Resilience of HPV Vaccine Uptake in Denmark: Decline and Recovery

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Abstract

Background. Immunization programs' resilience to shocks is central their success, but little empirical evidence documents resilience in action. We sought to characterize the decline of HPV vaccination in Denmark after negative media coverage and recovery during a national information campaign.

Methods. We conducted a population-based retrospective cohort study of all girls born in Denmark from 1997-2006 (*N*=328,779), aged 12-15. The outcome measure was HPV vaccine uptake (first dose), as reported to the Danish national health registry from 2009-2019, when HPV vaccine was freely available to girls in primary care clinics in Denmark. Events that created 4 natural time periods for study were HPV vaccine reaching the uptake of other vaccines in the national program (2009), some negative media coverage of HPV vaccination (2013), extensive negative media coverage (2015), and a national information campaign about the vaccine's safety and effectiveness (2017-2019).

Results. In the period with some negative media coverage, HPV vaccine uptake fell to 83.6% (95% CI:78.0%-89.7%) of baseline uptake. In the period with extensive negative media coverage, uptake fell even further to 49.6% (95% CI:44.5%-55.2%) of baseline uptake. After the information campaign, HPV vaccine uptake recovered to its baseline level (109.2%, 95% CI:90.1%-132.4%) due in part to catch-up doses. Despite the recovery, an estimated 26,000 fewer girls initiated the vaccine than if uptake had not declined.

Conclusions. The experience in Denmark offers one of the first opportunities to document how a nation grappled with negative media coverage of HPV vaccination and the steadying impact of action by national authorities.

Key words. HPV vaccination, resilience, vaccine hesitancy, safety

Introduction

Vaccination is one of the most important public health achievements of the Twentieth Century [1], preventing millions of deaths annually. HPV vaccination can prevent six cancers, including an estimated 90% of cervical cancer [2]. National recommendations call for routine delivery of vaccination at age 11 or 12 because HPV infections are increasingly prevalent starting at age 13 [3], and HPV vaccine generates a stronger immune response at younger ages [4]. Central to realizing the full impact of HPV vaccine and other vaccines is achieving high uptake that is timely and stable [5] in order to ensure herd immunity [6].

Unsubstantiated safety scares that spread through social and traditional media can sometimes lead to sharp and lasting declines in vaccine uptake if not met with immediate and concerted efforts [7]. Despite clear evidence of HPV vaccine's safety and efficacy in independent reviews [8,9], safety scares have been associated with large declines in HPV vaccine uptake in several countries, including Japan, Columbia, and Ireland [10–12]. In Denmark, most girls received the first dose of HPV vaccine in the first calendar year of eligibility, but this number declined substantially during an unfounded safety scare [13,14]. While 75% of cohorts 1999 and 2000 began HPV initiation in the year they turned age 12, the corresponding figure for cohort 2004 was just 25%.

Few documented examples exist of vaccination programs recovering from a safety scare, [15] and as a result we have little understanding of resiliency in vaccination programs. Denmark's troubles with HPV vaccine offer an important opportunity to understand a vaccine program's resilience in action. Some have speculated that negative media coverage in Denmark led to the decline in uptake. Our study had two aims. First, we sought to confirm the role of two major negative media events. Second, we attempted to establish whether a national information campaign about HPV vaccine safety and effectiveness was associated with recovery in uptake.

Methods

Setting and population

HPV vaccine became part of the Danish national childhood vaccine program starting on January 1, 2009, delivered for free by family physicians to adolescent girls aged 12-15 and born 1996 or later [16]. The program first provided quadrivalent HPV vaccine (late 2008-January 2016), then bivalent HPV vaccine (February 2016 to October 2017), and then nonavalent HPV vaccine (November 2017-current). Initially, HPV vaccine had a three-dose schedule, which dropped to a two-dose schedule for girls who initiated HPV vaccination before age 15 [17]. In Denmark, parental consent is required for vaccination before age 15 [18]. Our study population was all girls residing in Denmark who were born from 1997 to 2006 (*N*=328,779).

