Reduction of low and high grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland

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ABSTRACT

Background

In Scotland, a national HPV immunisation programme began in 2008 for 12-13 year olds, with a catch-up campaign from 2008-2011 for those under the age of 18. To monitor the impact of HPV immunisation on cervical disease at the population level, a programme of national surveillance was established.

Methods

We analysed colposcopy data from a cohort of women born between 1988-1992 who entered the Scottish Cervical Screening Programme (SCSP) and were aged 20-21 in 2008-2012.

Results

By linking datasets from the SCSP and colposcopy services, we observed a significant reduction in diagnoses of cervical intraepithelial neoplasia 1 (CIN 1) (RR 0.71, 95% CI 0.58 to 0.87, p=0.0008), CIN 2 (RR 0.5, 95% CI 0.4, 0.63, p<0.0001) and CIN 3 (RR 0.45, 95% CI 0.35 to 0.58, p< 0.0001) for women who received 3 doses of vaccine compared with unvaccinated women.

Conclusions

To our knowledge, this is one of the first studies to show a reduction of low and high grade cervical intraepithelial neoplasia associated with high uptake of the HPV bivalent vaccine at the population level. These data are very encouraging for countries that have achieved high HPV vaccine uptake.

Keywords: human papillomavirus; vaccine; cervical intraepithelial neoplasia

INTRODUCTION

In the UK, cervical cancer is the second most common cancer in women under 35 years (Cancer Research UK, 2010). Human papillomavirus (HPV) types 16 and 18 are known to be essential for the development of at least 70% of cervical cancers (Smith *et al,* 2007) but may contribute in excess of 80% of cervical cancers in Scotland (Cuschieri *et al,* 2010). The prophylactic bivalent vaccine prevents infection with HPV types 16 and 18 and has been shown to induce strong and sustained neutralising antibody responses which prevent cervical HPV 16 and 18 infection and confer protection against consequent viral-induced cervical intraepithelial neoplasia (CIN) (Paavonen *et al,* 2009). The vaccine may also afford immunological cross-protection against other high-risk oncogenic HPV types which are phylogenetically related to HPV 16 and 18, including HPV 31, 33 and 45 (Malagon *et al,* 2012; Kavanagh *et al,* 2014).

The quadrivalent HPV vaccine has been provided in Australia through the national HPV vaccination programme since April 2007. Early indications from the HPV vaccination programme suggest that there has been a decrease in high-grade cervical cytological abnormalities (HGA coded as CIN of grade 2 or worse or CGIN) of the cervix in girls younger than 18 years (Brotherton *et al*, 2011). Although the study did not directly link pathology results with immunisation status, it provided evidence that high uptake of the HPV vaccine (approximately 70%) was temporally correlated with a decrease in cervical cancer precursors at the population level.

Since 2008, school-based uptake of bivalent HPV vaccine in girls aged 12-13 in Scotland has been impressive, with vaccine uptake sustained at levels >90% (NHS Information Services Division, 2011; Sinka *et al,* 2014). Furthermore, a three-year (from September 2008 to 2011) catch-up campaign offered vaccination to all girls aged 13 to 17, with uptake recorded at between 80% and 30% in younger and older

girls at age of vaccination respectively (NHS Information Services Division, 2012). In order to estimate vaccine impact it is important to ascertain the effect of the vaccination programme on the whole population, with particular focus on the age group where these changes will be initially observed. In Scotland cervical screening is offered 3-yearly to all women aged 20 to 60 years. Therefore it is one of the few countries in the world able to detect an early impact of the vaccine through population-based surveillance.

Scotland has a population of 5.2 million and almost all care is provided by the National Health Service (NHS). Preventive health programmes operate population registers based on birth and patient care registration systems with a common unique person identifier. One of the major strengths of Scottish health data is the ability to perform robust data linkage in a national population, using Community Health Index (CHI) (Bhopal *et al,* 2012). In this study we have used such linkage to complete preliminary analysis of the impact of the bivalent vaccine on HPV-associated disease at the population level. These attributes allow us to demonstrate early impact of high HPV immunisation coverage to show significant reductions in the diagnosis of low and high grade CIN level.

