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Impact and cost-effectiveness of strategies to accelerate cervical cancer elimination: A model-based analysis

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ABSTRACT

Following the global call for action by the World Health Organization to eliminate cervical cancer (CC), we evaluated how each CC policy decision in Norway influenced the timing of CC elimination, and whether introducing nonavalent human papillomavirus (HPV) vaccine would accelerate elimination timing and be cost-effective. We used a multi-modeling approach that captured HPV transmission and cervical carcinogenesis to estimate the CC incidence associated with six past and future CC prevention policy decisions compared with a pre-vaccination scenario involving 3-yearly cytology-based screening. Scenarios examined the introduction of routine HPV vaccination of 12-year-old girls with quadrivalent vaccine in 2009, a temporary catch-up program for females aged up to 26 years in 2016–2018 with bivalent vaccine, the universal switch to bivalent vaccine in 2017, expansion to include 12-year-old boys in 2018, the switch from cytology- to HPV-based screening for women aged 34–69 in 2020, and the potential switch to nonavalent vaccine in 2021. Introducing routine female vaccination in 2009 enabled elimination to be achieved by 2056 and prevented 17,300 cases. Cumulatively, subsequent policy decisions accelerated elimination to 2039. According to our modeling assumptions, switching to the nonavalent vaccine would not be considered 'good value for money' at relevant cost-effectiveness thresholds in Norway unless the incremental cost was $19 per dose or less (range: $17–24) compared to the bivalent vaccine. CC control policies implemented over the last decade in Norway may have accelerated the timeframe to elimination by more than 17 years and prevented over 23,800 cases by 2110.

1. Introduction

The recent global call for action by the World Health Organization (WHO) Director-General to eliminate cervical cancer as a public health problem (i.e., achieve incidence rates of <4 cases per 100,000 woman-years) requires country-specific evaluation of cervical cancer control programs (Brisson and Drolet, 2019; World Health Organization, 2018). It is important to note that definitions of disease elimination and eradication, where disease transmission is reduced to zero (Dowdle, 1998), differ from 'elimination as a public health problem', defined as "achieving the measurable global targets set by the World Health Organization for a specific disease, based on population data" (World Health Organization, 2020).

Considering the long time period between acquiring a human papillomavirus (HPV) infection and the development of cervical cancer (Schiffman et al., 2007), mathematical simulation modeling is a

Abbreviations: 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; ASR, age-standardized rate; CC, cervical cancer; GDP, gross domestic product; HPV, human papillomavirus; ICER, incremental cost-effectiveness ratio; LMICs, low-and-middle income countries; LY, life year; NOK, Norwegian kroner; QALY, quality-adjusted life year; SCC, squamous cell carcinoma; WHO, World Health Organization; UN, United Nations; US, United States; USD, US dollars.

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powerful tool to help understand the cervical cancer burden under past and future primary and secondary prevention efforts in a country. Such models have been used to support the planning of WHO's elimination goals in Australia, the United States (US), and 78 low-and-middle income countries (LMICs) (Brisson et al., 2020; Canfell et al., 2020; Hall et al., 2019; Burger et al., 2020). These analyses suggest that elimination of cervical cancer could be achieved globally within a century by achieving coverage targets for HPV vaccination (90% of girls vaccinated by age 15), cervical screening (70% of screen-eligible females screened twice-lifetime), and treatment (90% of identified disease treated) by 2030 (Brisson et al., 2020; Simms et al., 2019). Modeled evaluations provide insight into the specific drivers of the timing of elimination among these targeted programs. HPV vaccination plays a critical role in achieving elimination in the longer term but scaled-up cervical screening expedites the timing of elimination (Brisson et al., 2020; Burger et al., 2020). In settings with limited treatment access, scaling up cervical cancer treatment plays an additional, crucial role in saving lives in the short term (Canfell et al., 2020). In high-income countries, where some of these targets have been achieved, detailed country-specific modeling has found that improvements in screening coverage (e.g., reducing the proportion of women who are never screened) and test performance (e.g., transitioning from cytology- to HPV-based screening) tend to have a greater effect on elimination timing compared to increases in vaccination coverage (either via higher coverage in girls or extending vaccination to boys or adults) (Hall et al., 2019; Burger et al., 2020; Hall et al., 2018). For example, transitioning from cytology-based to primary HPV screening was predicted to bring forward elimination by around 5–6 years in Australia and the US, whereas large changes in vaccination coverage shifted the elimination year by no more than two years (Hall et al., 2019; Burger et al., 2020; Hall et al., 2018). Given the long natural history of cervical cancer, it is likely that even dramatic changes to vaccination could take 10 years or more to provide quantifiable population-level impact.

Similar to other high-income countries, Norway, with a decades-long organized cytology-based screening program, has reduced cervical cancer incidence considerably (Vaccarella et al., 2014; Lönnberg et al., 2015). The 2009 implementation of routine girls-only adolescent HPV vaccination program has achieved high coverage, such that Norway has the potential to eliminate cervical cancer in the near term (Feiring et al., 2018). However, the potential for, and timing of, cervical cancer elimination is affected by screening and vaccination coverage levels and potentially also multiple in-country decisions, such as the type of HPV vaccine or primary cervical cancer screening modality offered, the introduction of temporary HPV vaccination catch-up programs, and the expansion of the routine vaccination program to include boys (Burger et al., 2014). Since 2018, Norway has begun to gradually implement primary HPV-based screening for women aged 34–69 years (Burger et al., 2012). Together, these policies will likely lead to declines in cervical cancer incidence in Norway; however, future policies could further improve the effectiveness and efficiency of cervical cancer elimination efforts.

