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Quadrivalent HPV vaccine effectiveness against anogenital warts: A registry-based study of 2,2 million individuals

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ABSTRACT

Background: In 2009, Norway initiated routine quadrivalent HPV (qHPV) vaccination for girls at 12–13 years of age to protect against virus types causing cervical cancer, HPV16/18, and HPV6/11 which cause anogenital warts (AGW). We wanted to investigate qHPV vaccine effectiveness (VE) against AGW in females before and after first AGW episode and to assess the impact of female vaccination in males.

Materials and methods: QHPV vaccination and AGW episodes were collected for the time period 2006–2016 for birth cohorts 1975–2003. Cox models were applied to age at first, as well as at second AGW episode. Finally, we estimated the impact of the female vaccination program on unvaccinated males.

Results: The VE against the first episode of AGW was strongly dependent on vaccination age, with hazard ratios (HRs) compared to unvaccinated individuals of 0.2, 0.2, 0.3, 0.5, 1.0, 1.3, and 2.7, for age groups of ⩽13, 14–15, 16–17, 18–19, 20–24, 25–29, and 30+ years at first vaccination, respectively. Among women who had suffered a first episode of AGW, subsequent qHPV vaccination did not protect against a second episode, with HRs of 0.8, 1.0, and 1.4, for age groups of ⩽17, 18–24, and 25+ years at first vaccination. A gradually decreasing AGW risk was seen in unvaccinated male cohorts neighboring the first routinely vaccinated female 1997 cohort.

Conclusions: When administered before 14 years of age, qHPV vaccination reduced the probability of AGW about fivefold. The effect decreased sharply with vaccination age, and was not significant among women vaccinated after age 20 years. QHPV administered after the first AGW episode did not protect against a second AGW episode. Herd effects were indicated in unvaccinated males, as we observed a gradual decrease in AGW rates from the 1993 male birth cohort and onwards.

1. Introduction

Human papillomavirus (HPV) is a highly infectious virus mainly transmitted through sexual contact [1]. The average lifetime probability of acquiring HPV among sexually active individuals have been reported to be over 80 % [2]. Of the more than 200 HPV genotypes identified, 40 may infect the anogenital tract [3,4]. HPV6 or HPV11 have been detected in more than 85 % of cases of anogenital warts (AGW) [5]. Although not lethal, AGW may be very burdensome and long-lasting if not treated [6]. More than 10 % of Nordic women between 18 and 45 years of age have reported ever having had clinically diagnosed AGW [7]. The warts are most prevalent among people around 20 years of age [7]. In Norway, AGW are most commonly treated by podophyllotoxin and imiquimod solutions. The recurrence rates are reported to be at least 20 % within the first 12 weeks after primary treatment with different modalities [8].

The quadrivalent HPV vaccine Gardasil, which targets HPV 6, 11, 16, and 18, was licensed in Norway in October 2006, and self-paid opportunistic vaccination with a recommended three-dose schedule has since been available. From 2009 to 2017 the qHPV vaccine was offered to school girls in the seventh grade (12–13 years of age) as part of the Norwegian childhood vaccination program. A catch-up vaccination program with the bivalent vaccine Cervarix, targeting HPV 16 and 18, was effective from November 2016 through June 2019, targeting women born 1991 and later who had not been previously vaccinated in the routine program. In 2017, the bivalent vaccine replaced the qHPV vaccine in the vaccination program, and since 2018 the HPV vaccination in Norway has been gender neutral including boys in the seventh grade

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[9].

The first evidence of HPV vaccine effectiveness against cervical cancer was recently published with data from countries that introduced multi-cohort HPV vaccination early [10,11]. In Norway, where the single cohort vaccination strategy of 12–13 years old girls was implemented from 2009, the first vaccinated cohort (the 1997 cohort) is 25 years of age in 2022. As cervical cancer before this age is quite rare, there are still some years before we in Norway can observe any effect of the vaccine against cervical cancer with certainty. AGW have a much shorter time between infection and diagnosis than cancer (about 6 months for AGW vs decades for cancer [12]). AGW are therefore used to investigate effect of the vaccine while waiting for the effect to be seen in cancer.

Several studies have used population-based registry data linking vaccination status to AGW episodes for all individuals to evaluate the qHPV vaccine effectiveness against AGW [13–22]. The effectiveness has been shown to be strong, but highly dependent on vaccination age, with strongest effect if given before age of sexual debut [14,15,18,21]. The effect of the vaccine used as secondary prevention against AGW, i.e given after the first AGW episode, is less clear. A recent meta-analysis found no significant effect of the qHPV vaccine in patients with previous AGW [23]. However, this analysis was based on two randomized control trials (RCTs) with qHPV vaccination of only 225 individuals with previous AGW. Using population-based registry data, the number of vaccination registrations after AGW can be substantially higher, leading to a higher power to detect any effect of the vaccine after AGW.

