Screening in birth cohorts with HPV vaccinated women within the cervical cancer screening programme

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Introduction

In 2009, the Netherlands began the human papillomavirus (HPV) vaccination programme for girls. In 2023, the first HPV vaccinated women were invited to participate in the cervical cancer screening programme (BVO BMHK). Over the coming years, an increasing number of women who were previously vaccinated will join the programme. The risk of cervical cancer and high-grade abnormalities is expected to significantly decrease in these cohorts. To ensure a balance between the costs, burdens, and benefits of the screening programme, it may be desirable to downscale the screening intensity for vaccinated women or for cohorts in which both vaccinated and unvaccinated women participate.

Commissioned by the National Institute for Public Health and the Environment (RIVM), the National Evaluation of the Cervical Cancer Screening Programme (LEBA) team at Erasmus MC and the modelling team for HPV and cervical cancer at Amsterdam UMC have investigated through models the impact of adjusting one or more rounds of the screening schedule (up to age 45) in partially vaccinated cohorts. The goal was to determine which interventions are cost-effective and to provide insights into the practical effects of these interventions.

Research Questions:

1. Are there interventions that could improve the cost-effectiveness of the policy for screening birth cohorts with HPV vaccinated women (assuming full participation and compliance with the programme)?
2. What is the estimated effect of implementing these interventions in practice (assuming partial participation and compliance with the programme)?

Both the Erasmus MC and Amsterdam UMC models are calibrated to the same epidemiological data from the Netherlands, but they operate in different ways and are based on different assumptions. By comparing the results of the two models, more robust conclusions can be drawn. When both models lead to a similar conclusion, this can be seen as a stronger argument for adopting that conclusion than if only one model had been used.

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Methods

In this study, 25 different screening strategies were modelled for birth cohorts from 1993 to 2002. Both Amsterdam UMC and Erasmus MC performed the analyses using a combination of two different models: an hrHPV transmission model and a cancer progression model that calculates the disease progression from HPV infection to cervical cancer. These two models are referred to together as the AUMC model and the EMC model (also known as the STDSIM-MISCAN-Cervix model). (1-4)

Models

An important difference between the models is that the background risk of developing cervical cancer is higher in the AUMC model than in the EMC model. Background risk is the risk someone has of developing cervical cancer in the absence of screening. These assumptions cannot be verified in the current context in the Netherlands, as they relate to a non-existent situation (i.e., a situation without screening). Therefore, it cannot be said which of the two models best describes this strategy, but with knowledge of these differences in background risk, the variations in outcomes between the models can be partially explained.

Strategies

25 alternative strategies were simulated, and these strategies were compared to the current programme (base case, BC) (Table 1). Almost all the strategies focus on skipping one or two rounds at ages 30, 35, or 40, in order to stay as close as possible to the current screening programme. This facilitates the potential implementation of an alternative (more cost-effective) strategy. The strategies differ from the current programme in that they skip one or more rounds or make fixed rounds into flexible rounds. In a flexible round, a woman is only invited if she was hrHPV-positive in the previous round or if she did not participate, as is the case for ages 45 and 55 in the current programme. One of the strategies is fully risk-based (RB), meaning that every round up to 45 years is flexible.

The strategies were modelled for two different target groups: mixed cohort (MC) and vaccinated cohort (V). While a MC strategy applies to all women, both vaccinated and unvaccinated, a V strategy applies only to vaccinated women: unvaccinated women are still screened according to the current schedule in these strategies. The strategies are modelled not only for vaccinated but also for unvaccinated women because the screening programme could perhaps also be downscaled for unvaccinated women, partly due to herd immunity.

All 25 strategies were modelled in the main analysis under full (100%) participation. Additionally, the strategies were also modelled under partial participation as part of sensitivity analyses.

