Changes in HPV prevalence following a national bivalent HPV vaccination programme in Scotland: a 7-year cross-sectional study

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Abstract

Background

In September 2008, Scotland launched routine human papillomavirus (HPV) vaccination, targeted at 12-13-year-old girls, of whom 92.4% were fully vaccinated in 2008/9. In this study, we report on vaccine effectiveness of the bivalent vaccine in these vaccinated women who attended for routine cervical screening at age 20-21.

Methods

In this seven year cross-sectional study (covering birth cohorts 1988-1995) we sampled approximately 1000 samples per year from those attending cervical screening at age 20-21 and tested each for HPV. By linkage to vaccination records we ascertain prevalence by birth cohort and vaccination status. Estimates of vaccine effectiveness (VE) for HPV 16/18, HPV 31/33/45, other high-risk types and any HPV are calculated using logistic regression.

Findings

In total, 8584 samples were HPV genotyped. HPV 16/18 prevalence reduced substantially from 30.0% (95% CI 26.9-33.1) in 1988 cohort to 4.5% (95% CI 3.5-5.7) in 1995 giving a VE=89.1% (95% CI: 85.1-92.3%) for those vaccinated at age 12-13. All cross protective types showed significant VE (HPV 31: VE=93.8% (95% CI: 83.8-98.5); HPV 33: VE=79.1% (95% CI 64.2-89.0); HPV 45: VE=82.6% (95% CI 61.5-93.9)). Unvaccinated individuals born in 1995 have a reduced odds of HPV16/18 infection compared to those in 1988 (adjusted OR=0.13; 95% CI: 0.06-0.27) and reduced odds of HPV 31/33/45 (OR=0.45, 95% CI: 0.23-0.89).

Interpretation

Bivalent vaccination has led to a startling reduction in vaccine and cross-protective types which have almost disappeared in this population, 7 years following vaccination. We also evidence herd protection against the vaccine specific and cross-protective types, in unvaccinated individuals born in 1995. The success of the vaccination programme and the evidence presented must now be considered in cost-effectiveness models informing vaccine choice and models to shape the future of cervical screening programmes.

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Research in context

Evidence before this study

Two systematic reviews and meta-analyses have collated population-based data demonstrating early evidence of the effectiveness of the HPV vaccination programme in high-income countries. These studies showed a significant reduction in HPV 16/18 associated with vaccine. Although reduction in HPV 31 was suggested, there was no evidence of a reduction in HPV 31, 33 and 45 as a group. Studies included in these reviews covered both the bivalent and quadrivalent vaccines, had differing levels of vaccine uptake, were often ecological studies comparing prevalence in different time frames and were focused on those vaccinated at older ages as part of catch-up cohorts.

On 8 March 2016, we conducted a PubMed search using the same strategy outlined in the 2015 review - ("papillomavirus vaccine", "papillomavirus vaccination", "HPV vaccine", or "HPV vaccination") and ("program evaluation", "population surveillance", "sentinel surveillance", "incidence", or "prevalence"), with 151 articles published in the intervening period (1 Feb 2014-8 March 2016), and found a further 6 studies, including our own work, reporting population-based HPV prevalence in vaccinated populations from England, Scotland, Sweden, Australia and USA (2 studies) with all bar the UK studies evaluating the impact of the quadrivalent vaccine. The populations studied were generally vaccinated during catch-up campaigns and were attending cervical screening at age 25 or above, or were vaccinated at an earlier age and observed as part of screening high risk populations or through national surveys using self-collected samples. For the majority of studies, individual vaccination status was not known, rather changes in HPV prevalence pre- and post-vaccination were examined. No studies have currently presented population-based evidence for those vaccinated at age 12/13 where vaccine status is known. With the exception of our own work, no statistically significant evidence of vaccine effectiveness for the grouping of the cross-protective types was found in the aforementioned studies.

