The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study

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Summary

Background Human papillomavirus (HPV) immunisation with a bivalent vaccine (Cervarix) was introduced in England, UK, in Sept 1, 2008: routine vaccination was offered to girls aged 12–13 years with a catch-up programme for females aged 14–18 years in 2008–10. We quantified the early effect of this immunisation programme on cervical cancer and cervical carcinoma in situ, namely grade 3 cervical intraepithelial neoplasia (CIN3), registrations.

Methods In this observational study, we used an extension of the age-period-cohort Poisson model to estimate the relative risk of cervical cancer in three vaccinated cohorts compared with earlier cohorts that were not eligible for HPV vaccination. Data from a population-based cancer registry were extracted on Jan 26, 2021, and were assessed for diagnoses of cervical cancer and CIN3 from Jan 1, 2006 to June 30, 2019 in women aged 20–64 years and who were a resident in England. We used three vaccinated cohorts to account for differences in the school year in which the vaccine was offered and its national coverage. Adjustment for confounding was made using information on changes in cervical screening policy and historical events that affected cervical cancer incidence. Results were compared across models with different adjustments for confounders.

Findings We used data from a total of 13·7 million-years of follow-up of women aged 20 years to younger than 30 years. The estimated relative reduction in cervical cancer rates by age at vaccine offer were 34% (95% CI 25–41) for age 16–18 years (school year 12–13), 62% (52–71) for age 14–16 years (school year 10–11), and 87% (72–94) for age 12–13 years (school year 8), compared with the reference unvaccinated cohort. The corresponding risk reductions for CIN3 were 39% (95% CI 36–41) for those offered at age 16–18 years, 75% (72–77) for age 14–16 years, and 97% (96–98) for age 12–13 years. These results remained similar across models. We estimated that by June 30, 2019 there had been 448 (339–556) fewer than expected cervical cancers and 17 235 (15 919–18 552) fewer than expected cases of CIN3 in vaccinated cohorts in England.

Interpretation We observed a substantial reduction in cervical cancer and incidence of CIN3 in young women after the introduction of the HPV immunisation programme in England, especially in individuals who were offered the vaccine at age 12–13 years. The HPV immunisation programme has successfully almost eliminated cervical cancer in women born since Sept 1, 1995.

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Introduction

Human papillomavirus (HPV) vaccination has been introduced in over 100 countries and underlies the WHO's global strategy for the elimination of cervical cancer.[1,2] In 2019, the global market for vaccines against HPV infections reached approximately 41·4 million doses, with the bivalent one having an estimated market share, by volume, of around 23%.[3] Vaccines have been shown in randomised controlled trials to prevent type-specific HPV infections and cervical intraepithelial neoplasia (CIN) in previously HPV uninfected cohorts, but there is an absence of high-quality empirical evidence regarding their effect on cervical cancer incidence.

HPV immunisation was introduced in England, UK, in Sept 1, 2008 using the bivalent HPV vaccine (Cervarix). The goal was to reduce cervical cancer incidence by preventing persistent infections from the two most common high-risk types of HPV (16 and 18), which are responsible for approximately 80% of all cervical cancers in the UK.[4] Since the HPV vaccine is most effective when given before any exposure to HPV viruses (ie, before sexual activity starts) routine vaccination was offered to girls aged 12–13 years (school year 8). In England, students are 12 years of age at the start of year 8 (from Sept 1) and turn 13 years during the school year. A catch-up service was offered to girls aged 17–18 years (born Sept 1, 1990–Aug 31 1991) in the

Research in context

Evidence before this study

Randomised controlled trials and surveillance studies have shown the usefulness of Human Papilloma Virus (HPV) vaccination at preventing HPV infection and cervical intraepithelial neoplasia (CIN), but direct evidence of its effect on cervical cancer incidence is incomplete. Preliminary evidence that showed that vaccination protects against HPV-associated cancers was provided by a combined passive follow-up of women participating in two Finnish vaccination trials (one using the quadrivalent vaccine and the other the bivalent vaccine) compared with an unvaccinated cohort; however, the number of people with cancer was too small to estimate efficacy with precision. An analysis of cervical cancer rates in Sweden showed reduced risk of cervical cancer in individuals who received Gardasil (a quadrivalent HPV vaccine) but estimates of efficacy varied depending on the adjustments made.

Added value of this study

We observed a substantial reduction in cervical cancer and incidence of CIN3 in young women after the introduction of HPV immunisation in England, especially in individuals who were offered the vaccine at age 12–13 years. Our study provides the first direct evidence of the prevention of cervical cancer using Cervarix (a bivalent HPV vaccine). We defined our cohorts to account for the age at which women were offered HPV immunisation and the differences in national vaccination coverage. This definition allowed us to estimate the effect of the routine vaccination programme carried out in girls aged 12–13 years (school year 8) separately from the additional catch-up campaigns that targeted girls aged 14–16 years (school years 10–11) and 16–18 years (school years 12–13), who might have already been exposed to HPV before vaccination and among whom coverage was lower.