Procedures

Our retrospective cohort study examined four key time periods in the Danish media and HPV vaccination landscape between 2009 and 2019. The first time period is *baseline*, from January 2009 to January 2013 (T_1). This period is when HPV vaccine uptake was similar to uptake for other vaccines in the Danish childhood vaccination program and before the negative media coverage began.

The second time period is *some negative media*, from February 2013 to February 2015 (T_2). The period starts when the first stories critical of HPV vaccine appeared in mainstream media [19]. Several newspaper articles suggested that HPV vaccine had serious side effects or suggested conflicts of interests of physicians who had advocated for HPV vaccination and its adoption into the Danish vaccine program [14,19].

The third time period is *extensive negative media*, from March 2015 to April 2017 (T_3). On March 26, 2015, TV2 Denmark aired a sensationalized documentary in Danish entitled: “De Vaccinerede Piger – Syge og Svigtede” (“The Vaccinated Girls – Sick and Abandoned”) [20]. The documentary presented personal stories of young women who believed they had illnesses caused by HPV vaccination, and the

documentary suggested that Danish health authorities had not been forthcoming about serious adverse events from the vaccine. Prior to the documentary airing, promotions for it appeared on TV2 Denmark along with trailers and related stories, and extensive media coverage followed on the possible association between HPV vaccine and severe adverse events [13,14]. By the end of April 2015, Danish media outlets had referenced the TV documentary 170 times [14]. The rise in negative news articles after the documentary (1329 negative articles in 2015, compared to 140 in 2014 [14]) supports a distinction between T_2 and T_3. A synopsis of the TV documentary appears in the online Appendix.

The fourth time period is *information campaign*, from May 2017 to February 2019 (T_4). Danish health authorities began a national information campaign on May 10, 2017 with the stated objective: "to prevent cases of cervical cancer in Denmark by increasing the uptake of HPV vaccination" [21]. The campaign was a collaborative effort by the Danish Health Agency, the Danish Cancer Society, and the Danish Medical Association, funded by Health and Senior Citizen's Committee of the Danish Parliament. The campaign was based on an analysis provided by an external consultancy agency. Based on a media analysis, surveys, and information obtained from focus groups. It was concluded that extraordinary efforts were needed to bring vaccine uptake back to 90%, and that digital platforms and social media, traditionally not used by Danish health authorities, had to be used. It was also concluded that it would be difficult to change the minds of people unwilling to get their children HPV vaccine (14%), while individuals hesitant about the vaccine (34%) would be the ideal target group for the campaign [22], particularly mothers of unvaccinated girls.

The campaign shared facts about HPV infections, cervical cancer, and HPV vaccination (Table 1); used social media to disseminate information, primarily by creating a website and a Facebook page, while promoting twitter hashtags, such as #stophpv; and made extensive use of personal stories from women who had suffered from cervical cancer and precancerous cervix stages. From the outset, the campaign website featured three personal stories, and the campaign shared many additional personal stories on its

Facebook page. Moreover, the campaign presented information that specifically targeted parents who had postponed HPV vaccination of their children.

Measures

Statens Serum Institute (SSI) provided data on the monthly number of first doses of HPV vaccine provided in Denmark by birth-year cohort of recipients. SSI is a research institution under the auspices of the Danish Ministry of Health that is responsible for the purchase and supply of vaccines to the Danish national vaccination program, including HPV vaccine. Vaccination data were at the aggregate level and thus were fully anonymized. Statistics Denmark provided data on birth-year cohort size, the number of girls residing in Denmark on January 1 in the calendar year in which they turned 12. We used these data sources to calculate HPV vaccine uptake, the percentage of girls who had received at least one dose of HPV vaccine in a time period or by a certain age. Danish vaccination data in the Danish vaccination register are highly accurate [23].

Data analysis

First, we characterized HPV vaccination uptake by birth year and age among all adolescent girls in Denmark born between 1997 and 2006. Next, we modeled the time variation in HPV vaccine uptake, adjusting for seasonal variation and age of unvaccinated girls.