Added value of this study

This study is the first to present population-based evidence of the effectiveness of the bivalent HPV vaccine in girls vaccinated routinely at age 12/13 and attending for cervical screening at age 20. We have shown that the vaccine-specific types HPV16/18 and the cross-protective types (31/33/45) have almost disappeared in this population, 7 years following the receipt of vaccine and present evidence of herd protection for all these types. We also demonstrate significant vaccine effect for the cross-protective types individually.

Implications of all the available evidence

These reductions in the most carcinogenic types of HPV, which are implicated in 90% of cervical cancers in Scotland, have clear implications for cervical screening in that the predictive value of cytology and HPV based screening strategies will reduce. Defining optimal screening intervals, age range, test and triage strategies for vaccinated women should be priorities for research. Our findings should inform the evaluation of screening programmes in vaccinated populations with high levels of uptake. There may be a time when current cytology or HPV based cervical screening programmes are no longer cost-effective. In addition, the levels of vaccine effectiveness observed, in particular for the cross-protective types may have implications for the comparative cost effectiveness assessment of the bivalent, quadrivalent and nonavalent HPV vaccines and our findings should be incorporated in the baseline assumptions of such evaluative models. If when evaluated under such models, the cross-protective benefit is shown to improve cost-effectiveness then the bivalent vaccine remains a strong candidate for consideration in HPV immunisation programmes.

Introduction

Human papillomavirus (HPV) types 16 and 18 are responsible for 70-80% of cervical cancers in the UK[1]. HPV vaccination prevents infection with HPV 16 and 18[2-4] and is associated with a reduction in all grades of histological and cytological abnormalities according to data from population-based immunisation programmes[5, 6]. The bivalent vaccine also provides immunological cross-protection against HPV 31, 33 and 45, high-risk oncogenic HPV types phylogenetically related to HPV 16 and 18, although the duration and scale of long-term cross-protective immunity has been vigorously debated[3, 7-9]. The persistence of the cross-reactive antibody titres against HPV 31 and 45 after bivalent HPV vaccination has been demonstrated up to 9.4 years after the initial dose in the clinical trial setting[10]. These data are particularly relevant for Scotland since at least 90% of invasive cervical cancers are attributable to HPV 16, 18, 31, 33 and 45[11].

To date, HPV vaccine impact data[2-4, 7, 12] through national vaccination programmes are largely obtained from females immunised as part of "catch-up" cohorts which, in Scotland, included girls up to age 18. While data derived from catch-up populations have been encouraging, they are likely to underestimate the effect as some females will have been exposed to HPV before vaccination. Cervical screening programmes, which constitute a critical and enriched resource for both monitoring HPV prevalence and outcomes, mostly screen from age 25 or older. Assessment of vaccine impact, prior to screening, has been possible either ecologically by conducting HPV testing in higher risk populations attending chlamydia screening[13-15] or via national surveys[16] reliant on self-reported vaccine status and self-collected samples. There has thus far been limited opportunity to observe changes in prevalence in women routinely vaccinated at age 12/13.

Until June 2016, cervical screening started aged 20 in Scotland. Therefore, using the ability to link individual screening and vaccination records, we can now report on effectiveness of the bivalent vaccine on both low- and high-risk HPV infections in 12/13-year old girls, of whom 92.4% were fully vaccinated in 2008/9[17]. Timely production and analyses of these data have significant implications for service planning and cost-effectiveness modelling to inform future cervical disease prevention policy.

Methods

In September 2008, Scotland began school-based routine HPV vaccination, targeted at 12-13-year-old girls. Between 1 September 2008 and 31 August 2011, a 3-year catch-up programme for older girls (aged 13–18 years, born between 01/09/90 to 31/08/95) was also delivered, both at school and, for school leavers, at Health Board-run vaccination clinics or general practices. The 3-year catch-up programme attained a high uptake (87%) for all three doses among those vaccinated in school but a lower uptake (32%) was achieved in school leavers[18]. Bivalent vaccination was delivered until September 2012 when a switch was made to quadrivalent vaccination. All females in our study period were eligible for the bivalent vaccination.

