The impact of bivalent HPV vaccine on cervical intraepithelial neoplasia by deprivation in Scotland: reducing the gap

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What is known?

- Cervical cancer disproportionately affects women from high deprivation backgrounds
- Uptake of the HPV vaccine in the catch-up programme was lower and not equitable compared to the routine programme in Scotland
- The HPV vaccine has previously been shown to be associated with significant reductions in HPV prevalence and cervical abnormalities in Scotland

What this study adds?

- We show a continued significant reduction in all grades of cervical intraepithelial neoplasia in vaccinated women with vaccine effect against CIN 3 greater in those from high deprivation backgrounds.
- The HPV vaccine has reduced health inequalities in cervical cancer despite inequitable uptake in the catch-up programme.

ABSTRACT

Background Cervical cancer disproportionately affects women from lower socio-economic backgrounds. A human papillomavirus (HPV) vaccination programme was introduced in Scotland in 2008 with uptake being lower and inequitable in a catch-up cohort run for the first three years of the programme compare to the routine programme. The socio-economic differences in vaccine uptake have the potential to further increase the inequality gap in regards to cervical disease.

Methods Vaccination status was linked to demographical, cytological and colposcopic data, which is routinely collected by the Scottish HPV surveillance system. Incidence rates and relative risk of cervical intraepithelial neoplasia (CIN) 1, 2 and 3 in unvaccinated and vaccinated women were stratified by birth year and deprivation status using Poisson regression.

Results Women who received three doses of HPV vaccine have significantly decreased risk of CIN 1, 2 and 3. Vaccine effectiveness was greater in those women from the most deprived backgrounds against CIN 2 and 3 lesions. Compared to the most deprived, unvaccinated women, the relative risk of CIN3 in fully vaccinated women in the same deprivation group was 0.29 (95% CI 0.2-0.43) compared to 0.62 (95% CI 0.4-0.97) in vaccinated women in the least deprived group.

Conclusions The HPV vaccine is associated with significant reductions in both low- and high-grade CIN for all deprivation categories. However, the effect on high-grade disease was most profound in the most deprived women. These data are welcoming and allays the concern that inequalities in cervical cancer may persist or increase following the introduction of the vaccine in Scotland.

INTRODUCTION

Cervical cancer is the most common cancer in women under the age of 35 in the UK with persistent high-risk (HR) human papillomavirus infection being the principle risk factor.[1, 2] HPV immunisation has been offered to all 12 to 13 year old girls in Scotland since September 2008 with uptake of all three doses of vaccine exceeding 90% each year within this routine cohort.[3] In addition, a catch-up programme was conducted simultaneously from September 2008 to August 2011 targeting girls aged 13-17. Overall uptake of three doses in this catch-up cohort was lower at 65% and varied by whether the individual was still at school at the time of vaccination and age.[3] The bivalent vaccine was used for the programme from 2008 to 2012; at which time it was changed to the quadrivalent vaccine. To assess the impact of the bivalent HPV vaccine on virological, cytological and histological outcomes, a national HPV surveillance system was created in tandem with the vaccination programme and all data collected to date are from girls who received the bivalent vaccine. Utilising data from the surveillance system we have shown a significant reduction in prevalence of HPV 16 and 18 and evidence of cross protection for HPV types 31, 33 and 45 associated with the bivalent HPV vaccine in 20 year old women attending for their first cervical screen.[4] In terms of disease outcomes, the bivalent vaccine has also been associated with a 55% reduction in high grade cervical intraepithelial neoplasia (CIN3) in women vaccinated as part of the catch-up programme [5] consistent with evidence from meta-analysis of data from nine countries.[6, 7] Furthermore in addition to the observed impacts on vaccinated women, early evidence of herd protection for HR-HPV infection in unvaccinated women has emerged in Scotland which is consistent with data from Australia.[8, 9]

Deprivation, as measured by the Scottish Index of Multiple Deprivation (SIMD), is associated with increased cervical cancer incidence and mortality - both more than two-fold higher in women residing in the most deprived areas compared to the least deprived areas in Scotland.[10] This disparity can also be observed at the global level with low-income countries having significantly higher rates of cervical cancer, four fold in some cases, when compared to high income countries.[11] These differences are likely to be multifactorial and include lower level of engagement with cervical screening, earlier age of sexual debut and increased likelihood of smoking in those from more deprived backgrounds. [12-15]

Although uptake of HPV vaccine in Scotland is generally high across all SIMD quintiles there is a lower likelihood of receiving all doses in the most deprived. In the first three years of the Scottish HPV immunisation programme, uptake of the first dose in the routine schools based cohort was high across all deprivation categories (~90%) but decreased linearly with increasing deprivation for doses two and three.[3] A similar pattern was seen in the catch-up programme where three dose uptake was 84.3-89.9% in those at school compared to ~30% in those who had left.[3] As school leavers are more likely to be from more deprived backgrounds, the substantially lower uptake in the out of school catch-up cohort coupled with the higher rates of cervical cancer in this group has the potential to widen the inequality gap between the least and most deprived women in Scotland with regards to incidence of cervical disease.

The objective of the present work was to determine the effect that the introduction of the bivalent HPV vaccine has had on the inequality gap by measuring the incidence rates of CIN1, CIN2 and CIN3 at first cervical screen stratified by deprivation category and vaccination status.

METHODS

OVERVIEW OF THE SCOTTISH HPV SURVEILLANCE SYSTEM

The methodology and processes involved in HPV surveillance in Scotland has been described previously.[4, 5] In summary, HPV surveillance is longitudinal and is facilitated by the use of an unique patient identifier, the community health index (CHI) number which allows for linkage of vaccination status to viral and disease outcomes.

Since 2008, the Information Services Division (ISD) of the Scottish National Health Service (NHS) provides Health Protection Scotland (HPS) with an annual update of the HPV surveillance cohort which contains anonymised data on all medically registered women born in Scotland between 1988 and, as of the end of 2015, 1994. These data are linked by ISD to HPV vaccination data from the Scottish Immunisation Call-Recall System (SIRS), the Child Health Schools Programme-System (CHSP-S) and the Scottish Index of Multiple Deprivation (SIMD) using the CHI number. The linked records are anonymised and assigned a unique reference number before HPS review.