Implications of all the available evidence

Our findings add evidence to the very limited literature showing that national HPV immunisation programmes can lead to a substantial reduction in cervical cancer incidence, especially if vaccination coverage is high and women are offered the vaccine at a younger age. Although it is still too early to assess the full effect of the English HPV vaccination programme, our results contribute towards a better understanding and recognition of the benefits of HPV immunisation.

academic year 2008–09 and those aged 14–18 years (born Sept 1, 1991–Aug 31, 1995) in the academic year 2009–10. Annual three-dose HPV immunisation coverage between the academic years of 2008–09 and 2011–12 was very high for those in school year 8 (range 80·9–88·0%) but lower for the catch-up cohorts (70·8–75·7% for school years 10–11 and 38·9–48·1% for school years 12–13).[5–7] The bivalent vaccine was replaced by the quadrivalent vaccine, Gardasil, in Sept 1, 2012 and is not evaluated in this paper.

By 10 years after the introduction of the HPV vaccination in England, there had been substantial reductions in HPV 16/18 and HPV 31/33/45 infections among women aged 16–24 years undergoing chlamydia screening.[8] In Scotland, a pronounced reduction in preinvasive cervical disease has been reported in women aged 20 years.[9] Early modelling suggested that HPV vaccination would have no discernible effect on cervical cancer rates for at least 8 years after vaccination but that there would be substantial reduction in incidence in women aged 20–29 years in the UK by the end of 2019.[10] In 2020, analysis of cervical cancer rates in Swedish women who did and did not receive the quadrivalent vaccine (Gardasil) showed reduced risk of cervical cancer but the magnitude of the effect was dependent on adjustments made for confounders.[11]

It has now been over 10 years since England introduced HPV immunisation. Although it is still premature to assess the full impact of the programme, we can now investigate its early effects on the incidence of cervical cancer. Others have shown the impact of HPV vaccination on HPV infection and CIN rates, [8,12] but the only direct evidence of its effect on cervical cancer relates to the quadrivalent vaccine.[11] We used population-based cancer registry data to estimate the early impact of the bivalent HPV immunisation programme (using Cervarix) on cervical cancer and, separately, cervical carcinoma in situ (CIN3) incidence in England.

Methods

Study design

We sought to estimate the effect of HPV vaccination on cervical cancer incidence from observed data. The individual-level relationship between being vaccinated and cervical cancer incidence is likely to be confounded by largely unmeasurable variables related to beliefs, behaviours, and lifestyle. By contrast, the relation between the offer of vaccination and cervical cancer diagnosis is confounded by recorded factors such as age, calendar time, and birth cohort (which determines whether or not women would have been offered HPV vaccination and also when they are first invited for cervical screening), but is independent of unobservable factors such as beliefs and lifestyle. We defined three vaccinated cohorts to account for the school year in which the vaccine was offered (at ages 12–13, 14–16, or 16–18 years) and differences in the vaccination coverage. We also included four unvaccinated cohorts based on date of birth and divided these so as to distinguish between groups of women who would have been offered cervical screening from different ages. The most recent unvaccinated cohort (born between May 1, 1989 and Aug 31, 1990) served as the comparator for the other cohorts.

In the absence of herd immunity and cross-protection against HPV types other than 16 and 18, the HPV

vaccination programme would be expected to reduce cervical cancer rates by an amount roughly equal to the product between 80% (ie, the approximate percentage of cervical cancers caused in England by HPV 16/18)[4] and the vaccine coverage. Using this approximation, we obtained a lower limit of expected effectiveness by assuming that any fewer than three doses provides no protection and an upper limit by assuming 100% efficacy (against disease caused by HPV 16/18) from a single dose. The expected reduction in cervical cancer incidence would then be around 36–48%, 59–64%, and 68–71% in the cohorts offered vaccination aged 16–18, 14–16, and 12–13 years, respectively.

The risk reduction in these last two groups might be larger than estimated based on screening coverage alone due to: herd immunity, partial cross-protection, or a higher prevalence of HPV 16/18 among those diagnosed at a younger age. By contrast, early vaccine effectiveness in women vaccinated at later ages will be lower than estimated previously because many of those who would develop cervical cancer in their 20s would have been infected before vaccination.

