EVIDENCE TO DECISION TABLE: PICO 8 AGE AT INITIATION GENERAL POPULATION

Should age 30 years vs. another age be used for a threshold to initiate cervical cancer screening in the general population?

POPULATION:	a threshold to initiate cervical cancer screening in the general population
INTERVENTION:	age 30 years
COMPARISON:	another age
MAIN OUTCOMES:	•Cervical cancer •Mortality •CIN 2+ •HPV infection •Preterm birth (early/late) •Acceptability (to all stakeholders) •Pre-cancer treatments •Adverse events related to pre-cancer treatments - Major infections or bleeding, Procedure associated pain, Cervical stenosis, Infertility, Spontaneous abortions (1st trimester/ 2nd trimester), Perinatal deaths, Premature rupture of membrane, Unnecessary interventions, Increased viral shedding in HIV infected women and, costs (number of tests), feasibility (Coverage of treatment, Coverage of screening), acceptability (stigmatization), equity
SETTING:	outpatient
PERSPECTIVE:	Population
BACKGROUND:	In 2014, the World Health Organization (WHO) published recommendations for screening and treatment of precancerous lesions and indicated that the age to start screening is 30 years. There are also other recommendations from WHO that may not be consistent with age 30.
CONFLICT OF INTERESTS:	

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

| JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	We conducted a systematic literature search from 1996 to August 2020 for systematic reviews of studies that report age stratified data for cervical cancer, histologically confirmed cervical precancer lesions, HSIL and ACIS, and/or HPV (any type). **Prevalence CIN 2, CIN 3** Zhao 2012 (pooled analysis of 17 population-based studies in China) of 30,207 women primarily in rural areas and never screened before; screened with VIA, HPV or cytology and histologically confirmed Prevalence of CIN 2 by age At 15-29: 1.4% At 30-34: 1.2% At 35-39: 1.5% At 40-44: 1.8% Prevalence of CIN 3+ (including cervical cancer) At 15-29: 0.7% At 30-34: 0.9% At 35-39: 1.3% At 40-44: 2.1% At 45-49: 2.4% At 50-59: 1.5% Prevalence of Invasive Cancer Arbyn 2020 (worldwide analysis from 185 countries from the Global Cancer Observatory 2018 database; ~570 000 cases of cervical cancer and ~311 000 deaths from disease in 2018. Cases per 100 000 women years by world At 20 years: 3 At 25 years: 5 At 30 years: 12 At 35 years: 19 At 40 years: 26 At 55 years: 36	The GDG agreed that the prevalence of histologically confirmed CIN 2 or CIN 3 before age 30 years may be lower or similar, but regression of CIN 2 before age 30 was higher than after age 30. Therefore the benefits of screening before age 30 for prevention of cervical cancer or histologically confirmed CIN 2/3 lesions was small.

At 60 years: 35 (then decreasing)
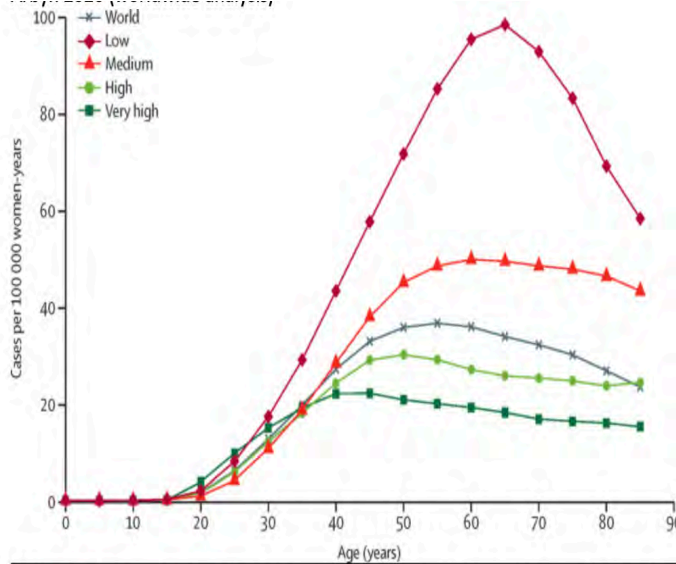
Figure 5: **Age-specific incidence of cervical cancer worldwide and in terms of the four-tier HDI**
The four tiers of HDI are the following: very high (HDI ≥0·8), high (HDI <0·8 to ≥0·7), medium (HDI <0·7 to ≥0·55), and low (HDI <0·55). HDI=Human Development Index.