We conducted a nation-wide registry-based cohort study including 2.2 million Norwegian residents to examine the vaccine effect before and after the first AGW episode in women, allowing the effect to depend on vaccination age. In addition, we studied a potential herd immunity among males caused by only females qHPV vaccination. This is the first study of the effectiveness of the HPV-vaccine using individual data in Norway.

2. Materials and methods

2.1. Study population and data collection

The study population were Norwegian males and females born 1975–2003 identified from the National Population Register. All individuals were followed up from January 2006 to December 2016, emigration, or death. The study design is illustrated in Fig. 1.

AGW data were obtained from the Norwegian Prescription Database (NorPD) and the Norwegian Patient Registry (NPR). Cases were defined as individuals with at least one prescription for podophyllotoxin (ATC code D06BB04), imiquimod (ATC code D06BB10), or sinecatechins (ATC code D06BB12), or at least one AGW diagnosis (ICD-10 code A63.0). For the NorPD data, we disregarded AGW prescriptions below 13 years of age (1 792 episodes). This was because the medications used to identify AGW prescriptions in our data also can be prescribed for other conditions, most notably other types of warts [24,25], which are more likely at lower ages [26]. An AGW episode was considered incident if preceded by at least 12 months without any registration of AGW diagnosis or treatment for AGW. For both NPR and NorPD the month of each prescription/diagnosis was retrieved.

From the Norwegian Immunisation Registry (SYSVAK) and NorPD we obtained the date (month, year) of each qHPV vaccine prescribed/administered to each individual. We used at least one dose of qHPV vaccine as the exposure in our primary analyses since there is evidence that a single dose of qHPV vaccine offers substantial protection against

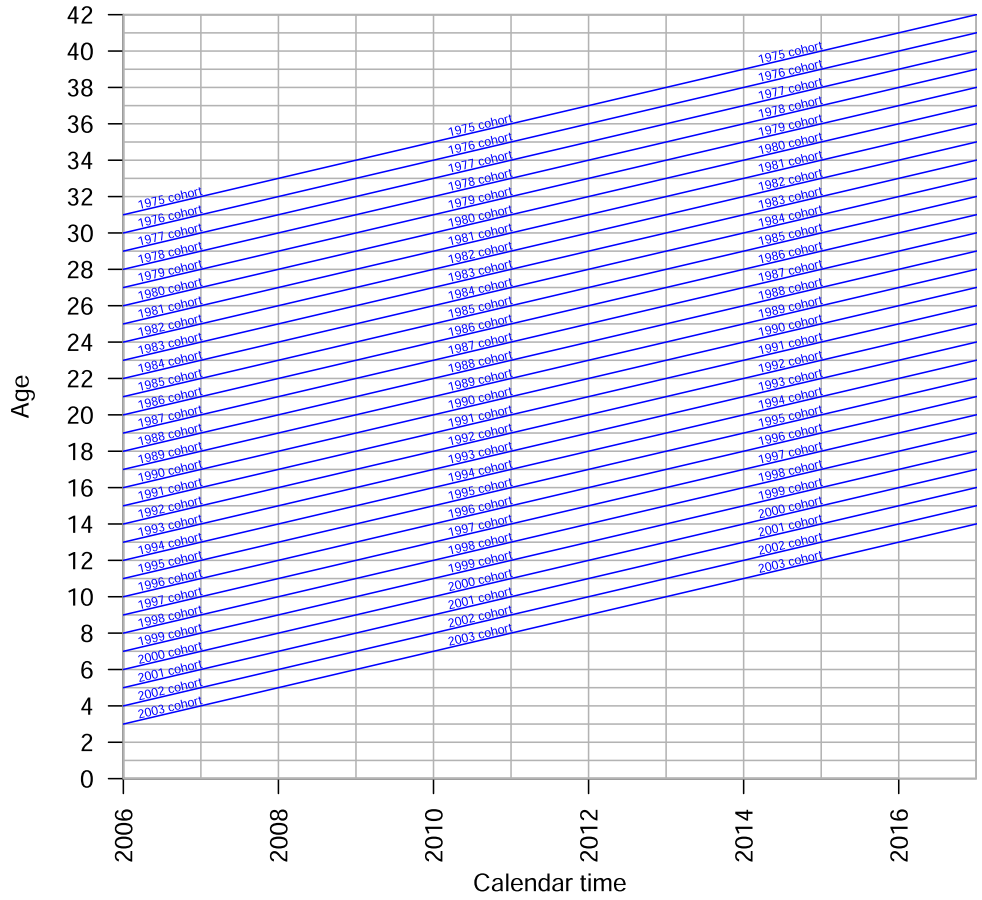

Fig. 1. Lexis diagram of the study population. The study included all male and female birth cohorts 1975–2003. The individuals were followed up from the beginning of 2006 to the end of 2016.

