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Impact of Delaying Effective and Cost-Effective Policy Decisions: An Example From Cervical Cancer Prevention in Norway

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Abstract

Introduction. Delayed implementation of evidence-driven interventions has consequences that can be formally evaluated. In Norway, programs to prevent cervical cancer (CC)—screening and treatment of precancerous lesions and prophylactic vaccination against human papillomavirus (HPV) infection—have been implemented, but each encountered delays in policy implementation. To examine the effect of these delays, we project the outcomes that would have been achieved with timely implementation of two policy changes compared with the de facto delays in implementation (in Norway). **Methods.** We used a multimodeling approach that combined HPV transmission and cervical carcinogenesis to estimate the health outcomes and timeline for CC elimination associated with the implementation of two CC prevention policy decisions: a multicohort vaccination program of women up to age 26 years with bivalent vaccine in 2009 compared with actual "delayed" implementation in 2016, and a switch from cytology to primary HPV-based testing in 2015 compared with "delayed" rollout in 2020. **Results.** Timely implementation of two policy changes compared with current Norwegian prevention policy timeline could have averted approximately 970 additional cases (range of top 10 sets: 830–1060) and accelerated the CC elimination timeline by around 4 years (from 2039 to 2035). **Conclusions.** If delaying implementation of effective and cost-effective interventions is being considered, the decision-making process should include quantitative analyses on the effects of delays.

Keywords
cervical cancer, vaccination, screening

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Introduction

Public health decision making involves weighing trade-offs to improve health outcomes in more than one dimension: not only quantifying and weighing losses against gains associated with an intervention but also quantifying and weighing losses against gains of the intervention implementation timeline. Delayed implementation of evidence-driven interventions has consequences, whether the risk of potential health losses or the benefit of careful planning to minimize those losses, that can be formally evaluated in the decision making process.

Cervical cancer (CC) is preventable through either screening and treatment of precancerous lesions caused by persistent human papillomavirus (HPV) infection or prophylactic vaccination against HPV. Both types of prevention policies have been implemented in Norway—organized CC screening in 1995 and HPV vaccination in 2009—but opportunities to integrate new technologies in screening and expand vaccination programs to target additional subgroups have been subject to long prioritization and decision-making processes that consequently

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delayed policy implementation, despite evidence demonstrating their effectiveness and cost-effectiveness.[1]

In a recent evaluation of how five CC prevention policy decisions in Norway influenced projected CC elimination as a public health problem (defined as "achieving the measurable global targets set by the World Health Organization for a specific disease"),[2–4] we projected that the cumulative impact of policy decisions between 2009 and 2020 accelerated the timing of elimination by 17 years compared with pre-2009 policies.[5] However, this analysis reflected the actual timeline of implementation in Norway, which included significant delays between when sufficient evidence was available to recommend a policy change and the decision to implement.

For example, although the quadrivalent HPV vaccine (4vHPV) was deemed to have sufficient evidence to recommend it in 2007 for girls up to 16 years of age,[6] it was offered routinely to 12-year-old Norwegian girls beginning in 2009. Although a multicohort "catch-up" vaccination program up to age 16 was recommended at the same time as routine vaccination by a group of HPV experts in Norway,[6,7] others advised caution against launching a multicohort vaccination programs before effect against CC was demonstrated, despite knowledge this evidence would not be available for at least a decade.[8–12] In fact, this evidence was not published until 2020.[13] As a result of the ensuing discourse, the suggested introduction of HPV vaccination beyond age 12 in 2009 was abandoned and a temporary multicohort vaccination program of young women up to age 26 years was implemented from 2016 to 2018.[14] This decision has already resulted in delayed protection against HPV infection and HPV-related genital warts in Norway as compared with Denmark, where multicohort HPV vaccination up to age 26 was implemented in 2008.[15,16] The differences in cervical precancerous lesions and cancers is expected to emerge in due time.[16]

Moreover, in 2009, following international HPV-based guideline recommendations,[17] a Norwegian advisory board recommended replacing primary cytology-based screening with primary HPV-based screening for women aged 34 to 69 years[18] based on available data from six European countries on the safety and efficacy of using HPV DNA testing,[19] but the regional randomized pilot implementation study was not initiated until 2015 in Norway. Furthermore, the program planned for a gradual expansion to include all regions in Norway and is expected to be completed in 2022.

