Early effect of the HPV bivalent vaccine on high-risk HPV prevalence and high-grade cervical abnormalities in Scotland

NHS National Services Scotland

Aim

A national HPV immunisation programme was initiated in Scotland in 2008 for 12-13 year olds with a three year 'catch up' for those under the age of 18. 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%. A three-year (September 2008 to 2011) catch-up campaign offered vaccination to all girls aged 13 to 17, with uptake in this cohort recorded at between 30% and 80% in older and younger girls respectively.

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. As age at screening debut is currently 20 in Scotland, we are now able to determine the impact of a national immunisation programme on rates of HPV infection and HPV associated disease.

Methods

As part of the HPS HPV epidemiology and surveillance strategy, cohorts of young women born between 1988 and 1992 were assessed to determine vaccine impact.

Liquid-based cytology (LBC) samples from women attending their first cervical smear were genotyped for HPV and data linkage enabled HPV prevalence to be stratified by immunisation status. In addition, we analysed data from the National Colposcopy Clinical Information and Audit System (NCCIAS), a national colposcopy database which contains, data on referral cytology, interventions and histology results associated with any colposcopy visit.

This 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, derived from the postcode of residence, was attributed to each record allowing assignment of the Scottish Index of Multiple Deprivation (SIMD) to each individual in the cohorts.

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).

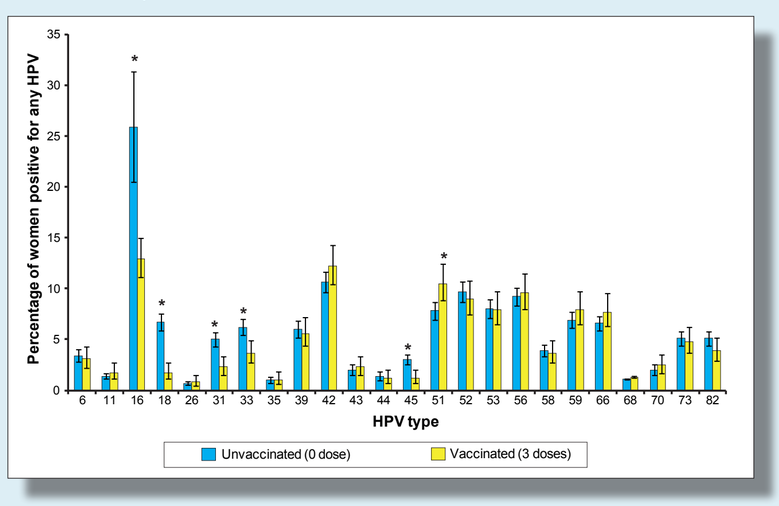
The relative risk of CIN 1, 2 and 3 in the vaccinated population compared to the unvaccinated population was calculated using Poisson regression adjusting for cohort year and deprivation score (assessed via the SIMD quintiles of the area of residence).

Results

In those women who have been fully vaccinated, there is a statistically significant reduction in the percentage of women positive for HPV 16, 18, 31, 33 and 45 (figure 1). Given that HPV types 31, 33 and 45 are genetically related to HPV 16 and 18, this suggests that vaccination with bivalent vaccine may provide immunological cross-protection against other high-risk HPVs.

There was a reduction in incidence of CIN 3, which 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 1). 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).

Figure 1: HPV types in anonymised LBC samples from women attending their first screening appointment in Scotland, 2009-2012 (*denotes statistically significant difference).



The adjusted analysis (Table 1) 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= 0.055).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 1). 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 1: 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