SIMD is an index of multiple deprivation in Scotland which takes into account employment, income, health, crime, housing, education and access to services in small areas termed datazones. This deprivation index is then mapped to individuals based on their postcode of residence and quintiles of the score calculated overall. Individuals scoring SIMD 1 represent those that reside in the 20% most deprived areas while SIMD 5 represents those that reside in the 20% least deprived areas.

LINKAGE

The national Scottish Cervical Screening Call and Recall System (SCCRS) is an information technology system used by the Scottish cervical screening programme. It contains longitudinal cervical screening records for all eligible women in Scotland and incorporates pathology, virology, recall and management information for all eligible women in Scotland. ISD send records of all 20 and 21 year olds attending for their first cervical screen to HPS on an annual basis covering the birth cohorts from 1988 to 1994. If a woman is referred to colposcopy, her results are captured in the National Colposcopy Clinical Information and Audit System (NCCIAS). HPS receives NCCIAS data for those in the monitored HPV surveillance cohorts on a quarterly basis and up to 12 to 18 months of follow is available for each woman.

ANALYSIS OF CIN IN WOMEN ATTENDING FOR FIRST SMEAR ACCORDING TO DEPRIVATION AND VACCNATION STATUS

Incident abnormal histological episodes (CIN 1, CIN 2 and CIN 3) occurring within the first year following the first cervical screen in women aged 20 or 21 years born between 1988 to 1994 were considered for each woman.

The incidence rates of CIN 1, CIN 2 and CIN 3 per 1000 person-years were calculated by comparing the numbers of each diagnosis to the person-time contribution of each screened women. Incidence rates and associated 95% confidence intervals were stratified by SIMD quintile and the number of doses received. The relative risk of each grade of CIN in vaccinated women compared to unvaccinated women was calculated using Poisson regression, adjusting for birth cohort to model potential sociological differences between cohorts with person-time contribution used as an offset. As the relative risks of each grade of CIN were calculated with reference to those with no disease, the person-time contribution of women with a different disease outcome to the one being assessed was not included in the calculation of the rates. Adjusted relative risks were calculated using a similar approach but with the inclusion of an interaction term between SIMD quintile and the number of doses received to consider potential differences on the impact of the vaccination on disease by deprivation quintile. All statistical analyses were performed in R version 3.2.0.

Sensitivity analyses were performed for each grade of CIN; one model including only unvaccinated women, one including only those born from 1988 to August 1990 who would be unvaccinated as they were ineligible for vaccine and one including only those women born from 1991 to 1994 who were mostly vaccinated. These analyses were undertaken to remove potential sociological and temporal differences which may exist between those women who are vaccinated and unvaccinated which may confound vaccine effect.

RESULTS

Table 1 presents the characteristics of the women included in the study. Almost all women born in 1988 and 1989 were unvaccinated as they were not eligible to receive vaccine and therefore represent a baseline of CIN incidence in women attending for first screen in Scotland. As expected, the proportion of women receiving three doses of HPV vaccine increased with each new birth cohort from 1988 (0.03%) to 1994 (80.3%). Additionally, the numbers of each grade of CIN have decreased from 1988 to 1994. The proportion of unvaccinated women was higher in the most deprived quintile (58.7%) compared to the least deprived quintile (53.4%) with vaccine uptake increasing with increased affluence. The proportion of partially vaccinated women is also higher in the high deprivation categories. Figure 1 shows the proportion of screened women who are fully vaccinated increases with decreasing deprivation for each birth cohort. The number of women with CIN1, CIN 2 and CIN 3 generally decreases with decreasing deprivation.

Table 1: Overview of characteristics of women included in study

Birth year	Screened	Unvaccinated	1 dose	2 doses	3 doses	CIN1	CIN2	CIN3
1988	21830	99.95%	0.01%	0.01%	0.03%	274	276	248
1989	20223	99.64%	0.12%	0.08%	0.15%	229	253	183
1990	20542	81.45%	1.46%	2.69%	14.40%	216	224	201
1991	20284	30.64%	3.02%	6.72%	59.61%	169	161	141
1992	19807	20.37%	2.49%	5.02%	72.11%	148	113	90
1993	19560	22.98%	2.82%	5.10%	69.10%	163	130	74
1994	15461*	14.50%	1.74%	3.46%	80.30%	97	65	40
SIMD quintile								
SIMD 1: Most deprived	30285	58.70%	2.54%	4.50%	34.26%	335	386	291
SIMD 2	28859	56.09%	1.86%	3.60%	38.45%	280	295	262
SIMD 3	26503	53.06%	1.49%	3.13%	42.31%	239	199	180
SIMD 4	24557	52.86%	1.18%	2.72%	43.24%	207	191	137
SIMD 5: Least deprived	27503	53.37%	0.96%	2.05%	43.62%	235	151	107
TOTAL	137707	54.96%	1.64%	3.24%	40.16%	1296	1222	977

*The numbers of screened women is lower in 1994 as these women had less follow-up time at data extraction

Figure 2 (rates available in supplementary table S1) presents the incidence rates of CIN 1, CIN 2 and CIN 3 per 1000 person-years. Across all SIMD quintiles, the rate of cervical lesions is lower in fully vaccinated women compared to unvaccinated women. The difference in incidence rate between unvaccinated and fully vaccinated women is greater in those women diagnosed with more severe disease (CIN 2 and CIN 3) (Figure 2B and 2C). The

decrease in incidence is more profound in the most deprived; for CIN 3 the rate in the unvaccinated and most deprived individuals (SIMD 1) is 14.5 per 1000 person-years (95% CI 12.7-16.4) compared to 3.3 per 1000 person-years (95% CI 2.3-4.7) ($p<0.001$) in those vaccinated (Figure 2C). The corresponding results in the most affluent group (SIMD 5) is a shift from 5.1 per 1000 person-years (95% CI 4-6.5) ($p<0.001$) in the unvaccinated to 2.5 per 1000 person-years (95% CI 1.7-3.6) ($p=0.037$) in the vaccinated. The pattern of impact is similar for CIN 2 (Figure 2B).