Although gradual expansion of new policies can reassure quality aspects related to implementation of novel technology and mitigate unintended consequences, health losses associated with these delays cannot be ignored. Delays or more "limited indications" may be justified with quantified analyses but remain a policy decision with consequences.

To provide an example application of the effect of delayed decision making and implementation, we quantified the health losses and impact on the CC elimination timeframe for the existing "delayed" prevention policy timeline of two policy changes compared with a "timely" implementation, that is, the earliest year implementation of high quality could have been started, of these policies in Norway.

Methods

We used a multimodeling approach that captured HPV transmission and cervical carcinogenesis, described previously,[5,20,21] to evaluate the impact associated with the timing of implementing two policies in Norway: 1) a multicohort HPV vaccination program of women up to age 26 years; and 2) the switch from primary 3-yearly cytology to primary 5-yearly HPV-based testing for women aged 34 to 69 years (maintaining primary 3-yearly cytology for women aged 25–33 years). Given our country-level modeling framework, the second (latter) policy was modeled with a simplifying assumption of full nationwide implementation of the screening program switch in 2020 as the time-point of the gradual implementation experienced in Norway, beginning in a limited capacity in 2015 and ongoing in the largest regions of Norway to 2022. Similarly, the model implemented multicohort vaccination in 2017 as the midpoint of the 3-

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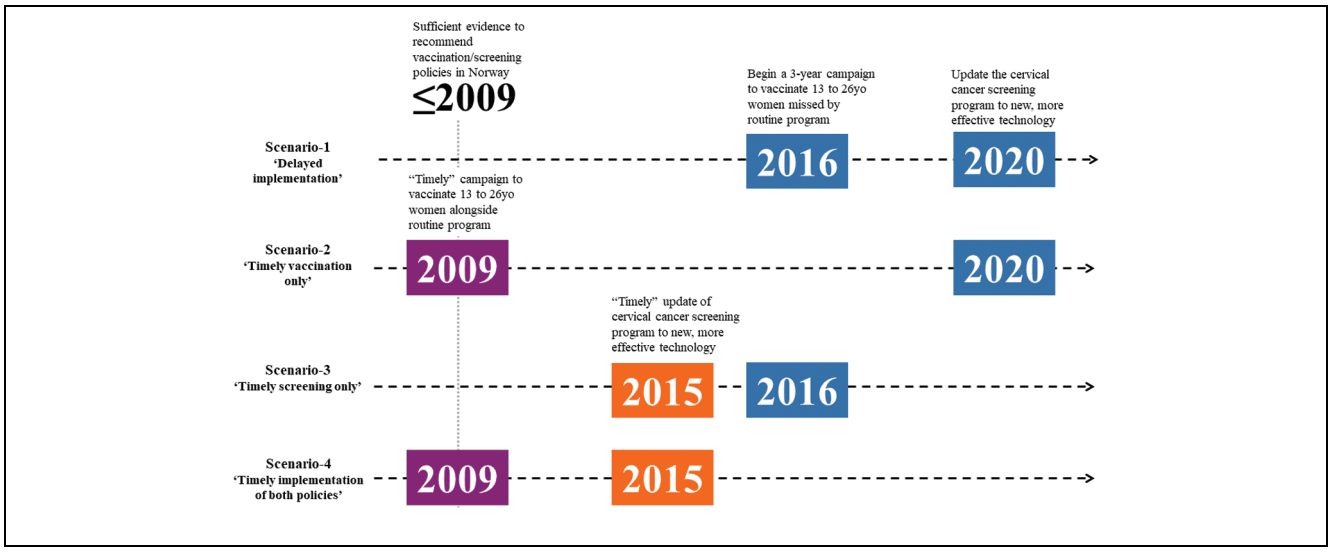