Tabel 1 *Strategies that have been modelled for the mixed cohorts or only for vaccinated women within these cohorts. The programme from age 45 onwards remains unchanged compared to the current screening.*

Strategy	Description
BC (Base case)	The current programme
RB (Risk Based)	Risk-based strategy, women are only invited after 10 years following an hrHPV-negative test, regardless of age
N30	Women are not invited at age 30
N35.1	Women are not invited at age 35
N35.2	Women are not invited at age 35, unless the hrHPV test at age 30 was positive
N40.1	Women are not invited at age 40
N40.2	Women are not invited at age 40, unless the hrHPV test at age 35 was positive
30.1	Women are only invited at age 30
30.2	Women are only invited at age 30, and at age 35 if the hrHPV test at age 30 was positive
30.3	Women are only invited at age 30, and at age 40 if the hrHPV test at age 30 was positive
35.1	Women are only invited at age 35
35.2	Women are only invited at age 35, and at age 40 if the hrHPV test at age 35 was positive
40	Women are only invited at age 40

Measured outcomes

The extent to which screening rounds could be skipped depends on the trade-off between the benefits and burdens of screening, as simulated by the models. The benefits include the number of cancer cases prevented, gained life-years (LY), and gained Quality-Adjusted Life-Years (QALYs) (i.e., a life year adjusted for health-related quality of life). The burdens of screening include the number of referrals, the costs, and the (unnecessary) anxiety experienced by participants. Cost-effectiveness is represented by an Incremental Cost-Effectiveness Ratio (ICER), which is calculated as the additional cost per (QA)LY of a strategy compared to a less expensive strategy. This determines how much an extra (QA)LY costs if a more expensive strategy is implemented. Since future costs and effects are valued less than current ones, future costs and effects in screening carry less weight; this is called discounting. Effects of? ((QA)LYs) are discounted at 1,5%, and costs at 3%.

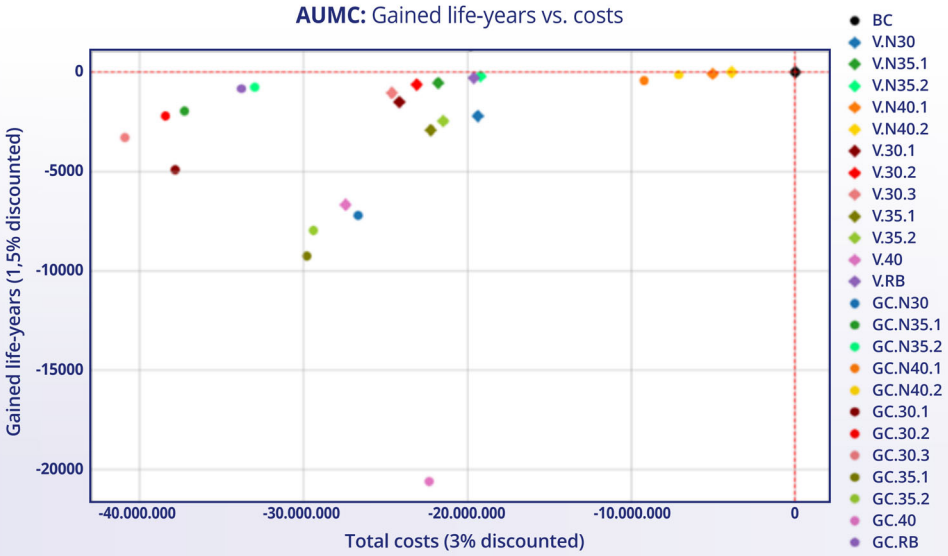

Figure 1 *Life-years gained compared to the current programme (discounted by 1,5%) and costs compared to the current programme (discounted by 3%) in the case of full participation in the screening programme according to the AUMC model.*

Key results

Full participation

Reducing the intensity of screening leads to lower costs and a loss in gained life-years[1] (Figure 1 and Figure 2). The loss in life-years due to downscaling is greater in the AUMC model, as de-intensifying screening leads to more cancer cases than in the EMC model. In the AUMC model, the reduction in costs from downscaling is smaller than in the EMC model because more cancer cases occur, and the costs of diagnosing and treating cancer are high.

1 The strategies are compared with the current programme, including vaccination effects. Any form of cost-effective scaling down of the screening programme results in more gained life-years than in a strategy without vaccination.