For CIN 1, there was no significant evidence of a differential vaccine impact on incidence between SIMD quintile (Figure 2A, test of interaction SIMD and vaccine status, p-value=0.275) therefore only a main effects model was considered (Table 2). Calculation of adjusted relative risks (RR) showed a significant effect of 3 doses of vaccine associated with a reduction of CIN 1 burden (RR=0.83, 95% CI 0.69-0.98) ($p=0.028$). After adjustment for vaccine status and cohort year, the effect of deprivation remains, with those in the least deprived cohort less likely to have CIN 1 (SIMD 5 RR=0.78, 95% CI 0.66-0.92) ($p=0.003$). Sensitivity analyses did not significantly alter the relative risk estimates (Supplementary tables S2-S4).

Table 2: Rates (per 1000 person year) and adjusted RR of CIN 1 by birth cohort, SIMD quintile and number of doses of vaccine received

		Person-years	Number of CIN 1	Rate per 1000 person years (95% CI)	Adjusted RR (95% CI)	p-value
Number of doses	0	72601	835	11.5 (10.7-12.3)	1	-
	1	2152	16	7.4 (4.2-12.1)	0.752 (0.453-1.248)	0.271
	2	4281	43	10.0 (7.3-13.5)	1.031 (0.744-1.428)	0.855
	3	53325	402	7.5 (6.8-8.3)	0.825 (0.695-0.979)	0.028
Birth cohort	1988	20917	274	13.1 (11.6-14.7)	1	-
	1989	19465	229	11.8 (10.3-13.4)	0.901 (0.756-1.073)	0.242
	1990	19825	216	10.9 (9.5-12.4)	0.859 (0.717-1.029)	0.098
	1991	19768	169	8.6 (7.3-9.9)	0.736 (0.590-0.917)	0.006
	1992	19436	148	7.6 (6.4-8.9)	0.671 (0.529-0.851)	0.001
	1993	18921	163	8.6 (7.3-10.0)	0.756 (0.601- 0.951)	0.017
	1994	14028	97	6.9 (5.6-8.4)	0.622 (0.475-0.815)	0.001
SIMD quintile	**SIMD 1: Most deprived**	28842	335	11.6 (10.4-12.9)	1	-
	SIMD 2	27669	280	10.1 (9.0-11.4)	0.878 (0.750-1.030)	0.110
	SIMD 3	25527	239	9.4 (8.2-10.6)	0.822 (0.696-0.971)	0.021
	SIMD 4	23706	207	8.7 (7.6-10.0)	0.765 (0.643-0.910)	0.002
	SIMD 5: Least deprived	26614	235	8.8 (7.7-10.0)	0.777 (0.657-0.918)	0.00307

Considering CIN 2 and CIN 3, there is evidence for a differential impact of vaccination across the deprivation quintiles (test of interaction SIMD and vaccine status for CIN 2 and CIN 3 both p-value <0.001). Compared to the most deprived and unvaccinated individuals, the least deprived and unvaccinated women have reduced risk of CIN 2 (RR=0.47, 95% CI 0.38-0.59) (p<0.001) (Table 3, Table 4). In those vaccinated and most deprived, there is a reduced risk of CIN 2 (RR=0.45 95% CI 0.33-0.6) (p<0.001) compared to most deprived and unvaccinated while those women who were vaccinated and least deprived had a similar reduction in disease (RR=0.38 95% CI 0.25-0.58) (p<0.001) compared to unvaccinated women in SIMD 5. For CIN 2, the significance of the interaction between SIMD and vaccine impact is likely driven by the low incidence in the unvaccinated women from the SIMD 3

group (Figure 2B), which then affects the vaccine impact in this group (RR=0.71; 95% CI 0.51-0.99) (p=0.041).

Table 3: Rates (per 1000 person year) and adjusted RR* of CIN 2 and 3 by birth cohort

Birth cohort	Number of CIN 2	Person-years	Rate per 1000 person years (95% CI)	Adjusted RR (95% CI)	p-value		Number of CIN 3	Person-years	Rate per 1000 person years (95% CI)	Adjusted RR (95% CI)	p-value
1988	276	20904	13.2 (11.7-14.9)	1	-		248	20891	11.9 (10.4-13.4)	1	-
1989	253	19474	13 (11.4-14.7)	0.99 (0.84-1.18)	0.924		183	19438	9.4 (8.1-10.9)	0.8 (0.661-0.968)	0.022
1990	224	19818	11.3 (9.9-12.9)	0.93 (0.78-1.11)	0.435		201	19800	10.2 (8.8-11.7)	0.946 (0.785-1.141)	0.565
1991	161	19755	8.2 (6.9-9.5)	0.89 (0.72-1.11)	0.294		141	19748	7.1 (6-8.4)	0.941 (0.748-1.185)	0.606
1992	113	19414	5.8 (4.8-7)	0.7 (0.55-0.9)	0.005		90	19394	4.6 (3.7-5.7)	0.692 (0.527-0.908)	0.008
1993	130	18884	6.9 (5.8-8.2)	0.81 (0.64-1.03)	0.081		74	18857	3.9 (3.1-4.9)	0.567 (0.426-0.754)	<0.001
1994	65	14007	4.6 (3.6-5.9)	0.61 (0.45-0.82)	0.001		40	13993	2.9 (2-3.9)	0.476 (0.331-0.685)	<0.001

***The relative risk (RR) for each birth cohort is adjusted for the interaction of Scottish Index of Multiple Deprivation (SIMD) quintile and number of doses of vaccine received.**

For CIN 3, the differential impact of the vaccine by deprivation quintile is clear (Table 3, Table 4). Compared to the most deprived and unvaccinated group, those vaccinated in the same deprivation quintile have a significantly reduced risk (RR=0.29 95% CI 0.2 -0.43) (p<0.001). The impact for those vaccinated in the least deprived group (SIMD 5) is less evident (RR=0.62 95% CI 0.4-0.97) (p=0.037) when compared to unvaccinated, least deprived group illustrated by Figure 2C and reflective of the lower incidence rate in the unvaccinated individuals in SIMD 5. Sensitivity analyses of the models for CIN 2 and CIN 3 showed small differences to the relative risk estimates compared to the full model but did not change the overall conclusions (Supplementary tables S2-S4).

Table 4: Rates (per 1000 person year) and adjusted RR* of CIN 2 and 3 by the combination of Scottish Index of Multiple Deprivation (SIMD) quintile and number of doses of vaccine received.

