natural history and implications for contemporary cervical cancer screening programs. Clinical Medicine. 2020;22:100293. (https://doi.org/10.1016/j.eclinm.2020.100293).

Table 2 Relative importance of carcinogenic human papillomavirus (HPV) types

Rank	HPV type	HPV species	IARC group	Prevalence in cancer	Prevalence in normal	Reported odds ratio	Computed odds ratio	Reported attributable fraction
1	HPV 16	α-9	1	0.558	0.026	47.6	47.3	0.624
2	HPV 18	α-7	1	0.143	0.010	15.7	16.5	0.153
3	HPV 45	α-7	1	0.048	0.006	8.3	8.4	0.048
4	HPV 33	α-9	1	0.040	0.006	7.1	6.9	0.039
5	HPV 58	α-9	1	0.040	0.008	5.1	5.2	0.037
6	HPV 31	α-9	1	0.035	0.010	3.7	3.6	0.029
7	HPV 52	α-9	1	0.032	0.010	3.3	3.3	0.026
8	HPV 35	α-9	1	0.016	0.004	3.9	4.0	0.014
9	HPV 59	α-7	1	0.012	0.004	2.9	3.0	0.009
10	HPV 39	α-7	1	0.013	0.006	2.0	2.2	0.008
11	HPV 68	α-7	2A	0.006	0.004	1.5	1.5	0.002
12	HPV 51	α-5	1	0.010	0.009	1.2	1.1	0.002
13	HPV 56	α-6	1	0.008	0.006	1.3	1.3	0.002
14	HPV 73	α-11	2B	0.005	0.003	1.8	1.7	0.002

Group 1: carcinogenic; Group 2A probably carcinogenic; Group 2B: possibly carcinogenic to humans.
Source: adapted from IARC Handbook[4].

Table 3 Ranking of the 12 carcinogenic HPV types (Group 1) as per WHO TPPs (1a, 1b, 1c, 1d)

HPV type	IARC classification of carcinogenicity	WHO-TPPs Type groups
HPV16	**1**	**1a**
HPV18	1	1b
HPV45	1	1b
HPV33	1	1c
HPV58	1	1c
HPV31	1	1c
HPV52	1	1c
HPV35	1	1c
HPV59	1	1d
HPV39	1	1d
HPV51	1	1d
HPV56	1	1d

Certain countries already apply a principle of grouping of HPV types according their carcinogenic risk in their guidelines for triaging HPV-positive women (for instance Sweden and Denmark; see Table 4).

[4] International Agency for Research on Cancer. IARC handbooks of cancer prevention: cervical cancer screening, Vol. 18. Lyon, France: IARC Press; 2022:67 (https://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Cervical-Cancer-Screening-2022).

Table 4 Extended genotyping to triage HPV-positive women used in current guidelines

Group label	Included HPV types
Swedish guidelines	
Highly oncogenic	16/18/45
Medium oncogenic	31/33/52/58
Lower oncogenic	35/39/51/59/66/68
Danish guidelines	
Highest risk group	16/18/45/31/33/52
Lower risk group	35/39/51/58/59/66/68

Since 2025, extended genotyping is recommended also in the United States of America (USA) *(1)*.

Table 5 presents the lists of HPV assays that are currently considered as clinically validated for use in screening on clinician-taken cervical samples, including the extent of HPV genotyping provided by the test.

Table 5 Genotyping capacity of currently validated HPV assays that can be used in cervical cancer screening

HPV assay genotyping capacity	**Nb targeted**	**IARC group of carcinogenic HPV Types**	**Genotyping Details**
No genotyping			
HC2	13	12 group 1 & 1 group 2A	None
GP5+/6+ PCR-EIA	14	12 group 1, 1 group 2A, 1 group 2B	None
APTIMA HPV Assay	14	12 group 1, 1 group 2A, 1 group 2B	none
Limited genotyping			
Cobas 4800, 6800	14	12 group 1, 1 group 2A, 1 group 2B	HPV16, 18, 31/33/35/39/45/51/56/59/66/68
Abbott RealTime High Risk HPV	14	12 group 1, 1 group 2A, 1 group 2B	HPV16, 18, 31/33/35/39/45/51/56/59/66/68
HPV-Risk Assay	15	12 group 1, 1 group 2A, 1 group 2B	HPV16, 18, 31/33/39/45/52/56/58/59/66/67/68
REALQUALITY RQ-HPV Screen	14	12 group 1, 1 group 2A, 1 group 2B	HPV16,18, 31/33/35/39/45/51/56/59/66/68
OncoPredict HPV SCR	13	12 group 1, 1 group 2A	HPV16,18, 31/33/35/39/45/51/56/59/68
Extended genotyping			
BD Onclarity	14	12 group 1, 1 group 2A, 1 group 2B	HPV16, 18, 31, 45, 51, 52; HPV33/58; 35/39/68; 56/59/66
Alinity	14	12 group 1, 1 group 2A, 1 group 2B	HPV 16,18, 45; 31/33/52/58; 35/39/51/56/59/66/68
Xpert HPV	14	12 group 1, 1 group 2A, 1 group 2B	HPV16; 18/45; 31/33/35/52/58; 51/59; HPV39/56/66/68

Full genotyping	Nb types targeted	IARC group of oncogenic HPV types	Genotyping details
Anyplex II HR	14	12 group 1, 1 group 2A, 1 group 2B	All 14 types included in GP5+/6+ PCR
PapilloCheck	15	12 group 1, 1 group 2A, 1 group 2B	All 14 types included in GP5+/6+ PCR plus HPV53
EuroArray (partially validated)	30	12 group 1, 1 group 2A, 1 group 2B	All 14 types included in GP5+/6+ PCR plus 4 2B types (26, 53, 73, 82); plus 12 other types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, 89)
CLART HPV4s	16	12 group 1, 1 group 2A, 1 group 2B	All 14 types included in GP5+/6+ PCR plus HPV6,11
Riatol qPCR	17	12 group 1, 1 group 2A, 1 group 2B	All 14 types included in GP5+/6+ PCR plus HPV6,11,53 (67)
OncPredict QT	12	12 group 1	Neither potentially nor possible oncogenic types

Source: adapted from Arbyn et al., 2021 (28)

Additional HPV tests with WHO prequalification that are not included in Table 5, include the CareHPV test, which provides a pooled (non-genotyped) result for 12 cHPV types, including HPV66 and HPV68, and the Aptima HPV16 18/45 Genotype Assay, which provides limited genotyping for HPV16 (individually) and HPV18/45 (pooled).

1.5.3 *List of eligible studies*

The following studies were identified during the systematic review started on request of, or with support from, European Society of Gynaecological Oncology, the French High Council for Health, Cancer Council of New South Wales (Sydney, Australia), the Belgian Cancer Centre, the Risk-based Screening for Cervical Cancer (RISCC) project (RISCC Horizon 2020 project, European Commission) and WHO (cervical cancer screening guideline group).

Inclusion criteria were as follows: women who were cHPV-positive identified through primary cervical cancer screening, who had received at least one triage test or combination of triage tests, with occurrence of cervical histologically confirmed lesions monitored among triage-positive and triage-negative women; timelines were documented.

- Wheeler et al, 2014 (NMHPVPR study, USA) *(2)*
- Schiffmanet al, 2015 (KPCN, USA) *(3)*; Demarco et al, 2018 (KPCN, USA) *(4)*; Schiffman et al, 2016 (KPCN, USA) *(5)*; Demarco et al, 2020 (KPCN, USA) *(6)*
- Wright et al; 2019 *(7)*; Stoler et al, 2023a *(8)* and 2023b *(9)* (Onclarity study, USA); Stoler et al, 2019 (Onclarity study, USA) *(10)*
- Safaeian et al, 2021 (Impact study, USA) *(11)*; Wright et al, 2022 (Impact study, USA) *(12)*
- Monsonego et al, 2015 (Athena study, USA) *(13)*; Stoler et al, 2020 (Athena study, USA) *(14)*
- Bulkmans et al, 2005 (POBASCAM, the Netherlands) *(15)*
- Kjaer et al, 2014 (Denmark) *(16)*; Thomsen et al, 2015 (Denmark) *(17)*; Sand et al, 2019 *(18)*
- Mistro et al, 2018 (NTCC, Italy) *(19)*
- Kitchener et al, 2014 (ARTISTC, UK) *(20)*
- Hashim et al, 2020 (Norway) *(21)*

Previous reviews: Bzhalava et al, 2013 *(22)*, Cuzick and Wheeler, 2016 *(23)*.

1.5.4 *Data collection*

An excel file ("WHOextgenotF2_empty.xlsx") was developed and used to collect data from data owners. The file contained two worksheets:

- Worksheet "hier", used for hierarchically ranked HPV types or groups of HPV types, according to the IARC list included in Fig. 1. We first considered HPV16, where we counted all women with baseline HPV16 infection, irrespective of whether it concerned a single or multiple infections. Next we considered HPV18, where we counted all women with HPV18, but not with HPV16. All other types (classified at a lower level) could be present or absent.
- Worksheet "explanation_hier", containing information about the variable names, value labels and instructions on how to use the data-entry form.

Table 6 includes the data sets for the general population of women, which were received and processed comprising genotyping information from 72 384 cHPV-positive women.

Table 6 Overview of received study data included in the analysis

N	Study	Countries	N° subjects screened	N° HIV	hrHPV+	FU (Y)	Tests	Stratifier
1	PAVE	9 countries: Latin America, Africa, Asia	50 657	8355	7535	1	Screenfire	VIA
2	NATHIC	Belgium	346 781	-	49 897	9	RIATOL qPCR	cytology
3	IRIS	USA		-	3757	3	HC2/Cobas/Onclarity	cytology
4	Slovenia	Slovenia	4118	-	540	9	Alinity	cytology
5	ARTISTIC	UK	24 193	-	3547	20	HC2/Linear Array	cytology
6	Denmark	Denmark	78 764	-	7108	1	Onclarity	cytology

1.5.5 *Processing and compilation of received data*

Studies included in the current analysis and publications for reference

PAVE study
Involved countries: nine countries across Africa, Latin America and Asia (Brazil, Cambodia, Dominican Republic, El Salvador, Eswatini, Honduras, Malawi, Nigeria and Tanzania).

- De Sanjosé et al, 2024 *(24)*
- Befano et al, 2025 *(25)*

NATHIC study
Involved country: Belgium.

- Arbyn et al, 2009 *(26)*
- Benoy et al, 2019 *(27)*
- Arbyn et al, 2021 *(28)*

IRIS study
Country involved: USA.

- Gage et al, 2022 *(29)*

Slovenian study
Country involved: Slovenia.

- Ostrbenk et al, 2025 *(30)*

ARTISTIC trial
Country involved: UK.

- Gilham C et al, 2023 *(31)*.