Data

Data for cervical cancer (International Classification of Diseases-10 C53) and CIN3 (International Classification of Diseases-10 D06) diagnosed between Jan 1, 2006 and June 30, 2019 in women aged 20–64 years and resident in England were extracted on Jan 26, 2021 from the dataset produced by the National Cancer Registration and Analysis Service,[13] Public Health England (PHE). Midyear population estimates were obtained from the Office for National Statistics.[14]

We used an extension of the age-period-cohort Poisson model[15,16] to estimate the effect of HPV vaccination on incidence rates of cervical cancer and, separately, CIN3. In addition to the usual functions of age, period, and cohort, we included age-by-cohort and age-by-period interactions to handle historical events (discussed below) known to have an effect on cervical cancer incidence. Cancer cases were aggregated by months of age, period, and cohort and the corresponding population estimates (person-time) were included after a logarithmic transformation as an offset; 95% CIs used robust standard errors.[17,18] Models included a combination of the following covariates. We considered seven age groups: 20·0 years to younger than 24·5 years, 24·5 years to younger than 26·0 years, 26·0 years to younger than 30·0 years, 30·0 years to younger than 35·0 years, 35·0 years to younger than 45·0 years, 45·0 years to younger than 55·0 years, and 55·0 years to younger than 65·0 years. In particular, the cutoff point of 24·5 years was included to account for the pronounced increase in cancer diagnosis in the months following the first invitation to screening[19] and the fact that, since 2012, women have received their first invitation at age 24·5 years. Older age groups were retained in the analysis so that we could capture trends in CIN3 and cervical cancer diagnosis and registration over time. This information was useful for estimation of historical events, seasonal variation in registrations, and any under-registration due to inclusion of more recent data. Sensitivity analyses were done using restricted cubic splines.[20,21]

The three main period effects were: (1) linear trend in time (drift), centred on Jan 1–31 2016. (2) Four dummy variables to capture seasonal variations in diagnoses (all ranges include the full month): January–March, April–June, July–September, and October–December. (3) Four dummy variables to adjust for possible under-registration of recent cancer diagnoses (all ranges include the full month): January 2006–December 2017 (complete registration), January 2018–September 2018, October 2018–March 2019, April 2019–June 2019 (least complete registration).

We defined seven birth cohorts corresponding to differences in the age at first invitation to screening and the school years in which HPV vaccination was offered. Changes in age at first screening invitation greatly affect age-specific cancer rates.[19] In England, the national cervical cancer screening programme was introduced in 1988 for women aged 20–64 years. In 2004, the age of first invitation to screening was increased to 25·0 years. Since the new policy was implemented over a 15-month period commencing in August 2004, women born between September, 1984, and October, 1985, were first invited for screening either from their 20th birthday or on their 25th birthday. In 2012, the age at first screening invitation changed once more, this time to 24·5 years. Therefore, we defined seven birth cohorts depending on whether or not vaccination was offered, the age at first screening invitation, and age at HPV vaccination offer (figure 1).

Two age-by-period interactions were made. First, a dummy variable for women aged 20 years to younger than 50 years between Jan 1 and June 30, 2009 to account for the increase in cervical screening from the so-called Jade Goody effect (publicity surrounding the last months and death of the celebrity Jade Goody from cervical cancer).[22] Second, a dummy variable for women aged 24·5 years and older between March 1 and June 30, 2019 to account for the expected increase in incidence due to the cervical screening awareness campaign launched on March 5, 2019 by PHE.[23]

For age-by-cohort interactions, we included a set of dummy variables to account for increased diagnosis of prevalent cancer cases arising from policy changes in the age of first invitation to screening.[19] We assumed that an invitation for first screening increases cancer detection substantially for 6 months and to a lesser extent for a further 6 months. Specifically, we considered dummy variables for the following cohort-related and age-related groups: (1) women in cohort 2 aged 25·0 years to younger than 25·5 years; (2) women in cohort 2 aged 25·5 years

to younger than 26·0 years; (3) women in cohort 3 aged 25·0 years to younger than 25·5 years; (4) women in cohort 3 aged 25·5 years to younger than 26·0 years; (5) women in cohorts 4–7 aged 24·5 years to younger than 25·0 years; (6) women in cohorts 4–7 aged 25·0 years to younger than 25·5 years. The purpose of these six dummy variables was to capture the increase in diagnoses made within 6 months and 6–12 months of a first invitation to cervical screening.