We aimed to assess how the HPV vaccination and cervical cancer screening policy decisions in Norway over the last decade have influenced the timing of cervical cancer elimination, and whether elimination could be expedited by switching the routine program from the bivalent HPV vaccine (2vHPV) to the nonavalent HPV vaccine (9vHPV). As the value of implementing a new policy is an explicit component of priority-setting in Norway, we also evaluated the cost-effectiveness of a potential switch of the routine HPV vaccination program from 2vHPV to 9vHPV.

2. Methods

2.1. Analytic overview

We used a multi-modeling approach that captured HPV transmission and cervical carcinogenesis, described previously (Burger et al., 2020; Burger et al., 2019) and in Appendix A, to evaluate the impact associated with six past and future cervical cancer prevention policy decisions in Norway compared with a pre-vaccination scenario involving 3-yearly cytology-based screening for women at different ages (Fig. 1). We conducted two distinct analyses: (1) a health impact analysis of past and future policies; and (2) a cost-effectiveness analysis of a future policy. Our 'impact analysis' quantified the effects of both past and future policies on cervical cancer burden over time, while our 'cost-effectiveness analysis' estimated the discounted lifetime costs and health benefits of a potential switch to 9vHPV vaccination compared with the current 2vHPV-based program.

2.2. Scenarios and model assumptions

Each scenario was layered incrementally and chronologically to examine the cumulative impact of policy decisions over time, i.e., each successive scenario included the policy change(s) from previous scenario(s). Scenario-1 examined the introduction of routine HPV vaccination of 12-year-old girls with the quadrivalent vaccine (4vHPV) in 2009; Scenario-2 reflected the addition of a temporary catch-up vaccination program for women up to 26 years in 2016–2018 with 2vHPV; Scenario-3 captured the routine vaccination program switch from the 4vHPV to 2vHPV in 2017; Scenario-4 reflected the expansion of the routine vaccination program to include 12-year-old boys in 2018; Scenario-5 reflected the switch from 3-yearly cytology- to 5-yearly primary HPV-based screening for women aged 34–69 (maintaining primary cytology for women aged 25–33) years assuming full implementation in 2020 (rather than gradually over 2018–2025); and Scenario-6 reflected a future potential routine vaccination program switch from the 2vHPV to 9vHPV in 2021.

All scenarios were conducted in the context of current HPV vaccination and screening coverage (Appendices B–D). As screening behavior based on 5-year recommended intervals associated with the new primary HPV guidelines is unknown (i.e., Scenario-5) (Andreassen et al., 2019), we assumed that a similar proportion of Norwegian women would over-screen (28.2%), under-screen (15%), or never attend screening (6%) (Pedersen et al., 2018a; Pedersen et al., 2017), with the majority of screening-compliant women (50.8%) centered around the new 5-yearly interval (Appendix B). We assumed observed historical vaccination two-dose coverage rates from 2009 to 2018 for girls in the routine and catch-up programs and from 2018 for boys (The Norwegian Immunization Registry, 2020), and assumed that the preliminary 2019 routine program 1-dose coverage rates (90% and 89% for girls and boys, respectively) remain unchanged indefinitely (Appendices C and D).

To capture the direct and indirect impacts of HPV vaccination, we used an agent-based dynamic model of partnership acquisition and HPV transmission, contextualized using primary data on Norwegian sexual behavior patterns (Hansen et al., 2020). The model, which is stratified by genotype (HPV-16, -18, -31, -33, -45, -52, -58), was calibrated using a likelihood-based method to fit empirical outcomes of HPV prevalence observed in Norway and neighboring countries when Norwegian data was unavailable (Appendix A). To capture the impacts of vaccination and alternative screening strategies on long-term cervical cancer outcomes, we linked transmission model outputs to a previously developed microsimulation model of HPV-induced cervical carcinogenesis that tracks a birth cohort of individual women through a series of monthly transitions over their lifetimes, beginning at age 9 years (Campos et al., 2014), adapted to reflect Norwegian epidemiologic data (Burger et al., 2012; Pedersen et al., 2018a; Pedersen et al., 2016). HPV infections and precancer are stratified by genotype (HPV-16, -18, -31, -33, -45, -52, -58, other high-risk genotypes, and non-high-risk genotypes). Progression to cancer required infection with a high-risk genotype. Cancer detection occurs at either the local, regional, or distant stage (Campos et al., 2014). We selected the best-fitting natural history parameter set for the base-case analysis, prioritized to fit HPV type distribution in Norway