Danish screening study
Country involved: Denmark.
Bonde Et al, 2020 *(32)*

Computation of the accuracy of HPV genotyping tests (sensitivity and specificity for CIN3+ cervical cancer)

We calculated the relative sensitivity and specificity of genotyping for HPV16 (WHO TPP group 1a); HPV16 and HPV18/45 (WHO TPP groups 1a and 1b); HPV16, HPV18/45 and WHO TPP group 1c; and all four WHO TPP groups 1a, 1b, 1c and 1d.

We considered the quartet HPV31/33/52/58 without HPV35 to be similar to WHO TPP group 1c when extended genotyping was performed with Onclarity or Alinity. The combination of the HPV39/51/56/59/68 was similar to WHO TPP group 1d when HPV testing was performed with ScreenFire.

1.6 Results

1.6.1 *Computation of the risk of CIN3+ and cervical cancer of strategic combinations of HPV genotypes to triage cHPV*

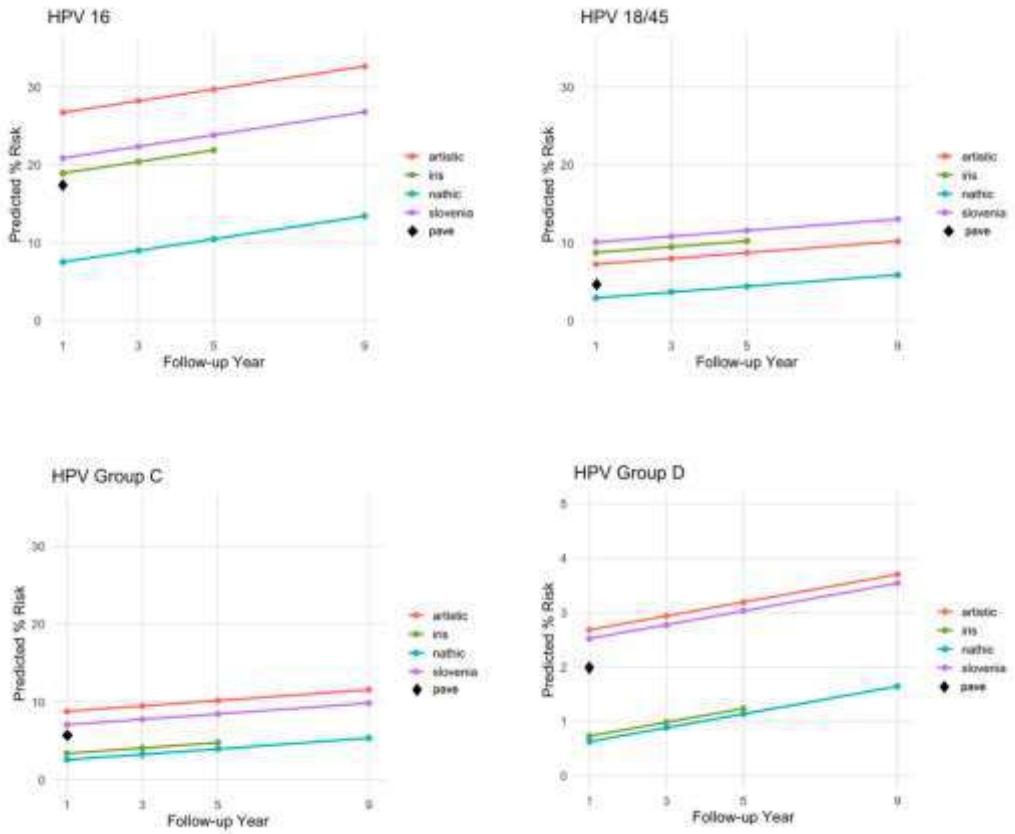
Fig.3 plots the detection rate of CIN3+ when an HPV type of WHO TPP group 1a (HPV16,) 1b (HPV18/45), 1c (HPV31/33/35/52/58) or 1d (HPV39/51/56/59) is present. Often, HPV tests with extended genotyping do not exactly separate the exact WHO TPPs groups. In such cases, types were grouped in look-alike WHO TPPs groups as described in the previous section.

Four studies (NATHIC, ARTISTIC, IRIS and Slovenia) contributed data varying from three to 20 years. The other three studies contributed only cross-sectional findings with CIN3+ detected by triaging HPV-positive women during one screening episode.

Modelling approach for Figs. 3 and 4

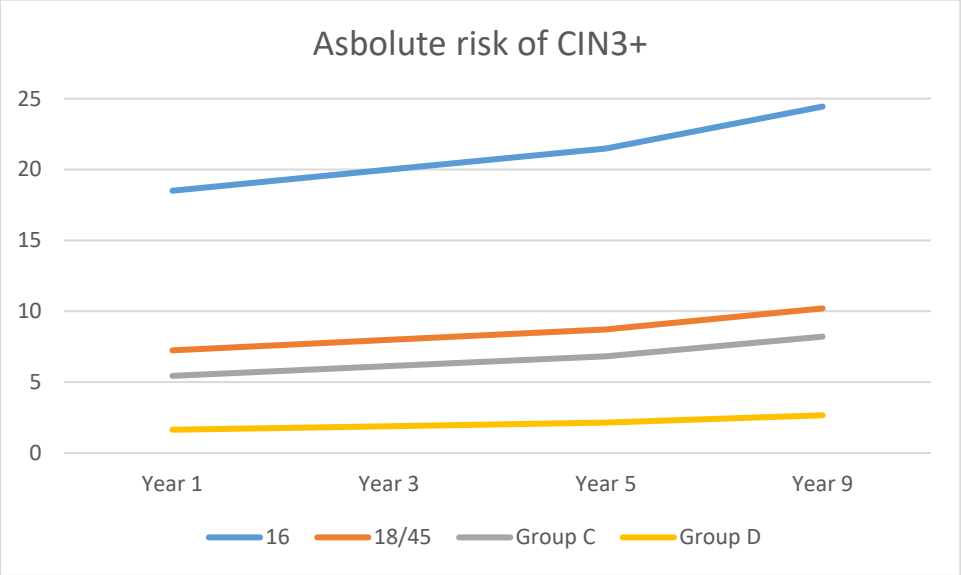
For the ARTISTIC, NATHIC and Slovenia studies, risks at each year were estimated through the Kaplan-Meier statistic, assuming that at each year, the reported N is the number of individuals returning for follow-up. Variance of these estimates are obtained using Greenwood's formula. For the IRIS study, risks at each year were predicted through the prevalence-incidence (PI)-Mixture model with standard errors of each estimate provided by the model. A generalized linear model (GLM) was performed with inverse variance weighting to combine these four studies with follow-up time and study as covariates in the model. Combined risk estimates by HPV type group were obtained by averaging the study covariates in the GLM model.

Fig. 3 Detection of CIN3+ by WHO TPP cHPV groups 1a, 1b, 1c and 1d in one cross-sectional study and four longitudinal studies with follow-up up to nine years



Lower detection rate from left to right and from top to bottom.

Fig. 4 Modelled combined risk CIN3+ estimates by WHO TPP cHPV groups 1a, 1b, 1c and 1d from four longitudinal studies (ARTISTIC, IRIS, NATHIC, Slovenia)



Figs. 5, 6, 7 and 8 show the meta-analysis of the HPV type group-specific risks of CIN3+.

Fig. 5 Baseline CIN3+ risk associated with HPV16 (group 1a) infection, pooled from a random-effect meta-analysis of six studies

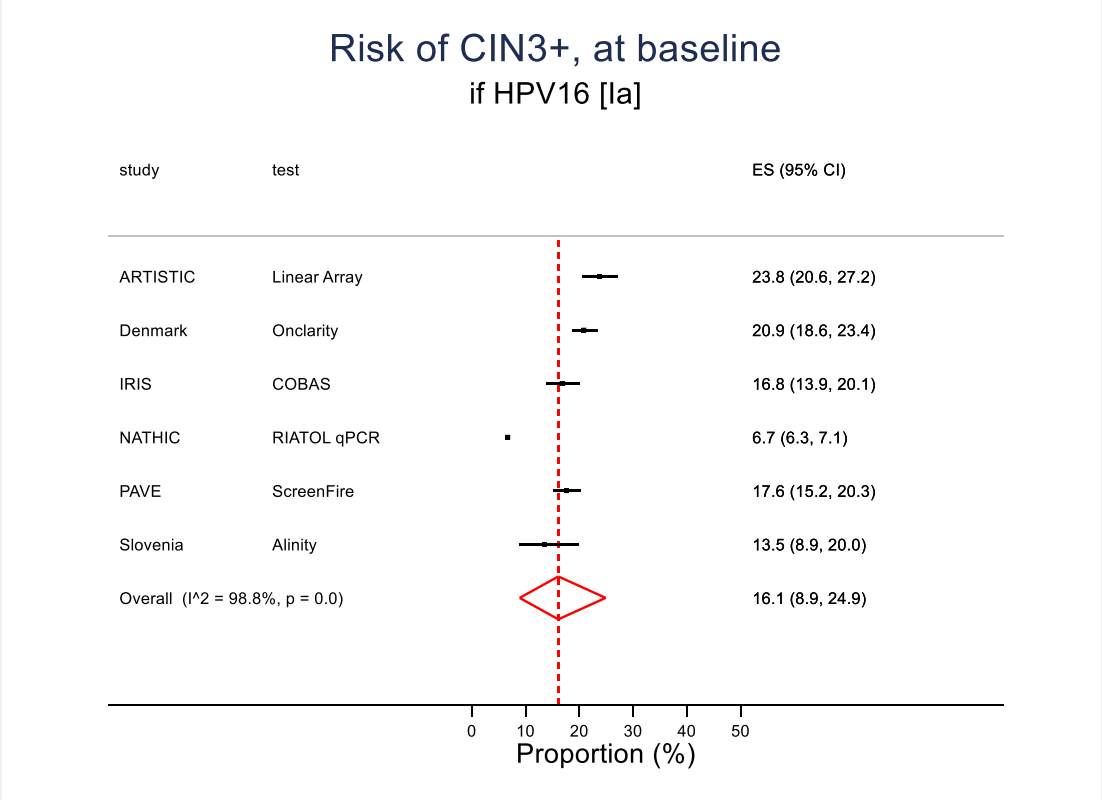


Fig. 6 Baseline CIN3+ risk associated with HPV18/45 (group 1b) infection, pooled from a random-effect meta-analysis of six studies