Since 2009, Health Protection Scotland (HPS) has co-ordinated a national HPV immunisation surveillance programme[19] to assess the impact of HPV vaccine on viral and disease outcomes[3-5, 20, 21]. This includes the assessment of type-specific HPV prevalence in females attending for their first cervical screen. This has been achieved by yearly (cross-sectional) collection and HPV genotyping of approximately 1000 residual liquid-based cytology (LBC) samples from women aged 20–21 from the years 2009 to 2015. Each sampling year covers at least two birth year cohorts for example, in 2009, individuals from 1988 and 1989 birth cohorts were sampled and in 2015, the collection primarily covered individuals from the 1994 and 1995 cohorts. Vaccinated girls mainly entered the cervical screening programme from 2011 and the inclusion of samples from 2009 and 2010 provides a relevant comparator group of those not offered vaccination through the National Health Service (NHS) immunisation programme.

Residual LBC samples from cervical screening were collected from all 8 NHS cytopathology laboratories in Scotland. Each laboratory collected residual samples over a 1-2 month period, staggered throughout the year, to balance the workload. The target number from each laboratory was dictated by the size of the population served by the laboratory, ensuring a geographically representative sample. Each laboratory collected sequential residual LBC samples from women aged 20-21 attending in those months until they had met their target. Apart from age, no other information was known about the women at the point of collection. Samples were given a laboratory identification number and underwent HPV genotyping at the Scottish HPV Reference Laboratory (SHPVRL). Oversampling was conducted in 2009 to establish a baseline. The 2015 collection was extended into 2016 to maximise capture of those vaccinated at age 12-13, prior to the change in screening policy to start at age 25.

All individuals resident in Scotland are listed on the Community Health Index (CHI) population register, allowing all patients using the NHS in Scotland to be uniquely identified by their CHI number. Cytopathology laboratories sent the laboratory identification number and the CHI number of samples selected for testing to the Information Services Division of the Scottish National Health Service. CHI numbers were used to assign month and year of birth and to obtain vaccination data (dates of and type of vaccine) from the Scottish Immunisation Recall System. The postal code of the patient's residence on attendance for screening was used to rank the geographic data zone for each sample according to the Scottish Index of Multiple Deprivation[22] (SIMD) – the Scottish Governments official tool to identify areas of multiple deprivation based on combining information on seven domains covering employment, income, crime, housing, health, education and access. Each individual is categorised into SIMD quintiles (SIMD 1 = most deprived and SIMD 5 = least deprived). An anonymous patient identifier was then assigned to all records, the CHI and postcode were removed, and the resulting data sent to HPS. HPV test results and laboratory identification number were transferred to HPS from SHPVRL and were linked to vaccination data using the laboratory identification number which was then removed from the data set before analysis. No patient identifiable HPV results were available to anyone involved in the linkage or analysis.

HPV genotyping was performed using a PCR based technology with luminex detection - the Optiplex HPV genotyping kit, (Diamex, Heidelberg, Germany). This assay has a high analytical sensitivity, detecting 24 HPV types - high-risk carcinogenic types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59); probable carcinogenic types (HPV 68); and some possibly carcinogenic types (HPV 26, 53, 66, 70, 73, and 82) – as defined by the International Agency for Research on Cancer[23]. This assay can also detect 5 low-risk HPV types (HPV 6, 11, 42, 43, and 44).

HPV genotyping was performed on all collections from 2009-15. In addition any sample collected in 2015/16 and found to be positive for HPV 16/18 by the Optiplex genotyping test, was also tested by the clinically validated Abbott RealTime High Risk HPV (HR-HPV) assay (RealTime; Abbott, Wiesbaden, Germany). This was to gain preliminary insight into the likely clinical significance of any residual HPV 16/18 infections in routinely vaccinated females. This test has a detection remit for high-risk and probable carcinogenic types with the sensitivity calibrated to detect high-grade lesions[24].