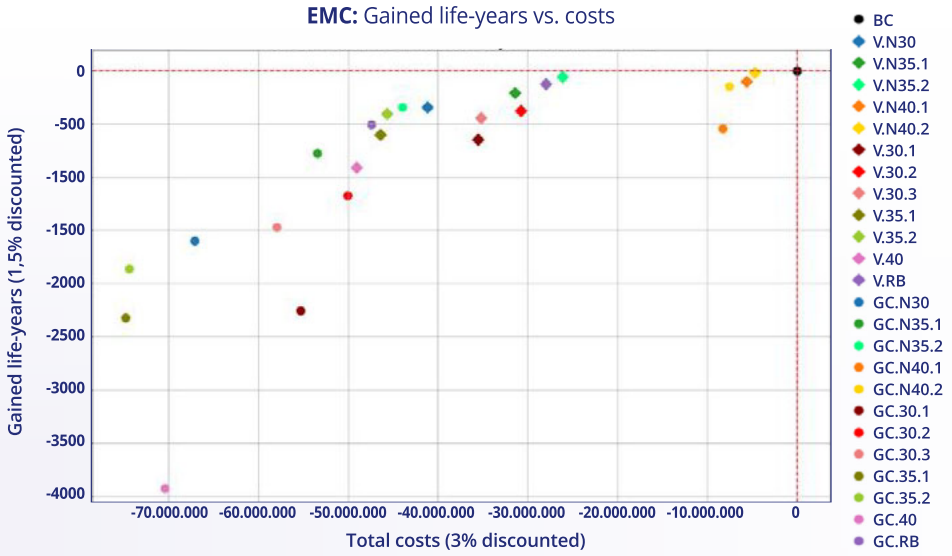

Figure 2 *Life-years gained compared to the current programme (discounted by 1,5%) and costs compared to the current programme (discounted by 3%) in the case of full participation in the screening programme according to the EMC model.*

Figure 3 and Figure 4 show the number of QALYs gained versus the costs per strategy compared to the current programme for the AUMC model and the EMC model, respectively. According to the AUMC model, downscaling the programme (typically) results in a loss of QALYs because more cancer cases occur. According to the EMC model, scaling down the programme results in a gain in QALYs because less (unnecessary) anxiety is experienced during screening.

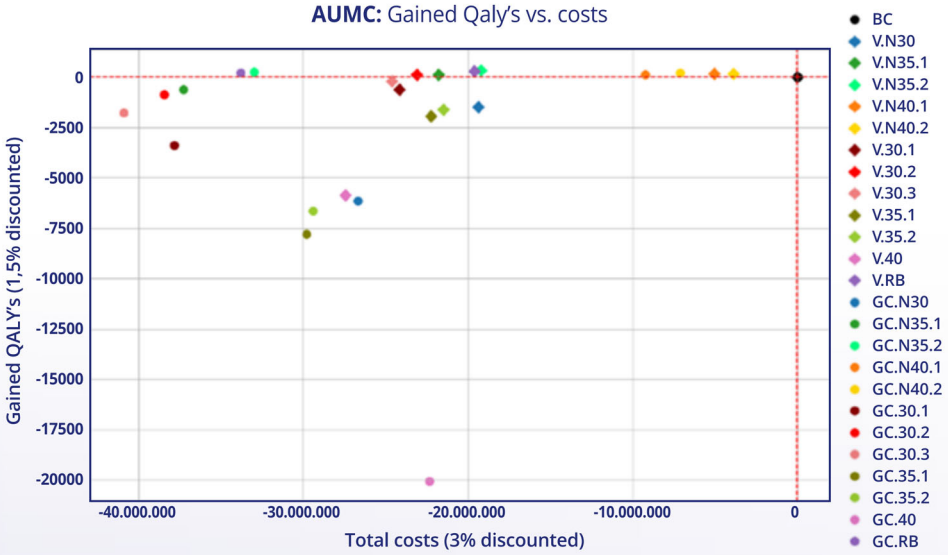

Figure 3 *QALYs gained compared to the current programme (discounted by 1,5%) and costs compared to the current programme (discounted by 3%) in the case of full participation in the screening programme according to the AUMC model.*
Abbreviations: *QALY, Quality-Adjusted Life Year.*