METHODS

HPV surveillance cohorts.

As part of the Health Protection Scotland (HPS) HPV surveillance strategy, cohorts of young women born between 1988 and 1992 were assessed to determine vaccine impact. The study identification number and the patient Community Health Index reference (CHI, a unique national patient identifier) were sent to Information Services Division (ISD) of the National Health Service (NHS) in Scotland, who used CHI to link the national Scottish Immunisation call Recall System

(SIRS) and Child Health Schools Programme-System (CHSP-S) data to screening and colposcopy attendance. This is described more fully elsewhere (Kavanagh *et al.,* 2014).

The range of ages spans the period of eligibility for vaccination (1990-1992 i.e. the catch-up cohort) and also provides mainly unvaccinated individuals (1988 and 1989) from the early cohorts, for comparison. Geographical data-zone (Scottish Government, 2005) derived from the postcode of residence, was attributed to each record allowing assignment of the Scottish Index of Multiple Deprivation (SIMD) (Scottish Government) to each individual in the cohorts.

Vaccination status derived from Child Health Schools Programme-System (CHSP-S) or the Scottish Immunisation Recall System (SIRS) which act as the call and recall register for immunisation programmes in Scotland is linked to all individuals in the cohort.

Data linkage of the cohort.

Women are referred directly by the Scottish Cervical Call and Recall System (SCCRS) to colposcopy for further investigation on the basis of high grade dyskaryosis, repeat low grade dykaryosis or borderline nuclear abnormality (BNA). Colposcopy data are collected routinely for all referred individuals in NHS Scotland via the National Colposcopy Clinical Information and Audit System (NCCIAS). This information is episode based and comprises patient demographics, appointment details, clinical data including referral, clinical signs and symptoms, colposcopy assessment and findings, biopsy results, cytology results, treatments and the follow-up care management plan.

NHS Information Services Division (ISD) provided an extract of this data to HPS, matching NCCIAS patients to the HPV surveillance cohort via an anonymous

reference number. Extracts from NCCIAS are received by HPS on a quarterly basis, with the data in this study based on linked referrals to the end of May 2013.

Statistical analysis.

We restricted our analysis to those individuals in the cohort with a cervical screening attendance date in SCCRS after the age of eligibility (age 20). In the NCCIAS dataset, individuals may have more than one linked histological episode to the index referral cytology. We restricted our analysis to the incident abnormal histological episode. Incidence rates per 1000 person-year were calculated by comparing the number of cases of each diagnosis to the number of individuals screened, adjusting for the person-time contribution of each individual as those born in the early cohorts have more time to develop an outcome. This contribution was calculated as the number of months between the individual attending for their first screen and the date of referral for the incident abnormal histological episode if present (which could occur following a later screening attendance, or alternatively to 31st May 2013 (the latest month for which referrals were extracted), whichever occurred first. Incidence rates per 1000 person year were stratified by vaccination status and birth cohort.

The relative risk of CIN in the vaccinated population compared to the unvaccinated population was calculated using Poisson regression adjusting for cohort year to model potential changes in sociological behaviour which may exist from one birth cohort to the next, deprivation score (assessed via the SIMD quintiles of the area of residence where 1 is most deprived and 5 is least deprived) and age. Person-time contribution was used as an offset. Individuals were censored at the date of referral for an incident abnormal histological episode (all grades) or the 31st May 2013. As the risk of an abnormal histological episode may change over time, age is included as a

time dependent co-variate, with person-time contribution and the number of abnormal histological episodes stratified by the age of the individual in months as they move through the study. For each grade of CIN, interaction tests were carried out to consider differences in the vaccine effect between cohort years and between deprivation (SIMD quintile).