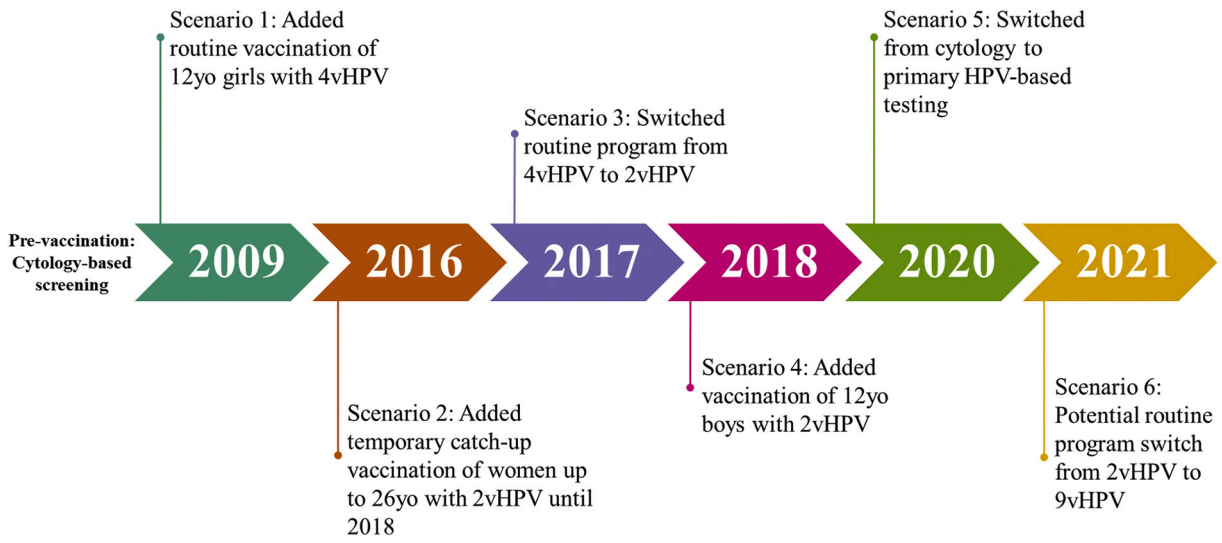

Fig. 1. Timeline of current and future policies in Norway: analytic scenarios. Note: HPV = human papillomavirus; 4vHPV = quadrivalent HPV vaccine; 2vHPV = bivalent HPV vaccine; 9vHPV = nonavalent HPV vaccine. Norway initiated a pilot primary HPV-based screening program in 2015. Following the pilot program, Norway implemented a nationwide gradual switch to primary HPV-based testing that began in 2018 and is expected to be completed by 2023–2025, whereas Scenario-5 assumed an immediate switch from pre-vaccination cytology-based screening to HPV-based testing among women aged 34–69 years in 2020 (maintaining primary cytology for women aged 25–33).

(Appendix A), and the top ten best-fitting natural history parameter sets to capture uncertainty in the calibrated parameters for selected scenarios (Molden et al., 2016). Our base case assumed a two-dose schedule (three-dose schedule prior to 2017 and for women aged 15 years and older), vaccine efficacy of 100% against HPV-16/18 infections for all vaccines (FUTURE II Study Group, 2007; Paavonen et al., 2009; Naud et al., 2014), and 95% against other vaccine-targeted types in 9vHPV (Joura et al., 2015; Petrosky et al., 2015). We assumed that 4vHPV provided 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 (Feiring et al., 2018); whereas we assumed the 2vHPV provided a higher cross-protection of 93.8%, 79.1%, and 82.6% for these types (Kavanagh et al., 2014). The duration of protection for type-specific vaccine efficacy was assumed to be lifelong. We conducted a validation of 4vHPV efficacy and cross-protection assumptions to available primary data (Feiring et al., 2018) on the prevalence of vaccine-type HPV in multiple birth cohorts of vaccinated and unvaccinated girls in Norway five years after the introduction of the routine 4vHPV vaccination program (Appendix E).

2.3. Health impact on cervical cancer incidence

We estimated the health impact on cervical cancer burden in terms of both age-standardized rate (ASR) of cervical cancer incidence per 100,000 woman-years and the number of cervical cancer cases averted between 2009 and 2110 (inclusive). We defined the elimination year as the year in which ASR of cervical cancer incidence consistently decreased to <4 new cases per 100,000 woman-years. Base-case results were age-standardized to the standard Norway population (0–84 years) (Cancer Registry of Norway, 2019). We calculated the number of newly diagnosed cervical cancer cases each year by applying the Norway female population projections for 2009 to 2110 from the UN Development Program (United Nations Population Division, 2019). We conducted sensitivity analyses to assess the effect of alternative population structures on the elimination year; in particular the World Female Population 2015 (0–99 years) (United Nations Population Division, 2019), the benchmark population structure in use for global predictions by WHO (Brisson et al., 2020; Canfell et al., 2020); and the Segi standard population (0–84 years) (Segi et al., 1969; Doll et al., 1966), a common population structure in prior analyses included for comparability (Hall et al., 2019) (Appendix F). We also conducted sensitivity analyses to assess the effect of increasing current screening compliance (Appendix B) in the base case to perfect screening compliance for ever-screeners (94% of screening-age population), maintaining the current level of never-screeners (6% of screening-age population).