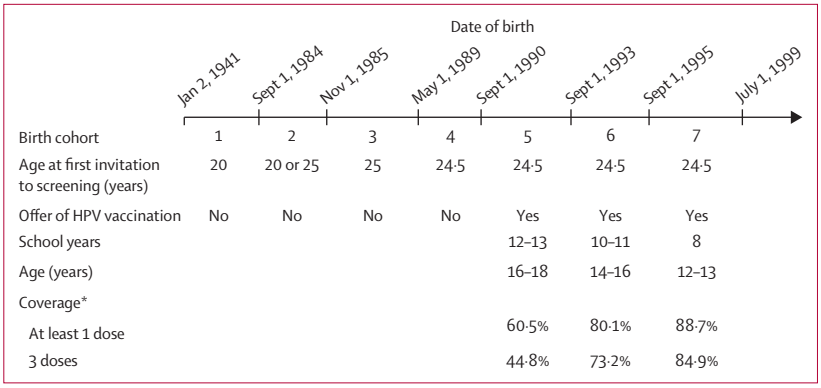
Modelling strategy

Working from a statistical analysis plan, analysis code was written before the authors had access to the data. After testing on simulated data consisting of artificial cancer records, the code was sent to PHE for running on the real data and the results were shared. Analysis code was subsequently revised and run on a later data extract. We present both the findings of the original (blinded) model and those of the subsequent models (revised after seeing the results of modelling on a preliminary data extract) in this Article.

The main analysis considered three models that differ only in terms of adjustments made for under-registration (we were concerned that cancers diagnosed in late 2018 and the first 6 months of 2019 might not have been registered by the date of data extraction, but felt that any such under-registration should affect all ages equally) and the PHE awareness campaign. Model 1 includes all main effects for age and cohort, age-by-cohort interactions, linear trend (drift), dummy variables for the Jade Goody effect, and seasonal effects. Model 2 (adjustment for under-registration) is model 1 but with additional dummy variables for possible under-registration. We planned to use this model before we saw any of the data. Model 3 (adjustment for the awareness campaign) is model 1 but with an additional age-by-period dummy variable for the PHE's awareness campaign.

Using each of these models, we estimated the number of cancers and CIN3 averted since the start of the HPV vaccination programme. This was done by comparing the expected number of events in the vaccinated cohorts (with different effects for each cohort) with the corresponding expected numbers when the cohort effects were forced to be the same as in the last unvaccinated cohort (ie, the reference group). The point estimates and 95% confidence intervals were derived using the margins command in Stata (version 16.1).

As part of our sensitivity analysis, for CIN3, we fitted models to the subsample of women aged 24·5 years and over as CIN3 is diagnosed almost exclusively through screening and rates of CIN3 in women aged 20·0–24·5 years decreased substantially as screening in this age group was phased out. Additional sensitivity analyses evaluated the robustness of our models (eg, by changing the number and location of the cubic spline knots). The National Cancer Registration and Analysis Service (NCRAS) has legal permission from the Secretary of State for Health and Social Care to collect and use personally identifiable information about patients and their cancer without asking for direct consent. This permission is because it is in the



Birth cohort	1	2	3	4	5	6	7
Age at first invitation to screening (years)	20	20 or 25	25	24·5	24·5	24·5	24·5
Offer of HPV vaccination	No	No	No	No	Yes	Yes	Yes
School years					12–13	10–11	8
Age (years)					16–18	14–16	12–13
Coverage*							
At least 1 dose					60·5%	80·1%	88·7%
3 doses					44·8%	73·2%	84·9%

Figure 1: **Schematic representation of the birth cohorts**
*Vaccine coverages include (when data are available) mop-up vaccinations (ie, when females are vaccinated in a later year than the one in which they were first offered vaccination).

	Cervical cancer	CIN3	Women-years in population (millions)
Total			
Diagnoses	27 946	318 058	214·8
Birth cohort			
Cohort 1: invited from age 20·0 years and unvaccinated	23 665	205 291	175·5
Cohort 2: invited from age 20·0 years or 25·0 years and unvaccinated	930	20 723	5·7
Cohort 3: invited from age 25·0 years and unvaccinated	2150	56 103	15·2
Cohort 4: invited from age 24·5 years and unvaccinated	563	17 279	4·6
Cohort 5: invited from age 24·5 years and offered vaccine in school years 12–13	561	16 959	8·0
Cohort 6: invited from age 24·5 years and offered vaccine in school years 10–11	70	1654	3·3
Cohort 7: not invited before age 24·5 years and offered vaccine in school year 8	7	49	2·5
Age at diagnosis, years			
20·0 to <24·5	329	9886	20·9
24·5 to <26·0	1579	57 938	7·5
26·0 to <30·0	3360	88 606	19·7
30·0 to <65·0	22 678	161 628	166·7
Year of diagnosis*			
2006–2010	9893	118 851	77·9
2011–2015	10 433	125 168	79·9
2016	2124	21 979	16·2
2017	2124	20 917	16·3
2018	2185	20 245	16·3
January–June, 2019	1187	10 898	8·2

CIN=cervical intraepithelial neoplasia. *Years denote the range from Jan 1 to Dec 31, except for 2019, which is Jan 1 to June 30.