AGW [27]. Individuals who were not registered with any dose of qHPV vaccine in NorPD or SYSVAK were considered unvaccinated. We disregarded information about other HPV vaccination, i.e bivalent and nanovalent vaccine, because there were very few vaccinated with nanovalent vaccine, and the vast majority (97 %) of the ones vaccinated with the bivalent vaccine (34 948 individuals) were vaccinated in the last two month of the study (as part of the catch-up program). By also taking into consideration that the bivalent vaccine gives direct protection only against HPV16/18, and not against HPV6/11, that cause most of the anogenital warts, we assumed that the impact of other HPV vaccination on AGW is neglible in our data.

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway.

2.2. VE against first AGW episode

To evaluate vaccine effectiveness, we used only female individuals. The risk of AGW was assessed using a Cox model where the hazard function for getting first AGW depended on the age itself, vaccination status, vaccination age, as well as calendar time. The age was modelled by the baseline hazard rate, whereas vaccination age, vaccination status and calendar time were treated as covariates, with the latter two treated as time-dependent covariates. Specifically, we defined the hazard function at age a as

$$\lambda(a|v_{ai}, w_i, t_{ai}) = \lambda_0(a)\exp(v_{ai} \cdot f(w_i) + t_{ai}), \quad (1)$$

where $\lambda_0(a)$ is the baseline hazard, v_{ai} is an indicator with value 1 if the individual was vaccinated at age a_i, and 0 if it was not, w_i is the individual's vaccination age, and t_{ai} is years since start of the study when the individual reached age a. The start time for the individual was age at 1 January 2006, and stop time age at first AGW episode, or age at censoring, i.e age at emigration, death, or 1 December 2016 (end of study), whichever occurred first. The dependence on vaccination age was captured by the function $f(w_i)$. For this, vaccination age was treated as a discrete variable, estimating one effect per vaccination age group, or as a continuous variable, estimating the vaccine effect using a natural cubic spline.

There will be an uncertain lag time l from vaccination to a potential protective effect of the vaccine. We selected a lag time of six months as this is close to the average AGW incubation time reported elsewhere [5]. To further examine the appropriate lag time, we analysed models where $v_{ai} = 1$ from the same month as the first vaccination dose was given, as well as from one month, two months, and up to 12 months after the first dose. A lag time of six months gave the best model fit (Cox concordance index, Supplementary Fig. 5). To examine how much the results depended on the chosen lag time, we performed a sensitivity analysis with a range of lag time values (Supplementary Table 4).

Stratified analyses were performed to examine differences in VE between cohorts offered routine school-based vaccination (women born 1997–2003) and earlier cohorts that were not offered routine vaccination (women born 1977–1996). We also performed an analyses where individuals receiving only one dose of the vaccine were removed, so that all vaccinated individuals received at least two doses.

Predictions of the cumulative hazard rate for various vaccination ages w were obtained by entering the estimates of the $\lambda_0(a)$ and $f(w)$ into the hazard function (1), and setting $v_a = 0$ for $a < w + l$ and $v_a = 1$ for $a \geq w + l$ (where l was the chosen time lag from vaccination to vaccine effect), before integrating over ages.

2.3. VE against second AGW episode

To analyse VE after first AGW we included only women who had one AGW episode, and who had not been vaccinated before the first AGW episode. We applied the same Cox model as described above (1), except that the start time now was age at first AGW episode, and stop time was age at second AGW episode, or age at censoring date (if the individual did not have a second AGW episode). We applied the same lag time of six months from vaccination to effect of the vaccine. A stratified analysis was preformed using cohorts not offered routine vaccination (women born 1977–1996). We did not perform an analysis of the school-based vaccinated birth cohorts 1997–2003, as they only reached 19 years of age in the study period, and the power to detect VE against AGW was considered limited.

2.4. Impact of female HPV vaccination on AGW among unvaccinated males

As boys were not part of the routine vaccination program in the study period, most males (0.1 %) in this data set have not been vaccinated, which makes this cohort well suited for examination of potential herd immunity from vaccination of girls. Since the 1997 female birth cohort was the first to receive qHPV vaccination in the routine program, we used adjacent male birth cohorts, i.e boys born just before or after 1997. Each birth cohort was analysed separately with a basic Cox model with no covariates, i.e the hazard rate was simply the baseline hazard rate:

$$\lambda(a) = \lambda_0(a). \quad (2)$$

2.5. Implementation and code availability

The data was analysed using R [28]. Model fitting was done using the `coxph` function of the **survival** library and the `ns` (natural cubic splines) function from the **splines** library. R code is available in github (github.com/staaln/qhpv-agw).

