Association between HPV vaccination and cervical screening policy changes and cervical cancer incidence and grade-3 cervical intraepithelial neoplasia incidence in England, 2006–2020: a population-based trends analysis

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Summary

Background Monitoring trends in diseases after the implementation of new public health interventions or policy changes is crucial for public health planning and surveillance. In this study we look at variations in rates of cervical cancer and grade-3 cervical intraepithelial neoplasia (CIN3) incidence between 2006 and 2020 in England and relate them to predictions based on the changes in HPV vaccination and cervical screening policy.

Methods Using population-based registry data, we estimated incidence rates and their 95% confidence intervals for cervical cancer and CIN3 by age group and by either year of diagnosis or 1-year birth cohort. Trends were compared over time and across birth cohorts by calculating relative changes with respect to reference time points. We also tested if trends in women offered HPV vaccination were significantly different across outcomes (cervical cancer and CIN3) and age groups. To do this, we used Poisson regression with adjustments for interval censoring, overdispersion and correlation between observations.

Findings There were 5558 cancers and 164,682 cases of CIN3 from 53.4 million women-years of observation in the age group 20–29.99 years. We found no evidence of increased cervical cancer rates over the age of 26 in cohorts not offered cervical screening until age 24.5 or 25 years. Substantial and increasing reductions in CIN3s and cervical cancers were observed in the cohorts offered HPV vaccination and were consistent with an 80% (95% CI: 72.9%–87.1%) decrease in cervical neoplasia in the routine vaccination group.

Interpretation Plots against different time scales (e.g., calendar year and date of birth) may provide important insights that could otherwise be missed. Our findings are consistent with a sustained high effectiveness of the HPV immunization programme as the catch-up vaccination cohorts age.

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Keywords: Immunization; Vaccination; Papillomaviruses; HPV; Registries; Cervical cancer; Cervical intraepithelial neoplasia; Trends; Incidence; Rates; Screening; Health policy; Data visualisation; Cohort effects

Introduction

The World Health Organization (WHO)'s global strategy towards the elimination of cervical cancer as a public health concern aims for all its member states to lower incidence of cervical cancer below 4 cases per 100,000 women per year. The strategy relies on three key areas: (1) vaccination against human papillomavirus (HPV), (2) screening and treatment of pre-cancerous lesions, and (3) treatment and palliative care.[2]

In England, the National Health Service (NHS) has recently pledged to reach this target by 2040 and is planning to do so by boosting the uptake of both HPV vaccination and cervical screening.[3] A national HPV vaccination programme has been running in England

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Research in context

Evidence before this study

We searched PubMed and Google Scholar with the key terms ("cervical cancer" OR "CIN" OR "cervical intraepithelial neoplasia") AND "incidence" AND ("policy" OR "vaccination" OR "immunization") AND "England" to identify studies with objectives similar to ours. We found good evidence of the dramatic impact that changes in screening policy had up to March 2018 on age-specific incidence of cervical cancer and CIN3 by calendar year and how they affected cervical screening rates. A large increase in diagnoses of cervical cancer was observed at age 25 years following the change in the age of first screening invitation from "within three years of the 20th birthday" to "exactly on the 25th birthday". There was also evidence of the high effectiveness of the national HPV vaccination programme by broad birth cohorts. In a study published in 2021, cervical cancer incidence was estimated to be 87% (95% confidence interval: 72%–94%) lower among women offered the HPV vaccine at a younger age (age 12–13 years) when compared with those in the reference unvaccinated cohort.[1]

Added value of this study

Here we used population-based cancer registry data up to the end of 2020 to unify the evidence related to policy changes in cervical screening and the introduction of HPV vaccination and illustrate trends by single year of birth and single calendar year. By looking at changes in incidence rates as compared to the last birth cohort not offered HPV vaccination, we showed how similar the effectiveness of the HPV immunization programme has been for both CIN3 and cervical cancer.

Implications of all the available evidence

Although changes in screening policy had substantial effects on cervical disease rates, there was little biological variation in rates prior to the introduction of HPV vaccination. Since then, the reduction in incidence has been dramatic, such that those offered vaccination at age 12–13 years have around 80% lower rates than they would have had in the absence of a national vaccination programme.

since September 2008. It started by routinely offering the bivalent Cervarix vaccine to 12–13-year-old girls, along with a catch-up campaign in 2008–2010 targeting females aged 14–18 years. Since then, the programme has gone through several major changes in terms of vaccine offered (switching to the quadrivalent Gardasil in 2012 and fully transitioning to the nine-valent Gardasil 9 in 2022), the target population (e.g., including 12–13-year-old boys too from 2019) and dosing schedule (reducing the initial full course of 3 doses to 2 in 2014 and then to 1 in 2023).[4] Recent studies[1,5] have shown that the programme has greatly reduced cervical cancer and CIN3 incidence, most notably among females who were offered the vaccine at a younger age (12–13 years). However, since the vaccine does not protect against all HPV types and it was not offered to women born before September 1990 anyway, regular screens to detect precancerous lesions are still recommended to both vaccinated and unvaccinated women.[6]