As a sensitivity analysis, we considered only the abnormal histological episodes which followed the first cervical screen in only those who attended for screening at age 20 or 21. The odds of CIN in the vaccinated population compared to the unvaccinated population were then calculated using logistic regression adjusting for cohort year and deprivation score for grades CIN 1, 2 and 3 individually. This analysis considers a more homogeneous population in terms of age and attendance for screening, and age at histological examination. All statistical analysis was conducted in R version 3.0.3 (R Development 2014).

RESULTS

Cohort analysis.

Across all 5 birth cohorts (n=200867), 53.5% (n=106052) attended for their first cervical screen at age 20 or above (Table 1). Attendance was lowest for the youngest cohort i.e. those born in 1992 (36.3%) with these individuals having less follow-up time at screening attendance, at the time of data extraction. Across all 5 cohorts, 72% were unvaccinated and 24% received 3 doses of vaccination, with vaccine uptake varying significantly by cohort year. 99% of those born in 1988 and 1989 were unvaccinated since the programme was not targeted at these individuals. A proportion of those born in 1990 and all of those born in 1991 and 1992 were eligible

for vaccination. Vaccine uptake increased yearly and was highest for the 1992 cohort where 74% of individuals received 3 doses (Table 1).

The first result for an abnormal referral (this includes a result of CIN 1 or worse) occurring after the date of first screen for each individual was considered. Those with a date of referral prior to the date of first screen were excluded (n=10), reducing the total cohort size from 106052 to 106042. Of the 10 excluded individuals, five individuals had CIN1 and were all unvaccinated, four individuals had CIN2, three of whom were unvaccinated and one individual had CIN 3 who was unvaccinated. In total there were 4854 abnormal histology (CIN 1-3) episodes; 1753 were CIN 1, 1698 CIN2 and 1403 CIN3 (Table 1).

Incidence and relative risk of CIN 1, 2 and 3.

Incidence rates for CIN 1, 2 and 3 diagnosis per 1000 person year by number of vaccinations received and birth cohort were estimated (Figure 1). For those fully vaccinated in 1990-1992, there is a clear reduction in incidence of CIN 3 between unvaccinated and fully vaccinated individuals e.g. in 1991, the incidence in the unvaccinated is 7.93 per 1000 person years (p1000py) (95% CI: 6.13, 10.10) compared to 3.66 p1000py (95% CI: 2.80, 4.69) in those receiving 3 doses. This reduction in incidence of CIN 3 was statistically significant in both the unadjusted and adjusted models (3 dose unadjusted RR 0.59, 95% CI: 0.48, 0.72, $p<0.0001$; 3 dose adjusted RR 0.45, 95% CI: 0.35, 0.58, $p<0.0001$) (Table 2). Although those receiving 2 doses of vaccine had a lower incidence rate of CIN 3 than the unvaccinated group in the 1990-1992 cohorts, the adjusted relative risk was not statistically significant (2 dose adjusted RR 0.77, 95% CI: 0.49, 1.21, $p=0.25$).

The adjusted analysis (Table 2) also showed a statistically significant difference in relative risk of diagnoses of CIN 2 (RR 0.5, 95% CI 0.4, 0.63, $p<0.0001$)

and CIN 1 (RR 0.71, 95% CI 0.58, 0.870, p= 0.0008) associated with 3 doses of vaccine compared with those who were unvaccinated. Two doses of vaccine were associated with a reduced risk of both CIN 2 and CIN 1 but this was not statistically significant (CIN 2: RR 0.81, 95% CI 0.54, 1.22, p= 0.32 and CIN 1: RR 0.65, 95% CI 0.42, 1.01, p= 0.056).

Relative risk of CIN 1, 2 and 3 diagnosis was significantly lower for the least deprived women (SIMD 5) compared to the most deprived (SIMD 1), even when differences in vaccination were accounted for (Table 2). For each outcome, the relative risk of a diagnosis was significantly lower among women from affluent areas compared to women from very deprived areas.