3. Results

Out of a total of 2 187 724 men and women, 228 778 (10.5 %) individuals received qHPV vaccine. The vast majority of these were women born 1997–2003 vaccinated at ages 12 or 13, i.e. as part of the routine vaccination program (Table 1). We observed a total of 48 388 women (4.6 %) with at least one AGW episode, of which 7 260 (15 %) experienced at least one recurrent episode (Table 2).

3.1. VE against first AGW episode among women

Women who had *not* had AGW before receiving qHPV vaccine had a significantly reduced risk of AGW as compared to unvaccinated women if they received qHPV vaccine before age 20 (HRs with 95 % CI of 0.2 (0.2–0.3), 0.2 (0.2–0.3), 0.3 (0.2–0.3), and 0.5 (0.4–0.7), for age groups of ⩽13, 14–15, 16–17, and 18–19 years at first vaccination, respectively). However, women who had not had AGW and who received qHPV at age 20 or later did not have a reduced risk of AGW compared to unvaccinated women (HRs with 95 % CI of 1.0 (0.8–1.4), 1.3 (0.8–2.2), and 2.7 (1.1–6.6), for age groups of 20–24, 25–29, 30 + years at first vaccination, respectively) (Table 3, upper panel). VE modelled by a natural cubic spline showed the same pattern, i.e for the lowest vaccination ages the HR was around 0.3, but increased markedly from around 16 years of age (Fig. 2, left panel). Predicted cumulative hazard at 40 years of age was reduced from around 10 % if no vaccination was given to 2–3 % if vaccination was given at 12 years of age (Fig. 3). There were minor differences between vaccination ages of 12–16 years, but after 16 years the cumulative hazard was increasing markedly with vaccination age. The stratified analyses showed that the VE for the birth cohorts 1975–1996, i.e cohorts not offered routine vaccination, was lower than for birth cohorts 1997–2003, i.e those offered routine vaccination (Supplementary Tables 5 and 6). Analyses excluding individuals receiving only one dose of qHPV gave almost identical results to analyses where these individuals where included (Supplementary Table 7).

Table 1
Number of females vaccinated with at least one dose of quadrivalent HPV vaccine in the time period 2006–2016 by birth year and age at first vaccination dose.

	Age										
Birth year	<12	12	13	14	15–19	20–24	25–29	30+	Total	Population[a]	%[b]
1975	·	·	·	·	·	·	·	72	72	36578	0.2
1976	·	·	·	·	·	·	·	70	70	35555	0.2
1977	·	·	·	·	·	·	·	60	60	35179	0.2
1978	·	·	·	·	·	·	8	84	92	36332	0.3
1979	·	·	·	·	·	·	48	102	150	37038	0.4
1980	·	·	·	·	·	·	79	89	168	37734	0.4
1981	·	·	·	·	·	·	155	136	291	37865	0.8
1982	·	·	·	·	·	28	201	128	357	38749	0.9
1983	·	·	·	·	·	103	80	97	280	38551	0.7
1984	·	·	·	·	·	150	64	107	321	39341	0.8
1985	·	·	·	·	·	114	105	104	323	39787	0.8
1986	·	·	·	·	·	142	162	87	391	40266	1.0
1987	·	·	·	·	7	168	302	24	501	41174	1.2
1988	·	·	·	·	85	180	368	·	633	42093	1.5
1989	·	·	·	·	194	183	465	·	842	41732	2.0
1990	·	·	·	·	346	223	504	·	1073	41701	2.6
1991	·	·	·	·	524	319	151	·	994	39726	2.5
1992	·	·	·	8	758	410	33	·	1209	37821	3.2
1993	·	·	6	102	849	415	·	·	1372	36240	3.8
1994	·	2	62	140	1015	365	·	·	1584	35180	4.5
1995	·	23	98	187	1146	318	·	·	1772	34455	5.1
1996	4	40	323	458	1316	193	·	·	2334	34266	6.8
1997	22	12022	8966	785	455	9	·	·	22259	33268	66.9
1998	37	16165	7771	128	395	·	·	·	24496	32416	75.6
1999	40	17240	7750	147	445	·	·	·	25622	32570	78.7
2000	77	17774	7821	183	423	·	·	·	26278	32539	80.8
2001	87	17919	7673	157	399	·	·	·	26235	31373	83.6
2002	67	18577	7365	225	61	·	·	·	26295	30944	85.0
2003	84	19101	7390	101	·	·	·	·	26676	31548	84.6
Total	418	118863	55225	2621	8418	3320	2725	1160	192750	1062039	18.1

[a] For each birth year, number of women resident in Norway at any time during 2006–2016.
[b] For each birth year, percentage of women qHPV vaccinated at any age.