Calculating initiation

We defined the HPV vaccine initiation rate as the total number of initiations in a month divided by the number of girls who become eligible for HPV vaccination in the same calendar year, then multiplied by twelve to annualize the rate. This approach provided an approximate snapshot of uptake that can temporarily exceed 100% if the number of initiations is sufficiently large (e.g., due to catch-up doses). The average initiation rate over a calendar year is identical to the total number of initiations in that calendar year divided by the number of girls who turned 12 in that calendar year. The advantage of the

monthly initiation rate is that we can compute similar averages over periods that are not made up of whole calendar years.

Estimating relative uptake

We modeled HPV vaccine uptake using two components: a baseline component that is common for all birth-year cohorts, and a time-specific component that captured time variation in uptake that is driven by other factors than seasonality and age. Let N_c denote the size of cohort c, and let $x_{c,i}$ be the number of HPV vaccine initiation doses of cohort $c = 1997, \ldots, 2006$ in month $i = 1, \ldots, 48$. Here $i = 1$ corresponds to January in the year in which the girls turn 12, and $i = 48$ corresponds to December in the year in which they turn 15. We took $x_{c,i}$ to be Poisson distributed, with the expected number of vaccinations given by

$$\mathbb{E}x_{c,i} = \delta_t \gamma_i N_c, \qquad 0 < \delta_t \gamma_i < 1.$$

Here γ_i is the baseline distribution of vaccinations over the 48 months we followed each of the cohorts. The variation in γ_i is tied to seasonality and age-specific uptake. The second term, δ_t, is the time-specific effect, where is calendar time and is key in our analysis. It shows how uptake varied over the sample period, and its time variation can be compared with events that may have influenced HPV vaccine uptake in Denmark. δ_t is a measure of relative uptake between time periods. We normalize $\sum_{t \in T_1} \delta_t = 1$, so that δ_t can be interpreted as uptake relative to the average uptake before February 2013 (baseline), where coverage was about 94% for Danish girls. Estimation is facilitated by a multinomial transformation that averts estimation of the time-and-month specific effects, γ_i, and computed robust standard errors [24], see the online Appendix.

We computed average HPV vaccine uptake for each of the four periods as $\bar{\delta}(k) = \frac{1}{n_k} \sum_{t \in T_k} \hat{\delta}_t$, $k = 1, 2, 3, 4$, and the average uptake in period k relative to the baseline period, by investigating the ratio

$$r_k = \frac{n_k^{-1} \sum_{t \in T_k} \hat{\delta}_t}{n_1^{-1} \sum_{t \in T_1} \hat{\delta}_t}, \qquad k = 2, 3, 4,$$

where T_k represents subperiod k. We computed confidence intervals around this ratio, see the online Appendix.

Estimating cumulative missed opportunities

In addition to relative uptake between periods, we sought to quantify the absolute change in vaccine uptake. We calculated missed opportunities for HPV vaccine initiation by comparing the actual number of vaccinated girls relative to a counterfactual number of vaccinated girls, where the latter was based on the assumptions that all birth-year cohorts had the same uptake as girls born in 1997, 1998, or 1999. The counterfactual number of vaccinated girls in cohort c in the i^{th} month of vaccination is simply

$$x^*_{c,i} = \frac{x_{1997,i} + x_{1998,i} + x_{1999,i}}{N_{1997} + N_{1998} + N_{1999}} N_c,$$

and by aggregating over cohorts for a given point in time, $X^*_t = \sum_{i:t=\tau(c,i)} x^*_{c,i}$, we arrived at the expected number of vaccinations in calendar month t, in the counterfactual scenario. We then compared this number to the actual number of vaccinations: $X_t = \sum_{i:t=\tau(c,i)} x_{c,i}$. A figure of their difference, $X_t - X^*_t$, appears in the online appendix. We then calculated the evolution of the cumulative difference

$$\sum_{s \leq t} X_s - X^*_s.$$

Finally, we plotted this cumulative number of missed opportunities to show how far the country was behind or ahead of baseline.