Figure 1 Timeline of current and "timely" policies in Norway: analytic scenarios.
Note: HPV, human papillomavirus; HPV switch, switch from 3-yearly cytology to 5-yearly primary HPV-based screening for women aged 34 to 69 (maintaining primary cytology for women aged 25–33) years; multicohort, a multicohort vaccination program for women up to 26 years. The gray vertical dotted line represents the timeframe when Norway recommended routine HPV vaccination for adolescent girls, as well as when other high-income countries (e.g., Australia, Denmark, the United States) adopted and implemented HPV vaccination including a multicohort "catch-up" vaccination program. In 2009, the Norwegian advisory board also recommended replacing primary cytology-based screening with primary HPV-based screening for women aged 34 to 69 years, in which capacity-readiness planning could have begun. The implementation year for primary HPV screening represents the year in which the switch began for cohorts eligible to receive screening in that year and following years. Each scenario also incorporated the following policy changes implemented in Norway between 2009 and 2020: the introduction of routine HPV vaccination of 12-year-old girls with quadrivalent vaccine (4vHPV) in 2009; the routine vaccination program switch from the 4vHPV to bivalent vaccine (2vHPV) in 2017; and the expansion of the routine vaccination program to include 12-year-old boys in 2018.

year campaign (Supplemental Appendix A). We compared the health outcomes and CC elimination timeline associated with the "timely" implementation of these policy changes to the "delayed" implementation. A total of four scenarios were evaluated to isolate the impact of each delay (Figure 1) compared with a prevaccination scenario involving 3-yearly cytology-based screening for women at different ages: 1) current policy implementation timeline; 2) "timely" multicohort vaccination only; 3) "timely" switch to primary HPV-based screening only; and 4) "timely" implementation of both policies. For the multicohort vaccination program, we assumed "timely" implementation occurred in 2009 (rather than 2016–2018) alongside the routine program roll-out. For the switch to primary HPV-based testing, we assumed "timely" implementation of primary HPV screening occurred nationwide in 2015 (rather than the base-case assumption of 2020). For the "timely" implementation of multicohort vaccination in 2009, all birth cohorts were assumed to receive the bivalent vaccine (2vHPV), which they were offered in 2016 to 2018.

All scenarios incorporated the following policy changes implemented in Norway: 1) the introduction of routine HPV vaccination of 12-year-old girls with 4vHPV in 2009; 2) the routine vaccination program switch from 4vHPV to 2vHPV in 2017; and 3) the expansion of the routine vaccination program to include 12-year-old boys in 2018. We assumed "timely" implementation of the multicohort vaccination program reached the coverage achieved by 12-year-olds in 2009 for 13- to 18-year-olds (70%) and the coverage achieved by 26-year-olds in 2016 to 2018 for 19- to 26-year-olds (56%).[5] Additionally, we examined this scenario assuming the lower vaccination coverage levels achieved by the 2016 to 2018 multicohort vaccination program for the same age cohorts in 2009 (Supplemental Appendix A). Otherwise, all scenarios were conducted in the context of current HPV vaccination and screening coverage.[5] Importantly, the "timely" implementation of the multicohort vaccination scenario included direct protection of seven additional birth cohorts that were age-ineligible for vaccination at the time of the current policy timeline in 2016.