SIMD quintile	Number of doses	Number of CIN 2	Person-years	Rate per 1000 person years (95% CI)	Adjusted RR (95% CI)	p-value		Number of CIN 3	Person-years	Rate per 1000 person years (95% CI)	Adjusted RR (95% CI)	p-value
SIMD 1: Most deprived	**0**	296	16830	17.6 (15.6-19.7)	1	-		243	16816	14.5 (12.7-16.4)	1	-
SIMD 2	**0**	215	15500	13.9 (12.1-15.9)	0.79 (0.66-0.94)	0.008		204	15490	13.2 (11.4-15.1)	0.909 (0.755-1.095)	0.316
SIMD 3	**0**	128	13528	9.5 (7.9-11.3)	0.54 (0.44-0.66)	<0.001		127	13523	9.4 (7.8-11.2)	0.65 (0.524-0.805)	<0.001
SIMD 4	**0**	139	12516	11.1 (9.3-13.1)	0.63 (0.51-0.77)	<0.001		104	12495	8.3 (6.8-10.1)	0.571 (0.454-0.719)	<0.001
SIMD 5: Least deprived	**0**	118	14207	8.3 (6.9-9.9)	0.47 (0.38-0.59)	<0.001		73	14188	5.1 (4-6.5)	0.357 (0.275-0.463)	<0.001
SIMD 1: Most deprived	**1**	15	727	20.6 (11.5-34)	1.39 (0.82-2.36)	0.225		5	725	6.9 (2.2-16.1)	0.58 (0.237-1.416)	0.232
SIMD 2	**1**	1	517	1.9 (0.1-10.8)	0.16 (0.02-1.16)	0.070		9	517	17.4 (8-33)	1.551 (0.789-3.051)	0.203
SIMD 3	**1**	7	377	18.6 (7.5-38.2)	2.26 (1.05-4.87)	0.038		6	375	16 (5.9-34.8)	1.969 (0.862-4.5)	0.108
SIMD 4	**1**	4	279	14.3 (3.9-36.7)	1.48 (0.54-4.01)	0.444		1	278	3.6 (0.1-20)	0.493 (0.069-3.544)	0.482
SIMD 5: Least deprived	**1**	0	253	0	0	-		1	253	4 (0.1-22)	0.884 (0.123-6.376)	0.903
SIMD 1: Most deprived	**2**	11	1296	8.5 (4.2-15.2)	0.57 (0.31-1.05)	0.072		10	1295	7.7 (3.7-14.2)	0.641 (0.337-1.22)	0.175
SIMD 2	**2**	20	987	20.3 (12.4-31.3)	1.71 (1.07-2.74)	0.025		7	984	7.1 (2.9-14.7)	0.633 (0.295-1.356)	0.239
SIMD 3	**2**	5	801	6.2 (2.1-14.6)	0.76 (0.31-1.87)	0.552		9	803	11.2 (5.1-21.3)	1.38 (0.695-2.739)	0.357
SIMD 4	**2**	5	648	7.7 (2.5-18)	0.8 (0.33-1.97)	0.631		2	649	3.1 (0.4-11.1)	0.423 (0.104-1.722)	0.230
SIMD 5: Least deprived	**2**	3	543	5.5 (1.1-16.2)	0.76 (0.24-2.4)	0.639		4	543	7.4 (2-18.9)	1.605 (0.584-4.417)	0.359

SIMD 1: Most deprived	**3**	64	9975	6.4 (4.9-8.2)	0.45 (0.33-0.6)	<0.001		33	9960	3.3 (2.3-4.7)	0.292 (0.199-0.43)	<0.001
SIMD 2	**3**	59	10658	5.5 (4.2-7.1)	0.49 (0.36-0.67)	<0.001		42	10640	3.9 (2.8-5.3)	0.384 (0.268-0.549)	<0.001
SIMD 3	**3**	59	10802	5.5 (4.2-7)	0.71 (0.51-0.99)	0.041		38	10789	3.5 (2.5-4.8)	0.477 (0.325-0.702)	<0.001
SIMD 4	**3**	43	10240	4.2 (3-5.7)	0.47 (0.32-0.67)	<0.001		30	10231	2.9 (2-4.2)	0.45 (0.294-0.691)	<0.001
SIMD 5: Least deprived	**3**	30	11572	2.6 (1.7-3.7)	0.38 (0.25-0.58)	<0.001		29	11566	2.5 (1.7-3.6)	0.62 (0.395-0.972)	0.037

*The relative risk (RR) for each combination of number of doses and SIMD is adjusted for birth cohort.

DISCUSSION

The uptake of cervical screening in Scotland in women aged 20-60 has gradually decreased over the last 10 years and dropped below 70% for the time since 2007.[16] Therefore, HPV vaccination is increasingly important in the primary prevention of cervical cancer. We have shown that the bivalent vaccine is significantly associated with reductions of CIN 1, CIN 2 and CIN 3, with vaccine effectiveness against CIN 2 and CIN 3 greater in those women from the most deprived categories. These findings are welcome due to the higher rates of cervical cancer and poorer outcomes in women in SIMD 1. Our findings also allay the concern that HPV immunisation would further widen the inequality gap between the least and most deprived women with regards to rates of cervical disease.[2] Paired with evidence of herd immunity against HPV 16 and 18 in the unvaccinated population from those born 1993 onwards,[8] those most at risk are benefitting from protection against cervical disease. Nevertheless, there remains a cohort of unvaccinated women in SIMD 1 in which there are higher rates of cervical disease compared to the unvaccinated least deprived women, albeit a small number, and therefore the benefits of regular screening must be reiterated.

We have previously shown that bivalent HPV vaccine is associated with reductions in low and high grade cervical abnormalities.[5] Evidence of reductions in cervical abnormalities is also being demonstrated elsewhere. An Australian study presented quadrivalent vaccine effectiveness of 46% against high grade cervical abnormalities and a study in the United States reported vaccine effectiveness estimates against HPV 16/18- attributable CIN 2+ of between 21% to 72%, depending on time between vaccination and diagnosis of CIN 2+.[17, 18] We observed no significant reduction in CIN 1, 2 or 3 in women who were partially vaccinated despite a reduction in HPV prevalence in those women in a study of Scottish data. This may be confounded by differences in sociological factors which may exist between those who received only a partial number of doses compared to those who receive the full regimen and the fact only a small number women are partially vaccinated in Scotland.[19] As further data accrue, we aim to investigate the impact of partial vaccination on disease outcomes.