The sample collection of 1000 per year, was powered a priori to give at least a 99% power to detect a 15% reduction at first cervical screen in assumed overall HPV prevalence from 40 to 34%, a 25% reduction in high-risk HPV prevalence from 25 to 19%, and a 40% reduction in HPV 16/18 prevalence at first cervical screen from 12 to 7%. The prevalence of each

detectable HPV type, along with 95% CIs, was calculated and presented for each cohort year, study year, number of doses of vaccine received, SIMD quintile and age at vaccination.

Association between HPV outcome and the number of doses of vaccine received (0, 1, 2 or 3 doses) was measured by logistic regression to allow for adjustment for the impact deprivation score and birth cohort on HPV positivity. Both adjusted and unadjusted effects (odds ratios) are presented. Ordered factors were used to test for a linear change in positivity by dose, cohort and deprivation. Vaccine effectiveness was estimated stratified by age at vaccination (for those receiving 3 doses) and pooled for all ages for those with incomplete dosage (1 or 2 doses). The odds ratio (OR) of each HPV outcome relative to those unvaccinated in all birth cohorts was calculated for each group adjusted for deprivation score using logistic regression. Vaccine effectiveness is then calculated as VE=100*(1-OR).

The HPV groupings considered as outcomes were positivity for any of the following HPV types - HPV 16/18; HPV 31/33/45; other non-vaccine HR-HPV types (35/39/51/52/56/58/59/68); or any type detected by the genotyping HPV assay. In addition, HPV 31, 33 and 45 were evaluated individually. Potential herd immunity was evaluated in women who were not vaccinated during 2009–2015 by using logistic regression and testing for a linear trend over the successive annual cohorts for the prevalence of HPV 16/18, the cross-protective types, other non-vaccine high-risk types, and any HPV. Descriptive analysis of HPV 16/18 positivity using the RealTime and Optiplex on samples collected in 2015 was performed.

National surveillance was approved through the NHS National Clinical Governance committees and Caldicott Guardians at individual NHS Boards. Data linkage of information was approved by the NHS National Services Scotland (NSS) CHI advisory group.

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Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Over the seven surveillance years, 8708 LBC samples were collected. Sixty-one entries were excluded as SIMD quintile could not be linked and a further 63 could not be HPV genotyped. The remaining 8584 samples were successfully HPV genotyped and formed the study population. Supplementary Table 1 describes the breakdown by year. In the 2009 collection year, females attending for first smear born in 1988 and 1989 were not eligible for routine vaccination hence 98.5% were unvaccinated. The proportion of vaccinated individuals increased with study year; 33.6% of those in 2011 were vaccinated with 3 doses compared to 86.0% in 2015 (Supplementary Table 1). The data are consistently distributed by SIMD quintile (~20% expected in each group).