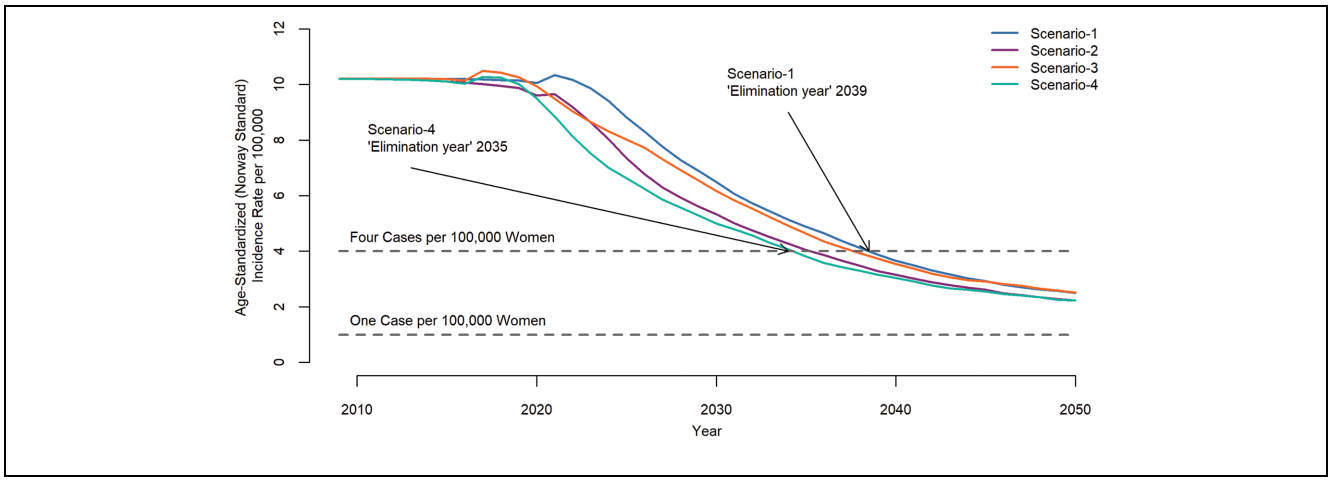

Figure 2 Time to CC elimination in Norway.

In our multimodeling approach, we used an agent-based dynamic model of partnership acquisition and HPV transmission, stratified by HPV genotype, to capture direct and indirect impacts of HPV vaccination, using primary data on Norwegian sexual behavior patterns.[22] The model was calibrated using a likelihood-based method to fit empirical outcomes of HPV prevalence.[5] In order to capture impacts on long-term CC outcomes, we linked the outputs of this transmission model to a previously developed microsimulation model of HPV-induced cervical carcinogenesis, also stratified by HPV genotype, that tracks a birth cohort of individual women through a series of monthly transitions over their lifetimes, beginning at age 9 years,[23] adapted to reflect Norwegian epidemiologic data.[1,24,25] Progression to cancer required infection with a high-risk HPV genotype. Cancer detection occurs at either the local, regional, or distant stages.[23] We selected the best-fitting natural history parameter set for the base-case analysis, prioritized to fit HPV type distribution in Norway,[5] and the top 10 best-fitting natural history parameter sets were simulated to capture uncertainty in the calibrated parameters for selected scenarios.[26]

We assumed vaccine efficacy of 100% against HPV-16/18 infections for 2vHPV and 4vHPV,[27–29] with lifelong duration of protection. We assumed that 4vHPV provided lifelong cross-protection against HPV infection of 89.3%, 47.8%, and 53.7% for HPV types 31, 33, and 45, respectively, based on a Norwegian analysis,[30] whereas we assumed the 2vHPV provided a higher cross-protection of 93.8%, 79.1%, and 82.6% for these types.[31]

We estimated the health impact on CC burden in terms of age-standardized rate (ASR) of CC incidence per 100,000 woman-years and the number of CC cases and deaths between 2009 and 2050 (inclusive). We defined the elimination year as the year in which ASR of CC incidence consistently decreased to <4 new cases per 100,000 woman-years.[3,4] Age-specific results were age-standardized by year using the standard Norway population in 2014 as the reference population, per the practice of the Cancer in Norway incidence and prevalence reports published by the Cancer Registry of Norway.[32]

Role of the Funding Source

The funder had no role in initiating, planning, analyses, interpretation of results, or decision to submit this study.