Inequalities in cervical screening uptake in the UK and in other developed countries are well documented with women from deprived backgrounds less likely to attend.[20-24] Several factors have been identified which contribute to non-attendance of women at cervical screening including perception of risk of developing cervical cancer being low, the potential

for embarrassment and pain, a lack of knowledge about the purposes of cervical screening and anxiety about the results.[23, 24] These factors may disproportionately affect more deprived women due to lower educational attainment which has been shown to be associated with non-attendance at cervical screening.[25] Notably, a recent analysis of Scottish data showed that screening uptake, in vaccine eligible women, is higher in the most deprived women.[26] This contrast with previous research may be related to differences in the usage of health services or increased movement of the least deprived women.[26] It is welcoming that the Scottish data so far indicate that inequitable uptake of vaccine in the catch-up cohort and cervical screening has not led to a widening of the difference in rates of CIN between the most and least deprived.

A major strength of our study is that we utilised data from large national databases which were linked to immunisation status via a unique patient identifier, allowing the impact of the HPV vaccine to be assessed directly. There are, however, some limitations associated with the study. The lack of sexual history data and the fact that all women included in the study received vaccine as part of the catch-up campaign may lead to lower estimates of vaccine effect than is likely to be observed in those routinely vaccinated at age 12. Another limitation is that the majority of unvaccinated women are from the 1988 and 1989 cohort; comparisons of rates between unvaccinated and vaccinated women is partly a temporal comparison, therefore, the differences may be confounded by changes in behaviours and sexual practices over time. This is partly adjusted for in the Poisson regression analysis by including birth cohort but cannot fully account for sexual history and practices. However, results of the National Survey of Sexual Attitudes and Lifestyles (NATSAL) study have actually shown an increase in the number of sexual partners in women over time, which is known to increase the risk of HR-HPV infection. Thus the decrease is unlikely to be due to changes in sexual practices alone.[27] Results from sensitivity analyses (Supplementary tables S2-S4) show that temporal changes and/or sociological differences are unlikely to have had a substantial effect on our conclusions.

While SIMD is an effective method of estimating deprivation it does have limitations. A SIMD score is assigned based on postcode of residence and therefore shows an individual is from a deprived area but it may not accurately represent an individual's true deprivation status.[28] Also, as seven different aspects of deprivation are considered, an individual may be categorised as being deprived based on aspects which are not as relevant to the likelihood

of receiving HPV immunisation and attending for cervical screening. For example, an individual may be from an area which scores low on crime and housing conditions but scores more highly on geographical access and education which may be more influential on individual's health seeking behaviour.

Our results are derived from those who have attended for their first screen at age 20-21 and are thus not wholly representative of the Scottish population where around half of all cancers are detected in those who have never attended for screening. Excluding women who attend their first cervical screen later in life will also underestimate the true burden of cervical disease and may bias our sample towards less deprived, vaccinated women. Studies in Scotland and the US have shown that screening uptake is higher in vaccinated women and therefore vaccine effect may be overestimated in our study.[26, 29] It should be noted that deprived women who engage with cervical screening may be socially and culturally different to those that do not, potentially confounding the vaccine effect in the most deprived but this is tempered by the inclusion of the 1988 and 1989 birth cohorts who were ineligible to receive vaccine.

The bivalent HPV vaccine in Scotland is associated with a reduction in the inequality in cervical disease between deprivation groups by decreasing the incidence of high grade cervical lesions in the most deprived women who attend screening to rates comparable to a level in the least deprived category. Our results are encouraging for other countries, including those with inequitable uptake.

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Dr Syed Ahmed is the clinical lead for the work. Dr Kevin Pollock and Ross Cameron conceived the original idea for the work. Testing of samples and data collection was co-ordinated by Dr Kate Cuschieri. Data collation, management and linkage were performed by Cameron Watt. Data analysis and interpretation was undertaken by Ross Cameron, Dr Kim Kavanagh and Dr Chris Robertson. Drafting of the article was undertaken by Ross Cameron and all authors critically revised the article and approved the final manuscript.

Ethical approval was not required for this study as it did not involve human subjects.

REFERENCES

1. Dunne EF and Park IU. HPV and HPV-associated diseases. *Infect Dis Clin N Am* 2013;27:765-778.

2. National Services Scotland Information Services Division. Cancer Statistics. 2016. http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Cancer_in_Scotland_summary_m.pdf. [Accessed: November 2016]

3. Sinka K, Kavanagh K, Gordon R, et al. Achieving high and equitable coverage of adolescent HPV vaccine in Scotland. *J Epidemiol Commun* 2013;68:57-63

4. Kavanagh K, Pollock KGJ, Potts A, et al. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. *Brit J Cancer* 2014;110(11):2804-11.

5. Pollock KGJ, Kavanagh K, Potts A, et al. Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. *Brit J Cancer* 2014;111:1824-1830.

6. Mesher D, Soldan K, Lehtinen M, et al. Population-level effects of human papillomavirus vaccination programs on infections with nonvaccine genotypes. *Emerg Infect Dis* 2016;22:1732-1740.

7. Drolet M, Bérnard E, Boily MC, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2015; S1473-3099(14)71073-4.

8. Cameron RL, Kavanagh K, Pan J, et al. Human papillomavirus prevalence and herd immunity after introduction of vaccination program, Scotland, 2009–2013. *Emerg Infect Dis*. 2016 Jan [30/11/2016]. http://dx.doi.org/10.3201/eid2201.150736

9. Tabrizi SN, Brotherton JML, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. *Lancet Infect Dis*. 2014;14(10):958-66.

10. National Services Scotland Information Services Division. Cancer of the cervix uteri (ICD-10 C53) Scotland: age-standardised incidence and mortality rates (EASRs), by SIMD 2012. 2015. https://www.isdscotland.org/Health-Topics/Cancer/Publications/2015-11-17/dim_cancer_cervix.xls

11. Forman D, de Martel C, Lacey CJ et al. Global burden of human papillomavirus and related diseases. *Vaccine* 2012 Nov 20;30:Suppl-23.