Although in England cervical screening was introduced in 1964, it was only in 1988 that it evolved into a well-organised national screening programme. This meant moving from mostly opportunistic screenings, with no quality control, to a computerised call/recall system with an agreed-upon policy inviting women aged 20–64 years at regular intervals of 3–5 years, depending on the specific local health authorities' practices.[7] In 2003 the recommended age at first invitation to screening was increased to 25 years and the intervals between routine screenings were standardised across the country: every 3 years for 25–49-years-olds and every 5 years for 50–64-years-olds. These changes were implemented from August 2004 over a 15-month period and were not retrospective in that women already screened at age 20 would be reinvited at 23.[8] In practice, prior to this change the age at first invitation was anywhere between 20.0 and 22.99, so that a woman aged 22.0 in August 2004 who had not yet been invited would, if affected by the new policy, not receive the invitation until she turned 25. Thus, the proportion of women screened for the first time before age 24.5 or between 24.5 and 26.0 changed gradually by date of birth. For those born in 1980–1981, 49% were screened by age 24.5 and a further 8% by age 26. For subsequent birth cohorts these figures were respectively 41% and 17% for 1982–1983; 18% and 38% for 1984–1985; and 6% and 52% for 1986–1987 (data extracted from Fig. 2 of Castañon et al.).[9] In December 2012 the UK National Screening Committee (UK NSC) suggested a further minor alteration to the policy by recommending the age at first screening invitation to be anticipated by 6 months, that is at age 24.5 years.[10]

Previous research found that 59% of cervical cancers in women under age 30 years were screen detected, with most (61%) being diagnosed immediately after the first screening test.[11] Changes in the age of first invitation to screening were also found to be significantly associated with a higher detection of prevalent cervical cancers.[8] The majority of the increased rates under age 30 years were however among women with stage I cancer, which was reassuring as it implied better chances for treatment and fertility preserving.[8,11] Indeed 8-year survival of young women with stage 1A cervical cancer was estimated to be over 99.5%.[12]

Especially in view of the NHS's 2040 target, it is important to monitor trends in incidence of cervical disease and to have a better understanding of the factors that may drive their changes. In this paper we used an ecological design to examine how the screening policy on age at first invitation to screening and the introduction of HPV vaccination have affected incidence rates of invasive cervical cancer and CIN3 over time and across birth cohorts. Our findings reflect changes at the population level, which include both direct and indirect effects of vaccination.

Methods

Data

Our study focused on women aged 20 to <30 years who were resident in England between 1 January 2006 and 31 December 2020. We retrieved the data from 2 sources: the National Disease Registration Service (NDRS) and the UK's Office for National Statistics (ONS). The former collects information on all tumours (with the exception of some benign neoplasms) that are diagnosed in England each year. The data are received from across the NHS (England's National Health Service) and form part of a population-based cancer registry. All diagnoses are recorded using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) coding system.[13] For our study the NDRS provided information on the numbers of invasive cervical cancers (ICD-10 C53) and of CIN3s (ICD-10 D06) by year of diagnosis and by birth cohort. From the ONS's web site we then downloaded mid-year population estimates for England stratified by gender and single year of age (i.e., 1-year age groups).[14] Here we used the population figures released on 25th June 2021, that is before the 2021 Census data were available; post-census adjustments are however very unlikely to lead to any major difference in our analysis. More details about how the ONS derives and updates the mid-year population estimates are provided in the Supplementary Material.

For the analysis by birth cohort, we restricted the attention to women born between 1 September 1981 and 31 August 1996 and took advantage of the fact that a woman's date of birth determined the age at which she would have been first invited to screening and her HPV vaccination eligibility (Fig. 1 and Table 1). For example, only those born since 1 September 1990 would have been targeted by the HPV vaccination programme either routinely (≥ September 1995) or as part of catch-up campaigns (September 1990–August 1995).

Statistical methods

We calculated the incidence rates and their 95% confidence intervals for cervical cancer and CIN3 by age group (20 to <24.5, 24.5 to <26, and 26 to <30 years) and by either year of diagnosis or 1-year birth cohort. An incidence rate I is defined as the number of new cases of the disease under study during a certain period of time divided by the population at risk during that period. In dynamic cohorts where people may enter and exit the risk set at different time points (due for example to birth, migration or death), the denominator of I is usually calculated by summing up each person's time at risk (known as person-time or person-years if the unit of time is a year). When individual-level data are not available, the total sum of person-time at risk is approximated by the mid-period population estimate

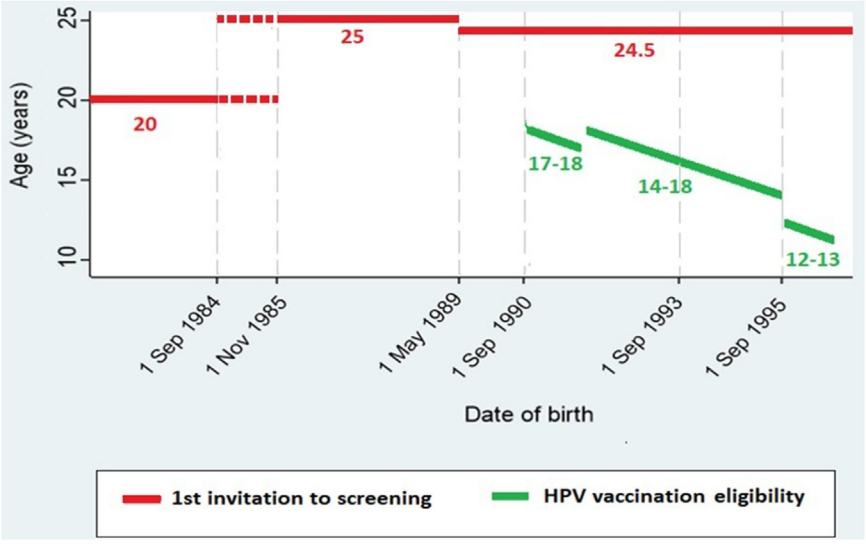

Fig. 1: **Age at first invitation to screening and age at HPV vaccination eligibility by date of birth.** Dashed red lines represent uncertainty due to the implementation of the policy change that increased the age at first invitation to screening from 20 to 25 years.