Table 2 also shows that there was a significant reduction in all grades of CIN in those born in 1989. Furthermore, for CIN3 there are significant reductions in those born in the 1989 and 1992 cohorts but not in those born in 1990 and 1991. Generally the trend is downwards and conducting a test for linear trend shows that for each of CIN 1, 2 and 3 there is a significant linear change over the cohort years (p=0.0126; p<0.0001 and p=0.0009 respectively).

There was no significant interaction between the number of vaccine doses and deprivation (SIMD score) on occurrence of CIN 1, 2 or 3 (p-value of interaction tests p=0.65, p=0.811 and p=0.63 respectively) nor between the number of vaccine doses and the birth cohorts (p-value of interaction tests p=0.48, p=0.1 and p=0.86 respectively).

Sensitivity analysis.

We conducted a sensitivity analysis of only those individuals screened at age 20 or 21 and consider only incident abnormal histology occurring within 6 months of their first screen. This reduced our total cohort size to 91677 of which 73% were

unvaccinated and 23% fully vaccinated. Within this reduced cohort, there were 602 CIN 1, 617 CIN 2 and 575 CIN 3 diagnoses. In adjusted analyses, women vaccinated with 3 doses had a statistically significant reduced risk of being diagnosed with CIN 1, 2 and 3 (Table 3), similar to that observed in the age-adjusted model (table 2) although the confidence intervals were wider due to the smaller cohort size. As in the full model, 2 doses of vaccine was associated with a reduction in each of CIN 1, 2 and 3 but this was not statistically significant (p=0.176, p=0.121, p=0.352 respectively).

In this analysis, there was no significant change in the numbers of CIN 1 and 2 by cohort year (p-values of the linear test of trend were 0.497and 0.4463 respectively). For CIN 3, there was evidence of a linear trend (p= 0.044) driven by the large reduction in the 1992 cohort coupled with marginal reductions in the preceding birth cohorts.

DISCUSSION

In this study, we have completed a preliminary analysis of the impact of the bivalent vaccine on HPV-associated cervical disease at the population level. To our knowledge, this is the first population-based study to report a statistically significant decrease in incidence of cervical intra-epithelial neoplasia grades 1, 2 and 3 (29%, 50% and 55% respectively) in women aged 20-21, associated with three doses of bivalent HPV vaccine administered during a catch-up campaign.

The vaccinated women in this cohort received the HPV vaccine through a national catch-up campaign, with mean uptake across all age groups for all 3 doses recorded as 66% (NHS Information Services Division, 2012). Since 2008, the uptake rate of the HPV vaccine in the routine cohort (immunised at age 12 to 13 years) has consistently achieved > 90% (NHS Information Services Division, 2011) and therefore any effect on HPV-associated disease is likely to be even more profound

than that observed in the catch-up cohort. These data are very encouraging for countries that have achieved high HPV vaccine uptake.

Long-term surveillance of the effects of HPV vaccination in the population commenced in Scotland in 2008 and incorporates the study of both HPV prevalence in residual liquid-based cytology samples from screening (Kavanagh *et al,* 2013), and the monitoring of HPV-associated disease through national screening and colposcopy services. Preliminary analysis of HPV prevalence in the Scottish catch-up cohort corroborates previous studies (Paavonen *et al*, 2009; Wheeler *et al,* 2012) and shows that the bivalent vaccine is strongly associated with a reduction in both HPV 16 and 18, while affording cross-protection against HPV 31, 33 and 45 (Kavanagh *et al,* 2014) .

Our analysis focused on the risk of CIN 1, 2 and 3 dependent on the number of doses of vaccine received adjusted for cohort year, deprivation and age at observation. Cohort year is used to model the possible background patterns of changes in sociological behaviour which may exist from one birth cohort to the next. This may influence the levels of CIN 1, 2 and 3 observed i.e. those born in 1988 have two invitations to be screened and 3 years of opportunistic screening between those periods while those people born in 1989 will not have the same screening opportunities, hence the reduction in all grades of CIN in the 1989 cohort. In the sensitivity analyses, which considered a more homogeneous population, there was no significant change in the numbers of CIN 1 and 2 by cohort year.