2.4. Cost-effectiveness of future policy

In the context of primary HPV-based testing, the most recent cervical cancer prevention policy change in Norway, we evaluated the additional health benefits and costs of vaccination of boys and girls with 9vHPV (Scenario-6) compared to vaccination of boys and girls with 2vHPV, including cross-protection (Scenario-5), assuming an additional vaccine cost per dose of 45 US dollars (USD) for 9vHPV compared to 2vHPV. The price differential between the two vaccines was based on the maximum retail price for pharmacies provided by the Norwegian Medicines Agency (Norwegian Medicines Agency, 2007; Norwegian Medicines Agency, 2015) after excluding 25% value-added tax as recommended in Norwegian guidelines for evaluating health technologies; however, we explored the impact of alternative incremental vaccine prices in sensitivity analysis. All scenarios assumed a vaccine delivery cost per dose of 12 USD. Costs were reported in 2018 Norwegian kroner (NOK) and converted to USD using the average annual 2018 exchange rate (USD1 = NOK8.1325) (World Bank, 2019). A full list of cost assumptions in 2018 USD is presented in Appendix G.

We calculated the incremental cost-effectiveness ratio (ICER) defined as the additional cost of 9vHPV strategy (Scenario-6) divided by the additional health benefits (i.e., quality-adjusted life years; QALYs) compared with 2vHPV strategy (Scenario-5). We assumed a cost-effectiveness threshold of 47,341 USD per QALY, which has been suggested as the severity-specific threshold for a low-severity disease such as cervical cancer in Norway (due to the relatively good prognosis) (Norwegian Ministry of Health and Care Services, 2015; Norwegian Ministry of Health and Care Services, 2016) (Appendix H). In sensitivity analysis, we varied the incremental vaccine price between 2vHPV and 9vHPV and compared ICERs to alternative cost-effectiveness thresholds, including Norway's gross domestic product (GDP) per capita (81,734 USD (World Bank, 2019)) and a maximum suggested severity-specific threshold (101,445 USD). In line with good-modeling practice, we reported the discounted and undiscounted cost-effectiveness analysis

results, in terms of lifetime costs, QALYs, and life years (LYs) from a societal perspective (direct medical and non-medical costs associated with screening). Model outcomes were aggregated over multiple birth cohorts to capture the discounted (4% annually) lifetime costs and benefits, including QALYs (utility weights for the general population and cervical cancer by stage of diagnosis (Burger et al., 2014); Appendix H), of women born up to 2110 (over their lifetimes).

3. Results

3.1. Impact on cervical cancer incidence

Without new policy interventions starting in 2009, Norway would not have achieved cervical cancer elimination. With only the 2009 policy of routine vaccination for 12-year-old girls using 4vHPV, the model predicted that Norway would reach the cervical cancer elimination threshold by 2056 (Fig. 2; Scenario-1). Subsequent changes to vaccination accelerated elimination timing by eight years in total: five years from adding the temporary catch-up for females aged up to 26 years with 2vHPV (Scenario-2, elimination in 2051), two years from switching to 2vHPV (elimination in 2049), and one year from adding 12-year-old boys to the routine vaccination program (elimination in 2048). Switching to primary HPV screening for women aged 34–69 years (Scenario-5) accelerated cervical cancer elimination by an additional nine years compared with Norway's vaccination policies and a cytology-based program (elimination in 2039). An examination of the top ten parameter sets found the time to elimination for Scenario-5 to vary between 2036 and 2041, with the majority of simulations (60%) achieving elimination by 2039–2040. A hypothetical switch from 2vHPV to 9vHPV in 2021 had no impact on elimination timing, but reached a lower cervical cancer incidence of 0.8/100,000 (range of top ten sets: 0.7–1.0/100,000) woman-years as compared with 1.3/100,000 (range of top ten sets: 1.2–1.5/100,000) woman-years with 2vHPV by 2110 (Appendix I).

The current policy context in Norway (Scenario-5) is projected to cumulatively avert over 22,800 cases of cervical cancer and 7500 cervical cancer-related deaths compared with the pre-vaccination scenario over the period 2009–2110 (Table 1). A potential, future switch to 9vHPV (Scenario-6), assuming high protection against seven high-risk HPV genotypes, was projected to avert 1000, or 4%, additional cases compared with 2vHPV (Scenario-5).

The elimination year varied by up to 10 years when we used different populations and age ranges for age standardization. For example, our projections for the Norway elimination year were 4–10 years earlier when we used the World Female Population 2015 (age 0–99 years) structure, the benchmark population structure used for global predictions by WHO, and elimination with the current policies in place (Scenario-5) was predicted to occur in 2035 compared to 2039. When we used the Segi population structure, our projections for the Norway

Table 1
Cervical cancer cases and deaths averted compared with pre-vaccination prevention policy in Norway over the period 2009 to 2110 inclusive, by policy scenario (percent reduction compared with status quo in parentheses).