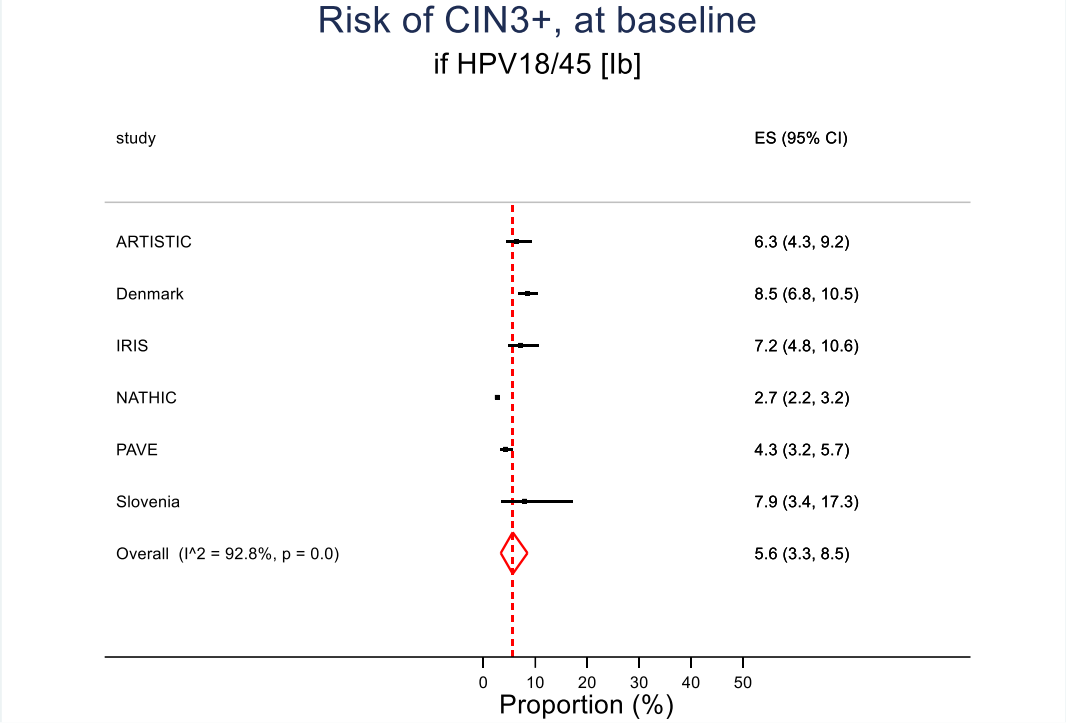
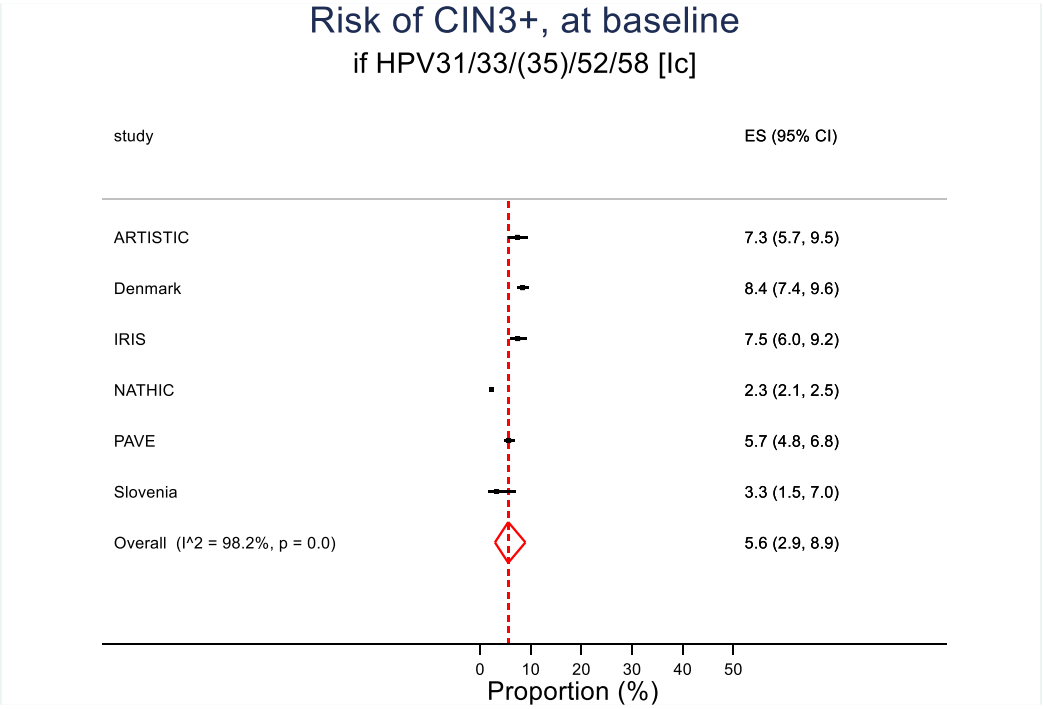
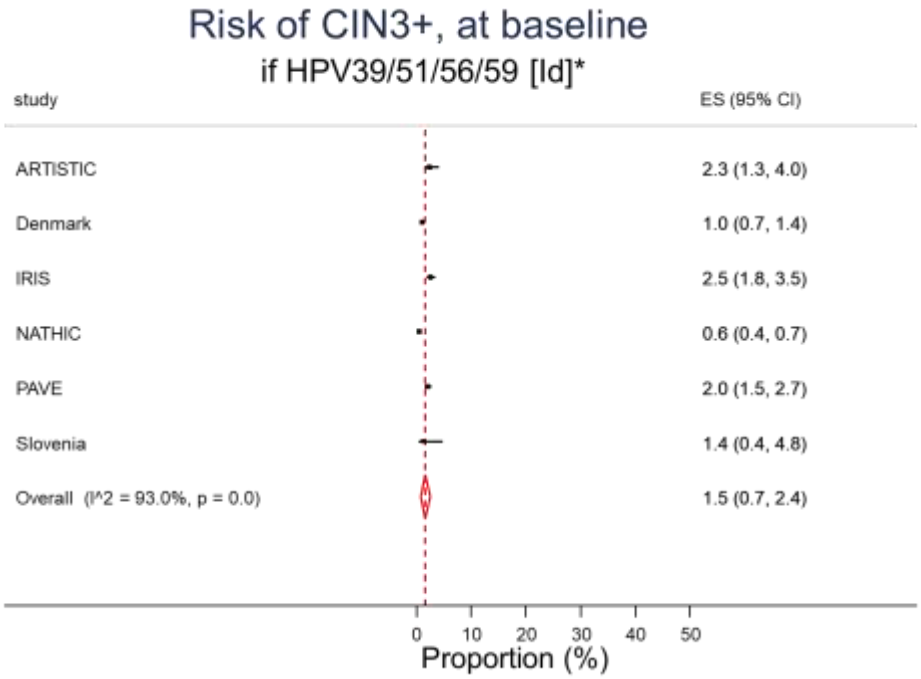


Fig. 7 Baseline CIN3+ risk associated with HPV 31/33/35/52/58 (group 1c) infection, pooled from a random-effect meta-analysis of six studies



In Slovenia (Alinity), Denmark (Onclarity), IRIS (Onclarity) HPV assays were used that do not identify HPV35 together with the other cHPV types on group 1c.

Fig. 8 Baseline CIN3+ risk associated with HPV 39/51/56/59 (group 1d) infection, pooled from a random-effect meta-analysis of six studies



In Slovenia (Alinity), Denmark (Onclarity) and IRIS (Onclarity), HPV assays were used that identify HPV35/66/68 together with the other cHPV types on group 1d.

Table 7 shows the risk of CIN3+ with HPV groups 1a, 1b, 1c and 1d positivity.

Table 7 Pooled baseline CIN3+ risk associated with HPV positivity for hierarchically ranked types grouped in four groups according to level of carcinogenicity

			Pooled CIN3+ risk, in % (95% CI)
Risk of CIN3+		**Look-alike**	**all studies**
HPV group	HPV types	HPV groups	
1a	HPV16		20.5 (11.2-31.7)
1b	HPV18/45		7.1 (4.2-10.7)
1c	HPV31/33/35/52/53	-HPV35	7.3 (4.0-11.4)
1d	HPV39/51/56/59	+HPV35/66/68	1.9 (1.0-3.2)

1.7 Discussion

Aggregated data were received from six studies, comprising genotyping information of approximately 72 000 women with a cHPV-positive result at HPV-based cervical cancer screening, from four continents.

Meta-analytical pooling of the cross-sectional findings showed that HPV16 (WHO TPP group 1a) is associated with a very high immediate risk of CIN3+ lesions (around 18%), exceeding the risks associated with other HPV type groups. At the opposite end of the spectrum, we observed that HPV types belonging to the 1d group were associated with a quite limited immediate risk (around 1%) of CIN3+. The HPV type groups 1b and 1c, with an intermediate carcinogenic potential, show an average absolute risk of 7% and 5% respectively. The average absolute risk of CIN3+ after nine years of follow-up were 24%, 10%, 8% and 2% for groups 1a, 1b, 1c and 1d respectively. While cross-sectional risks for CIN3+ were not very different, a differential probability of developing invasive cervical cancer is expected between groups 1b and 1c. It would be interesting to assess the risk

associated with HPV18 alone and with the duplet HPV16/18, and to explore geographical differences in the longer-term risks of CIN3+ and cancer associated with HPV45 to challenge the impact of triage recommendations for women with 1a and 1b infections.

A weakness of our study on the performance of triage of screen-positive women by WHO TPPs groups is the lack of availability of existing extended genotyping HPV assays. At present, none of currently available and clinically validated HPV tests with extended HPV genotyping capacity can distinguish the WHO TPP groups 1c and 1d. Only fully genotyping HPV assays allowed us to compute the risks correlated with different carcinogenic groups. Nevertheless, we were able to compose look-alike groups using the typing details of the tests concerned. This means that triage recommendations will require fine-tuning according to the available HPV assay in a specific screening programme.

We want to express our gratitude to data owners and researchers for the willingness and efforts to transfer data.

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2. Evidence summary 2. Modelling results on benefits, harms and cost-effectiveness of extended genotyping algorithms

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2.1 Background

To support countries in implementing the Global Strategy for the elimination of cervical cancer screening as a public health problem, WHO updated their guidelines for cervical screening in 2021 *(1)*, recommending universal adoption of primary human papillomavirus (HPV) testing.

These updated guidelines were, in part, informed from our earlier modelling using the Policy1-Cervix platform, which found that primary HPV screening approaches were the most effective and cost-effective, reducing cervical cancer age-standardized mortality rates by 63–67% when offered every five years in the general population of women. For the general population of women, WHO recommends primary HPV in either in a screen-and-treat approach or a screen-triage-and-treat approach every five or 10 years for women aged 30–50. Our earlier modelling using Policy1-Cervix-HIV *(2)* also supported updated WHO guidelines for women living with HIV, which now recommend primary HPV testing in a screen-triage-and-treat approach every three or five years for women aged 25–50 *(1)*. Primary HPV testing opens up options for self-collection, which has been shown to increase acceptability of cervical screening in low- and middle-income countries (LMICs) *(3)* and increase participation in women who are under-screened or never screened in Australia *(4)*. Primary HPV testing also allows the option of point-of-care testing, which could allow for screen-and-treat management and reduce loss-to-follow-up for women in rural and remote areas. However, challenges remain for LMICs in scaling-up primary HPV testing. The cost-per-test can be a barrier for countries, particularly LMICs. New technologies have been rapidly entering the market – in a landscape report published in 2024, a total of 264 clinically-validated HPV tests were commercially available *(5)*. To support the development of new testing technologies, the WHO released target product profiles (TPPs) for HPV screening tests in 2024, describing minimal and preferred characteristics of HPV tests to ensure new technologies are optimally designed to enable countries to reach the target of 70% cervical screening coverage *(6)*. One such characteristic described in the TPPs included classifying the 12 carcinogenic HPV (cHPV) types into four categories based on relative attributable fraction in cervical cancer, informed by the International Agency for Research on Cancer handbook *(7)*: group 1a contains HPV16, group 1b contains HPV18/45, group 1c contains HPV31, 33, 35, 52 and 58 and group 1d contains HPV39, 51, 56 and 59. According to the TPPs, as a minimum, new tests should detect at least eight of the carcinogenic types across groups 1a−1c (8-type test) in a single output signal; however, preferred characteristics would identify all 12 carcinogenic types across groups 1a−1d (12-type test), with at least four output categories based on the four risk categories.