Prevalence of HPV
Bruni 2010 (review of 114 studies of women with normal cytological findings)

Variable	Women, no.		HPV prevalence, % (95% CI)	
	Total tested	HPV positive	Crude	Adjusted[a]
Mean age of enrolled women				
<25 years	27,343	5960	21.8 (21.3–22.3)	24.0 (23.5–24.5)
25–34 years	60,475	8901	14.7 (14.4–15.0)	13.9 (13.6–14.1)
35–44 years	263,740	27,962	10.6 (10.5–10.7)	9.1 (9.0–9.2)
45–54 years	658,695	28,691	4.4 (4.3–4.4)	4.2 (4.2–4.3)
≥55 years	328	44	13.4 (9.9–17.6)	7.5 (5.0–11.0)

By less and more developed regions
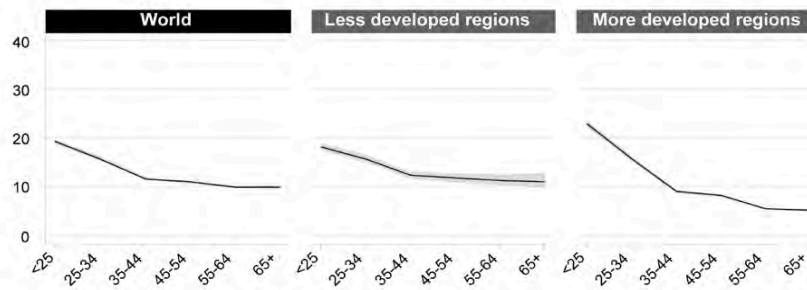
Progression of CIN 2 and Regression of CIN 2
Analysis from 2 sysetmatic reviews

Age group (years)	No. participants	Regression rate	No. studies	Population	Length of follow-up	Source
< 25	754	44.7%	7	Women with CIN I, II, and III	28 to 30 months	Bekos 2018
<30	1069	60.0%	4	Non-pregnancy women with CIN II	24 months	Tianio 2018
<30	938	52.8%	7	Women with CIN I, II, and III	28 to 30 months	Bekos 2019
<30	131	70.0%	2	Non-pregnancy women with CIN II	36 months	Tianio 2018
>30	401	44.0%	7	Non-pregnancy women with CIN II	24 months	Tianio 2018
<35	1,058	51.9%	7	Women with CIN I, II, and III	28 to 30 months	Bekos 2020
>=35	172	46.2%	7	Women with CIN I, II, and III	28 to 30 months	Bekos 2021

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See above.	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Although there was no evidence comparing different age groups at initiation of screening, we had evidence from systematic reviews of large databases and primary studies of incidence and prevalence of cervical cancer and CIN at different age groups provided moderate certainty evidence. Modelling at different age groups was also available.	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The outcomes previously identified in the 2014 screening and treatment guidelines, using methods from the WHO Handbook for Guideline Development were agreed on by the GDG as the outcomes of importance for these new PICO questions. The importance of the outcomes was identified as: •Cervical cancer •Mortality •Preterm birth (early/late) •Pre-cancer treatments (and related adverse events, see below) •CIN 2+ •HPV infection •Adverse events related to pre-cancer treatments - Major infections or bleeding, Procedure associated pain, Cervical stenosis, Infertility, Spontaneous abortions (1st trimester/ 2nd trimester), Perinatal deaths, Premature rupture of membrane, Unnecessary interventions, Increased viral shedding in HIV infected women •Acceptability (to all stakeholders) A systematic review of qualitative research was conducted (43 studies), but there was very little data reporting the value of outcomes (data was primarily for acceptability of tests/treatments – see below). **A survey of 561 women** was conducted online via SurveyMonkey in 2020, and was completed anonymously. All women aged 15 years and older, regardless of their prior cervical cancer screening or treatment status were eligible to participate. Survey results from 275 respondents found that some of the key concerns from women who had never been screened before were fear of the test itself higher costs of test(22.91%) and the fear of having cancer(22.91%).	The Guideline Development Group agreed that greater value should be placed on cervical cancer incidence and mortality, and less value on treatment of CIN (and subsequent harms) and reproductive outcomes. However, in young women of reproductive age, although more value is placed on reproductive outcomes, there was still greater value placed on cervical cancer and mortality.

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was found. However, there was evidence from modelling showing that the differences in cost when starting screening later than age 30 were small to negligible.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	From the modelling, strategies initiating at age 30 or 35 were on the cost-effectiveness frontier. 	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence. The GDG agreed that there would likely not be no impact on equity depending on age at screening.	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence found. The GDG agreed that starting at any age would be acceptable to most women.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence found. However, the GDG agreed that the need for greater resources when starting at age 30 versus 35 may impact feasibility, but it is likely feasible in most settings.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	●

CONCLUSIONS

Recommendation

5. WHO recommends starting regular cervical cancer screening at the age of 30 years among the general population of women.
[Strong recommendation, moderate-certainty evidence in effects]

Justification

On the age at which to start screening, there is evidence from modelling and large databases measuring the incidence of cervical cancer and CIN that supports the initiation of screening at the age of 30 years (moderate-certainty evidence). Starting screening at this age is likely to be acceptable to stakeholders, is feasible and needs fewer resources than starting at an earlier age.