12. Kavanagh K, Sinka K, Cuschieri K, et al. Estimation of HPV prevalence in young women in Scotland; monitoring of future vaccine impact. *BMC Infect Dis*. 2013;13:519.

13. O'Leary MC, Sinka K, Robertson C, et al. HPV type-specific prevalence using a urine assay in unvaccinated male and female 11- to 18-year olds in Scotland. *Brit J Cancer*. 2011 Mar 29;104(7):1221-6.

14. Tanton C, Soldan K, Beddows S, et al. High-Risk Human Papillomavirus (HPV) Infection and Cervical Cancer Prevention in Britain: Evidence of Differential Uptake of Interventions from a Probability Survey. *Cancer Epidem Biomar*. 2015;24(5):842-53.

15. Douglas E, Waller J, Duffy SW, et al. Socioeconomic inequalities in breast and cervical screening coverage in England: are we closing the gap? *J Med Screen*. 2016;23(2):98-103.

16. National Services Scotland Information Services Division. Scottish Cervical Screening Programme. 2016. https://www.isdscotland.org/Health-Topics/Cancer/Publications/2016-09-06/Annual_uptake_data.xlsx [Accessed: November 2016]

17. Crowe E, Pandeya N, Brotherton JM, et al. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. *Brit Med J*. 2014;348:g1458

18. Hariri S, Bennett NM, Niccolai LM, et al. Reduction in HPV 16/18-associated high grade cervical lesions following HPV vaccine introduction in the United States - 2008-2012. *Vaccine* 2015;33:1608-1613

19. Cuschieri K, Kavanagh K, Moore C, et al. Impact of partial bivalent HPV vaccination on vaccine-type infection: A population-based analysis. *Br J Cancer*. 2016;114(11):1261-1264

20. Tanton C, Soldan K, Beddows S, et al. High-Risk Human Papillomavirus (HPV) Infection and Cervical Cancer Prevention in Britain: Evidence of Differential Uptake of Interventions from a Probability Survey. *Cancer Epidem Biomark*. 2015;24:842-853

21. Webb R, Richardson J, and Pickles A. A population-based study of primary care predictors of non-attendance for cervical screening. *J Med Screen* 2004;11:135-140

22. Sutton S. and Rutherford C. Sociodemographic and attitudinal correlates of cervical screening uptake in a national sample of women in Britain. *Soc Sci Med*. 2005;61:2460-2465

23. Orbell S, Crombie I, Robertson A, et al. Assessing the effectiveness of a screening campaign: who is missed by 80% cervical screening coverage? *J Roy Soc Med* 1995;88:389-394

24. Cooper M. Reasons for non-attendance at cervical screening. *Nursing Standard* 2011;25:41-46

25. Moser K, Patnick J, and Beral V. Inequalities in reported use of breast and cervical screening in Great Britain: analysis of cross sectional survey data. *Brit Med J* 2009;338:b2025

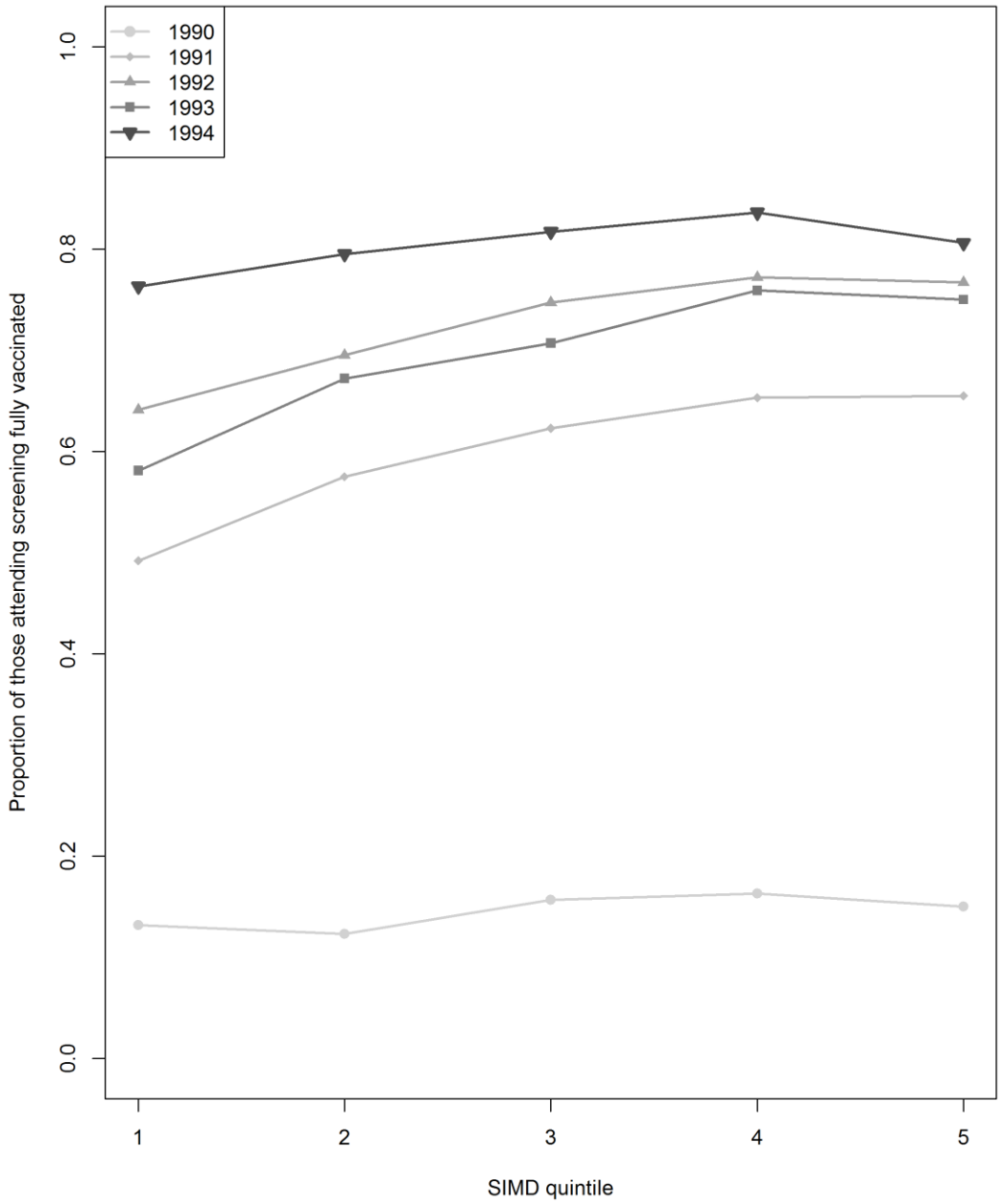
26. Mercer CH, Tanton C, Prah P, et al. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). *The Lancet* 2013;382(9907):1781-94.