Other challenges for LMICs are around follow-up of women who require treatment or surveillance. Our earlier modelling was based on a normative approach, which assumed follow-up of at-risk women was 90% at all points in the management pathway. However, some settings might experience challenges in reaching and maintaining 90% follow-up, especially in algorithms that require longer-term follow-up after triage, or for women after treatment for pre-cancer.

2.2 Aims

The two main aims were as follows:

AIM1: to evaluate the impact of screening algorithms that allow for differential management based on HPV type-specific positivity for 8-and 12-type HPV tests.

AIM2: to explore the resilience of screening algorithms when follow-up of at-risk women is low for all recommended primary HPV DNA testing approaches, both for the 2021 guidelines algorithms and updated extended genotyping algorithms.

2.3 Methods

We used the Policy1-Cervix platform, an extensively validated dynamic model of HPV transmission, vaccination, HPV type-specific natural history, cancer survival, screening, diagnosis and treatment *(2,8–15)* to predict outcomes for each strategy across the lifetime of females aged 10–84 who turn 30 in 2030 (born in 2000) across all 78 LMICs. The Policy1-Cervix model was used to inform the 2021 update of the WHO cervical screening guidelines, and was one of three models used by the Cervical Cancer Elimination Modeling Consortium (CCEMC) to evaluate the impact of cervical cancer elimination targets in 78 LMICs and was reviewed and endorsed by the WHO Advisory Committee on Immunization and Vaccines related Implementation Research for the use in modelling elimination targets for WHO, and subsequently for global modelling of therapeutic HPV vaccination *(16)*. Details of the modelled approach on the calibration to 78 LMICs is described in detail in the earlier CCEMC publications *(8,17)*.

To ensure adequate communication between the different expert groups involved in informing the update of cervical screening and treatment guidelines, regular meetings were held between the modelling team, representatives from the WHO secretariat and representatives from the systematic review teams. Regular meetings were also held between Guideline Development Group (GDG) members and the systematic review, modelling and costing teams to discuss the priority management algorithms.

2.3.1 *Screening strategies*

For both AIM1 and AIM2, we considered the benefits, harms and cost-effectiveness of six screening algorithms involving the use of limited or extended genotyping testing as identified by the GDG, compared to no screening:

1) HPV screen-and-treat using a 12-type test (1a–d] (12-type treat)
2) HPV screen-and-treat using an 8-type test (1a–c) (8-type treat)
3) HPV screen-triage-and-treat using a 12-type test (12-type [1a–d] triage)
4) HPV screen-and-treat for 1a–1c, screen-triage-and-treat for 1d using a 12-type test (12-type extended genotyping (1a–c) treat, 1d triage)
5) HPV screen-and-treat for 1a–b, screen-triage-and-treat for 1c–d using a 12-type test (12-type limited genotyping [1a–b] treat [1c–d] triage)
6) HPV screen-and-treat for 1a-b, screen-triage-and-treat for 1c using an 8-type test ('8-type LG (1a-b) treat, 1c triage').

In scenarios involving triage, we considered visual inspection with acetic acid (VIA) triage, cytology triage and colposcopy triage.. We assume screening is offered every five years for women aged 30–50, every 10 years for women aged 30–50 or every 10 years for women aged 35 and 45 years, as per the 2021 updated guidelines. We also present outcomes for the strategies included in the 2021 Guidelines update *(1)*, including primary VIA and primary cytology strategies.

2.3.2 *Screening adherence*

For both aims, we assumed that 70% of women attend each routine screening visit, but that 10% would be never-screeners (i.e. the 70% are selected from the 90% of ever-screeners).

AIM1: Taking a normative approach, we made the favourable assumption that women tested with HPV and referred for triage follow-up or treatment with a procedure that could feasibly be

performed on the same day, such as ablation or VIA triage, would attend with a compliance rate of 95%. We assumed that same-day test and treatment would be available for all primary VIA scenarios and therefore made the favourable assumption that 100% adherence would be achieved in women eligible for same-day treatment after primary VIA. We assumed 90% of screen-detected cervical cancer cases would receive adequate treatment, but access to cancer treatment for symptomatically detected cancers would remain unchanged from the status-quo (rates vary by country, averaging up to 33% across all 78 LMICs). This assumption was made because of the huge logistical challenges involved in scaling-up access to cancer treatment for all women in LMICs.

AIM2: We evaluated outcomes when follow-up rates for at-risk women is reduced to 60% or 30%. Lower follow-up rates are applied to women referred to excisional treatment (due to being ineligible for ablative treatment), women referred for separate-visit triage within a few weeks and women referred for separate-visit follow-up at 12 months (including women who were triage negative, and women after pre-cancer treatment). Lower follow-up rates were not applied when triage or treatment can be offered at point-of-care. This includes primary VIA screening, primary HPV in a screen-and-treat approach or primary HPV when triage with VIA or colposcopy is used (assuming a portable colposcopy unit is utilised in these instances); cytology is always assumed to require a separate visit. Lower follow-up rates are applied in all instances when 12-month follow-up is recommended, for instance in cases where women test HPV positive and triage negative, or after treatment for pre-cancer.

2.3.3 *Outcomes assessed*

For both AIM1 and AIM2, we report on outcomes over the lifetime of unvaccinated women who would turn 30 in 2030, the first cohort to be fully affected by scale-up of cervical screening by 2030. Outcomes assessed include the lifetime number of cervical cancer cases and deaths and age-standardized incidence and mortality rates as a measure of the benefits. We assessed the number of pre-cancer treatments needed to avert a cervical cancer death (number needed to treat [NNT]) as a measure of the harms associated with screening. We report on the cost and cost-effectiveness of each strategy as a cost per health-adjusted life year (HALY) saved, assuming 0% discounting for effects and 3% discounting for costs as recommended by WHO for health economic evaluation of vaccination programmes *(18,19)*, and assuming discounting starts from age 30. We present results at a population-weighted average across 78 LMICs, which we refer to as a "normative approach", using 2015 population structure for population-weighted contribution of each country. There is no defined willingness-to-pay (WTP) when presenting cost-effectiveness at this multi-country average level; however, as a reference point for a potential WTP threshold in this population, the population-weighted average gross domestic product (GDP) per capita for 2019 across the 78 LMICs is US$ 2093, and 71 of 78 [91%] LMICs had a GDP per capita equal to or above US$ 518, considering countries GDP per-capita being related to the countries willingness-to-pay *(18,19)*.

2.4 Results

2.4.1 *Results: AIM1 – benefits, harms, cost-effectiveness of primary HPV testing with limited or extended genotyping*

Cervical cancer incidence and mortality – benefits

Over the lifetime of a cohort of 100 000 unscreened women in 78 LMICs, 1950 cervical cancer cases and 1456 deaths are predicted to occur (Table 1). For all screening frequencies, primary HPV testing algorithms resulted in similar reductions in cancer cases and deaths over the lifetime of birth cohorts; for example, when considering five-yearly screening (Table 1a), reductions in cancer cases ranged from 48−56% and reduction in deaths ranged from 57−64% across 14 primary HPV algorithms considered. All primary HPV testing approaches reduced cancer cases and deaths by at

least 10% points more than primary cytology or primary VIA strategies. When considering five-yearly intervals, 12-type screen-and-treat was the most effective strategy, with a 56% reduction in cervical cancer incidence and a 64% reduction in cervical cancer deaths predicted over the lifetime of birth cohorts compared to no screening. Eight-type screen-and-treat was slightly less effective, with a 52% reduction in cases (4% absolute percentage points lower) and 59% reduction (5% absolute percentage points lower) in deaths over the lifetime of a birth cohort compared to no screening. Twelve-type (1a−d) triage approaches resulted in 48−52% reduction in cancer cases and 57−61% reduction in deaths (ranges representing variation in triage test considered). Similar patterns were observed when considering 10-yearly intervals for women aged 30−50 years (Table 1b) and 10-yearly intervals for women aged 35−45 years (Table 1c).

The 12-type (1a-c) treat, 1d triage with colposcopy strategy has effectiveness very similar to that observed with 12-type screen-and-treat. This is due to assumptions around treatment offered to women who are referred to colposcopy. Specifically, we assume that women who are referred to colposcopy but in which the transformation zone is not visible (i.e. colposcopy unsatisfactory) are assumed to receive endocervical curettage at the same visit, followed by excisional treatment within a few weeks if histology confirms CIN2 or CIN3. Conversely, all women managed under 12-type screen-and-treat will receive ablation, unless they are confirmed ineligible after visual assessment. We believe the incremental benefit of excisional treatment for women who have an unsatisfactory colposcopy (generally older women) is making the strategy appear slightly more effective than 12-type screen-and-treat. The difference is very marginal, and in practice will likely be more impacted by variables associated with implementation success.

Table 1 Tabular summary of the lifetime number of cervical cancer cases, cervical cancer deaths, pre-cancer treatments, number of pre-cancer treatments needed to prevent a cervical cancer death (NNT), costs and resilience over the life time of a cohort of 100 000 women across 78 LMICs, assuming (a) five-yearly screening for women aged 30–50 years, (b) 10-yearly screening for women aged 30–50 years, (c) 10-yearly screening for women aged 35–45 years, (d) for scenarios evaluated in the earlier guidelines involving three or five-yearly primary VIA or primary cytology, no longer recommended for any setting, and (e) the colour code designed to provide an overall impression of strategies that are performing well—best-performing strategies in a column are coloured green (best = largest cancer incidence/mortality reduction or the lowest number of pre-cancer treatments, NNTs or costs)—followed by teal, yellow and then red for the worst-performing strategies..