Although there was a significant reduction in all grades of CIN associated with 3 doses of vaccine in this cohort, no statistically significant reduction was observed in individuals who were partially immunised. However, almost all of the women who received two doses of vaccine in this cohort were immunised at 0 and 1 month. Further data are required to assess what protective effect is afforded by <3 doses of

vaccine since only 3.8% of women in our cohort were partially vaccinated. We hope to elucidate the long-term efficacy of a 2-dose vaccine regimen through the analysis of updated quarterly colposcopy extracts to the national surveillance programme since studies suggest a 2-dose regimen may be both protective and cost-effective (Romanowski *et al,* 2011; Kreimer *et al*, 2011) .

HPV vaccination and regular cervical screening offers the best combination for prevention of cervical cancer. However, knowledge and awareness of HPV infection, cervical cancer and screening in young girls who have been vaccinated against the virus, is surprisingly low (Bowyer *et al*, 2013). This has prompted concerns that those girls who have been vaccinated may not realise they still require regular cervical screening (Marlow *et al*, 2007; Henderson *et al*, 2011). Reassuringly, we found that there was no reduction in the initial uptake of cervical screening in those women who were born in 1990 and had been vaccinated in the catch-up cohort. Nevertheless, it is imperative that health education initiatives continue to emphasise the importance of attendance at cervical screening for vaccinated women. This is especially important, given the association of increased levels of HPV positivity and poor attendance at cervical screening with increased deprivation (O'Leary *et al,* 2011; Baker & Middleton, 2003).

One of the main limitations with attributing reductions in CIN to vaccination is that women born in 1991 and 1992 who were fully vaccinated, would likely have been at school up to the age of 18 while the majority of the unvaccinated women in these cohorts would likely have left school at age 16. Coupled with this is the observation from a baseline prevalence study prior to vaccination that the levels of HPV positivity among girls aged 16-18 who had left school was much higher compared to those who were still at school (O'Leary *et al,* 2011). Thus the comparison of fully vaccinated with unvaccinated cohorts is confounded with leaving

school, but no individual adjustment can be made for this with the data available in this study. Attributing the reduction in severe disease solely to vaccination will over-estimate the impact of the vaccination but given that this study reports a 55% reduction in the relative risk of CIN 3 associated with 3 doses of vaccine, it is extremely unlikely that all of this effect is confounded with leaving school early.

Our work builds upon previous studies which assessed high-grade abnormalities and CIN data in both vaccinated and unvaccinated individuals, respectively (Kavanagh *et al,* 2014; Powell *et al,* 2012; Crowe *et al*, 2014; Baldur-Felskov *et al*, 2014). To our knowledge, this is the first study to report vaccine effectiveness findings against cervical lesions for the bivalent vaccine in a population rather than in a trial setting. The strengths of our analyses are that we have a largely complete population-based dataset on cervical screening that we can then directly link to disease and vaccination status through use of our national databases. Scotland is therefore in a strong position to assess the ongoing impact of the HPV vaccine on HPV-associated disease in the years ahead, including assessment in 2015 of vaccine impact in the routinely immunised girls. These data are generalisable to countries that have achieved high HPV vaccine uptake such as Australia, Portugal and Rwanda (Hopkins & Wood, 2013). This study highlights the gains that can be achieved if action is taken to overcome recognised barriers to high vaccine uptake.

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CONFLICTS OF INTEREST

None declared.