Policy scenario	Cervical cancer cases averted	Cervical cancer deaths averted
Scenario-1	17,300 (50%)	5,200 (43%)
Scenario-2	18,100 (53%)	5,500 (46%)
Scenario-3	18,900 (55%)	5,800 (48%)
Scenario-4	19,900 (58%)	6,200 (51%)
Scenario-5	22,800 (66%)	7,500 (61%)
Scenario-6	23,800 (69%)	7,700 (63%)

Note: Pre-vaccination cervical cancer prevention policy in Norway in 2009 (Scenario-0) is 3-yearly cytology-based screening (i.e., no vaccination). Scenario-0 is projected to result in 34,400 cases of cervical cancer and 12,200 cervical cancer-related deaths over the period 2009–2110. Scenario-1 = Added routine vaccination of 12-year-old girls with quadrivalent vaccine in 2009; Scenario-2 = Added temporary catch-up vaccination of women up to 26 years of age with bivalent vaccine in 2016; Scenario-3 = Switched routine program from quadrivalent to bivalent vaccine in 2017; Scenario-4 = Added routine vaccination of 12-year-old boys with bivalent vaccine in 2018; Scenario-5 = Switched from cytology to primary HPV-based testing in 2020; Scenario-6 = Potential routine program switch from bivalent to nonavalent vaccine in 2021. Cases and deaths averted were rounded to the nearest hundred and estimated for ages 9 to 89.

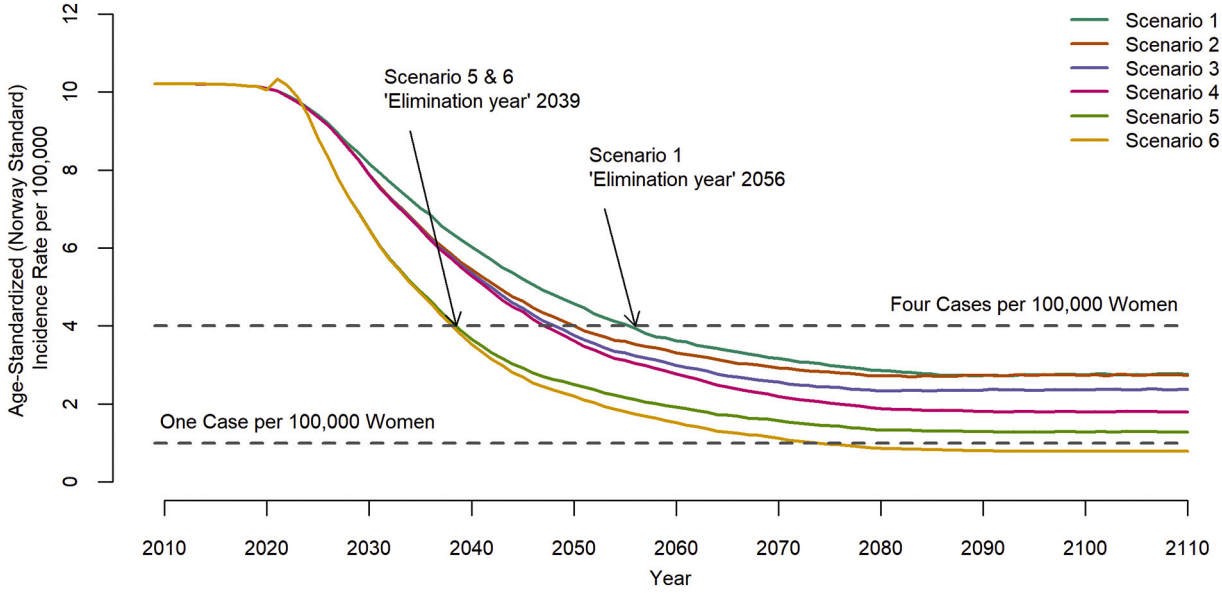

Fig. 2. Time to cervical cancer elimination in Norway. Note: Pre-vaccination cervical cancer prevention policy in Norway in 2009 (Scenario-0) is 3-yearly cytology-based screening. In the absence of additional interventions, we would expect the age-standardized cervical cancer incidence in Scenario-0 to be equivalent to the starting level of the analyzed scenarios. Scenario-1 = Added routine vaccination of 12-year-old girls with quadrivalent vaccine in 2009; Scenario-2 = Added temporary catch-up vaccination of women up to 26 years of age with bivalent vaccine in 2016; Scenario-3 = Switched routine program from quadrivalent to bivalent vaccine in 2017; Scenario-4 = Added routine vaccination of 12-year-old boys with bivalent vaccine in 2018; Scenario-5 = Switched from cytology to primary HPV-based testing in 2020; Scenario-6 = Potential routine program switch from bivalent to nonavalent vaccine in 2021.

elimination year were 4–9 years earlier. The elimination year was predicted to occur in 2038 compared to 2039 for Scenario-5 and Scenario-6 when we assumed perfect screening compliance for ever-screeners.

3.2. Cost-effectiveness analysis of switch to nonavalent vaccine

Assuming a low-disease severity cost-effectiveness threshold of 47,341 USD per QALY gained and an additional vaccine cost per dose of 45 USD, we found that switching the routine vaccination program to 9vHPV would not be considered 'good value for money' compared to the current 2vHPV in Norway (ICER of 174,500 USD per QALY gained) (Table 2). The ICER ranged from 126,100 to 198,500 USD across the top ten best-fitting natural history parameter sets. Switching to 9vHPV remained unattractive for both higher cost-effectiveness thresholds. When we did not include quality-of-life decrements, the switch to 9vHPV was even less attractive.