(a)

Primary test	Screening ages	Cervical cancer cases (% reduction)	Cervical cancer deaths (% reduction)	Pre-cancer treatments+	NNT to avert a cervical cancer death#	Discounted lifetime cost@ (US$ 2019)	Resilience - absolute percentage point difference in mortality benefits when follow-up is 30%
No Screening	**-**	1950 (-)	1456 (-)	None	None	$3	N/A
12-type (1a-d) treat ('Screen-and-treat')	**5yrly, 30-50 yrs (5X)**	852 (56%)	525 (64%)	49 967	54	$52	11%
8-type (1a-c) treat ('Screen-and-treat')	**5yrly, 30-50 yrs (5X)**	936 (52%)	600 (59%)	31 583	37	$47	9%
12-type (1a-d) triage with VIA	**5yrly, 30-50 yrs (5X)**	938 (52%)	578 (60%)	30 194	34	$51	28%
12-type (1a-d) triage with cytology	**5yrly, 30-50 yrs (5X)**	1017 (48%)	622 (57%)	20 532	25	$59	52%
12-type (1a-d) triage with colposcopy	**5yrly, 30-50 yrs (5X)**	939 (52%)	562 (61%)	33 170	37	$57	41%
12-type LG (1a-b) treat, (1c-d) triage with VIA	**5yrly, 30-50 yrs (5X)**	874 (55%)	539 (63%)	34 357	37	$51	15%
12-type LG (1a-b) treat, (1c-d) triage with cytology	**5yrly, 30-50 yrs (5X)**	902 (54%)	554 (62%)	26 495	29	$56	20%
12-type LG (1a-b) treat, (1c-d) triage with colposcopy	**5yrly, 30-50 yrs (5X)**	869 (55%)	529 (64%)	35 924	39	$55	16%
8-type LG (1a-b) treat, 1c triage with VIA	**5yrly, 30-50 yrs (5X)**	954 (51%)	612 (58%)	25 282	30	$47	12%
8-type LG (1a-b) treat, 1c triage with cytology	**5yrly, 30-50 yrs (5X)**	969 (50%)	622 (57%)	21 481	26	$50	16%
8-type LG (1a-b) treat, 1c triage with colposcopy	**5yrly, 30-50 yrs (5X)**	948 (51%)	604 (59%)	25 342	30	$49	13%
12-type EG (1a-c) treat, 1d triage with VIA	**5yrly, 30-50 yrs (5X)**	858 (56%)	528 (64%)	40 647	44	$51	12%
12-type EG (1a-c) treat, 1d triage with cytology	**5yrly, 30-50 yrs (5X)**	870 (55%)	535 (63%)	36 548	40	$53	14%
12-type EG (1a-c) treat, 1d triage with colposcopy	**5yrly, 30-50 yrs (5X)**	850 (56%)	522 (64%)	41 229	44	$53	11%

(b)

Primary test	Screening ages	Cervical cancer cases (% reduction)	Cervical cancer deaths (% reduction)	Pre-cancer treatments+	NNT to avert a cervical cancer death#	Discounted lifetime cost@ (US$ 2019)	Resilience - absolute percentage point difference in mortality benefits when follow-up is 30%
No Screening	-	1950 (-)	1456 (-)	None	None	$3	N/A
12-type (1a-d) treat ('Screen-and-treat')	**10yrly, 30-50 yrs (3X)**	1045 (46%)	665 (54%)	39 801	50	$35	14%
8-type (1a-c) treat ('Screen-and-treat')	**10yrly, 30-50 yrs (3X)**	1108 (43%)	725 (50%)	25 932	35	$32	13%
12-type (1a-d) triage with VIA	**10yrly, 30-50 yrs (3X)**	1143 (41%)	733 (50%)	24 210	33	$35	28%
12-type (1a-d) triage with cytology	**10yrly, 30-50 yrs (3X)**	1226 (37%)	782 (46%)	16 363	24	$41	43%
12-type (1a-d) triage with colposcopy	**10yrly, 30-50 yrs (3X)**	1139 (42%)	709 (51%)	26 481	35	$39	38%
12-type LG (1a-b) treat, (1c-d) triage with VIA	**10yrly, 30-50 yrs (3X)**	1070 (45%)	682 (53%)	27 779	36	$34	17%
12-type LG (1a-b) treat, (1c-d) triage with cytology	**10yrly, 30-50 yrs (3X)**	1092 (44%)	696 (52%)	21 503	28	$38	20%
12-type LG (1a-b) treat, (1c-d) triage with colposcopy	**10yrly, 30-50 yrs (3X)**	1060 (46%)	669 (54%)	28 867	37	$38	17%
8-type LG (1a-b) treat, 1c triage with VIA	**10yrly, 30-50 yrs (3X)**	1126 (42%)	737 (49%)	20 742	29	$31	15%
8-type LG (1a-b) treat, 1c triage with cytology	**10yrly, 30-50 yrs (3X)**	1139 (42%)	746 (49%)	17 626	25	$34	17%
8-type LG (1a-b) treat, 1c triage with colposcopy	**10yrly, 30-50 yrs (3X)**	1114 (43%)	725 (50%)	20 816	28	$33	14%
12-type EG (1a-c) treat, 1d triage with VIA	**10yrly, 30-50 yrs (3X)**	1053 (46%)	669 (54%)	32 990	42	$34	15%
12-type EG (1a-c) treat, 1d triage with cytology	**10yrly, 30-50 yrs (3X)**	1061 (46%)	674 (54%)	29 812	38	$36	16%
12-type EG (1a-c) treat, 1d triage with colposcopy	**10yrly, 30-50 yrs (3X)**	1041 (47%)	659 (55%)	33 222	42	$36	13%

(c)

Primary test	Screening ages	Cervical cancer cases (% reduction)	Cervical cancer deaths (% reduction)	Pre-cancer treatments+	NNT to avert a cervical cancer death#	Discounted lifetime cost@ (US$ 2019)	Resilience - absolute percentage point difference in mortality benefits
No Screening	-	1950 (-)	1456 (-)	None	None	$3	N/A
12-type (1a-d) treat ('Screen-and-treat')	**10yrly, 35-45 yrs (2X)**	1237 (37%)	827 (43%)	18 622	30	$21	13%
8-type (1a-c) treat ('Screen-and-treat')	**10yrly, 35-45 yrs (2X)**	1285 (34%)	872 (40%)	11 974	20	$20	12%
12-type (1a-d) triage with VIA	**10yrly, 35-45 yrs (2X)**	1319 (32%)	887 (39%)	11 729	21	$21	23%
12-type (1a-d) triage with cytology	**10yrly, 35-45 yrs (2X)**	1382 (29%)	924 (37%)	7 957	15	$24	34%
12-type (1a-d) triage with colposcopy	**10yrly, 35-45 yrs (2X)**	1310 (33%)	861 (41%)	12 476	21	$23	31%
12-type LG (1a-b) treat, (1c-d) triage with VIA	**10yrly, 35-45 yrs (2X)**	1254 (36%)	840 (42%)	13 213	21	$21	15%
12-type LG (1a-b) treat, (1c-d) triage with cytology	**10yrly, 35-45 yrs (2X)**	1274 (35%)	852 (42%)	10 194	17	$23	17%
12-type LG (1a-b) treat, (1c-d) triage with colposcopy	**10yrly, 35-45 yrs (2X)**	1246 (36%)	829 (43%)	13 496	22	$23	15%
8-type LG (1a-b) treat, 1c triage with VIA	**10yrly, 35-45 yrs (2X)**	1294 (34%)	880 (40%)	9798	17	$20	13%
8-type LG (1a-b) treat, 1c triage with cytology	**10yrly, 35-45 yrs (2X)**	1309 (33%)	889 (39%)	8332	15	$21	14%
8-type LG (1a-b) treat, 1c triage with colposcopy	**10yrly, 35-45 yrs (2X)**	1287 (34%)	872 (40%)	9657	17	$21	13%
12-type EG (1a-c) treat, 1d triage with VIA	**10yrly, 35-45 yrs (2X)**	1241 (36%)	830 (43%)	15 385	25	$21	14%
12-type EG (1a-c) treat, 1d triage with cytology	**10yrly, 35-45 yrs (2X)**	1250 (36%)	834 (43%)	13 843	22	$22	14%
12-type EG (1a-c) treat, 1d triage with colposcopy	**10yrly, 35-45 yrs (2X)**	1234 (37%)	822 (44%)	15 429	24	$22	12%

Women testing positive for HPV types referred for treatment are treated after assessment of eligibility for ablative treatment. Women referred for triage are treated after assessment of eligibility for ablative treatment if triage-positive, with the exception of women positive after cytology triage who are referred to colposcopy. +There could be multiple treatments in the same woman over her lifetime. @ Costs incurred over the lifetime of an average woman discounting by 3% per-annum from age 30. #NNT, number of women needed to treat to avert a death.

(d)

Primary test	Screening ages	Cervical cancer cases (% reduction)	Cervical cancer deaths (% reduction)	Pre-cancer treatments+	NNT to avert a cervical cancer death#	Discounted lifetime cost@ (US$ 2019)	Resilience - absolute percentage point difference in mortality benefits
No Screening	-	1,950 (-)	1,456 (-)	None	None	$3	N/A
Primary VIA (High sens)	**3yrly, 30-50 yrs (7X)**	1046 (46%)	645 (56%)	147627	182	$54	14%
Primary VIA (High sens)	**5yrly, 30-50 yrs (5X)**	1181 (39%)	722 (50%)	120 091	164	$41	16%
Primary VIA	**3yrly, 30-50 yrs (7X)**	1193 (39%)	769 (47%)	137 443	200	$51	13%
Primary VIA	**5yrly, 30-50 yrs (5X)**	1348 (31%)	876 (40%)	111 608	192	$39	13%
Cytology, HPV triage for ASCUS	**3yrly, 30-50 yrs (7X)**	1112 (43%)	703 (52%)	20 728	28	$81	31%
Cytology, HPV triage for ASCUS	**5yrly, 30-50 yrs (5X)**	1209 (38%)	758 (48%)	18 246	26	$59	32%

Women testing positive for HPV types referred for treatment are treated after assessment of eligibility for ablative treatment. Women referred for triage are treated after assessment of eligibility for ablative treatment if triage-positive, with the exception of women positive after cytology triage who are referred to colposcopy. +There could be multiple treatments in the same woman over her lifetime. @ Costs incurred over the lifetime of an average woman discounting by 3% per-annum from age 30. #NNT, number of women needed to treat to avert a death.