Table 2
Distribution of number of AGW episodes for the study population.

AGW episodes[a]	1	2	3	4	5	6	7
Females (%)	41128 (3.9)	5687 (0.5)	1217 (0.1)	275 (0.03)	66 (0.006)	13 (0.001)	2 (0.0002)
Males (%)	35607 (3.2)	6907 (0.6)	1564 (0.1)	361 (0.03)	74 (0.006)	15 (0.001)	2 (0.0002)

[a] AGW episodes were retrieved from the Norwegian Prescription Database, using ATC codes for podophyllotoxin, imiquimod and sinecatechins, and from the Norwegian Patient Registry, using ICD10 code A63.0 (anogenital warts).

Table 3
Hazard ratios (HR) for getting anogenital warts (AGW) relative to unvaccinated (including not yet vaccinated) individuals.

Vaccine effect *before* first AGW episode							
Vacc age:	⩽13	14–15	16–17	18–19	20–24	25–29	30+
HR	.2*	.2*	.3*	.5*	1.0	1.3	2.7
95 % CI	(.2-.3)	(.2-.3)	(.2-.3)	(.4-.7)	(.8–1.4)	(.8–2.2)	(1.1–6.6)
Vaccine effect *after* first AGW episode[†]							
Vacc age:		⩽17			18–24		25+
HR		.8			1.0		1.4
95 % CI		(0.5–1.4)			(.7–1.2)		(.9–2.0)

[†] When looking at vaccination effect after first AGW episode, only individuals with at least one AGW episode were included.
* $p < 0.05$.

3.2. VE against second AGW episode

QHPV vaccination after one episode of AGW did not reduce the risk of having a second episode of AGW, irrespective of age at vaccination (HRs with 95 % CIs of 0.8 (0.5–1.4), 1.0 (0.7–1.2) and 1.4 (0.9–2.0) for vaccination age groups of ⩽17, 18–24 and 25 + years, respectively) (Table 3, lower panel). The natural cubic spline for the HR showed a similar pattern, with values close to 1, and the 95 % CI covering 1, for all vaccination ages (Fig. 2, right panel).

3.3. AGW risk trends in unvaccinated males

We observed a modest but consistently decreasing risk of first AGW for each unvaccinated male cohort born from 1993 to 1999. The cumulative hazard rates at 20 years of age were 1.3 %, 1.2 %, 1.1 %, 1.0 %, and 0.7 % for the 1993–1997 cohorts, respectively. The 1998 and the 1999 cohort also showed decreasing risks, but were only followed up until 19 and 18 years of age, respectively (Fig. 4).