Results

HPV vaccine initiation

Most adolescent Danish girls who received HPV vaccine did so in the calendar year they became eligible (Table 2). The HPV vaccine initiation rate was very high during the baseline period, an average of 94.9% in 2012, the last calendar year of baseline period. During the two periods with negative media coverage, the HPV vaccine initiation rate fell to 83.3% and 50.5%. It then increased to 107.0% in the final period when the information campaign was active. This was due to an unusually large number of girls being vaccinated at age 14 and 15 who had missed initiation at an earlier age. HPV vaccine initiation was particularly low during the years 2015 and 2016 (Figure 1). HPV vaccine initiation was also subject to seasonal effects, with relatively few doses delivered during the summer vacation (July) and a peak during September.

During the baseline period, HPV vaccine uptake adjusted for seasonal and age effects fluctuated in a relatively narrow band (Figure 2). In the period with some negative media coverage, uptake decreased to 83.6% (95% CI: 78.0%, 89.7%) of baseline uptake. In the period with extensive negative media coverage, uptake fell even further, to 49.6% (95% CI: 44.5%, 55.2%) of baseline uptake. In the final period, when the information campaign was active, uptake increased again to a level statistically indistinguishable from baseline (109.2%, 95% CI: 90.1%, 132.4% of baseline).

That relative HPV vaccine uptake exceeded 100% in the last period suggests that the information campaign encouraged uptake and that a recovery is under way for the cohorts who missed initiation during the periods with negative media coverage. Despite the large number of HPV vaccine initiations in 2018, the uptake for girls who turned 12 in 2018 was just 46%. This compares favorably to 25% in 2016, but is far short of the equivalent figure for 2011 and 2012, where 75% of adolescent Danish girls began HPV initiation in the calendar year they became eligible.

Cumulative missed opportunities

Initially, cumulative missed opportunities were slightly above the average for cohorts 1997-1999 (red area in first period of Figure 3). This was due to girls born in 1997 who were vaccinated at an older age than was the case for cohorts 1998 and 1999 (see also Table 2). The cumulative number of vaccinations quickly recovered (as shown in the blue area of vaccination surplus). In the period of some negative media coverage, cumulative missed opportunities followed a slight and steady increase. In the period of extensive negative media coverage, the number of missed doses continued to swell. By the end of the third period in May 2017, over 36,000 girls had missed the opportunity to receive HPV vaccine as compared to vaccine delivery baseline. In the final period of the information campaign, the backlog of missed opportunities slowly shrank. A temporary increase in the number of missed opportunities in September/October 2017 was followed by an unusually large number of vaccinations in November 2017. Despite the recovery in vaccination provision by the end of the final time period in February 2019, the cumulative missed opportunities remained at around 26,000.

We translated these missed opportunities to additional cases of cervical cancer and deaths. Given 0.9% lifetime prevalence of cervical cancer in Danish women a quarter of whom die from the disease [25] and assuming 70% vaccine effectiveness against cervical cancer, these missed opportunities may lead to more than 180 cases of cervical cancer and more than 45 deaths that vaccination could have prevented.

4. Discussion

Our study of over 300,000 Danish adolescent girls showed clear patterns of decline and recovery in HPV vaccination uptake. Negative newspaper stories were associated with a 14% decline in HPV vaccine uptake relative to before the stories appeared, and a negative television documentary and media coverage that followed it were associated with uptake falling by half relative to baseline. The national

information campaign coincided with the recovery to pre-crisis levels of uptake. Despite this recovery, the periods with negative media coverage left over 26,000 older girls unvaccinated who would have otherwise received the vaccine. The missed doses will, over time, translate to over 180 avoidable cervical cancers and 45 deaths.