Date of birth	First invitation to screening		HPV vaccination	
	Age (in years)	Calendar years	Eligibility (campaign)	Age (in years)
1 Sep 1981–31 Aug 1982	20	2001/2002	No	
1 Sep 1982–31 Aug 1983	20	2002/2003	No	
1 Sep 1983–31 Aug 1984	20	2003/2004	No	
1 Sep 1984–31 Aug 1985	20 or 25	2004/2005 if invited at age 20, 2009/2010 if invited at age 25	No	
1 Sep 1985–31 Aug 1986	20 or 25	2005/2006 if invited at age 20, 2010/2011 if invited at age 25	No	
1 Sep 1986–31 Aug 1987	25	2011/2012	No	
1 Sep 1987–31 Aug 1988	25	2012/2013	No	
1 Sep 1988–31 Aug 1989	25 or 24.5	2013/2014	No	
1 Sep 1989–31 Aug 1990	24.5	2014/2015	No	
1 Sep 1990–31 Aug 1991	24.5	2015/2016	Yes (catch-up)	17–18
1 Sep 1991–31 Aug 1992	24.5	2016/2017	Yes (catch-up)	17–18
1 Sep 1992–31 Aug 1993	24.5	2017/2018	Yes (catch-up)	16–17
1 Sep 1993–31 Aug 1994	24.5	2018/2019	Yes (catch-up)	15–16
1 Sep 1994–31 Aug 1995	24.5	2019/2020	Yes (catch-up)	14–15
1 Sep 1995–31 Aug 1996	24.5	2020/2021	Yes (routine)	12–13

The policy on age at first screening invitation was changed in August 2004 but rolled out over 15 months, leading to some uncertainty on when women born in September 1984–August 1986 received their first invitation letter.

Table 1: **Summary information on when women would have been first invited to screening and HPV vaccine eligibility by birth cohort.**

multiplied by the length of the period. The mid-period population will include some people who have the disease under study and are therefore no longer truly at risk, but for cancer they are relatively few and can be ignored.[15,16] Hereafter we will therefore use the same person-years at risk for both cervical cancer and CIN3, meaning that women that are at risk of cervical cancer are also at risk for CIN3 and vice versa.

In order to estimate the incidence rates in our study, we had first to calculate the number of cervical cancers and that of CIN3s by age group and by either year of diagnosis or birth cohort and then divide those numbers by the appropriate women-years (WYs), which we approximated using mid-year population estimates as described above.

Details about how we calculated the WYs are reported in the Supplementary Material. The confidence intervals of the incidence rates were derived using the exact probability function of the Poisson distribution (the formula and method are described e.g., in 5.1.1 of Ahlbom's book).[17]

To compare trends over time and across birth cohorts, we calculated the rate ratios relative to reference time points. If R_{ay} denotes the incidence rate for age group a and year of diagnosis y and R_{ac} is the corresponding incidence rate for birth cohort c, then we considered R_{ay}/R_{ay*} and R_{ac}/R_{ac*} where $y*$ and $c*$ are reference points that we set to 2011 and 1989/90 respectively. It's worth noting that the choice of a reference point is arbitrary and only serves to identify an anchor to be used as the comparison group in the rate ratios. In our study we chose 2011 for the comparisons over calendar years because it was after the major changes to screening had occurred and before vaccinated cohorts were screened. To compare rates across birth cohorts, we chose as reference point the last cohort not offered vaccination (1989/90). To facilitate visual comparisons, we plotted the relative changes on the logarithmic scale.

In addition, we tested if the magnitude of HPV vaccination "effect" on time trends was similar across outcomes (cervical cancer and CIN3) and age groups. Specifically, we restricted the attention to women born since 1 September 1989 (i.e., those offered the vaccine plus the most recent 1-year pre-vaccination birth cohort) and considered 6 regressions: one for each combination of the three age groups and two outcomes (cervical cancer and CIN3). If N_1, N_2, and N_3 denote the count variables for cancers diagnosed respectively in age groups 20 to <24.5, 24.5 to <26, and 26 to <30 and M_1, M_2, and M_3 are the corresponding count variables for CIN3, then we specified a Poisson regression model for each of N_1, N_2, N_3, M_1, M_2, and M_3 as the response variable and year of birth as the independent variable and we included an offset to account for the women-years at risk. For cervical cancer the models accounted for interval censoring as for some of the youngest birth cohorts the cancer registry only released that the number of cases was ≤5, that is interval censored between 0 and 5, to prevent disclosure.[18] Instead of fitting the 6 regressions separately, we estimated them jointly as described in the Supplementary Material. Standard

errors were calculated using a robust estimator to adjust for overdispersion and correlation between observations. The joint estimation allows for formal testing of parameters across the models which would not be possible if the 6 regressions were fitted separately. For example, we were able to test whether for cervical cancer or CIN3 the slopes (i.e., the coefficients of the year of birth variable) were the same across the three age groups. As sensitivity analyses, we fitted additional Poisson models with constraints on different sets of parameters, e.g., equal slopes for both cervical cancer and CIN3 and all age groups.

All the analyses were performed using Stata, version 17.[19] In particular, the 95% confidence intervals were calculated using the *ci* command with the *poisson* and *exposure()* options, while the multi-equation model was fitted using the *intcount*[20] command with "robust" standard errors.

Role of the funding source

The funder had no role in study design, data collection and analysis, interpretation, decision to publish or preparation of the manuscript.