When the 9vHPV price was equal to the 2vHPV price, switching to 9vHPV was cost-saving, providing greater health benefits and lower lifetime costs, compared to 2vHPV (Fig. 3). The 9vHPV vaccination remained cost-saving until the vaccine cost 9 USD (range of top ten sets: 9–11 USD) or more per dose than 2vHPV. We found that, at the estimated cost-effectiveness threshold for cervical cancer in Norway (47,341 USD), switching to 9vHPV could be considered cost-effective when the incremental cost of 9vHPV was 19 USD per dose or less (range of top ten sets: 17–24 USD) compared to 2vHPV (assuming a two-dose schedule). For lower and higher disease-severity threshold values of 33,815 and 101,445 USD, switching to 9vHPV could be considered cost-effective if the incremental cost was not more than 16 USD (range of top ten sets: 15–20 USD) and 30 USD (range of top ten sets: 27–38 USD) per dose, respectively. Undiscounted values are presented in Appendix J.

4. Discussion

Our model-based analysis projected that Norway is on track to achieve cervical cancer elimination by 2039 under current and historic HPV vaccination and screening policies, including the recent implementation of primary HPV-based screening for women aged 34–69 years. Elimination would not have been possible in Norway without routine HPV vaccination of 12-year-old girls. The additional cervical cancer control policies in Norway implemented since then may have accelerated the timeframe to elimination by more than 17 years, just over half of which (nine years) is due to the introduction of primary HPV-testing. The acceleration due to primary HPV-testing, a more sensitive test compared with cytology-based screening, is primarily driven by preventing cases among mid-adult, unvaccinated women, which has been shown in previous analyses (Brisson et al., 2020; Hall et al., 2019; Burger et al., 2020). Although a potential future switch to 9vHPV in Norway is unlikely to accelerate the time to cervical cancer elimination, it yielded the lowest cervical cancer incidence by 2110 (0.8 cases per 100,000 woman-years in the base case, and consistently lower than Scenario-5 across the top ten best-fitting parameter sets), assuming there are no changes to screening recommendations for cohorts vaccinated with 9vHPV. However, in order to be considered cost-effective at a low disease-severity threshold, the additional cost of 9vHPV could not be more than 19 USD per dose compared to 2vHPV, but varied from 16 to 30 USD depending on the cost-effectiveness threshold value. Previous analyses have examined the health impact and cost-effectiveness of specific policy decisions in Norway, such as the decision to add boys to the routine program (Burger et al., 2014) or the switch to primary HPV-based testing (Burger et al., 2012), but, to our knowledge, this is the first study to project the timeframe to cervical cancer elimination according to detailed changes in screening and vaccination policies in Norway or examine the cost-effectiveness of switching to 9vHPV.

When using the WHO benchmark methodology (World Female Population 2015) as the population structure, we predicted cervical cancer elimination would be achieved in Norway in 2035, which can be compared to the projected timeframe in other settings. The projected time to elimination is similar to the 2034–2041 timeframe estimated in the US (Burger et al., 2020) and later than the approximate 2025 timeframe estimated in Australia (Hall et al., 2019). The comparative modeling exercise in the US found that the Harvard model projects earlier elimination than the Policy1-Cervix model, which may also impact the projected elimination timeline in the current analysis (Burger et al., 2020). The earlier elimination timeline in Australia may be due to the lower incidence of cervical cancer prior to vaccination, immediate implementation of a catch-up vaccination program (2007–2009) with the introduction of routine HPV vaccination, or earlier introduction of HPV screening. Earlier expansion to include boys in 2013 is unlikely to be an important factor as including male vaccination only affected timing by two years in Australia (Hall et al., 2019; Hall et al., 2018). The variation in timing of elimination by population structure in sensitivity analysis reflects how influential the included population age range and structure are on the projected timeframe. Importantly, switching older women to primary HPV-based testing was one of the most important policy levers to accelerate cervical cancer elimination in Norway, in Australia (Hall et al., 2019; Hall et al., 2018), and in the US (Burger et al., 2020), and delays should be avoided (Castañon et al., 2019).

Our analysis provides similar results to previous cost-effectiveness analyses of 9vHPV in high-income settings such as Canada (Drolet et al., 2014), Australia (Simms et al., 2016), and the United States (Brisson et al., 2016a). For example, in the US, switching to 9vHPV was found to be cost-saving assuming an incremental vaccine price of not more than 13 USD (2010) per dose compared to 4vHPV (Brisson et al., 2016a).