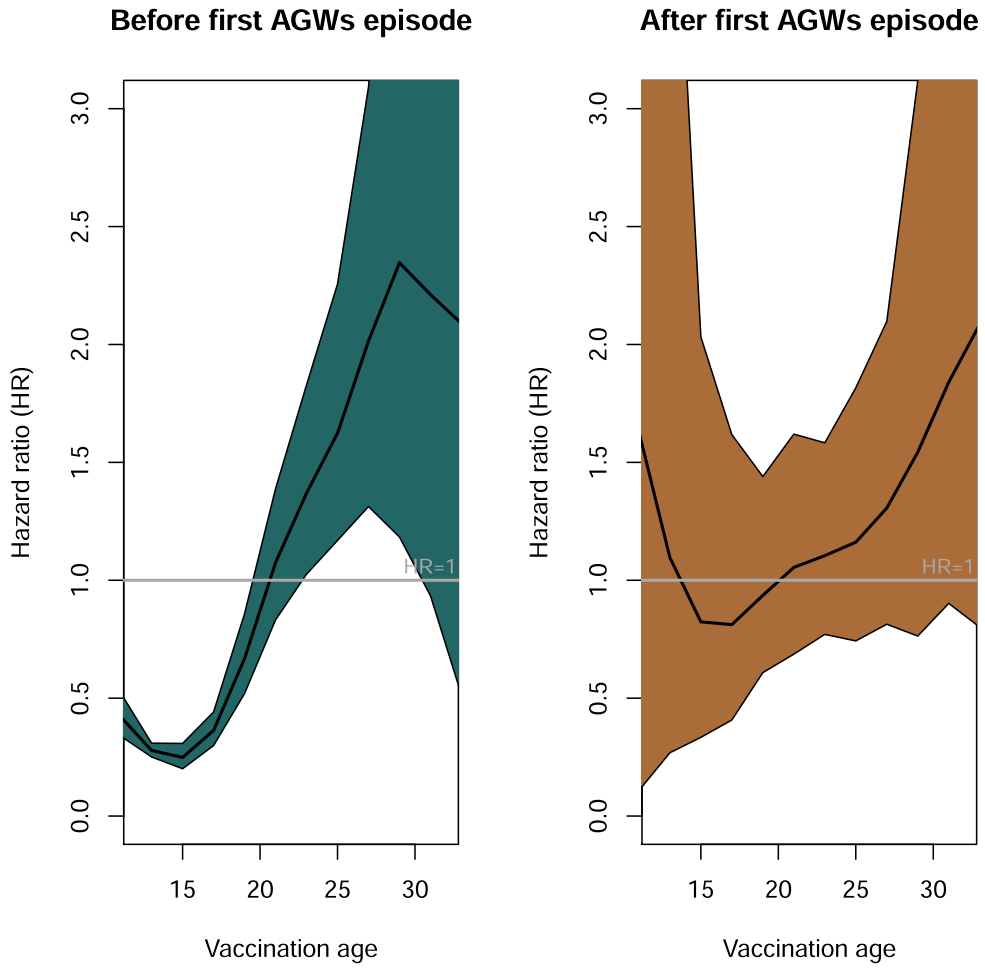

Fig. 2. Vaccine effect against anogenital warts (AGW) before and after first AGW episode. The vaccination age dependent hazard ratios (HR) are relative to unvaccinated (including not yet vaccinated) individuals. The shaded areas depict 95 % confidence bands. A grey horizontal line corresponding to HR = 1, i.e no vaccine effect, is drawn for reference.

4. Discussion

In this nationwide study of more than two million Norwegian males and females, of whom more than 190 000 individuals were vaccinated with the qHPV vaccine, we found a strong effect of the vaccine against AGW in females. However, the vaccine effect was strongly dependent on vaccination age. When given before 18 years of age, the HR for first AGW episode was 0.2–0.3, corresponding to a vaccine effectiveness (VE) of 70–80 %, while vaccination at age 20 years or older was not associated with a reduced risk of AGW. From vaccination age of 18 years the VE was markedly decreasing, with a non-significant VE after 20 years of age.

A similar vaccination age dependency has been shown in other studies, including studies on VE against cervical cancer [14,18,11,29]. Two main explanations for the reduced VE for women vaccinated late have been pointed out. Firstly, women vaccinated late have a much higher likelihood of already being exposed to HPV before vaccination [11]. We note that the age of first sexual intercourse of Norwegian women has been reported to have a median of 17 years and an interquartile range of 15–18 years [30]. This means that from 17–18 years of age a substantial proportion of girls most likely have been exposed to HPV, and may explain the decreasing VE observed from 18 years of age. Secondly, there may be a selection bias, as a higher proportion of women vaccinated at older age have been vaccinated outside the free-of-charge vaccination program, and it is possible that they have been vaccinated for reasons related to a higher risk of AGW or cervical cancer [11,21]. Taken together, these two factors may have caused the observed elevated risk for AGW among women vaccinated at age 25+. Our study thus supports the notion that HPV vaccination should be given early, most importantly before sexual debut age, for optimal protection, whether it is to avoid AGW, cancer or both. At older ages the vaccination effect is not significant, and may be biased due to disproportionate opportunistic vaccination of high-risk individuals.

In contrast to the VE against first AGW episode, we did not find any evidence for VE against recurrent AGW episodes. To the best of our knowledge, this is the first observational study using population based individual level registry data to evaluate VE against recurrent AGW. RCTs have been carried out [31,32,23], but these include a much smaller number of individuals than we had in our study (48 045 women with previous AGW, of whom 3 853 were vaccinated after AGW). Contrary to RCTs, observational studies may have biased VE estimates due to confounding factors. Such factors are likely to be present also in our study, as discussed in the previous paragraph. However, confounding may be less prominent in the analysis exclusively addressing women with previous AGW, since this entire population is at high risk of AGW. It is not known to which extent recurrent AGW are caused by reactivation of a non-cleared HPV virus, or infection with a new virus [33]. If reactivation is the mechanism, the prophylactic Gardasil vaccine is not expected to have any effect. If recurrent AGW are caused by a new HPV infection, the Gardasil vaccine is more likely to have an effect. The additional protection from the vaccine after an AGW episode will depend on the degree of natural immunity acquired from the first HPV