Results

Between 2006 and 2020 there were 5558 diagnoses of invasive cervical cancer and 164,682 of CIN3 in England among women aged 20 to <30 years. When we restricted the sample to those born between 1 September 1981 and 31 August 1996, we observed 4646 cancers and 140,673 CIN3s. For the analysis by birth cohort, we did not include women born in August 1981 or earlier and those born in September 1996 or later (912 cancers and 24,009 CIN3s).

Table 2 reports the number of diagnoses by calendar year and by birth cohort along with the women-years and crude incidence rates. The corresponding figures stratified by age group are shown in Supplementary Tables S1 and S2. Since across the calendar years the numbers of women-years were homogenous (and hence directly comparable) within each age group, we started by plotting the year- and age-specific number of cases (Fig. 2). We can see that cervical cancer and CIN3 have similar age-specific time trends, with a downward gradient in the younger age group, an inverted U shape for those aged 24.5 to <26 years and a clear spike among the older women in correspondence to the Jade Goody effect[21] in 2009. A similar direct comparison based solely on the number of cases was not possible for the analysis by date of birth as the women-years differ significantly across the birth cohorts, meaning that incidence rates should be considered instead. However, the analysis by birth cohort offers a great advantage when interpreting the results as there are clear cut-offs linking date of birth to changes in screening policy and the introduction of the HPV vaccination (Fig. 1 and Table 1). This is not the case when we look at trends by calendar year as multiple cohorts may be in the risk set at each time point (see the bottom part of Fig. 2).

	WY (1000s)[a]	Invasive cervical cancer		CIN3	
		N	Rate per 100K WY	N	Rate per 100K WY
Year of diagnosis					
2006	3354.8	274	8.2	9080	270.7
2007	3439.9	288	8.4	9879	287.2
2008	3516.1	332	9.4	10,512	299.0
2009	3542.6	454	12.8	13,842	390.7
2010	3572.8	371	10.4	11,819	330.8
2011	3612.0	404	11.2	12,287	340.2
2012	3622.1	434	12.0	12,715	351.0
2013	3619.1	465	12.8	14,322	395.7
2014	3626.2	484	13.3	14,493	399.7
2015	3630.4	489	13.5	13,642	375.8
2016	3623.2	411	11.3	11,221	309.7
2017	3609.0	385	10.7	9815	272.0
2018	3586.9	351	9.8	8612	240.1
2019	3563.4	242–247	6.8–6.9	7528	211.3
2020	3527.9	166–171	4.7–4.8	4915	139.3
Date of birth[b]					
1 Sep 1981–31 Aug 1982	2202.2	277	12.6	9727	441.7
1 Sep 1982–31 Aug 1983	2551.1	294	11.5	11,211	439.5
1 Sep 1983–31 Aug 1984	2902.4	376	13.0	11,993	413.2
1 Sep 1984–31 Aug 1985	3290.0	469	14.3	13,110	398.5
1 Sep 1985–31 Aug 1986	3557.5	501	14.1	13,662	384.0
1 Sep 1986–31 Aug 1987	3603.0	472	13.1	13,877	385.1
1 Sep 1987–31 Aug 1988	3653.4	493	13.5	14,230	389.5
1 Sep 1988–31 Aug 1989	3631.9	470	12.9	13,571	373.7
1 Sep 1989–31 Aug 1990	3663.1	443	12.1	13,303	363.2
1 Sep 1990–31 Aug 1991	3631.0	316	8.7	9074	249.9
1 Sep 1991–31 Aug 1992	3226.4	256	7.9	7618	236.1
1 Sep 1992–31 Aug 1993	2775.3	156	5.6	4763	171.6
1 Sep 1993–31 Aug 1994	2390.1	83	3.5	2753	115.2
1 Sep 1994–31 Aug 1995	1995.2	30–35	1.5–1.8	1480	74.2
1 Sep 1995–31 Aug 1996	1645.9	≤10	≤0.6	301	18.3

Some Ns and rates are reported as intervals to prevent disclosure of small numbers in other tables. [a]WY represents the population at risk, with women at risk of cervical cancer being at risk of CIN3 and vice versa. [b]Individuals with dates of birth before 1 September 1981 and after 31 August 1996 are excluded. This means that the women included in the analysis by date of birth are a sub-set of those considered for the analysis by year of diagnosis.

Table 2: **Number of diagnoses (N), women-years (WY), and crude incidence rates (N/WY) of invasive cervical cancer and CIN3 by year of diagnosis and by birth cohort.**

Fig. 3 displays the age-specific incidence rates and 95% confidence intervals for invasive cervical cancer and CIN3. To get a clearer picture of how the incidence trends compare across the age groups, we looked at relative changes (Fig. 4 and Supplementary Figure S1). We observed a very large decrease in incidence rates among women under age 24.5 years associated with the cessation of screening in that age group. Linked to that, there was a sharp increase in incidence for age 24.5 to <26 years. For 26 to 29-year-olds there was not much variation. Part of the decrease in rates observed around 2019/2020 is very likely due to the COVID-19