(e)

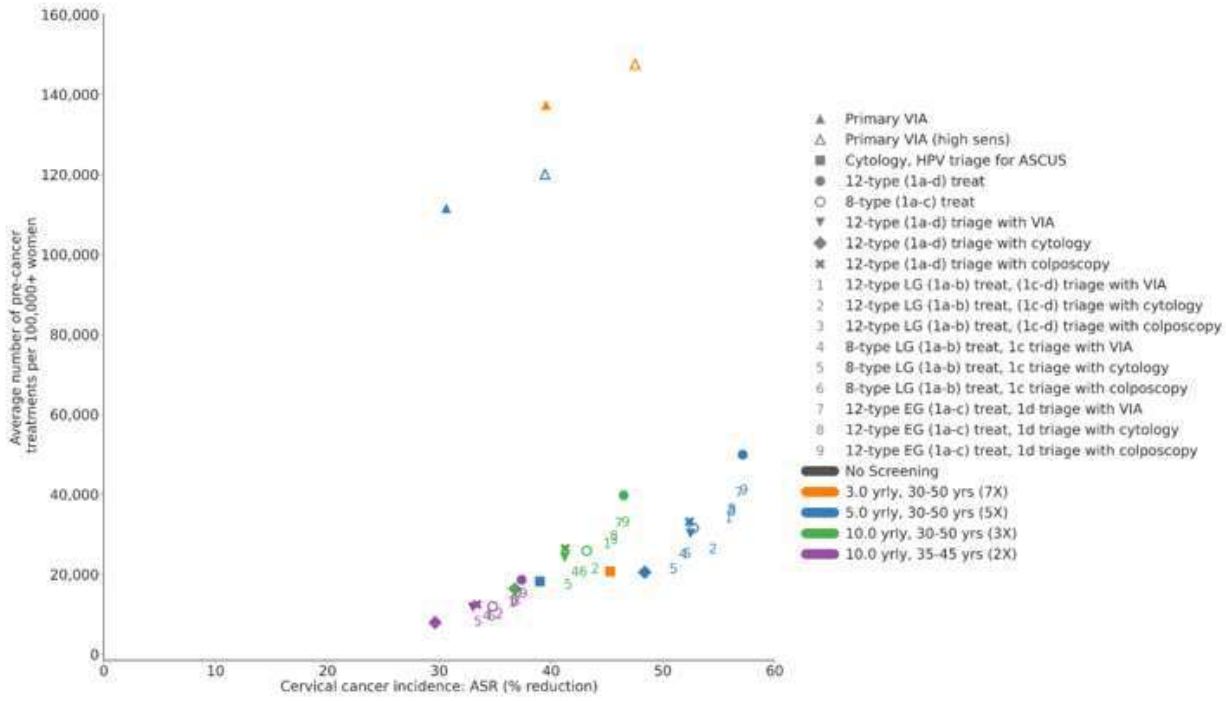
Cervical cancer cases (% reduction)	Cervical cancer deaths (% reduction)	Pre-cancer treatments	NNT to avert a cervical cancer death	Discounted lifetime cost (US$ 2019)	Resilience - absolute percentage point difference in mortality benefits when follow-up is 30%
<985 (>=50%)	<590 (>=60%)	<20,000	<27	<30	<=12%
985-1,179 [40-50%)	590-736 [50-60%)	20 000-40 000	27-50	30-45	(12-15%]
1,180-1,374 [30-40%)	737-953 [35-50%)	40 000-60 000	50-70	45-60	(15-30%]
>1,375 (<=30%)	>953 (<=35%)	>60 000	>70	>60	>30%

‘]’ indicates that the percentage in the range is inclusive; = ‘)’ indicates that it is not.

Balance of benefits and harms

Over the lifetime of a cohort of 100 000 women, when considering five-yearly screening, 12-type screen-and-treat is predicted to result in almost 50 000 pre-cancer treatments and the number of women needed to undergo cervical pre-cancer treatment to avert a cancer death (NNT) was predicted to be 54 (see Fig. 1 and Table 1). Eight-type screen-and-treat is predicted to result in just over 31 000 pre-cancer treatments and the NNT was predicted to be 37. When considering other triage and genotyping options, pre-cancer treatments ranged from 21 000 to 41 000 and NNTs ranged from 25 to 44. Similar patterns were observed when considering 10-yearly intervals for women aged 30−50 years (see Fig. 1 and Table 1b) and 10-yearly intervals for women aged 35−45 years (see Fig. 1 and Table 1c). Primary VIA strategies resulted in the largest number of pre-cancer treatments, with more than 110 000 pre-cancer treatments over the lifetime of the cohort of 100 000 women – more than double the lifetime number of pre-cancer treatments compared with any of the primary HPV or primary cytology strategies (see Fig. 1 and Table 1). It also generated at least 127 additional preterm deliveries over the lifetime of the cohort. The NNT to avert a cervical cancer death was >190 for primary VIA strategies, more than triple that predicted for any of the primary HPV testing strategies.

Fig. 1 Cervical cancer incidence age-standardized rate percentage reduction versus lifetime number of pre-cancer treatments for each strategy



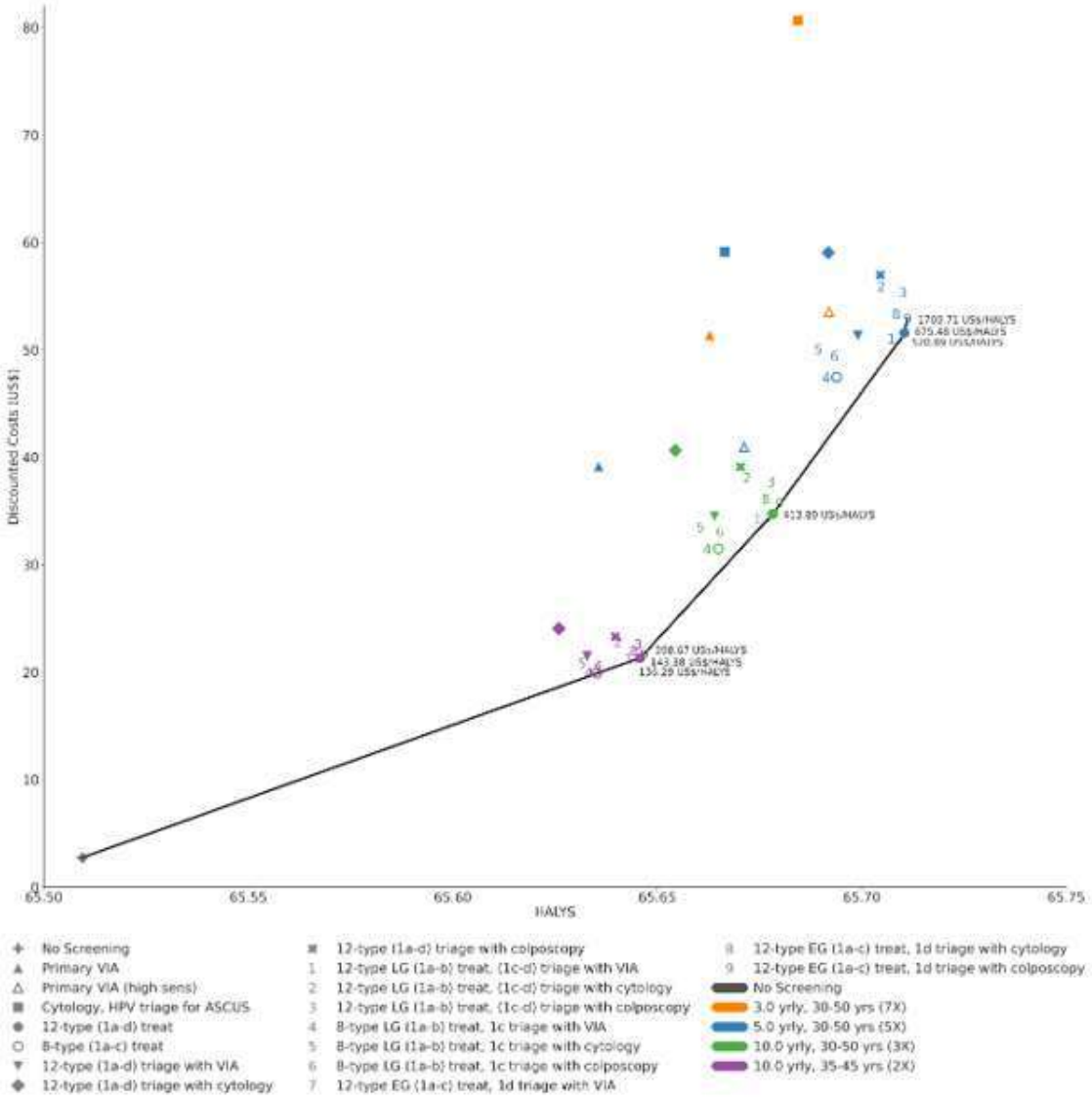
Cost-effectiveness

Primary HPV testing approaches generally cluster in a similar position on the cost-effectiveness frontier (Fig. 2). Twelve-type screen-and-treat was on the cost-effectiveness frontier and had an incremental cost-effectiveness ratio (ICER) of US$ 675/HALY saved when screening every five years from ages 30−50, an ICER of US$ 413/HALY saved when screening every 10 years from ages 30−50 and an ICER of US$ 143/HALY saved when screening every 10 years from ages 35−45. As a reference point for a potential WTP threshold across 78-LMICs, the population-weighted average GDP per capita for 2019 across the 78 LMIC is US$ 2093, and 71 of 78 [91%] of LMICs had a GDP per capita equal to or above US$ 518. Other 12-type and 8-type algorithms with triage at equivalent screening

intervals were very near the cost-effectiveness frontier and could be considered to have similar cost-effectiveness outcomes. Primary VIA, primary cytology and primary HPV with cytology triage strategies were furthest from the cost-effectiveness frontier.

When considering lower screening frequencies at 35 and 45 years (twice in a lifetime), 8-type screen-and-treat is closer to the frontier, almost landing on the frontier along with 12-type screen-and-treat.

Fig. 2 Cost-effectiveness plane (cost/HALY) plus 0% discount rate for effect, 3% discount rate for cost



2.4.2 *Results: AIM2 – resilience of primary HPV strategies to low follow-up rates*

Cervical cancer incidence and mortality – benefits

For all screening frequencies, primary HPV testing algorithms resulted in similar reductions (57−64%) in cancer deaths over the lifetime of birth cohorts when follow-up rates are 90% at all parts of the management pathway. For screen-and-treat approaches with either 12-type or 8-type tests, absolute percentage reduction in deaths compared to no-screening decline by <10% when follow-up rates decline to 60% and 9−11% when follow-up rates drop to 30%. For screen-triage-and-treat approaches with either 12-type or 8-type tests, absolute percentage reduction in deaths compared to no-screening decline by 10−30% when follow-up rates decline to 60% and 28−52% when follow-up rates drop to 30% (see Fig. 3 and Table 2).

Fig. 3 Percentage reduction in lifetime number of cancer deaths in five-yearly primary HPV screening strategies when follow-up rates at all parts of the management pathway are 90% (shown in green – baseline assumptions), 60% (blue) or 30% (red); shaded regions represent variability depending on triage test modelled (cytology, colposcopy or VIA triage)

Table 2 Summary table for lifetime number of cervical cancer deaths over the cohort of 100 000 women assuming (a) five-yearly screening for women aged 30–50 years, (b) 10-yearly screening for women aged 30–50 years, (c) 10-yearly screening for women aged 35–45 years, (d) for scenarios evaluated in the earlier guidelines involving three or five-yearly primary VIA or primary cytology, no longer recommended for any setting, and (e) green, yellow, and red colour-code grading details.