Table 1: **Characteristics of the cervical cancer and CIN3 cases included in our study**

	Cervical cancer			CIN3		
	20·0 to <24·5 years	24·5 to <26·0 years	26·0 to <30·0 years	20·0 to <24·5 years	24·5 to <26·0 years	26·0 to <30·0 years
Unvaccinated cohorts						
Cohort 1: invited from age 20·0 years and no vaccine	4·2 (70)	11·7 (246)	16·1 (1532)	233·8 (3893)	498·3 (10 522)	446·9 (42 443)
Cohort 2: invited from age 20·0 years or 25·0 years and no vaccine	2·5 (38)	27·0 (176)	20·4 (352)	100·6 (1504)	847·3 (5520)	489·0 (8443)
Cohort 3: invited from age 25·0 years and no vaccine	2·0 (109)	28·2 (557)	18·8 (987)	52·9 (2868)	1027·6 (20 298)	476·4 (25 020)
Cohort 4: invited from age 24·5 years and no vaccine	1·8 (37)	27·8 (211)	18·0 (315)	29·9 (629)	1141·7 (8680)	452·9 (7948)
Vaccinated cohorts						
Cohort 5: invited from age 24·5 years and offered vaccine in school years 12–13	1·0 (47)	20·0 (340)	11·5 (174)	15·9 (755)	673·2 (11 452)	312·8 (4752)
Cohort 6: invited from age 24·5 years and offered vaccine in school years 10–11	0·7 (21)	14·5 (49)	..	6·3 (188)	434·9 (1466)	..
Cohort 7: not invited before age 24·5 years and offered vaccine in school year 8	0·3 (7)	..	..	2·0 (49)	..	..

Data are incidence (number of cases). CIN=cervical intraepithelial neoplasia.

Table 2: **Crude incidence rates per 100 000 women-years by cohort and age group (for simplicity, restricted to age <30·0 years) for cervical cancer and CIN3**

public interest to use this information to improve the way cancer is diagnosed and treated. The proposal for this project was formally reviewed by the NCRAS Senior Leadership Team and deemed appropriate use of NCRAS data within the legal framework.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

During the study period there were 27 946 diagnoses of cervical cancer and 318 058 of CIN3 (table 1). The study included a total of 13·7 million-years of follow-up of women aged 20 years to younger than 30 years in the three vaccinated cohorts.

The crude incidence rates per 100 000 women-years (table 2) were particularly low for women offered the vaccine at age 12–13 years in cohort 7 (0·3 for cervical cancer and 2·0 for CIN3). We also noticed that crude incidence rates for both cervical cancer and CIN3 for women aged 24·5 years to younger than 26·0 years in cohorts 2 to 4 were much higher than in cohort 1, reflecting changes in age at first screening invitation. This finding is also shown in the significant age-by-cohort interaction results (appendix pp 2–5).

See Online for appendix

The estimated cohort-specific incidence rate ratios (IRRs) changed very little across the three models (table 3), all of which adjusted for confounding by age and period but differed in whether they explicitly allowed for under-registration or the effect of a campaign to increase screening participation. For simplicity of presentation, we report results from model 3 here. Incidence rates of cervical cancer were estimated to be 34% (95% CI 25–41) lower in cohort 5 (vaccine offered in school years 12–13), 62% (52–71) lower in cohort 6 (vaccine offered in school years 10–11), and 87% (72–94) lower in cohort 7 (vaccine offered in school year 8), compared with the unvaccinated cohort 4. The corresponding effectiveness of the vaccination programme in preventing CIN3 was reduced by 39% (95% CI 36–41) in cohort 5, 75% (72–77) in cohort 6, and 97% (96–98) in cohort 7.

When for CIN3, as part of our sensitivity analysis, we excluded women aged 20·0–24·5 years (it is no longer possible to estimate effects for cohort 7), the estimated incidence rate in model 3 for cohort 5 was 35% lower (down from 39%) and for cohort 6 was 66% lower (down from 75%) than that for cohort 4 (appendix p 5). The overall difference between the vaccinated cohorts 5 to 7 and the unvaccinated cohort 4 was significant ($p<0·0001$) in all models for cervical cancer and CIN3. This effect was also shown when we tested the joint effect of cohorts 5 and 6 versus cohort 4 in women with CIN3 aged 24·5 years and older ($p<0·0001$).

In our sensitivity analyses, the ranges of the estimated IRRs for cohort 5 were 0·66–0·69 for cervical cancer and 0·60–0·61 for CIN3, for cohort 6 were 0·32–0·40 and 0·21–0·27, and cohort 7 were 0·12–0·30 and 0·03–0·07 for CIN3 (appendix p 6). The greater variability observed in the results for cohort 7 is expected since women in that cohort were at most aged 24·5 years on March 31, 2019 and diagnosis of cervical cancer is rare in such young women.