	Unadjusted estimates			Adjusted* estimates		
	RR	95% CI	p-value	RR	95% CI	p-value
CIN 1						
Unvaccinated	1.00	-		1.00	--	
1 dose	1.33	(0.81, 2.18)	0.2530	0.98	(0.59, 1.63)	0.9491
2 doses	0.90	(0.59, 1.37)	0.6320	0.65	(0.42, 1.01)	0.0557
3 doses	1.00	(0.87, 1.16)	0.9620	0.71	(0.58, 0.87)	0.0008
1988	1.00	-		1.00	-	
1989	1.00	(0.89, 1.13)	0.9531	0.86	(0.76, 0.97)	0.0184
1990	1.18	(1.04, 1.34)	0.0112	0.93	(0.81, 1.07)	0.2852
1991	1.18	(1.01, 1.38)	0.0379	0.82	(0.67, 1.01)	0.0610
1992	1.30	(1.03, 1.66)	0.0306	0.66	(0.50, 0.89)	0.0059
SIMD 1	1.00	-		1.00	-	
SIMD 2	0.83	(0.72, 0.95)	0.0087	0.84	(0.73, 0.96)	0.0112
SIMD 3	0.83	(0.72, 0.96)	0.0110	0.84	(0.73, 0.97)	0.0174
SIMD 4	0.80	(0.69, 0.93)	0.0035	0.82	(0.70, 0.94)	0.0066
SIMD 5	0.74	(0.64, 0.86)	0.0001	0.76	(0.66, 0.88)	0.0002
CIN 2						
Unvaccinated				1.00	-	
1 dose	1.31	(0.80, 2.15)	0.2770	1.03	(0.62, 1.71)	0.9182
2 doses	1.05	(0.71, 1.55)	0.8000	0.81	(0.54, 1.22)	0.3203
3 doses	0.64	(0.54, 0.77)	<0.0001	0.50	(0.40, 0.63)	<0.0001
1988				1.00	-	
1989	1.01	(0.90-, 1.14)	0.8720	0.86	(0.76, 0.97)	0.0167
1990	0.95	(0.83, 1.09)	0.4790	0.78	(0.67, 0.90)	0.0005
1991	0.89	(0.75, 1.06)	0.1890	0.74	(0.59, 0.91)	0.0052
1992	0.98	(0.75, 1.28)	0.9020	0.58	(0.42, 0.79)	0.0006
SIMD 1				1.00	-	
SIMD 2	0.83	(0.72, 0.94)	0.0041	0.84	(0.73, 0.95)	0.0071
SIMD 3	0.67	(0.58, 0.78)	<0.0001	0.69	(0.60, 0.80)	<0.0001
SIMD 4	0.62	(0.53, 0.72)	<0.0001	0.64	(0.55, 0.74)	<0.0001
SIMD 5	0.45	(0.39, 0.53)	<0.0001	0.47	(0.40, 0.56)	<0.0001
CIN 3						
Unvaccinated				1.00	-	
1 dose	1.89	(1.20, 2.97)	0.0061	1.42	(0.89, 2.28)	0.1445
2 doses	1.03	(0.67, 1.58)	0.9064	0.77	(0.49, 1.21)	0.2500
3 doses	0.59	(0.48, 0.72)	<0.0001	0.45	(0.35, 0.58)	<0.0001
1988				1.00	-	
1989	0.95	(0.84, 1.09)	0.4890	0.84	(0.73, 0.96)	0.0098
1990	1.01	(0.87, 1.16)	0.9230	0.89	(0.76, 1.04)	0.1488
1991	0.94	(0.78, 1.13)	0.5080	0.86	(0.68, 1.08)	0.2034
1992	0.78	(0.57, 1.08)	0.1390	0.49	(0.34, 0.71)	0.0002
SIMD 1				1.00	-	
SIMD 2	0.94	(0.82, 1.08)	0.3860	0.95	(0.83, 1.10)	0.4922
SIMD 3	0.64	(0.54, 0.75)	<0.0001	0.66	(0.56, 0.77)	<0.0001
SIMD 4	0.59	(0.50, 0.70)	<0.0001	0.61	(0.52, 0.73)	<0.0001
SIMD 5	0.45	(0.38, 0.54)	<0.0001	0.47	(0.40, 0.57)	<0.0001

Conclusions

This study has revealed the first definitive evidence of a large reduction in HPV 16 and 18 in the target population after introduction of a national bivalent HPV immunisation programme and has also shown significant cross-protective effects for HPV 31, 33 and 45. Furthermore, we have completed a preliminary analysis of the impact of the vaccine on HPV-associated cervical disease at the population level. 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.

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 is likely to be cost-effective. 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 of vaccine impact in the routinely immunised 12-13 year old girls.

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Health Protection Scotland and Information Services Division have been brought together as 'Public Health and Intelligence (PHI)' within NHS National Services Scotland.

Health Protection Scotland