(a)

	% reduction in deaths versus status-quo (absolute % difference compared to 90% FU)	**% reduction in deaths versus status-quo (absolute % difference compared to 90% FU)**
Primary test	**Follow-up rates of 60%**	**Follow-up rates of 30%**
12-type (1a-d) treat ('Screen-and-treat')	58 (6)	53 (11)
8-type (1a-c) treat ('Screen-and-treat')	54 (5)	49 (10)
12-type (1a-d) triage with VIA	47 (13)	32 (28)
12-type (1a-d) triage with cytology	26 (31)	6 (51)
12-type (1a-d) triage with colposcopy	42 (19)	21 (40)
12-type LG (1a-b) treat, (1c-d) triage with VIA	55 (8)	48 (15)
12-type LG (1a-b) treat, (1c-d) triage with cytology	50 (12)	42 (20)
12-type LG (1a-b) treat, (1c-d) triage with colposcopy	55 (9)	47 (17)
8-type LG (1a-b) treat, 1c triage with VIA	52 (6)	46 (12)
8-type LG (1a-b) treat, 1c triage with cytology	48 (9)	42 (15)
8-type LG (1a-b) treat, 1c triage with colposcopy	52 (7)	46 (13)
12-type EG (1a-c) treat, 1d triage with VIA	57 (7)	52 (12)
12-type EG (1a-c) treat, 1d triage with cytology	56 (7)	50 (13)
12-type EG (1a-c) treat, 1d triage with colposcopy	58 (6)	53 (11)

(b)

	% reduction in deaths versus status-quo (absolute % difference compared to 90% FU)	**% reduction in deaths versus status-quo (absolute % difference compared to 90% FU)**
Primary test	**Follow-up rates of 60%**	**Follow-up rates of 30%**
12-type (1a-d) treat ('Screen-and-treat')	46 (8)	40 (14)
8-type (1a-c) treat ('Screen-and-treat')	43 (7)	38 (12)
12-type (1a-d) triage with VIA	34 (16)	21 (29)
12-type (1a-d) triage with cytology	17 (29)	3 (43)
12-type (1a-d) triage with colposcopy	29 (22)	13 (38)
12-type LG (1a-b) treat, (1c-d) triage with VIA	43 (10)	36 (17)
12-type LG (1a-b) treat, (1c-d) triage with cytology	39 (13)	32 (20)
12-type LG (1a-b) treat, (1c-d) triage with colposcopy	44 (10)	37 (17)
8-type LG (1a-b) treat, 1c triage with VIA	41 (8)	35 (14)
8-type LG (1a-b) treat, 1c triage with cytology	38 (11)	32 (17)
8-type LG (1a-b) treat, 1c triage with colposcopy	42 (8)	36 (14)
12-type EG (1a-c) treat, 1d triage with VIA	45 (9)	39 (15)
12-type EG (1a-c) treat, 1d triage with cytology	44 (10)	38 (16)
12-type EG (1a-c) treat, 1d triage with colposcopy	47 (8)	41 (14)

(c)

Primary test	**% reduction in deaths versus status-quo (absolute % difference compared to 90% FU)** **Follow-up rates of 60%**	**% reduction in deaths versus status-quo (absolute % difference compared to 90% FU)** **Follow-up rates of 30%**
12-type (1a-d) treat ('Screen-and-treat')	36 (7)	30 (13)
8-type (1a-c) treat ('Screen-and-treat')	33 (7)	29 (11)
12-type (1a-d) triage with VIA	26 (13)	16 (23)
12-type (1a-d) triage with cytology	13 (24)	3 (34)
12-type (1a-d) triage with colposcopy	23 (18)	10 (31)
12-type LG (1a-b) treat, (1c-d) triage with VIA	34 (8)	27 (15)
12-type LG (1a-b) treat, (1c-d) triage with cytology	31 (11)	25 (17)
12-type LG (1a-b) treat, (1c-d) triage with colposcopy	34 (9)	28 (15)
8-type LG (1a-b) treat, 1c triage with VIA	32 (8)	27 (13)
8-type LG (1a-b) treat, 1c triage with cytology	30 (9)	25 (14)
8-type LG (1a-b) treat, 1c triage with colposcopy	33 (7)	28 (12)
12-type EG (1a-c) treat, 1d triage with VIA	35 (8)	29 (14)
12-type EG (1a-c) treat, 1d triage with cytology	34 (9)	29 (14)
12-type EG (1a-c) treat, 1d triage with colposcopy	37 (7)	32 (12)

(d)

Primary test	**% reduction in deaths versus status-quo (absolute % difference compared to 90% FU) Follow-up rates of 60%**	**% reduction in deaths versus status-quo (absolute % difference compared to 90% FU) Follow-up rates of 30%**
Primary VIA (High sens) 3yrly, 30-50 yrs (7X)	49 (7)	42 (14)
Primary VIA (High sens) 5yrly, 30-50 yrs (5X)	42 (8)	34 (16)
Primary VIA 3yrly, 30-50 yrs (7X)	41 (6)	34 (13)
Primary VIA 5yrly, 30-50 yrs (5X)	33 (7)	27 (13)
Cytology, HPV triage for ASCUS 3yrly, 30-50 yrs	38 (14)	20 (32)
Cytology, HPV triage for ASCUS 5yrly, 30-50 yrs	32 (16)	16 (32)

(e)

Resilience - absolute percentage point difference in mortality benefits compared to equivalent scenario when follow-up is 90%
<=12%
(12-15%]
(15-30%]
>30%

']' indicates that the percentage in the range is inclusive; = ')' indicates that it is not.

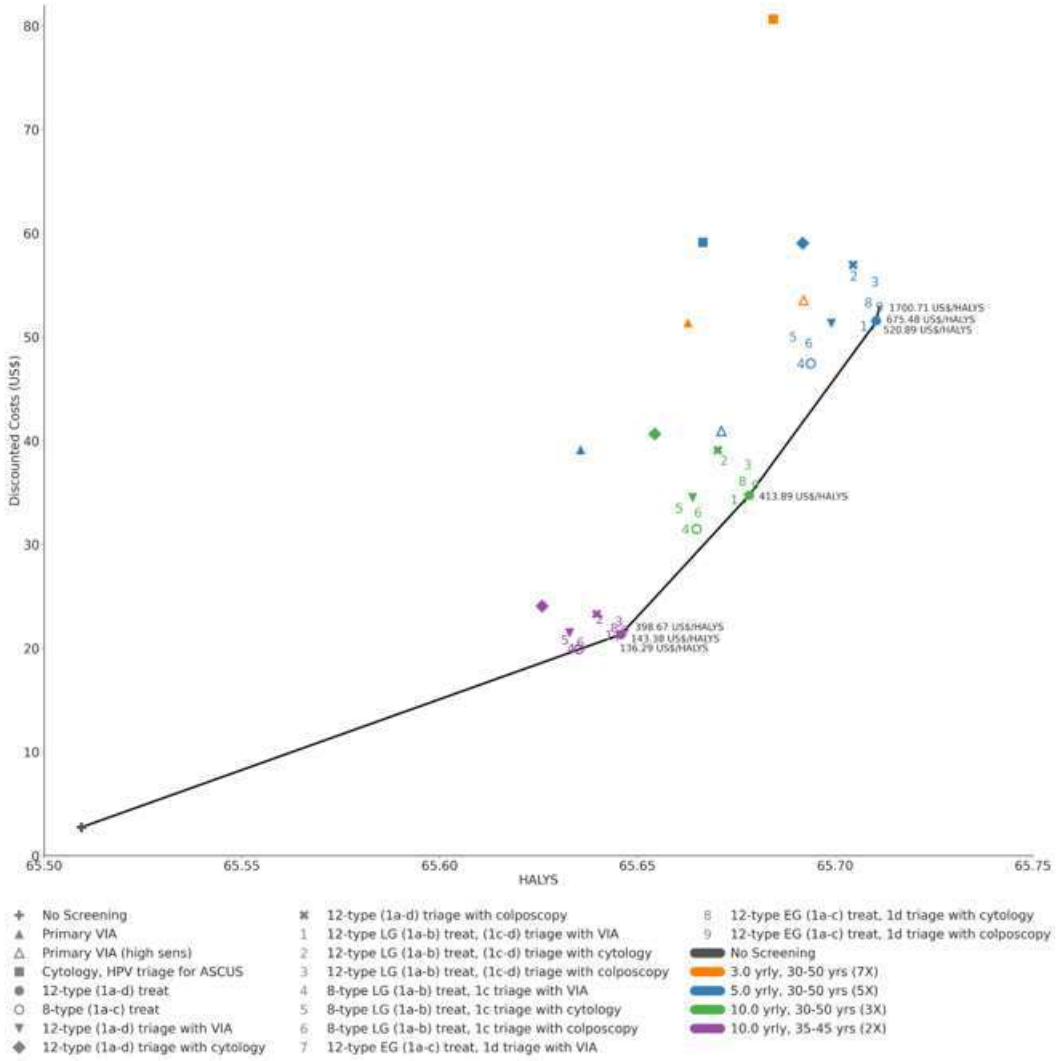
Cervical cancer incidence and mortality - benefits:

Cost-effectiveness

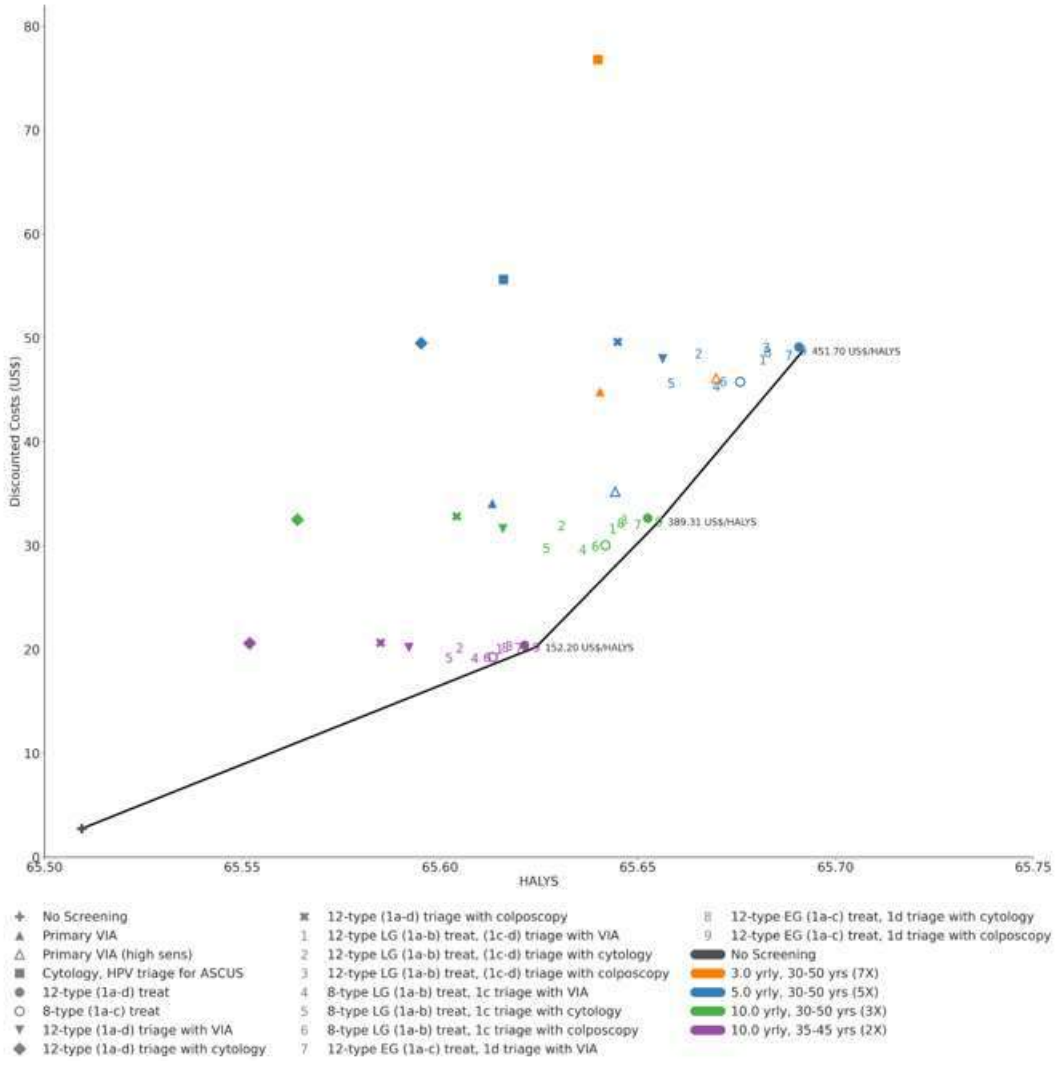
When considering 90% follow-up, all primary HPV testing algorithms appeared clustered near the cost-effectiveness frontier, while primary VIA and primary cytology strategies were furthest from the frontier, which was also found in our earlier evaluation of the 2021 updated guidelines (see Fig.4). When follow-up rates are 60%, strategies involving immediate treatment of groups 1a−1c, including screen-and-treat with either 8-type or 12-type tests, remain close to the frontier, while strategies involving triage of all HPV types (particularly cytology triage) move further from the frontier. When considering 30% follow-up, these screen-triage-and-treat strategies move even further from the frontier and are substantially less cost-effective than strategies involving immediate treatment of women positive for HPV types 1a−1c or treatment of types 1a−1d.

Fig. 4 Cost-effectiveness of algorithms assuming (a) 90% follow-up, (b) 60% follow-up, and (c) 30% follow-up

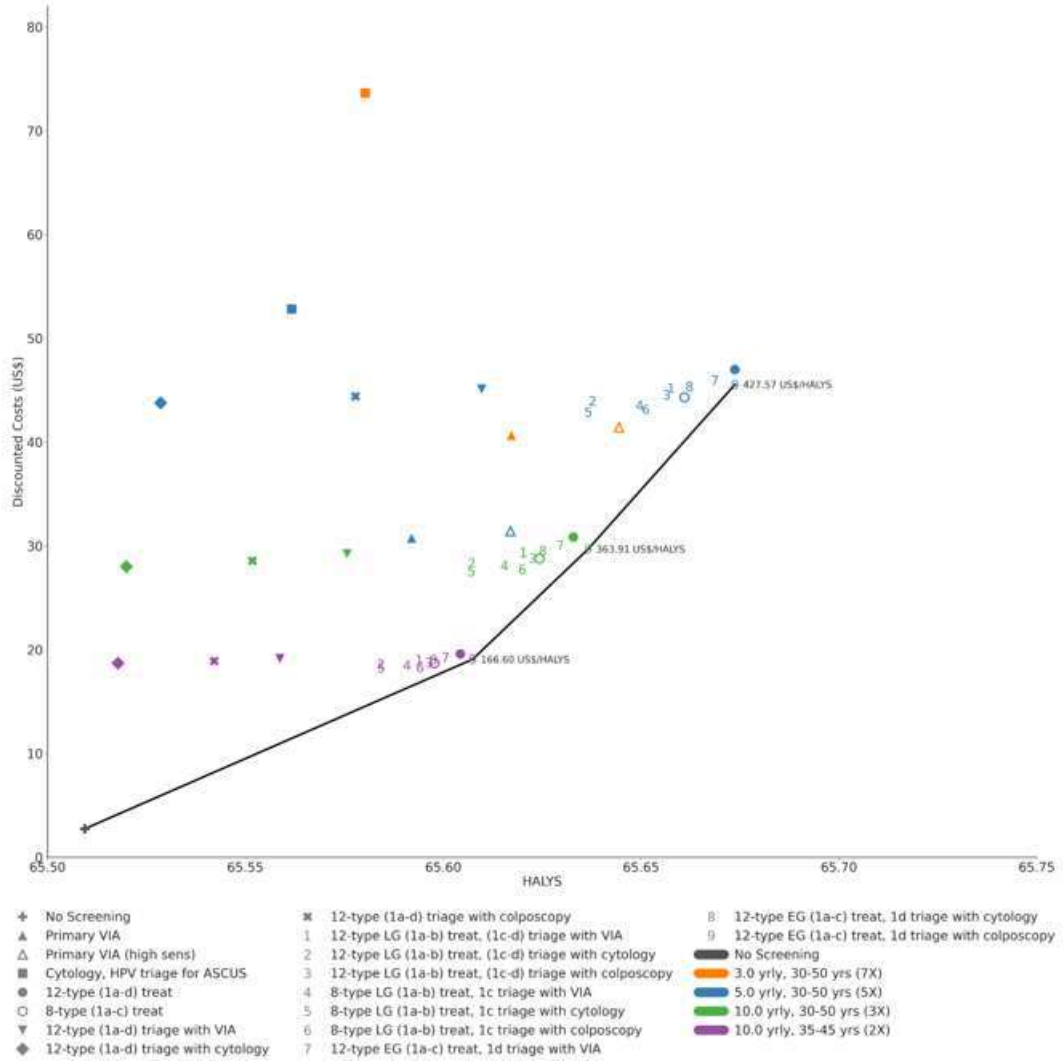
(a)



(b)


Discounted Costs (US$)
HALYS
451.70 US$/HALY$
389.31 US$/HALY$
152.20 US$/HALY$
No Screening
Primary VIA
Primary VIA (high sens)
Cytology, HPV triage for ASCUS
12-type (1a-d) treat
8-type (1a-c) treat
12-type (1a-d) triage with VIA
12-type (1a-d) triage with cytology
12-type (1a-d) triage with colposcopy
12-type LG (1a-b) treat, (1c-d) triage with VIA
12-type LG (1a-b) treat, (1c-d) triage with cytology
12-type LG (1a-b) treat, (1c-d) triage with colposcopy
8-type LG (1a-b) treat, 1c triage with VIA
8-type LG (1a-b) treat, 1c triage with cytology
8-type LG (1a-b) treat, 1c triage with colposcopy
12-type EG (1a-c) treat, 1d triage with VIA
12-type EG (1a-c) treat, 1d triage with cytology
12-type EG (1a-c) treat, 1d triage with colposcopy
No Screening
3.0 yrly, 30-50 yrs (7X)
5.0 yrly, 30-50 yrs (5X)
10.0 yrly, 30-50 yrs (3X)
10.0 yrly, 35-45 yrs (2X)

(c)


Discounted Costs (US$)
HALYS
427.57 US$/HALYS
363.91 US$/HALYS
166.60 US$/HALYS
No Screening
Primary VIA
Primary VIA (high sens)
Cytology, HPV triage for ASCUS
12-type (1a-d) treat
8-type (1a-c) treat
12-type (1a-d) triage with VIA
12-type (1a-d) triage with cytology
12-type (1a-d) triage with colposcopy
12-type LG (1a-b) treat, (1c-d) triage with VIA
12-type LG (1a-b) treat, (1c-d) triage with cytology
12-type LG (1a-b) treat, (1c-d) triage with colposcopy
8-type LG (1a-b) treat, 1c triage with VIA
8-type LG (1a-b) treat, 1c triage with cytology
8-type LG (1a-b) treat, 1c triage with colposcopy
12-type EG (1a-c) treat, 1d triage with VIA
12-type EG (1a-c) treat, 1d triage with cytology
12-type EG (1a-c) treat, 1d triage with colposcopy
No Screening
3.0 yrly, 30-50 yrs (7X)
5.0 yrly, 30-50 yrs (5X)
10.0 yrly, 30-50 yrs (3X)
10.0 yrly, 35-45 yrs (2X)

2.5 Discussion

When assuming 90% follow-up at all parts of the management pathway, we found that primary HPV testing approaches utilising limited or extended genotyping continued to generate the largest reductions in cervical cancer cases and deaths with more than 60% reduction in cervical cancer deaths, optimized benefits to harms and the most cost-effective compared to other primary testing approaches. 12-type (1a-c) treat, 1d triage with colposcopy with 5-yearly screening was the most effective and cost-effective approach. For all screening frequencies, 12-type HPV screen-and-treat is on the cost-effectiveness frontier and is the most cost-effective approach for a 10-yearly (3X) screening frequency. For 10-yearly (2x) screening, 8-type HPV screen-and-treat migrated closer to the cost-effectiveness frontier and could be considered to have similar cost-effectiveness to 12-type screen-and-treat.

When considering lower follow-up rates of screening strategies, 12-type (1a-c) treat, 1d triage with colposcopy was the most effective and cost-effective approach for all screening frequencies. Additionally, screen-and-treat approaches with either 12-type or 8-type tests experienced 11% or less absolute percentage reduction in deaths compared to no screening. These strategies also remained close to the cost-effectiveness frontier. For screen-triage-and-treat approaches with either 12-type or 8-type tests, absolute percentage reduction in deaths compared to no-screening decline by 10−30% when follow-up rates decline to 60% and 28−52% when follow-up rates drop to 30%. These strategies were also substantially less cost-effective and performed similarly or worse than primary VIA screening.

There are some limitations to this analysis. We took a normative approach and presented results at an average across all 78 LMICs. However, there are some variations in HPV type attributable fractions across regions and could influence individual countries decisions for management of different HPV type groups. However, our model fit well to global attributable fractions of HPV types in cervical cancer. We also incorporated test technology potential based on the WHO updated TPPs, therefore reflecting the most updated evidence on ideal test technology attributes.

In conclusion, primary HPV testing with more targeted genotyping approaches were effective, optimized benefits to harms and were cost-effective. These algorithms offer opportunities to tailor benefits and harms appropriate for settings, and provide additional options based on country health services capacity. 12-type (1a-c) treat, 1d triage with colposcopy, and primary HPV testing in a screen-and-treat approach with point-of-care HPV testing, using either 8-type or 12-type tests, are predicted to be more resilient than other approaches in settings which experience poor follow-up rates.

References for evidence summary 2

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