27. Palmer TJ, McFadden M, Pollock KGJ, et al. HPV immunisation and increased uptake of cervical screening in Scottish women; observational study of routinely collected national data. *Br J Cancer* 2016;114:576-580

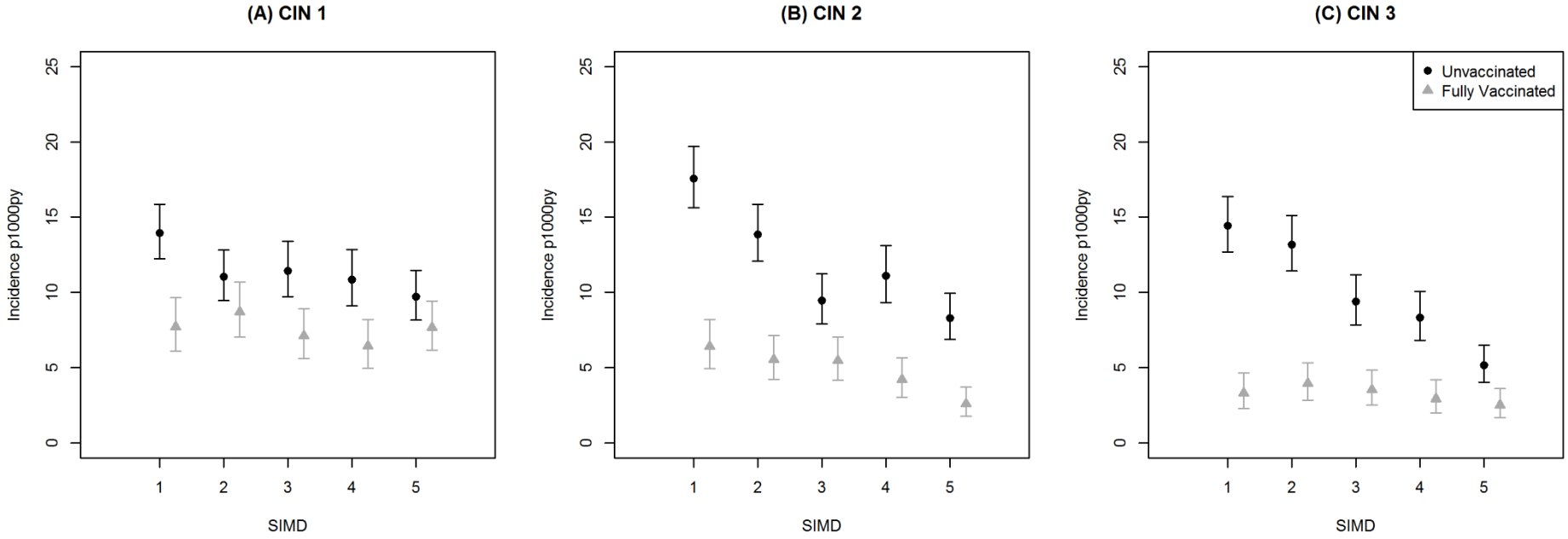
28. Scottish Government. The Scottish Index of Multiple Deprivation. 2016. http://www.gov.scot/Topics/Statistics/SIMD [Accessed: February 2016]

29. Ferris DG, Waller J, Dickinson A, et al. Impact of pap test compliance and cervical cancer screening intervals on human papillomavirus vaccine acceptance. *Low Genit Tract Dis* 2012;16(1):39–44.

Figure 1: Proportion of women who attended for first screen aged 20-21 who are fully vaccinated (3 doses) by birth cohort and deprivation (SIMD) quintile (based on location of residence SIMD 1: most deprived 20%, SIMD 5: least deprived 20%)



475 Figure 2: Incidence rate per 1000 person-years (p1000py) of (A) CIN 1,(B) CIN 2 and (C) CIN 3 by deprivation (SIMD) quintile (based on location of
476 residence SIMD 1: most deprived 20%, SIMD 5: least deprived 20%) in unvaccinated and fully vaccinated (3 doses) women



477

Supplementary tables

Table S1: Rates, unadjusted and adjusted relative risks of CIN1, CIN2 and CIN3 in 1 year following first smear in 20-21 year old women born between 1988 to 1994 by vaccination status and deprivation

CIN1		Rate per 1000py (95% CI)	
		Unvaccinated	Fully vaccinated
	SIMD 1	14 (12.2-15.9)	7.71 (6.08-9.63)
	SIMD 2	11.03 (9.44-12.82)	8.71 (7.03-10.67)
	SIMD 3	11.44 (9.71-13.39)	7.12 (5.62-8.9)
	SIMD 4	10.85 (9.11-12.83)	6.43 (4.97-8.18)
	SIMD 5	9.7 (8.15-11.46)	7.67 (6.16-9.43)
CIN 2			
	SIMD 1	17.58 (15.63-19.7)	6.41 (4.94-8.19)
	SIMD 2	13.86 (12.07-15.84)	5.53 (4.21-7.14)
	SIMD 3	9.46 (7.89-11.24)	5.46 (4.16-7.04)
	SIMD 4	11.1 (9.33-13.1)	4.2 (3.04-5.65)
	SIMD 5	8.3 (6.87-9.94)	2.59 (1.75-3.7)
CIN 3			
	SIMD 1	14.44 (12.68-16.37)	3.31 (2.28-4.65)
	SIMD 2	13.16 (11.42-15.1)	3.94 (2.84-5.33)
	SIMD 3	9.38 (7.82-11.17)	3.52 (2.49-4.83)
	SIMD 4	8.32 (6.8-10.1)	2.93 (1.98-4.18)
	SIMD 5	5.14 (4.03-6.46)	2.51 (1.68-3.6)