There are several limitations to this analysis. First, our national-level projections do not consider regional variations in Norway (Orumaa et al., 2019). The analysis is further limited by the lack of available data for specific model parameters in Norway, such as HPV prevalence in men. However, we relied on male HPV prevalence data from Denmark to calibrate the model (Hebnes et al., 2015), as cervical cancer epidemiology and prevention data (Pedersen et al., 2018b) as well as sexual behavior data among women (Hansen et al., 2020) have been shown to be similar. Moreover, our model platform reflects the most common cervical cancer histology, squamous cell carcinoma (SCC), and does not include the impact on adenocarcinomas, which may be increasing in Norway (Lönnberg et al., 2015). The inclusion of adenocarcinomas may delay our projected timeframe to elimination; however, both HPV vaccination and primary HPV-based screening are expected to also reduce the burden of adenocarcinoma. In addition, the contribution of the additional HPV genotypes targeted by 9vHPV in adenocarcinoma is

Table 2
Discounted costs (2018 USD)*, quality-adjusted life years (QALYs), life years (LYs), and cost-effectiveness of potential switch from bivalent (2vHPV) vaccine to nonavalent (9vHPV) vaccine in the routine girls and boys vaccination program in Norway.

Vaccine	Total costs	QALYs	LYs	Incremental costs	Incremental QALYs	Incremental LYs	Cost per QALY gained	Cost per LY saved
2vHPV	2,797,437,000	52,009,800	61,086,600					
9vHPV	2,911,589,400	52,010,400	61,087,000	114,152,500	700	500	174,500	233,300

Note: Scenarios in the context of primary HPV-based testing. Average annual 2018 exchange rate (USD1 = NOK8.1325) (World Bank, 2019). All values rounded to the nearest hundred. *The Norwegian Medicines Agency 2020 guidelines have been updated to recommend a diminishing discount rate for vaccination program evaluations; however, the 2018 guidelines that recommend a constant 4% annual discount rate remain valid through November 2020.

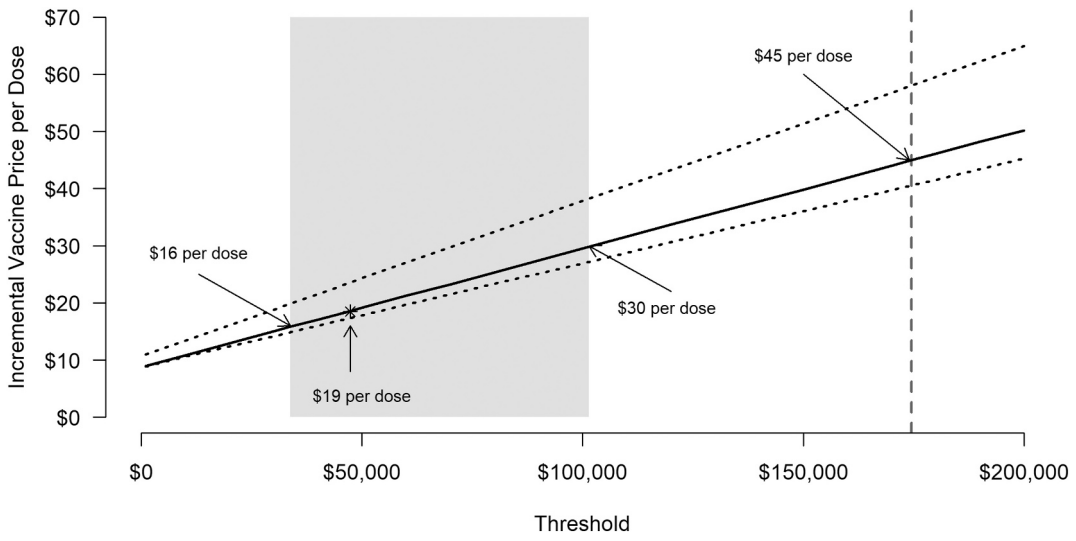

Fig. 3. Incremental vaccine price per dose for nonavalent (9vHPV) compared to bivalent (2vHPV) vaccine by cost-effectiveness threshold. Note: The dashed line represents the base-case incremental cost-effectiveness ratio of 174,500 USD for 9vHPV compared to 2vHPV that assumes an incremental vaccine cost per dose of 45 USD. The dotted lines represent the minimum and maximum incremental vaccine cost per dose across the top ten parameter sets. The shaded region represents the area of cost-effectiveness in Norway, with the minimum threshold equivalent to 33,815 USD for low-severity diseases and the maximum equivalent to 101,445 USD for high-severity diseases. *Reflects the threshold additional price of the vaccine assuming a low-severity threshold of 47,341 USD per QALY (Appendix H). Value next to each arrow reflects the additional cost of 9vHPV compared with 2vHPV. Average annual 2018 exchange rate (USD1 = NOK8.1325) (World Bank, 2019).

low; therefore, we do not expect this limitation to affect the conclusions of our analysis.

Although our calibrated model generally fit well to multiple epidemiological targets, several parameters may influence the results of this analysis more than others. For example, our model fits to the HPV type distribution in cervical cancer were lower than the primary data for Norway (Burger et al., 2012), albeit within the lower 95% confidence intervals of the empirical bounds of the primary data and similar to a recent Scandinavian analysis (Dovey de la Cour et al., 2019) (Appendix E). While these generally lower bound estimates may result in a conservative estimate of the time to cervical cancer elimination, these parameters may provide more optimistic estimates for switching to the 9vHPV in terms of its cost-effectiveness profile. For example, the relative contribution of HPV-16/18 were lower on the lower bound of our calibration target than reported from Norway, whereas the contribution of types not benefiting from 2vHPV cross-protection but included in the 9vHPV (i.e., HPV-52/58) were higher and, therefore, would provide more favorable incremental benefits (Appendix A). In addition, we did not allow vaccine efficacy to vary by age; however, since vaccine efficacy in the model is assumed to only prevent incident infections, older women effectively receive less benefit given the level of prevalent infections at the time of vaccination.