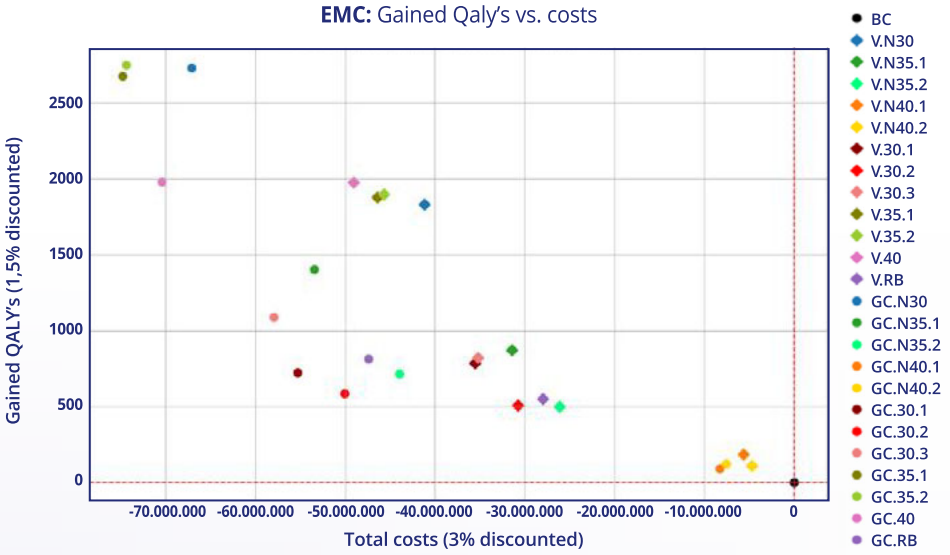

Figure 4 *QALYs gained compared to the current programme (discounted by 1,5%) and costs compared to the current programme (discounted by 3%) in the case of full participation in the screening programme according to the EMC model.*
Abbreviations: *QALY, Quality-Adjusted Life Year.*

Tabel 2 *The cost-effectiveness of efficient strategies under full participation, as calculated by the **AUMC model**. For the efficient strategies, the Incremental Cost-Effectiveness Ratio (ICER) is shown, based on gained life-years (LY) and quality-adjusted life-years (QALYs). In calculating the ICER, costs and effects were discounted by 3% and 1,5%, respectively.*

Screening strategies on the efficiency frontier	ICER (costs (€)/LY)	ICER (costs (€)/QALY)
GC.30.3	Ref.	Ref.
GC.30.2	2.252	2.673
GC.RB	3.426	4.360
GC.N35.2	10.309	40.414
V.N35.2	24.264	148.624
V.N40.2	78.724	n.a.
BC	4.709.168	n.a.

Tabel 3 *The cost-effectiveness of efficient strategies under full participation, as calculated by the **EMC model**. For the efficient strategies, the Incremental Cost-Effectiveness Ratio (ICER) is shown, based on gained life-years (LY) and quality-adjusted life-years (QALYs). In calculating the ICER, costs and effects were discounted by 3% and 1,5%, respectively.*

Screening strategies on the efficiency frontier	ICER (costs (€)/LY)	ICER (costs (€)/QALY)
GC.35.2	Ref.	Ref.
GC.N35.1	19.196	n.a.
V.35.2	21.001	n.a.
GC.N35.2	27.586	n.a.
V.N35.2	62.978	n.a.
BC	454.546	n.a.

Both models show that the strategies in which downscaling is based on hrHPV test results perform very favourably in the analysis, as these are cost-saving and result in little loss in life-years compared to the current programme (Table 2 and Table 3). The strategy where all hrHPV-negative women at age 30 are not invited again at age 35 (MC.N35.2) is the most cost-effective according to the AUMC model, assuming a gain of €50.000 per QALY. In the EMC model, every strategy results in a gain in QALYs and cost savings compared to the current programme. If a threshold of €50.000 per gained life-year is applied, the EMC model identifies the MC.N35.2 strategy, where women at age 35 are only invited if they were hrHPV-positive in the previous round, as the optimal strategy.

Partial participation

The previous analysis was conducted under full (100%) participation to map the effect among screening participants. Since not everyone participates in practice, a strategy under partial participation was also modelled. The analysis under partial participation uses data from attendance within 18 months. The partial participation strategy shows that there are differences in the conclusions of the EMC and AUMC models. The EMC model continues to show cost savings for every strategy compared to the current programme, while the AUMC model indicates that large-scale downscaling leads to additional costs due to a higher number of cancer cases (compared to the main analysis), resulting in higher treatment costs. This makes downscaling less cost-effective in the AUMC model. If a gained (QA)LY is worth €50.000, the current programme is the most cost-effective according to the ICERs (ICER BC: €22.409/LY and €32.892/QALY). The strategy that only downscales screening for vaccinated women based on hrHPV test results from a previous round (V.RB) is the most cost-effective in the AUMC model when a gained (QA)LY is worth €20.000. In the EMC model, the MC.N35.2 strategy, where women who test hrHPV-negative at age 30 are not invited again at age 35, remains the most cost-effective strategy.