	Cervical cancer			CIN3		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Unvaccinated cohorts						
Cohort 1: invited from age 20·0 years and no vaccine	0·99 (0·89–1·10)	1·00 (0·90–1·11)	0·99 (0·89–1·10)	0·97 (0·93–1·00)	0·98 (0·94–1·01)	0·97 (0·94–1·01)
Cohort 2: invited from age 20·0 years or 25 years and no vaccine	1·08 (0·95–1·22)	1·09 (0·97–1·23)	1·08 (0·96–1·22)	1·02 (0·98–1·06)	1·03 (0·99–1·07)	1·03 (0·99–1·06)
Cohort 3: invited from age 25·0 years and no vaccine	1·03 (0·93–1·15)	1·04 (0·94–1·16)	1·04 (0·93–1·15)	1·01 (0·97–1·04)	1·02 (0·98–1·05)	1·01 (0·98–1·05)
Cohort 4: invited from age 24·5 years and no vaccine (reference category)	1·00	1·00	1·00	1·00	1·00	1·00
Vaccinated cohorts						
Cohort 5: invited from age 24·5 years and offered vaccine in school years 12–13	0·67 (0·59–0·75)	0·66 (0·58–0·74)	0·66 (0·59–0·75)	0·61 (0·59–0·64)	0·61 (0·58–0·64)	0·61 (0·59–0·64)
Cohort 6: invited from age 24·5 years and offered vaccine in school years 10–11	0·39 (0·31–0·50)	0·37 (0·29–0·47)	0·38 (0·29–0·48)	0·26 (0·24–0·29)	0·24 (0·22–0·27)	0·25 (0·23–0·28)
Cohort 7: not invited before age 24·5 years and offered vaccine in school year 8	0·13 (0·06–0·27)	0·12 (0·06–0·26)	0·13 (0·06–0·28)	0·03 (0·02–0·04)	0·03 (0·02–0·04)	0·03 (0·02–0·04)

Data are IRR (95% CI). Model 1 adjusts for all main effects for age and cohort, age-by-cohort interactions, linear trend (drift), and dummy variables for the Jade Goody and seasonal effects. Model 2 contains all effects in model 1 plus adjustment for under-registration. Model 3 includes all effects in model 1 plus adjustment for the screening awareness campaign. The estimates are adjusted for the covariates included in the models, details in the methods. IRRs=incidence rate ratios. CIN=cervical intraepithelial neoplasia.

Table 3: **Estimated IRRs and 95% CIs of either cervical cancer or CIN3 among the vaccinated and unvaccinated birth cohorts.**

Model 2 (appendix pp 3, 4) showed no evidence of under-registration. The estimated IRRs for the two most recent period intervals (Oct 1, 2018–March 31, 2019 and April 1, 2019–June 30, 2019) compared with Jan 1, 2006–Dec 31, 2017 were significantly above 1 for both cervical cancer (IRR 1·13 [95% CI 1·06–1·21] and 1·20 [1·09–1·31], respectively) and CIN3 (1·14 [1·10–1·17] and 1·24 [1·20–1·29], respectively). The increased number of diagnoses registered in those two period intervals are most likely due to the significant rise in screening uptake following the PHE's awareness campaign launched on March 5, 2019 (see model 3 in appendix pp 3, 4).

Figure 2 shows the model 3 estimates of cumulative incidence for age 20 years to younger than 30 years for cohorts 4 to 7. Models 1 and 2 gave similar estimates (appendix p 7). From Model 3, we estimated that by June 30, 2019 there had been 448 (95% CI 339–556) fewer cervical cancers and 17 235 (15 919–18 552) fewer cases of CIN3 in vaccinated cohorts in England than would have been expected had the cohort effects been the same as in the most recent unvaccinated cohort (models 1 and 2 are presented in appendix p 8).