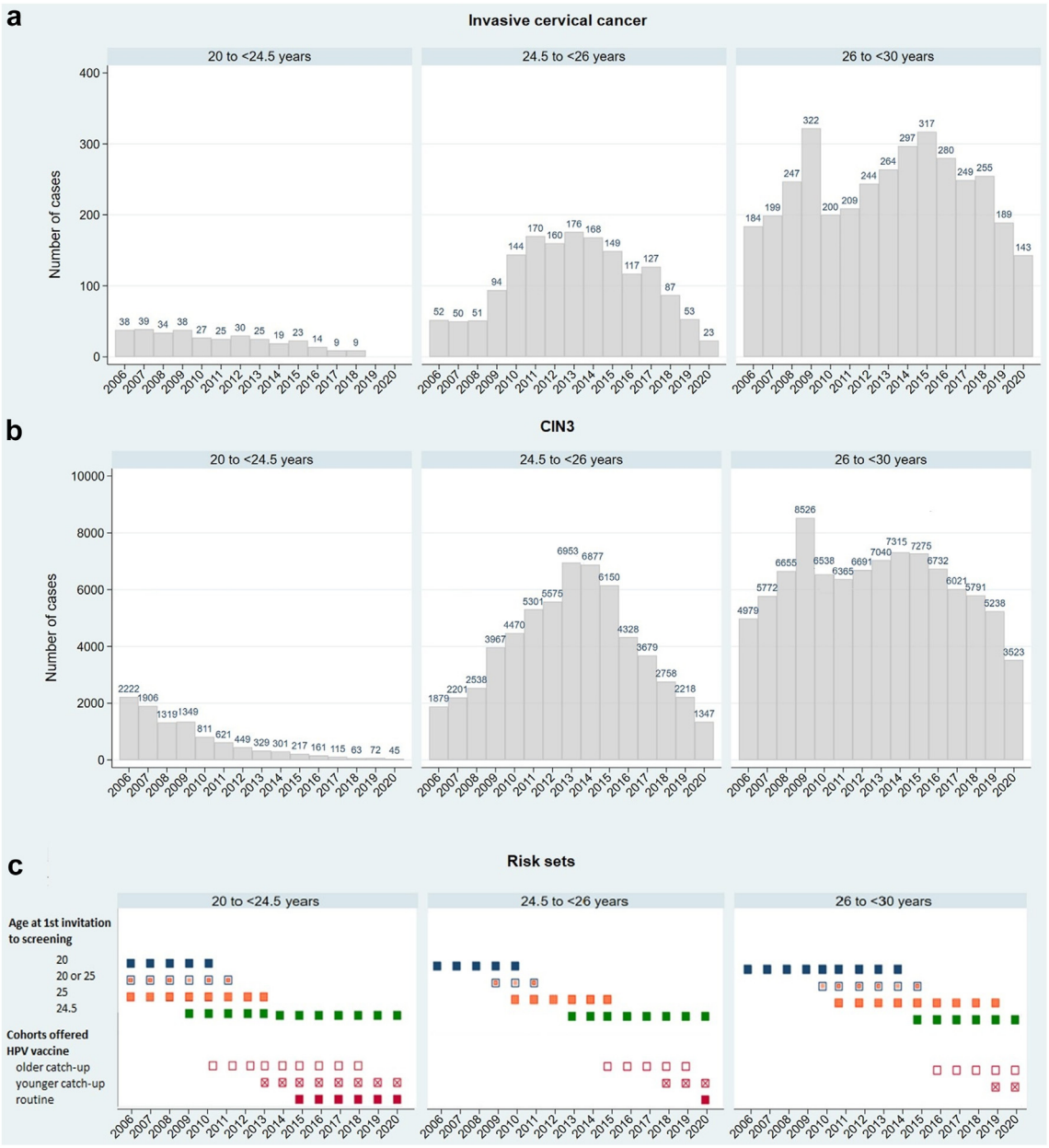

***Fig. 2:* Numbers of (a) invasive cervical cancers and (b) CIN3s by calendar year and age group.** The bottom part of the graph (c) shows the timelines of when women enter and exit the age-specific risk sets by age at first invitation to screening and HPV vaccination cohort. A square denotes presence in the risk set. For example, in 2020 all women aged 20 to <24.5 years would have been first invited to screening at age 24.5 and offered HPV vaccination at either age 12–13 (routine cohort) or 14–16 (younger catch-up cohort) years; those from the older catch-up vaccination cohort would be older than 24.5 so no longer in the risk set for that age group.

restrictions.[22] Supplementary Table S4 shows that there was roughly a 10% drop in invasive cervical cancer and CIN3 registrations in 2020 compared with 2019 among women aged 30 to <40.

It should also be noted that some fluctuations of the estimates, especially in the birth cohorts offered the HPV vaccine, are to be expected due to small numbers. For example, women born between 1 September 1994 and 31 August 1995 were at most aged 26 years and 4 months by the end of the study follow-up (31 December 2020). When we looked at the age group 26 to <30 years for that birth cohort we had only around 20,355 women-years (compared with 1.45 million women-years for those born 1 September 1981–31 August 1982). The