Uptake is generally high for vaccines globally, with HPV vaccination being an exception in facing substantial challenges [26]. Although declines in vaccination are uncommon, many ongoing crises are around HPV vaccination [10,12]. Denmark's large decline in HPV vaccination may be attributable to an unsubstantiated safety scare generated and amplified through traditional media channels of newspapers and television [14]. The underlying mechanisms for the decline remain unclear, but it is plausible that media reports generated concerns among the public that Danish authorities inadequately addressed. The media coverage may also have led people to attribute existing or new unexplained symptoms to vaccination [27]. Such an explanation is consistent with events in New Zealand where the volume of news articles on HPV vaccine was associated with adverse event reports [28]. Additional research is needed to understand the specific mechanisms through which unfounded safety scares undermine vaccine uptake, including the role of Denmark's decision early on to pay several people for harms they attributed to HPV vaccination [29].

Few studies have documented recovery in vaccination programs, and as a result it is poorly understood. Ireland also experienced an HPV vaccine crisis that has many similarities with the Danish crisis. Vaccine uptake fell rapidly following a TV documentary, entitled *Cervical cancer vaccine—is it safe?* which aired in December 2015, and Irish health authorities responded with a media campaign and the formation of a *HPV Vaccination Alliance* in August 2017 [11,30]. The Irish crisis has a connection to the Danish crisis because the Irish documentary used several clips from the Danish documentary. In the UK, the publication of a research article in 1998 that purportedly linked autism to MMR vaccination triggered a decline in uptake that only slowly recovered. Perhaps because of this experience, the UK was very proactive in managing public concern about the death of a young girl after HPV vaccination, through

causes unrelated to the vaccine, during the early roll-out of the vaccine in 2008. In contrast, Danish authorities were slow to respond to media stories questioning HPV vaccine safety, and early communication efforts relied on dry scientific information that was not engaging to the public. The authorities did not have a social media presence, effectively ceding that front to anti-vaccine activists. The Danish national information campaign, however, appeared to help HPV vaccination recover to pre-crisis levels. Introduction of nonavalent HPV vaccine in November 2017 may have also helped to accelerate the recovery. The sharp drop in vaccinations in October 2017 and the subsequent surge in November suggests that parents were willing to postpone vaccination, in order to allow their daughters to receive the more effective nonavalent vaccine. There may have been additional factors that contributed to the recovery that our methods cannot account for. Higher vaccination at the end of the study period may have been due to a reduction of negative media coverage or an effect specific to the 2003 and 2004 birth cohorts. The reduction in negative media coverage may also have been a product of the information campaign, which also thought to nudge media towards evidence-based communication [22].

Study strengths include use of nationally representative vaccination data for an entire country. Study limitations include the correlational nature of the study. Interrupted time series study designs allow limited causal inference due, in part, to the possibility of other unknown historical events that could correlate with the focal events. The threat of selection is, however, unlikely given the representativeness of the sample and the low rate of migration in and out of the country [31]. Our analyses were ecological in nature, meaning that inference at the level of individual patients requires some caution.

In conclusion, the Danish vaccination program has successfully weathered a serious decline in HPV vaccine uptake that was associated with negative media coverage. The national information campaign appears to have been successful, although other events may account for some of the recovery. The recovery, however, is not yet complete. Despite a large number of HPV vaccine initiations after the information campaign began, the percentage of girls who began HPV vaccination in the calendar year

they become eligible was much smaller than for earlier cohorts. To ensure resilience of vaccination programs, researchers and practitioners have suggested specific steps that countries can take [32,33]. Countries should have standing plans for addressing the inevitable safety scares that come at unpredictable times and from unpredictable sources. Tracking safety signals and public sentiment is also important to anticipating challenges to resilience. Experts suggest that countries should respond quickly and accurately to crises through a single spokesperson and use social media [33]. Healthcare providers should address questions and safety concerns proactively and receive training in how to recommend HPV vaccine to parents via presumptive announcements [34]. Finally, it is important to rely on advocacy organizations and their networks [35].

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Conflict of interests

Dr. Brewer has served as a paid advisor to and received research grants from Merck. The other authors had no conflicts to declare.