Other sensitivity analyses

The models used for the simulations are based on various assumptions, some of which are discussed here. Since, in reality, uncertainties exist, the robustness of the results and conclusions was tested through sensitivity analyses. These analyses were repeated with one change compared to the main analysis. The assumptions listed below were tested as part of sensitivity analyses and did not lead to any changes in the conclusions:

1. *Self-test use*: A strategy with 100% self-test use did not change the conclusions for either model.
2. *Test characteristics*: In a strategy where the sensitivity of the self-test was increased or decreased compared to an hrHPV test on a smear, no different conclusions were found for either model.
3. *Disutilities*: Although the use of the international instead of the Dutch disutility sets changed the number of QALYs gained per strategy, this did not lead to different conclusions for either model.
4. *Discounting*: This analysis, where (QA)LYs were 3% discounted, resulted in only a small change in the results and did not lead to a change in conclusions.

However, there were assumptions that led to a significant difference in results, prompting Amsterdam UMC to adjust its conclusions:

1. In a scenario without herd immunity, the most cost-effective strategy in the AUMC model shifted to a strategy with scaling down only for vaccinated women.
2. Two analyses with increased and decreased participation rates (compared to partial participation) showed that the cost-effectiveness of scaling down screening is highly dependent on participation, according to the AUMC model, which led to different conclusions.
3. Although cost-effectiveness is influenced by participation in the EMC model, the conclusions remained unchanged. In the absence of herd immunity, scaling down for the mixed cohort is less favourable, but MC.N35.2 remains a cost-effective option.

Conclusion

Two independent models from Amsterdam UMC and Erasmus MC were used to calculate the cost-effectiveness of downscaling screening in vaccinated cohorts. The inclusion of vaccinated women in the BVO BMHK allows for the possibility of downscaling the programme. Both models identify the best strategy under full participation as the one where mixed cohorts are invited at age 35 only if the hrHPV test at age 30 was positive (MC.N35.2). This would mean that women who are hrHPV-negative at age 30 would not need to be invited again at age 35.

In the AUMC model, under partial participation, strategies that only downscale screening for vaccinated women (V.N35.2, V.N40.2, and V.RB) are more cost-effective than GC.N35.2. This is because the AUMC model predicts that, in this case, a relatively large number of additional cancer cases would occur if the fixed round at age 35 is scrapped for unvaccinated women compared to when participation is full. This conclusion depends on the assumed attendance rate, also for rounds starting at age 45. In the EMC model, MC.N35.2 is still the most cost-effective under partial participation, regardless of the exact participation rate.

Both Erasmus MC and Amsterdam UMC conclude that vaccinated women who test hrHPV-negative at age 30 do not have to be invited again at age 35. Erasmus MC also concludes that unvaccinated women who test hrHPV-negative at age 30 do not have to be invited again at age 35, while Amsterdam UMC does not, due to the large additional number of cancer cases under partial participation and in a scenario without herd immunity, particularly among unvaccinated women.

Glossary

- **BVO BMHK**: Population-based Cervical Cancer Screening Programme
- **Disutility set**: Anxiety, discomfort, or disease burden experienced by people in a situation, expressed in values between 0 and 1.
- **Herd immunity**: When enough people in a population are immune to a disease, limiting its spread.
- **hrHPV**: High-risk human papillomavirus; HPV types with a high risk of developing cervical cancer.
- **ICER**: Incremental Cost-Effectiveness Ratio; the additional cost per (QA)LY of a strategy compared to a less expensive strategy. It determines how much an extra (QA)LY costs when a more expensive strategy is implemented.
- **QALY**: Quality-Adjusted Life Year; a life year adjusted for health-related quality of life by subtracting disutilities from the life year.
- **Discounting**: Since future costs and effects are valued less than those occurring now, future costs and effects in screening are discounted. This is applied as a percentage per year.

References

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