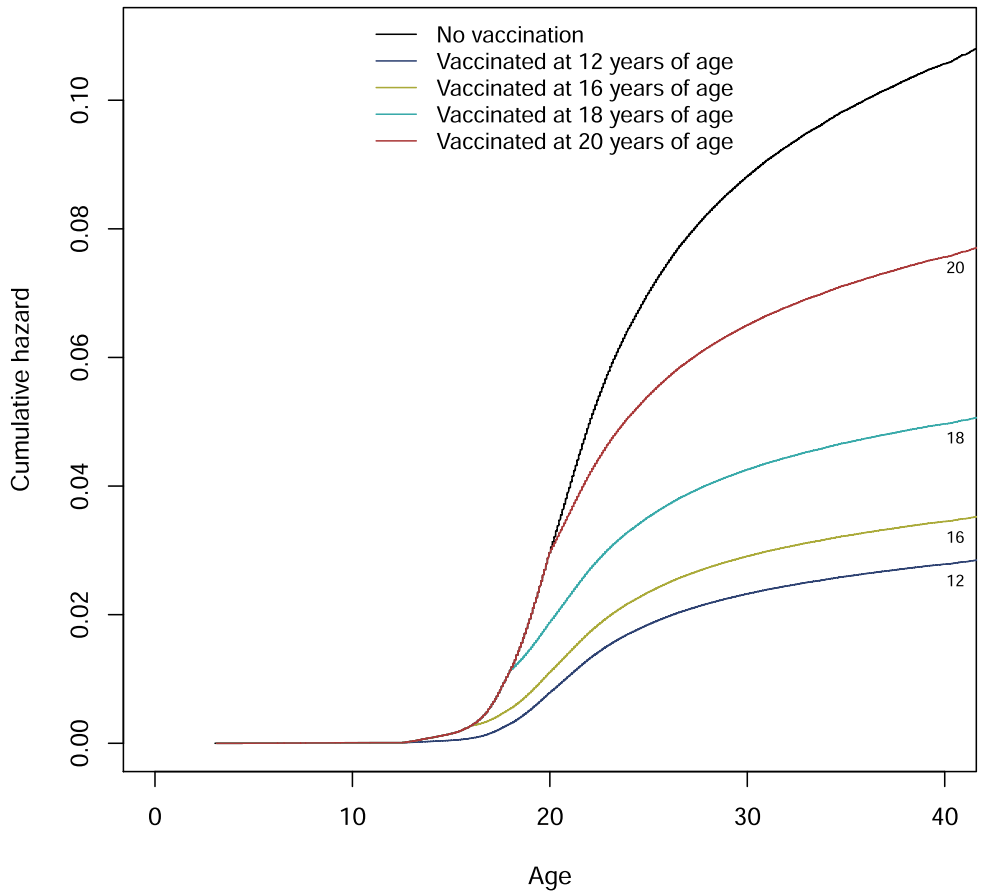

Fig. 3. Predicted cumulative hazard rates for anogenital warts for various qHPV vaccination ages. The predictions are based on vaccination age dependent hazard ratios within a Cox model.

infection. However, studies have been mixed on whether naturally acquired HPV antibodies may protect against subsequent HPV infection [34]. Possibly, the new AGW episode is caused by a different HPV type than the one causing the first episode, and against which the individual may be immune. However, this may not occur so often because the HPV6 attribution in AGW has been shown to be many times higher than the HPV11 attribution [35]. It is also important to note that HPV6 an HPV11 are phylogenetically very similar [36], implying that infection with one of the two types may give some natural immunity against the other one. The lack of effect of the vaccine when given after the first AGW episode that we find in our study, indicates that recurrent AGW are caused by reactivation of a latent HPV infection.

We observed a gradual decrease in the cumulative hazard of AGW among the unvaccinated male cohorts born from 1993 to 1999. This observation is consistent with herd protection from routine qHPV vaccination of girls, which started with the 1997 birth cohort, because most Nordic women have first sexual intercourse with a partner who is the same age or 1–4 years older than themselves [37]. This herd protection may increase further as more qHPV vaccinated birth cohorts of women reach the peak age of AGW, which in Norway is at age 20–25 [6]. The herd protection is also indicated by the stratified analyses, which showed lower VE in the cohorts offered routine school-based vaccination than in earlier cohorts that were not offered routine vaccination. The reduced VE may be due to lower prevalence of HPV6/11 relative to other HPV types in the qHPV vaccinated cohorts. If HPV6/11 prevalence has been reduced more than the prevalence of other AGW causing HPV types, the AGW attributable fractions of HPV6/11 have decreased, resulting in a smaller VE for the qHPV vaccine.

4.1. *Strengths and limitations*

The major strength of the study is the use of data from high-quality national registries, where vaccination information and AGW episodes were linked by the use of national identification numbers, thereby avoiding selection bias. This gave us a large sample size and the possibility of analysing the data at individual level.