Discussion

The introduction of national HPV immunisation programmes represents an important step forward in cervical cancer prevention. To the best of our knowledge, our study provides the first direct evidence of the effect of HPV vaccination using the bivalent Cervarix vaccine on cervical cancer incidence. We found a large reduction in cervical cancer rates in all three vaccinated cohorts and especially in those who were offered the vaccine in school year 8 (aged 12–13 years). The success of vaccination programmes relies not only on the efficacy of the vaccine but also on the proportion of the population vaccinated. There is growing evidence[24–27] that a single dose of HPV vaccine provides good protection against persistent infection with efficacy similar to that of three doses. Sankaranarayanan and colleagues[28] showed that the short-term protection from one dose of the quadrivalent HPV vaccine is similar to that from two or three doses, stressing that this dosing schedule merits further investigation.[29] Analogous findings have been reported for the bivalent vaccine.[30]

HPV one-dose annual coverage in England between 2008–09 and 2011–12 ranged between 85·9% and 90·6% in the routine cohorts (cohort 7) and between 55·6% and 81·9% in the catch-up cohorts.[6,7] It has remained high afterwards until the COVID-19 pandemic affected uptake in the 2019–20 academic year.[31] Additionally, unvaccinated women in the vaccine-eligible cohorts are likely to benefit from the indirect protection (herd immunity) of the vaccination programme. Empirical evidence suggesting herd immunity for HPV 16 and 18 and cross-protection against HPV 31, 33, and 45 has been reported in Scotland after the introduction of their HPV immunisation programme.[9]

In our study, whether or not women would have been offered HPV vaccination depends only on their birth cohort and this factor is unrelated to unobserved factors such as lifestyle and behaviour. There was still

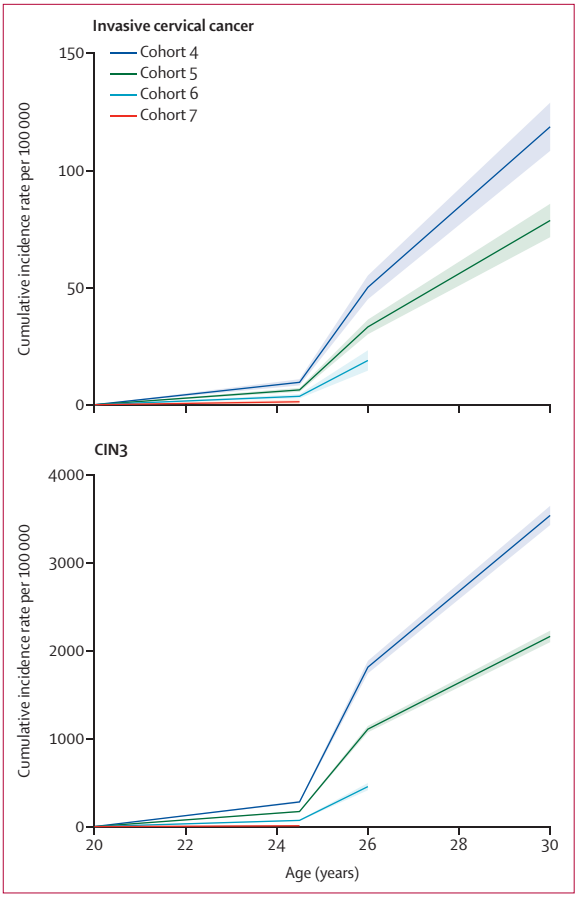


Figure 2: **Cumulative incidence rates of cervical cancer and CIN3 by birth cohort**

The shaded area indicates 95% CI. CIN=cervical intraepithelial neoplasia. Estimates from Model 3 with all other covariates fixed at their reference values.

confounding by age and period (and interactions of them) but, since they were observed, they could be handled by careful modelling. The incidence of cervical cancer varies rapidly with age and is affected by screen-detected cancers, particularly on first screen. The precise age of first screen and screening uptake changes over time. Even small alterations to cervical screening (or the reporting of cervical histology) or cancer registration could have substantial effect on trends in registered CIN3 in women in their 20s. Analysing published data based on incidence in 5-year age groups and calendar year of diagnosis would lead to a mix of vaccinated and unvaccinated cohorts in any one age group and this mixing would mask any effect of vaccination. Changes in vaccine uptake by age and the higher likelihood of pre-existing infection at the time of vaccination in women who go on to develop cervical cancers at relatively young ages are likely to modify the expected impact of vaccination, particularly in the catch-up cohorts. Therefore, we defined our cohorts to account for both the age at which women were offered HPV immunisation and the differences in achieved vaccination coverage. This definition allowed us to estimate the effect of the routine vaccination programme offered to girls aged 12–13 years (school year 8) separately from the catch-up campaigns that targeted girls aged 14–16 years and 16–18 years who might have already been exposed to HPV before vaccination. Careful modelling was required to accurately define the different birth cohorts and to adjust for changes to cervical screening and possible secular trends in cervical cancer at all ages before assessing the impact of vaccination.

From previous research,[19,22] we have detailed information on the effect that policy changes of age at first screening and particular events (eg, the death of Jade Goody) had on cervical cancer incidence, so in our regression models we made careful adjustment for this confounding. The cohort effect that we attribute to the offer and uptake of HPV vaccination could mirror changes in the underlying incidence of sexually transmitted infections, but national data on chlamydia, gonorrhoea, and genital herpes in young women between 2010 and 2019 did not show any strong decreasing trends.[32] Thus, we argue that our findings provide an unbiased estimate of the population-level effect of bivalent HPV vaccination (at different ages and with different levels of coverage) on subsequent cervical cancer rates.