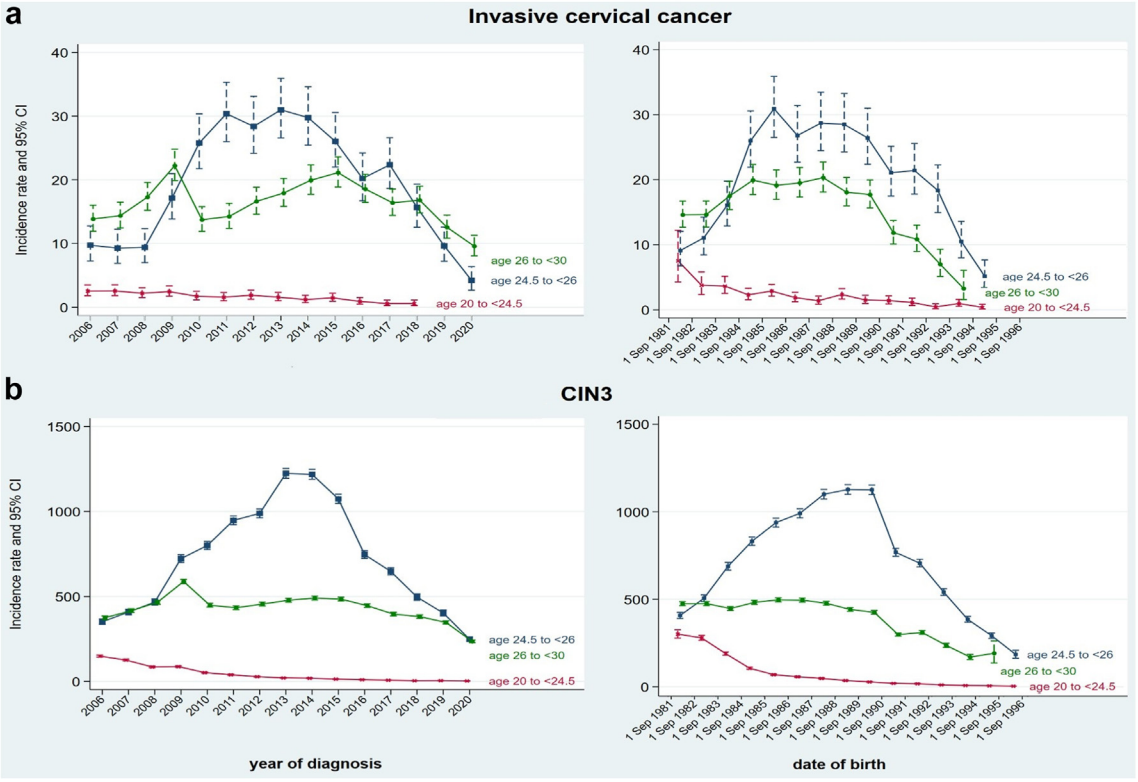

***Fig. 3:* Incidence rates per 100,000 women-years by age group and either calendar year or date of birth: a) of invasive cervical cancer and b) CIN3.** Vertical dashed lines represent 95% confidence intervals. The figures by date of birth are plotted at the mid-points of the 1-year birth intervals. Incidence rates are not displayed for years or birth cohorts where the number of cervical cancers or CIN3s was disclosed as ≤5.

CIN3 incidence rates for age 26 to <30 in cohorts 1993/94 and 1994/95 were respectively 169.6 (95% CI: 155.3–184.6) and 191.6 (95% CI: 136.2–261.9), with considerable overlap of the confidence intervals.

When we looked at age-specific trends in women born from September 1989 (i.e., the birth cohorts who had been offered the HPV vaccine and the most recent pre-vaccination cohort), we found highly significant negative slopes for both invasive cervical cancer and CIN3 across all age group with rates falling between 17.4% and 28.0% per year (unconstrained model in Table 3). This corresponds to reductions between 68.2% and 86.0% after 6 years. The estimates of the coefficients and their 95% confidence intervals obtained using this unconstrained model are reported in Supplementary Table S3. Sensitivity analyses showed that the model with a common slope across the 2 outcomes and 3 age groups did not fit well. In particular, we noticed that the age-specific slopes were statistically different for CIN3 ($p < 0.001$) but not for invasive cervical cancer ($p = 0.4$). When we refitted the model constraining only the age-specific slopes for cancer to be equal, the model fit greatly improved and the estimated cancer-specific slope was –0.268 (95% CI: –0.327 to –0.209), implying a reduction in rates of $100 \times (1 - \exp(-0.268))\% = 23.5\%$ per year and $100 \times (1 - \exp(-0.268 \times 6))\% = 80.0\%$ after 6 years (model with constrained slopes in Table 3).

Discussion

It is important to monitor trends in diseases after implementing new public health interventions or changes in policy. In this paper we looked at trend variations following the introduction of HPV vaccination and changes to cervical screening. Both have had dramatic effects on the rates of cervical cancer and CIN3 registrations.

In the absence of screening there will be very little CIN3 detected, and cancers will mostly only be detected once they have progressed to stage 1B or worse. Thus, if one stops screening under age X there will be very few cases of CIN3 or stage 1A cancer diagnosed under that age. If subsequently one screens a high proportion of the population exactly at age X (and assuming X is old enough) one will find a large number of prevalent CIN3 and stage 1A cancers (and maybe some stage 1B cancers too). This was observed when the age at first screening invitation was moved from age 20-22 to the 25th birthday and subsequently to age 24.5 years.[8]