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Table 1. The Danish national information campaign on HPV vaccination

Formative work	- Media analysis. - Survey. - Focus group studies. - Interviews.
Target audience	- Primary: mothers of girls ages 10-14, with doubts about HPV vaccination. - Fathers of girls ages 10-14, with doubts about HPV vaccination. - Unvaccinated girls ages 15-18. - Girls age 12.
Channels	- Media: Provide evidence-based communication about HPV vaccination and monitoring media coverage of HPV vaccination. - Digital platform with website and Facebook page. - Townhall meetings with participation of health professionals. - Promote communication between parents: “My daughter is HPV vaccinated because…”. - Printed materials to be distributed at physicians’ offices, schools, etc., with information and links to campaign website. - Materials for health professionals.
Messages	- At least 80% of all sexually active people will be infected with HPV one or more times during their lifetime. - HPV infections are most prevalent among adolescents. About four in ten Danes under the age of 30 are infected with HPV at the moment. - Each year, approximately 6,000 Danish women undergo cone surgery to remove cervical cancer precursors. - Every year, 100 Danish women die from cervical cancer. - HPV vaccination can prevent 70% of all cases of cervical cancer.

Table 2. HPV vaccine initiation from 2009 to 2019, by birth year cohort

Birth Year Cohort	*N*	First doses of HPV vaccine in year…											Coverage
		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	
1997	33,630	60%	29%	4%	1%	-	-	-	-	-	-	-	94%
1998	32,937	-	67%	23%	3%	1%	-	-	-	-	-	-	94%
1999	33,034	-	-	75%	16%	3%	1%	-	-	-	-	-	95%
2000	33,387	-	-	-	75%	17%	2%	1%	-	-	-	-	95%
2001	32,548	-	-	-	-	68%	18%	2%	1%	-	-	-	89%
2002	31,863	-	-	-	-	-	60%	17%	3%	4%	-	-	84%
2003	32,463	-	-	-	-	-	-	30%	17%	20%	13%	-	80%
2004	32,741	-	-	-	-	-	-	-	25%	33%	19%	2%	79%
2005	32,925	-	-	-	-	-	-	-	-	37%	34%	2%	73%
2006	33,251	-	-	-	-	-	-	-	-	-	46%	9%	55%
Total first doses per year		20,014	31,788	33,861	31,669	28,793	25,908	15,915	15,044	31,000	37,124	4,499	

Note. Percentages are HPV vaccine initiation for birth year cohorts (rows). The last column shows HPV vaccine initiation uptake by the year girls in the cohort turned 16 (or as of February 2019, whichever came first). Shading denotes the year the girls in the cohort turned 12 (darkest), 13, 14, and 15 (lightest). 2019 data are for January and February.

Figure 1. HPV vaccine initiation over time for each birth year cohort.