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Cohort Year	Attendance at cervical screening at age 20 or greater			% of screened population immunised				Number of cervical abnormalities amongst those screened		
	N screened	N total	% screened	Unvaccinated	1 dose	2 doses	3 doses	CIN 1	CIN 2	CIN 3
1988	26021	41948	62.00%	99.95%	0.01%	0.01%	0.03%	638	670	559
1989	22168	40618	54.60%	99.66%	0.12%	0.07%	0.15%	449	474	378
1990	23124	39377	58.72%	82.29%	1.41%	2.63%	13.67%	375	320	276
1991	20510	39672	51.70%	31.03%	3.02%	6.70%	59.24%	217	175	151
1992	14229	39252	36.30%	18.45%	2.41%	5.06%	74.08%	74	59	39
TOTAL	**106052***	200867	52.70%	71.77%	1.24%	2.57%	24.42%	1753	1698	1403

*reduces to 106042 when remove those with referral dates prior to first recorded screening date. This removed 5 CIN1 (all unvaccinated), 4 CIN 2 (3 unvaccinated, 1 fully-vaccinated) and 1 CIN3 (unvaccinated) – CIN figures in table are with these exclusions.

Table 1: Breakdown of each birth cohort in terms of number screened and the proportion vaccinated against HPV 16 and 18 (n=106052) and the number of cervical abnormalities (CIN 1-3) found in the follow-up period (to 31st May 2013).

	Unadjusted estimates			Adjusted* estimates				Unadjusted estimates			Adjusted* estimates				Unadjusted estimates			Adjusted* estimates		
	RR	95% CI	p-value	RR	95% CI	p-value		RR	95% CI	p-value	RR	95% CI	p-value		RR	95% CI	p-value	RR	95% CI	p-value
CIN 1							**CIN 2**							**CIN 3**						
Unvaccinated	1			1				1			1				1			1		
1 dose	1.33	(0.81, 2.18)	0.253	0.98	(0.59, 1.63)	0.9491		1.31	(0.8, 2.15)	0.277	1.03	(0.62, 1.71)	0.9182		1.89	(1.2, 2.97)	0.0061	1.42	(0.89, 2.28)	0.1445
2 doses	0.9	(0.59, 1.37)	0.632	0.65	(0.42, 1.01)	0.0557		1.05	(0.71, 1.55)	0.8	0.81	(0.54, 1.22)	0.3203		1.03	(0.67, 1.58)	0.9064	0.77	(0.49, 1.21)	0.25
3 doses	1	(0.87, 1.16)	0.962	0.71	(0.58, 0.87)	**0.0008**		0.64	(0.54, 0.77)	**<0.0001**	0.5	(0.40, 0.63)	**<0.0001**		0.59	(0.48, 0.72)	**<0.0001**	0.45	(0.35, 0.58)	**<0.0001**
1988	1	-		1	-						1	-						1	-	
1989	1	(0.89, 1.13)	0.9531	0.86	(0.76, 0.97)	**0.0184**		1.01	(0.9, 1.14)	0.872	0.86	(0.76, 0.97)	**0.0167**		0.95	(0.84, 1.09)	0.489	0.84	(0.73, 0.96)	**0.0098**
1990	1.18	(1.04, 1.34)	**0.0112**	0.93	(0.81, 1.07)	0.2852		0.95	(0.83, 1.09)	0.479	0.78	(0.67, 0.90)	**0.0005**		1.01	(0.87, 1.16)	0.923	0.89	(0.76, 1.04)	0.1488
1991	1.18	(1.01, 1.38)	**0.0379**	0.82	(0.67, 1.01)	**0.061**		0.89	(0.75, 1.06)	0.189	0.74	(0.59, 0.91)	**0.0052**		0.94	(0.78, 1.13)	0.508	0.86	(0.68, 1.08)	0.2034
1992	1.3	(1.03, 1.66)	**0.0306**	0.66	(0.50, 0.89)	**0.0059**		0.98	(0.75, 1.28)	0.902	0.58	(0.42, 0.79)	**0.0006**		0.78	(0.57, 1.08)	0.139	0.49	(0.34, 0.71)	**0.0002**
SIMD 1	1	-		1	-						1	-						1	-	
SIMD 2	0.83	(0.72, 0.95)	**0.0087**	0.84	(0.73, 0.96)	**0.0112**		0.83	(0.72, 0.94)	**0.0041**	0.84	(0.73, 0.95)	**0.0071**		0.94	(0.82, 1.08)	0.386	0.95	(0.83, 1.10)	0.4922
SIMD 3	0.83	(0.72, 0.96)	**0.011**	0.84	(0.73, 0.97)	**0.0174**		0.67	(0.58, 0.78)	**<0.0001**	0.69	(0.60, 0.80)	**<0.0001**		0.64	(0.54, 0.75)	**<0.0001**	0.66	(0.56, 0.77)	**<0.0001**
SIMD 4	0.8	(0.69, 0.93)	**0.0035**	0.82	(0.70, 0.94)	**0.0066**		0.62	(0.53, 0.72)	**<0.0001**	0.64	(0.55, 0.74)	**<0.0001**		0.59	(0.5, 0.7)	**<0.0001**	0.61	(0.52, 0.73)	**<0.0001**
SIMD 5	0.74	(0.64, 0.86)	**0.0001**	0.76	(0.66, 0.88)	**0.0002**		0.45	(0.39, 0.53)	**<0.0001**	0.47	(0.40, 0.56)	**<0.0001**		0.45	(0.38, 0.54)	**<0.0001**	0.47	(0.40, 0.57)	**<0.0001**