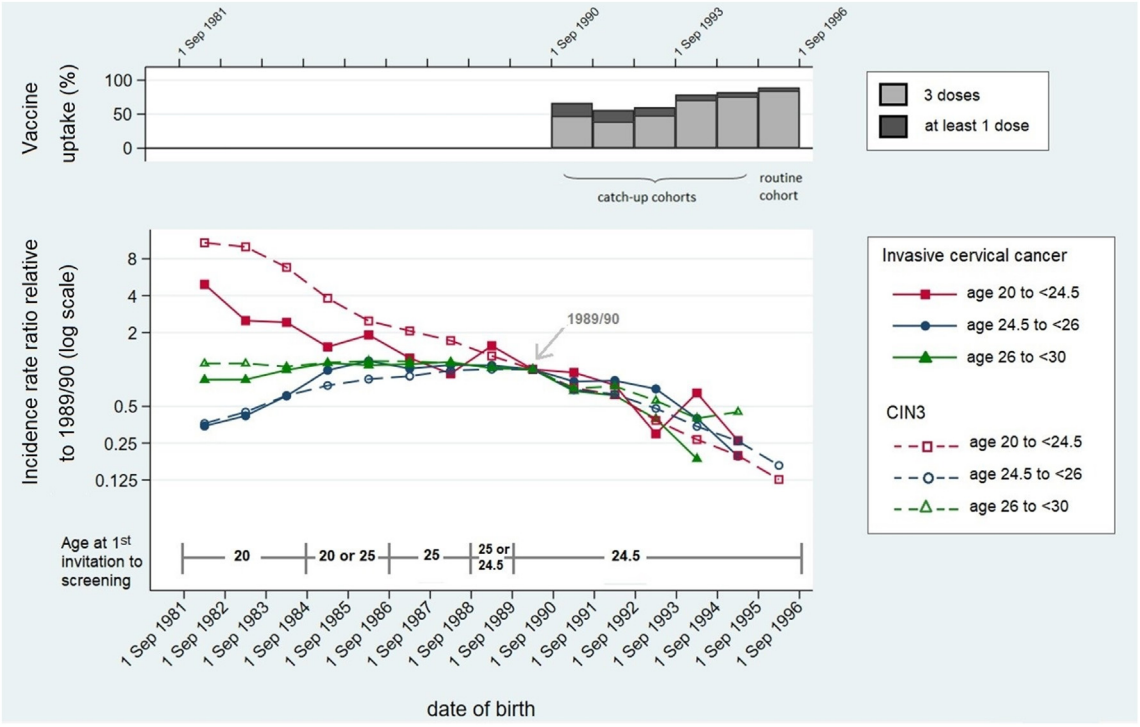

Fig. 4: **Trends by date of birth.** Age- and outcome-specific rate ratios relative to the 1989/90 birth cohort (larger graph) along with age at first invitation to screening (bottom) and vaccine uptake (smaller graph). For example, women born between 1 September 1995 and 31 August 1996 were first invited to cervical screening at age 24.5 years and were offered the HPV vaccine at age 12–13 years as part of the routine cohort. The 1989/90 birth cohort was taken as the reference point because it was the birth cohort just before those targeted by the HPV vaccination programme. Data on vaccine uptake refer to national figures and include (when information is available) mop-up vaccinations, as reported in Mesher (2018).[23]

There has been huge progress in data visualisation, but the analyses here make clear that a few simple plots can reveal a great deal of information and improve our understanding. They show how the substantial changes in cervical cancer and CIN3 rates in England between 2006 and 2020 can all be explained by external factors provided one looks at the data carefully. Difficulties arise because some events (such as the death of Jade Goody or the COVID-19 lockdown) affect a broad age group at a particular point in time, whereas others (such as changes to the age of first screening invitation or the introduction of HPV vaccination) affect those born between certain dates. For that reason, plotting data both against calendar time and against date of birth can be useful. Further, traditional age groupings (e.g., 5-year age bands: 20–24, 25–29, etc.) can blur important distinctions. For example, the change in policy to send out screening invitations 6 months before women turned 25, rather than on their 25th birthday, led to a very large rise in incidence of (presumably screen-detected prevalent) cervical cancer in women aged 24.5 to <25 but not in those younger than 24.5 years.[9] When considering trends over year of diagnosis, one can plot the numbers of cases because the denominator (population at risk) is of a similar size each year. On the contrary, when looking at trends over year of birth, it is important to plot rates because the numbers of diagnoses are not comparable. Plotting against year of diagnosis makes two events stand-out: one is the increase

	Unconstrained model[a]		Model with constrained slopes for cancer[b]	
	Estimate	(95% CI)	Estimate	(95% CI)
Annual percentage reduction				
Invasive cervical cancer				
Age 20 to <24.5	22.8	(14.6, 31.0)	23.5[c]	(19.0, 28.1)
Age 24.5 to <26	22.0	(15.4, 28.7)	23.5[c]	(19.0, 28.1)
Age 26 to <30	27.0	(22.1, 31.9)	23.5[c]	(19.0, 28.1)
CIN3				
Age 20 to <24.5	28.0	(26.6, 29.3)	28.0	(26.6, 29.3)
Age 24.5 to <26	22.9	(21.4, 24.4)	22.9	(21.4, 24.4)
Age 26 to <30	17.4	(13.7, 21.0)	17.4	(13.7, 21.0)
Log pseudo-likelihood	−268.8		−269.8	

In the unconstrained model all the parameters were free to vary, while in the constrained model the age-specific slopes for cancer were set to be equal. Figures between brackets represent 95% confidence intervals (95% CIs). [a]Model where both the intercepts and the slopes were allowed to vary between age groups, cervical cancer and CIN3. [b]Model where for cervical cancer we constrained the 3 age groups to share a common slope. The slopes for CIN3 and all the intercepts were allowed to vary. [c]Constrained to be equal.

Table 3: **Annual percentage reductions (100 × (1 − exp (slope))%) estimated from the unconstrained and constrained interval-censored Poisson regression models using data on women born between 1 September 1989 and 31 August 1996.**

in 2009 associated with the so-called "Jade Goody effect",[21] the other is the small numbers of registrations (particularly for CIN3) in 2020 which is likely due to the cessation of screening for a few months due to the COVID-19 lockdown. Neither of these features stand out from the plots against year of birth. Fig. 4, on the other hand, visually explains most of the trends in cervical cancer rates in young women between 2006 and 2020. By plotting the relative changes against the 1989/90 birth cohort, we can easily draw several conclusions.