Some limitations may be considered. We have already mentioned the potential bias in the VE estimates, as vaccinated individuals may have an overall higher risk of AGW than unvaccinated individuals of the same age. This is likely to be more of a problem for females vaccinated at older ages, who were not offered the vaccine for free as part of a routine program, which presumably leads to stronger self-selection for vaccination. Another limitation is that we use data from a prescription registry, which is not containing direct diagnoses of AGWs. However, using prescriptions for AGW treatment is a conventional way to estimate AGW incidences [13,14,38]. Further, we did not adjust for socioeconomic and lifestyle factors, which may be confounders, i.e associated with both vaccination and AGW rates. Adjusting for such factors may remove bias, especially in older, opportunistically vaccinated individuals.

5. Conclusions

This population-based study shows that the qHPV vaccine had a strong protective effect against AGW among women who were vaccinated before age 20 years. Our results also indicate herd protection among unvaccinated boys who were the same age or slightly older than women in birth cohorts with a high vaccination coverage.

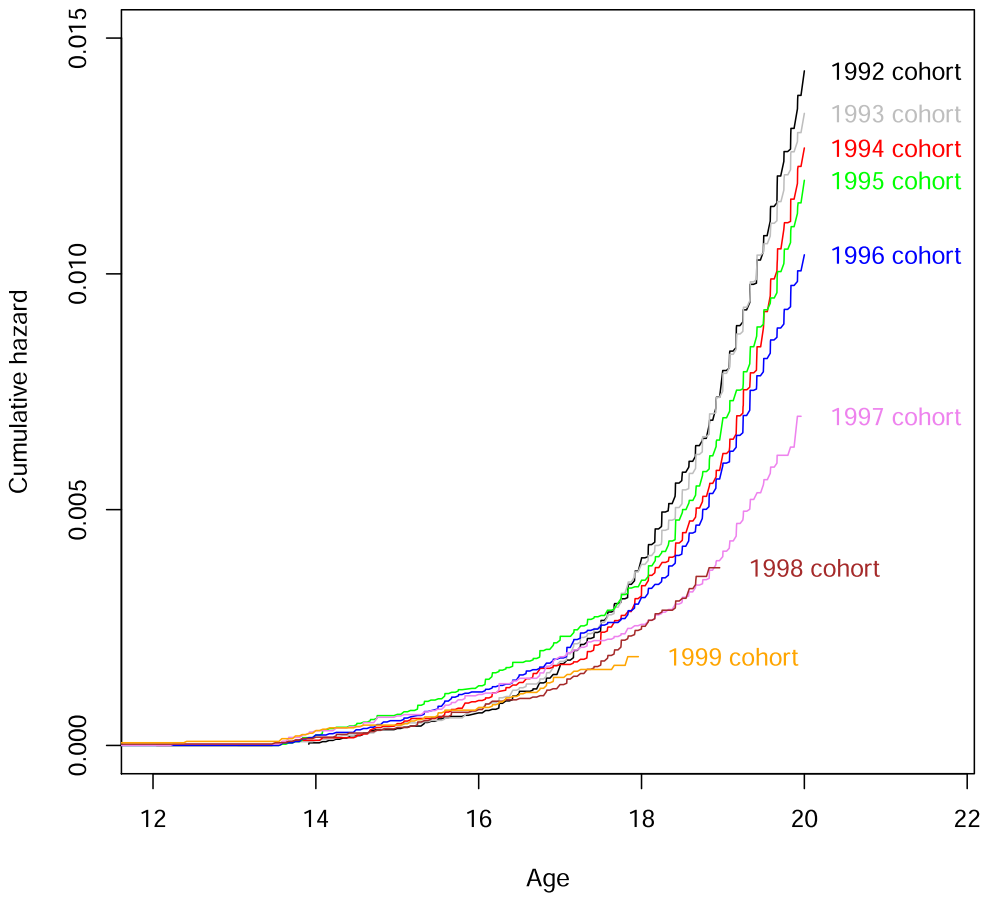

Fig. 4. Cumulative hazard for AGW among unvaccinated males born 1992–1999. Importantly, the female 1997 cohort was the first cohort included in the routine childhood HPV vaccination program.

6. Disclaimer/Acknowledgement

Data from the Norwegian Patient Registry, Norwegian Prescription Database, and Norwegian Immunization Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the aforementioned registries is intended nor should be inferred.

Declaration of Competing Interest

SN's, MO's, MN's, BTH's affiliated institute has received research grants from MSD Norway/Merck.

Data availability

The data that has been used is confidential.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2023.07.031.

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