Table 2: Unadjusted and adjusted estimates of the relative risk of CIN 1, 2 and 3 by number of vaccinations. *adjusted for cohort year, SIMD and age in months (time dependent covariate – not shown)

	OR	95% CI	p-value		OR	95% CI	p-value		OR	95% CI	p-value
CIN 1				**CIN 2**				**CIN 3**			
Unvaccinated	1	-		Unvaccinated	1	-		Unvaccinated	1	-	
1 dose	0.92	(0.45, 1.88)	0.8046		0.64	(0.28, 1.45)	0.276		1.91	(1.11, 3.29)	**0.0193**
2 doses	0.66	(0.36, 1.20)	0.1765		0.62	(0.34, 1.13)	0.1216		0.75	(0.41, 1.36)	0.3524
3 doses	0.59	(0.44, 0.79)	**0.0006**		0.4	(0.29, 0.55)	**<0.0001**		0.5	(0.36, 0.69)	**<0.0001**
1988	1	-			1	-			1	-	
1989	1	(0.80, 1.25)	0.9760		0.89	(0.72, 1.11)	0.2976		0.78	(0.62, 0.98)	**0.0332**
1990	0.91	(0.72, 1.16)	0.4567		0.85	(0.68, 1.06)	0.1552		0.92	(0.74, 1.15)	0.4744
1991	1.04	(0.77, 1.39)	0.8160		0.98	(0.73, 1.31)	0.8894		0.85	(0.63, 1.15)	0.2807
1992	1.14	(0.78, 1.67)	0.4737		0.79	(0.52, 1.21)	0.2809		0.56	(0.35, 0.89)	**0.0143**
SIMD 1	1	-			1	-			1	-	
SIMD 2	0.65	(0.51, 0.83)	**0.0005**		0.77	(0.62, 0.95)	0.0183		0.83	(0.66, 1.03)	0.095
SIMD 3	0.71	(0.56, 0.91)	**0.0074**		0.53	(0.41, 0.68)	**<0.0001**		0.6	(0.47, 0.78)	**<0.0001**
SIMD 4	0.74	(0.58, 0.94)	**0.0181**		0.57	(0.44, 0.73)	**<0.0001**		0.59	(0.46, 0.77)	**<0.0001**
SIMD 5	0.66	(0.52, 0.84)	**0.0013**		0.37	(0.28, 0.49)	**<0.0001**		0.33	(0.24, 0.46)	**<0.0001**

Table 3: Adjusted odds of CIN 1, 2 and 3 in the 6 months following the date of screening in those attending screening at age 20 or 21 who have 6 months of follow-up available

Figure 1: Incidence rates per 1000 person year (p1000py) and associated 95% confidence intervals of CIN 1, 2 and 3 stratified by birth cohort and vaccination status (unvaccinated versus fully vaccinated with 3 doses)