1. Age-specific trends in CIN3 and in invasive cervical cancer are very similar except for age 20 to <24.5 in the 1981/82 to 1987/88 birth cohorts. This is reassuring since we would generally expect trends in birth cohorts to be similar unless an increase in screen-detected pre-cancer at one age is leading to a decrease in invasive cancer at a later age.
2. Rates in women aged 26 to <30 were relatively stable (apart from a modest increase for cancer in birth cohorts from 1982/83 to 1984/85) prior to the introduction of HPV vaccination.
3. There was a steep rise in rates at ages 24.5 to <26 associated with a dramatic increase in screening activity at that age. Indeed, as reported by Castanon et al.,[9] among women born before 1980 the proportion of those who had a screening test between ages 19 and 35 years increased slowly with age and did not exceed 56% by age 26. By 1990/91, 67% of women were screened between ages 24.5 and 26 and the screening rate under age 24.5 became very low. As two reviewers pointed out, it would be nice to be able to look at screening activity by birth cohort. Unfortunately, such data are not available.
4. The decrease in rates in those aged 20 to <24.5 mirrors the cessation of screening at those ages. Here the fall in CIN3 is dramatic since without screening pre-cancerous lesions will not be detected. The relative fall in invasive cancer is less dramatic because a proportion of those cancers were always symptomatic and will still be diagnosed in the absence of screening.
5. The hump in invasive cancers in the 1985/86 birth cohort aged 20–24.5 could be because of the Jade Goody effect in those aged 24 in the first quarter of 2009.
6. The relative fall in rates following the introduction of HPV vaccination is similar at all ages and for both CIN3 and cervical cancer. The fall appears gradual as the birth cohorts were more likely to have been vaccinated and more likely still to have been vaccinated before first sexual activity. This trend was restricted to those born between 1 September 1989 and 31 August 1996. We do not anticipate that the average rate of decline in incidence rates will continue for more recent cohorts; rather we hope that rates will now remain at the current very low levels.

Sometimes data visualisation, such as presented here, can be so persuasive that formal regression modelling seems unnecessary. Of course, the visualisation is only as good as the data provided by the cancer registry, but it can also reveal potential issues such as under-registration in 2020. Where there are 5 or fewer cases, the cancer registry reveals only that there were ≤5 cases to prevent inadvertent disclosure. In this situation, it is hard to understand what would be disclosed if for instance one knew that there was only one cervical cancer in a woman aged 20–24.5 born between September 1995 and August 1996. Nevertheless, with large numbers in most cells, such interval censoring of the data does not create many problems for visualisation or analysis.

The relationships seen here of cancer rates with factors such as changes in cervical screening policy, the introduction of HPV vaccination and events such as Jade Goody's death and COVID-19 lockdown are only associations. It is natural to assume causality as it follows from the clear causal model, the strength of associations and the fact that in many cases both the timing and the magnitude of the effect could be predicted from the causal model. In any case, it is reassuring that there appeared to be no increase in cervical cancer over the age of 26 in cohorts not offered cervical screening until age 25 (or 24.5) compared with earlier cohorts offered screening from age 20. It is also very encouraging to see that there has been a substantial and increasing reduction in CIN3 and cervical cancer rates in the cohorts offered HPV vaccination, with the biggest apparent decrease in those offered vaccination aged 12–13 (where coverage was very high). These results are in line with the growing real-world evidence on the effectiveness of the HPV vaccination.[1,24,25] If we assume no herd immunity nor cross-protection against HPV types other than 16 and 18, the HPV immunization programme would be expected to reduce the incidence of cervical cancer by an amount close to the product between the vaccine uptake and the proportion of cervical cancers linked to HPV 16/18 in England (~80% in this age group). With 85% vaccine uptake, the reduction would therefore be around 68%. We observe even greater reduction in cervical cancer associated with the HPV vaccination programme in the routine cohort (vaccine offered at age 12–13 years). The results being above expectation might suggest the presence of herd immunity and/or cross-protection against HPV types not targeted by the vaccine.

Conclusion

Data visualisation is a useful tool for monitoring the impact of public health interventions. We showed that plots against different time scales (e.g., calendar year and date of birth) may provide important insights that

could otherwise be missed. Our findings confirm that the HPV vaccination programme has had a substantial effect on CIN3 and cervical cancer rates in England. The data are consistent with a sustained high effectiveness as the catch-up vaccination cohorts age and with an 80% reduction in cervical neoplasia in the routine vaccination group.

Contributors

PS proposed the original idea and together with MF and AC conceptualised the study. BN extracted the data. MF prepared the graphs and carried out the statistical analysis. MF and PS draft the manuscript, which was then critically reviewed by BN and AC. All authors approved the final submitted version.

Data sharing statement

The aggregated data on invasive cervical cancer and CIN3 come from the National Disease Registration Service (NDRS). Requests to access the data can be made through the NHS England's DARS service (https://digital.nhs.uk/services/data-access-request-service-dars). Mid-year female population estimates for England are freely downloadable from the ONS website (https://www.ons.gov.uk/).

Declaration of interests

This research was funded by a grant from Cancer Research UK (grant C8162/A27047 to PS). AC is employed by Lane Clark & Peacock LLP. PS was paid by Roche to participate in an advisory board on HPV testing. He is also on the Data Monitoring and Ethics Committee for the IARC India HPV Vaccine Trial, and the ESTAMPA screening study and the Steering Group for the Long-term follow-up of ARTISTIC cervical screening trial cohort. PS was a co-investigator on trials that received self-sampling swabs from Copan, and HPV vaccine from MSD.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lanepe.2024.101157.

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