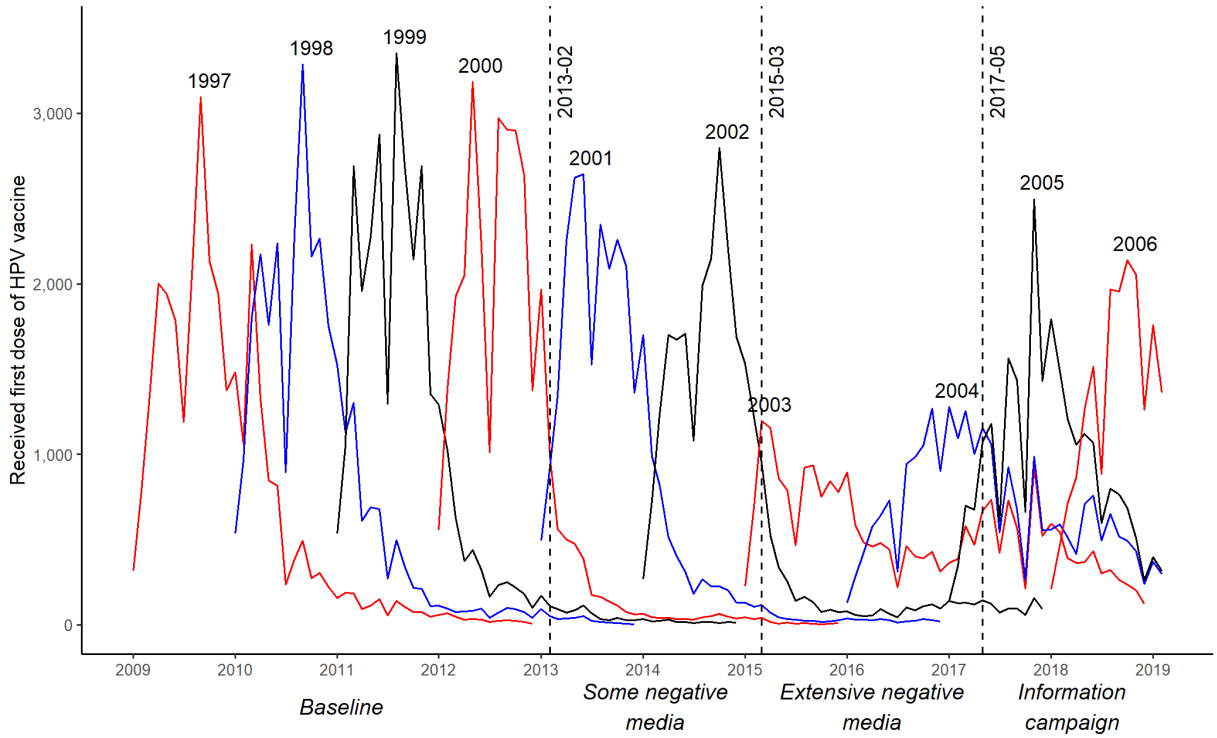
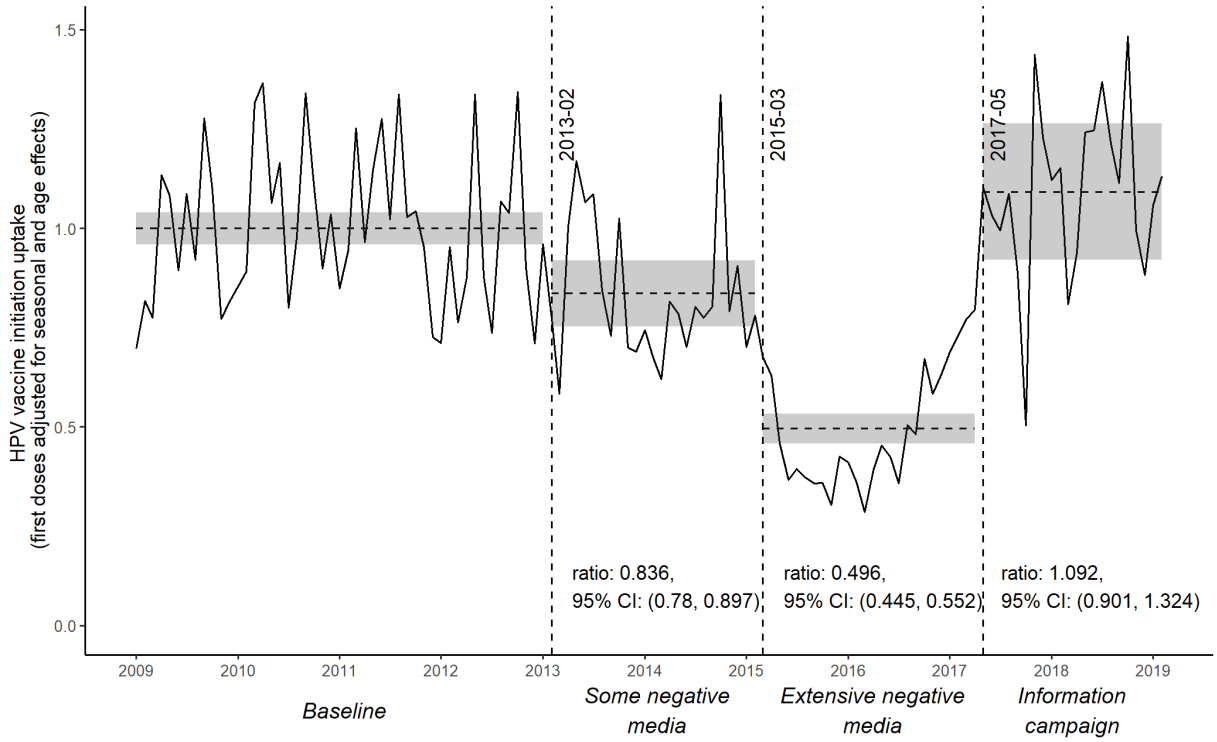
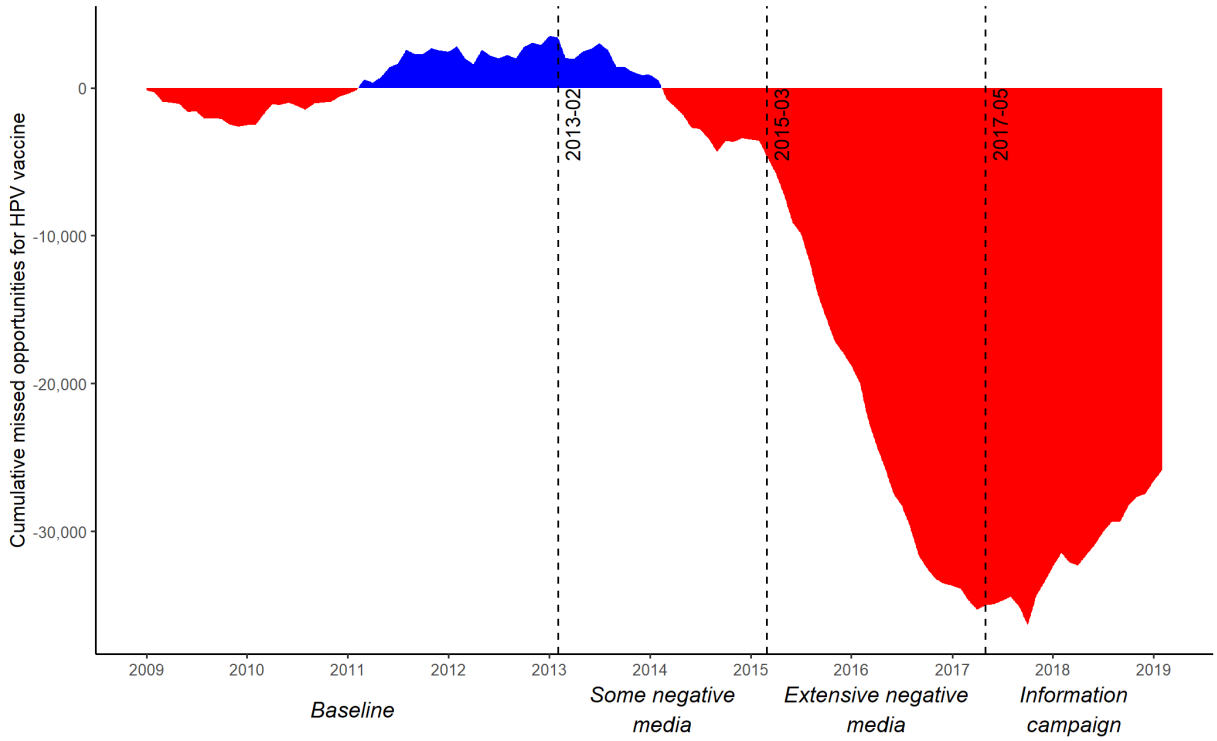


Figure 2. HPV vaccine initiation uptake in time periods defined by negative media coverage and national information campaign.



Outcome was first HPV vaccine dose by the calendar year the girl turned 16, adjusted for seasonality and age effects. Solid lines show HPV vaccine initiation uptake, scaled to the baseline period's average. Dotted horizontal lines show average HPV vaccine initiation uptake for the time period, and shaded areas show 95% confidence intervals.

Figure 3. Cumulative missed opportunities for HPV vaccine initiation in time periods defined by negative media coverage and national information campaign.



Missed opportunities are relative to the average HPV vaccine initiation for birth year cohorts 1997-1999.