Preliminary evidence that HPV vaccination protects against HPV-associated cancer was provided by a Finnish study that analysed data from passive follow-up of two randomised control trials of vaccine efficacy with a comparison cohort of unvaccinated women.[33] However, the women did not all receive the same vaccine (some were vaccinated with Cervarix and others with Gardasil) and the number of cases of cancer was too small to estimate efficacy with precision.

Our study has some limitations, the key one being that individual-level data for vaccination status were not available so we could not estimate individual-level efficacy. Additionally, we have no information on the HPV type in each of the cancers. As an observational study of routinely collected cancer registry records, there is a risk that the relationship between the offer of the HPV vaccine and subsequent diagnosis of cervical cancer is confounded by factors not accounted for in the analysis. However, as mentioned earlier, detailed information on changes in cervical screening policy and historical events that had an effect on cervical cancer incidence were available and allowed us to make careful adjustment for these known confounding factors.

The other main limitation is the relatively small numbers of individuals with cancers expected (in the absence of vaccination) in the vaccinated cohorts. This issue is most extreme for the group vaccinated aged 12–13 years for whom the expected number of cancers was under 60. Furthermore, since most of the follow-up for cohort 6 is while they are younger than age 25·0 years,

most of their cancers (and virtually all the CIN3) will have been screen-detected and so small differences in the exact age of first screening can have a big effect on the numbers of registered cases aged younger than 25·0 years. The adjusted IRRs of CIN3 for cohort 6 might be artefactually low due to decreased screening for women younger than age 24·75 years (even a 3 month delay in screening could have a big effect on the results for this cohort). We also noted that the IRRs in table 3 are lower for CIN3 than they are for cervical cancer (particularly so for cohorts 6 and 7). This finding is a somewhat surprising finding as the proportion of CIN3 due to HPV16/18 is less than the proportion of cervical cancer that is due to these HPV types. It might be an artefact, but it warrants further investigation (including HPV typing of CIN3 in younger women).

In our investigation, the risk reductions of cervical cancer expected in the catch-up cohorts (cohorts 5 and 6) under a scenario requiring three doses and assuming no cross-protection and no herd immunity (ie, 36% and 59%) fall well within the 95% CIs. However, the magnitude of the reduction reported for individuals offered the vaccine in school year 8 (87% for cancer and 97% for CIN3) was much greater than would be expected (68%) under that scenario and also than would be expected assuming a single dose provides 100% protection against HPV 16 and 18 (71%). Mesher and colleagues[4] found that, in the UK, the prevalence of HPV16/18 was particularly high (92·9% [95% CI 85·6–97·0]) among women diagnosed with cervical cancer before age 30 years. This effect could at least partly explain the magnitude of the reduction among those offered the vaccine in school year 8. Nevertheless, our results (especially those for CIN3) might also be explained by herd protection in unvaccinated women within vaccinated cohorts or cross-protection against HPV infections other than 16 and 18 as shown for high-grade disease[9] and type-specific HPV infection.[12] Regardless of the explanation, our findings should greatly reassure those still hesitant about the benefits of HPV vaccination. We have shown that HPV vaccination with high coverage in 12–13 year old girls has almost eliminated cervical cancer and cervical precancer up to age 25 (the extent of the observed data). Girls and women eligible for HPV vaccination should be encouraged to receive the vaccine, at any age but ideally when first offered it, to ensure that this hugely successful vaccination programme continues to benefit younger generations.

Contributors

PS and AC conceptualised the study and prepared the original study protocol, which was subsequently reviewed by KS, MC, JL-B, and LE-B and revised by PS, AC, and MF. PS and MF developed the statistical methods. MF wrote and tested the Stata code (checked by PS) for the data analysis and drafted the manuscript. BN and LE-B verified the integrity of the cancer registry data. BN extracted the data set and ran the Stata code on it. PS, AC, and MF interpreted the results and revised the manuscript. KS, MC, JL-B, BN, and LE-B critically reviewed the manuscript. All authors approved the final submitted version.

Declaration of interests

We declare no competing interests.

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Data sharing

The cancer registry data used in this paper are held by the National Cancer Registration and Analysis Service, PHE. Access to the data can be requested under PHE's data access arrangements through the Office for Data Release. Midyear population estimates are freely downloadable from the ONS website.

For the **Office for Data Release** see https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data

For the **ONS website** see https://www.ons.gov.uk

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