Results

In the context of the current prevention policy timeline in Norway (Scenario 1), the model predicted that Norway would reach the CC elimination threshold by 2039 (range of top 10 sets: 2036–2041; Figure 2 and Supplemental Appendix B). Implementation of a multicohort vaccination program of 13- to-26-year-old women (Scenario 2) in 2009 instead of 2016 would have accelerated CC elimination by 3 years (elimination in 2036; range of top 10 sets: 2032–2038). In contrast, nationwide implementation of the switch to primary HPV screening 5 years earlier (in 2015; Scenario 3) would have accelerated the elimination timeline by 1 year, to 2038 (range of top 10 sets: 2035–2040). If both policies combined had been implemented

Table 1 Cervical Cancer Cases and Deaths Averted Compared With Prevaccination Prevention Policy in Norway Over the Period 2009 to 2050 Inclusive[a]

Policy Scenario	Descriptive Name	Cervical Cancer Cases Averted and Percent Reduction[b]	Cervical Cancer Deaths Averted and Percent Reduction[b]
Scenario 1	Current policy timeline	4260 (3550–4530) 35% (33% to 35%)	910 (820–1090) 22% (22% to 23%)
Scenario 2	Timely multicohort HPV vaccination	4970 (4130–5470) 40% (39% to 40%)	1100 (4130–5470) 27% (26% to 28%)
Scenario 3	Timely switch to primary HPV screening	4530 (3830–5050) 37% (36% to 37%)	1030 (940–1240) 25% (25% to 26%)
Scenario 4	Timely vaccination and HPV screening	5230 (4400–5780) 43% (41% to 43%)	1220 (1090–1440) 30% (29% to 31%)

HPV, human papillomavirus.

[a]Values rounded to the nearest 10. Minimum and maximum values across the top 10 parameter sets in parentheses.

[b]Cases averted and percent reductions are calculated compared with a prevaccination scenario involving only 3-yearly cytology-based screening, that is, 12,300 cases and 4100 deaths. Scenario 2 and Scenario 4 assume 70% coverage among 13- to 18-year-olds and 56% coverage among 19- to 26-year-olds; results for alternative vaccination coverage levels (Appendix A) presented in Appendix C.

earlier (Scenario 4), Norway was projected to achieve the elimination threshold by 2035 (4 years earlier than currently projected; range of top 10 sets: 2031–2037). Assuming alternative coverage levels for the multicohort vaccination campaign in Scenario 2 and Scenario 4 had no impact on elimination timing.

Over the period 2009 to 2050, the current policy implementation timeline in Norway (Scenario 1) was projected to cumulatively avert 4260 (range of top 10 sets: 3550–4530) cases of CC and 910 (820–1090) CC-related deaths compared with a prevaccination scenario involving triennial cytology-based screening (Table 1). Compared with Scenario 1, timely implementation of a multicohort HPV vaccination program (Scenario 2) was projected to avert approximately 710 additional cases (580–750) or approximately 620 additional cases (510–660) when assuming alternative coverage levels (Supplemental Appendix C). Timely implementation of the switch to primary HPV-based testing (Scenario 3) was projected to avert 270 additional cases (250–320), while timely implementation of both policies combined (Scenario 4) was projected to avert approximately 970 additional cases (830–1060) or approximately 840 additional cases (770–980) when assuming alternative coverage levels (Supplemental Appendix C).

For women who aged out of screening by the year 2020 (i.e., women aged 65–69 in 2015 and therefore aged 70–74 in 2020) and never had the opportunity to receive primary HPV screening, the implementation delay resulted in an estimated 14.8 additional cases and 6.2 additional deaths among these cohorts (Scenarios 3 and 4).