Second, we evaluated the impact of 9vHPV in the context of cervical cancer elimination; however, switching to 9vHPV may also impact non-cervical cancers and genital warts. The impact of including non-cervical cancers on the ICER is affected by both the burden of the cancer and the HPV type attributed to the cancer. Relative to cervical cancer, HPV-16/18 contribute to a higher proportion of non-cervical cancers, which are protected by current vaccine types. Subsequently, five additional HPV types included in the 9vHPV among these lower-burden cancers may not lead to substantial impacts on disease burden and therefore the ICER. For example, among oropharyngeal cancers, the second highest-burden HPV-associated cancer in Norway, a recent genotyping study found that 96% of HPV-induced oropharyngeal cancers could be prevented by 2vHPV (with partial cross-protection), whereas 9vHPV could prevent an additional 2% of these cancers (Fossum et al., 2017). Importantly, genital warts, experienced by approximately one in ten Norwegians prior to 2009 (Kjaer et al., 2007), may also impact the relative value of 9vHPV as HPV-6/11 types are not included in 2vHPV. In a previous analysis, we found that, when including genital warts and recurrent respiratory papillomatosis related to HPV-6/11, the ICER dropped by approximately 32% (Burger et al., 2014), which would not change the conclusions of our current cost-effectiveness analysis at the current cost differential of 45 USD per dose. Furthermore, giving priority to the highest burden disease for interventions that affect multiple diseases is in line with the Norwegian priority-setting guidelines (Norwegian Medicines Agency, 2018). Therefore, as cervical cancer will still reflect the greatest burden of all HPV-related diseases under 2vHPV, it may be reasonable to assume that cervical precancer and cancer may drive the value-based tender negotiations, and prevention of genital warts may not be a standalone reason to recommend 9vHPV (Norwegian Institute of Public Health, 2007).

Third, we did not consider changes to sexual behavior, vaccine uptake, or correlations between vaccination and screening attendance, which may vary over time. A range of models developed independently for high-income country settings and incorporating a range of different sexual behavior assumptions and structure gave broadly similar predictions (Brisson et al., 2016b), and we do not anticipate additional uncertainty analysis around sexual behavior to have a large impact. HPV vaccination coverage in Norway is already high (89–90% among adolescent boys and girls) and may continue to increase in Norway, but is unlikely to accelerate elimination as found in a previous US-based analysis (Burger et al., 2020), and as suggested by a modeling meta-analysis that predicted vaccine-preventable HPV types will be eliminated at the coverage levels achieved in Norway (Brisson et al., 2016b). Previous work has identified that never-screened women are likely to have the highest cervical cancer burden if these women have lower vaccine uptake than frequently screened women (Malagón et al., 2015), which may have a greater impact on elimination timing. While the longer screening interval of five years for HPV-based screening and observed 10% increase after introducing self-sampling may yield higher screening coverage rates (Arbyn et al., 2018; Enerly et al., 2016), we found that the elimination was accelerated by one year when we assumed perfect screening compliance for ever-screeners. In addition, we assumed an immediate switch from pre-vaccination cytology-based screening to HPV-based testing among women aged 34–69 years in the year 2020; however, Norway began to gradually switch in a regional pilot implementation trial in 2015–2018; however, national scale-up

may not conclude until 2023–2025 (primarily driven by laboratory constraints and currently exacerbated by COVID-19 disruptions). Our assumption of an immediate switch helps to quantify the expected elimination timing, but the exact elimination timeframe is dependent on achieving this switch nationwide. The impact of de-intensified screening strategies on elimination timing will be the focus of future analyses.

In conclusion, the cervical cancer control policies implemented over the last decade in Norway, such as routine HPV vaccination and primary HPV-based testing, may have accelerated the timeframe to elimination by more than 17 years, such that cervical cancer rates may fall below 4 per 100,000 woman-years by the year 2039. A potential switch to 9vHPV may lead to greater benefits, but does not affect elimination timing and may not be cost-effective unless the additional cost of 9vHPV is substantially reduced.

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Contributions

AP, LIT, BF, IL, and EAB conceptualized the study. Data analysis was done by AP and EAB. AP and EAB drafted the manuscript with input from all authors. All authors approved the final version of the manuscript.

Declaration of Competing Interest

AP, KP, LIT, BF, IL, MAS, SS, JJK and EAB have no competing interests to declare. BTH and MN's affiliating institute (The Cancer Registry of Norway) received research grants from MSD Norway/Merck to perform HPV vaccine studies for the long-term follow-up study for the clinical trial population participating in vaccine trials and for vaccine impact in the general female population. The present study was conducted independently. MSD Norway/MSD had no role in initiating, planning, analyses, interpretation of results, or decision to submit this study.

Supplementary data

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