Table S2a: Adjusted RR of CIN 1, CIN 2 and CIN 3 by birth cohort and SIMD quintile in unvaccinated women

	CIN 1		CIN 2		CIN 3	
SIMD quintile	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**
1	1		1		1	
2	0.79 (0.65-0.96)	0.018	0.79 (0.66-0.94)	0.008	0.91 (0.75-1.1)	0.316
3	0.82 (0.67-1)	0.052	0.54 (0.44-0.66)	<0.001	0.65 (0.52-0.81)	<0.001
4	0.77 (0.62-0.95)	0.016	0.63 (0.51-0.77)	<0.001	0.57 (0.45-0.72)	<0.001
5	0.7 (0.56-0.86)	<0.001	0.47 (0.38-0.59)	<0.001	0.36 (0.27-0.46)	<0.001
Birth cohort						
1988	1		1		**1**	
1989	0.9 (0.75-1.07)	0.235	0.99 (0.83-1.17)	0.905	0.8 (0.66-0.97)	0.023
1990	0.84 (0.70-1.01)	0.07	0.87 (0.72-1.05)	0.14	0.94 (0.77-1.14)	0.5
1991	0.86 (0.66-1.12)	0.261	0.94 (0.73-1.22)	0.652	0.9 (0.68-1.18)	0.446
1992	0.68 (0.48-0.97)	0.031	0.84 (0.61-1.16)	0.29	0.81 (0.58-1.14)	0.234
1993	0.64 (0.45-0.9)	0.011	0.85 (0.63-1.15)	0.299	0.58 (0.4-0.85)	0.005
1994	0.66 (0.4-1.07)	0.094	0.59 (0.35-0.99)	0.046	0.53 (0.3-0.94)	0.031

Table S3a: Adjusted RR of CIN 1, CIN 2 and CIN 3 by birth cohort and SIMD quintile in women born 1988-1990

	CIN 1		CIN 2		CIN 3	
SIMD quintile	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**
1	1		1		1	
2	0.68 (0.52-0.88)	0.003	0.78 (0.62-0.99)	0.039	1 (0.78-1.29)	0.972
3	0.83 (0.64-1.07)	0.142	0.55 (0.42-0.72)	<0.001	0.7 (0.55-0.96)	0.024
4	0.77 (0.59-1)	0.05	0.65 (0.5-0.84)	0.001	0.66 (0.49-0.88)	<0.001
5	0.73 (0.56-0.94)	0.016	0.61 (0.47-0.79)	<0.001	0.42 (0.3-0.59)	<0.001
Birth cohort						
1988	1		1		1	
1989	0.9 (0.75-1.07)	0.237	0.99 (0.83-1.17)	0.902	0.8 (0.66-0.97)	0.021
1990	0.91 (0.58-1.43)	0.685	0.78 (0.48-1.28)	0.330	0.71 (0.42-1.22)	0.218

Table S4a: Adjusted RR of CIN 1 by birth cohort and SIMD quintile in women born 1991-1994

CIN 1		
Dose	**RR (95% CI)**	**p-value**
0	**1**	
1	0.67 (0.37-1.2)	0.175
2	1.05 (0.74-1.5)	0.789
3	0.79 (0.65-0.96)	0.016
SIMD		
1	1	
2	1.04 (0.82-1.32)	0.740
3	0.83 (0.64-1.07)	0.159
4	0.75 (0.57-0.99)	0.044
5	0.9 (0.7-1.15)	0.403
Birth cohort		
1991	1	
1992	0.92 (0.73-1.14)	0.44
1993	1.03 (0.83-1.28)	0.777
1994	0.85 (0.66-1.1)	0.213

Table S4b: Adjusted RR of CIN 2 and CIN 3 by birth cohort and the combination of SIMD quintile and number of doses of vaccine received in women born 1991-1994

		CIN 2		CIN 3	
Birth cohort		**Adjusted RR (95% CI)**	**p-value**	**Adjusted RR (95% CI)**	**p-value**
1991		1		1	
1992		0.8 (0.63-1.02)	0.067	0.74 (0.57-0.97)	0.029
1993		0.92 (0.73-1.16)	0.478	0.61 (0.46-0.81)	<0.001
1994		0.71 (0.53-0.95)	0.022	0.52 (0.37-0.75)	<0.001
SIMD quintile	**Number of doses**				
1	**0**	1	-	1	-
2	**0**	0.62 (0.43-0.9)	0.012	0.76 (0.51-1.14)	0.192
3	**0**	0.43 (0.28-0.68)	<0.001	0.49 (0.3-0.8)	0.005
4	**0**	0.51 (0.32-0.81)	0.004	0.51 (0.3-0.86)	0.012
5	**0**	0.21 (0.12-0.38)	<0.001	0.15 (0.07-0.33)	<0.001
1	**1**	1.02 (0.57-1.83)	0.949	0.54 (0.22-1.33)	0.180
2	**1**	0.2 (0.03-1.42)	0.106	1.9 (0.92-3.93)	0.082
3	**1**	1.84 (0.7-4.8)	0.214	1.76 (0.6-5.12)	0.301
4	**1**	1.36 (0.41-4.52)	0.614	0	0.992
5	**1**	0	0.992	2.39 (0.29-19.43)	0.415
1	**2**	0.31 (0.14-0.66)	0.003	0.59 (0.3-1.15)	0.122
2	**2**	1.88 (1.09-3.23)	0.023	0.75 (0.33-1.67)	0.476
3	**2**	0.86 (0.33-2.24)	0.752	1.43 (0.61-3.35)	0.416
4	**2**	0.74 (0.26-2.12)	0.569	0.49 (0.11-2.09)	0.332
5	**2**	0.55 (0.07-4.22)	0.566	4.01 (1.17-13.69)	0.027
1	**3**	0.32 (0.23-0.45)	<0.001	0.23 (0.15-0.36)	<0.001
2	**3**	0.45 (0.3-0.68)	<0.001	0.38 (0.25-0.6)	<0.001
3	**3**	0.68 (0.42-1.09)	0.107	0.49 (0.28-0.85)	0.011
4	**3**	0.38 (0.23-0.64)	<0.001	0.38 (0.21-0.69)	0.002
5	**3**	0.62 (0.32-1.21)	0.161	1.06 (0.46-2.46)	0.890