Discussion

Using CC in Norway as an example, this analysis serves to highlight the contribution of simulation models to estimate the impact of delayed implementation of effective and cost-effective interventions. Our model-based analysis projected that Norway, while on track to achieve CC elimination by 2039 under current and historic HPV vaccination and screening policies,[5] could have accelerated that timeline to the year 2035 with earlier implementation of multicohort vaccination (2009 rather than 2016) and nationwide primary HPV-based screening (2015 rather than 2020). The analyzed scenarios represent a retrospective analysis of the "bounds" of what could have been achieved for CC prevention policy in Norway, reflecting the authors' assumptions for the earliest possible point of high-quality implementation given sufficient evidence and expert consensus compared with the actual implementation timeframe for the two policies. Future applications in decision analysis could utilize simulation models to prospectively estimate the impacts of delayed implementation, for example, the incremental health losses associated with each additional year of delay or the tradeoffs between timeliness and quality-controlled implementation.

In particular, the immediate implementation of a multicohort "catch-up" vaccination program alongside the routine introduction of HPV vaccination was seen in other high-income countries, including Denmark, Australia, and the United States, and was the policy implemented in Norway in 2016. While there are likely

justifiable delays to implementing a technology change from cytology to primary HPV-based screening, including changes in clinical management algorithms, reallocation of resources, retraining staff, and redesigning data flow and communication systems with appropriate monitoring and evaluation, we assumed these activities followed the 2009 expert group recommendation with 2015 as the earliest identified point for introduction as the year of initial pilot implementation. Additionally, primary HPV testing, a more sensitive test compared with cytology-based screening, could have prevented additional cases among mid-adult, unvaccinated women, as shown in previous analyses.[21,33,34]

Our analysis provides similar results to previous analyses of delays to HPV-based screening implementation. For example, in the United Kingdom, authors found that a 1-year delay to the implementation of HPV-based screening missed the opportunity to prevent 581 cases of CC.[35]

Similar to our previous analysis,[5] there are several limitations to highlight. First, although Norway began to gradually switch from cytology-based screening to HPV-based testing among women aged 34 to 69 years in a regional randomized pilot implementation trial in 2015 to 2018, we assumed a nationwide switch in the specified year (2015 or 2020) as our multimodeling approach makes projections at the national level. However, national scale-up may not conclude in the largest regions in Norway until 2022. Furthermore, primary HPV-based screening may have a greater impact on health and expedite the elimination timeline compared with our current analysis with potential increases in screening coverage. Second, the analysis is limited by the lack of available data for specific model parameters in Norway. Specifically, we relied on male HPV prevalence data from Denmark to calibrate the model,[36] as CC epidemiology and prevention data[37] as well as sexual behavior data among women[22] have been shown to be similar.[5] Third, the multicohort vaccination coverage levels that could have been achieved in 2009 are uncertain. However, we examined two coverage scenario alternatives, and found that cervical cases averted varied by 2% to 3%. Fourth, we did not include the impacts of delaying the multicohort HPV vaccination program on non-cervical HPV-related diseases. Finally, the potential benefits of slower implementation in mitigating health losses were not included in our analysis.

In conclusion, despite demonstrable success in reducing HPV-related disease burden, the CC control policies implemented over the last decade in Norway incurred measurable losses in preventing CC cases and deaths due to delayed implementation. When the evidence is sufficient to recommend implementation (including clinical effectiveness, cost-effectiveness, and capacity readiness), policymakers should aim for swift implementation. If delaying implementation of effective and cost-effective interventions is being considered, the decision-making process should include quantitative analyses on the effects of delays.

Authors' Note

This study was conducted at the Center for Health Decision Science at the Harvard T.H. Chan School of Public Health. Preliminary results of this work were presented at the International Papillomavirus Society virtual conference (July 2020) and the Society for Medical Decision Making virtual conference (October 2020).

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Author Contributions

AP, MN, LT, and EAB conceptualized the study. AP and EAB conducted the analysis and drafted the manuscript with input from all authors. All authors approved the final version of the manuscript.

Supplemental Material

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