HPV 16/18 prevalence reduced substantially from 28.9% (95% CI: 26.7, 31.1%) in 2009 to 4.8% (95% CI: 3.8, 5.9%) in 2015 (unadjusted OR=0.12; linear p-value<0.0001; Table 1). Stratifying by birth cohort and vaccination status (Figure 1A) indicates a clear linear decline in HPV16/18 in successive birth cohorts (unadjusted OR (1995 cohort vs 1988 cohort) =0.11, linear p-value<0.0001; Table 1). The overall impact of vaccination on HPV16/18 prevalence, adjusted for birth cohort and SIMD, summarised in Table 2, shows a clear increase in 3 dose vaccine effectiveness (VE) in those receiving vaccine with earlier age of vaccination. For those vaccinated with 3 doses at age 18 resident in the most deprived areas (SIMD 1), VE=28.9% (95%CI: 4.5-47.8%) compared with VE=89.1% (95% CI: 85.1-92.3%) for the same group of women vaccinated at age 12/13. In the 1995 cohort, 59 (4.5%) of individuals were positive for HPV16/18 (58 HPV 16 positive, 1 HPV 18 positive) according to the Optiplex assay; 8 were unvaccinated, 1 person had 1 dose, 1 person had 2 doses and the remaining 49 individuals were fully vaccinated. When the 58 HPV 16/18 positive samples were tested with RealTime, only 7 individuals were positive for HPV 16, 4 of whom were fully vaccinated and 3 unvaccinated. Incomplete immunisation led to lower estimates of VE – 2 doses had an overall VE=39.0% (95% CI: 21.3-53.3%) and 1 dose VE=27.6% (95% CI: 0.7-48%) (Table 2). 97% of individuals receiving incomplete dosage were age 15 or older at first dose and the second dose occurred a median 49 days following the initial dose (IQR: 30 – 70 days).

The bivalent vaccine was also associated with substantial decreases in the prevalence of HPV 31/33/45 (Figure 1B). Prevalence reduced from 14.2% (95%CI: 12-16.7%) in the 1988 cohort to 2.6% (95% CI: 1.9-3.6%) in the 1995 cohort (Table 1). Again VE was lower in those vaccinated at older ages – VE=29.5% (95% CI: -6.2-55.3%) in those vaccinated at age 18, increasing to VE=85.1% (95% CI: 77.3-90.9%) in those vaccinated at age 12-13 (Table 2). Three dose vaccine effectiveness for the cross-protective types was therefore slightly lower, but comparable to, that for the vaccine types in girls vaccinated at age 12/13. Significant

vaccine effectiveness was observed for HPV 31, 33 and 45 individually in those vaccinated at age 12/13, with highest levels observed for HPV 31 and lowest for HPV 33 (HPV 31: VE=93.8% (95% CI: 83.8-98.5%); HPV 33: VE=79.1% (95% CI: 64.2-89.0%); HPV 45: VE=82.6% (95% CI: 61.5-93.9%)). For full details see Supplementary Table 1.

Figure 1C illustrates that although there were yearly fluctuations in the prevalence of HR-HPV types other than 16/18/31/33/45 of between 28% and 35%, there is no significant trend (Supplementary Table 3, linear test trend p=0.085) and there is little difference in prevalence between the unvaccinated and vaccinated groupings. Vaccination showed no effect on the odds of infection with these types (fully vaccinated adjusted OR=0.96 (95% CI: 0.83-1.1). VE calculations for other HR-HPV by age vaccination (Table 2) show fluctuations between negative and positive VE with all bar the age 16, 3 dose group, having confidence intervals which span 0 suggesting no vaccine effect on other HR-HPV levels.

Supplementary Figure 1 provides an overview of the changing epidemiology of the 24 HPV genotypes detected by HPV assay in young women spanning Scottish birth cohorts 1988-1995. The non-vaccine HR-HPV types show little evidence of trends that would indicate type replacement. For overall HPV positivity (i.e. positive for any of the 24 types) there is evidence of a declining trend with cohort year (linear p<0.0001, Supplementary Table 3) with levels decreasing from 56.9% (95%CI: 53.5-60.2%) in the 1988 cohort to 47.6% (95%CI: 44.9-50.3%) in the 1995 cohort, driven by the decline in HPV 16/18 and the cross-protective types 31/33/45 (Figure 1D). There is evidence that those vaccinated with 3 doses are significantly less likely to be infected with any HPV than those who are unvaccinated (adjusted OR=0.79, 95% CI: 0.69-0.9, Table 2). Across all HPV groupings, there is evidence (Table 2) that even when accounting for vaccination there remains an impact of deprivation on HPV positivity with those least deprived being less likely to be HPV positive.

Stratifying by birth cohort and vaccination status (Figure 1A) also provides an indication of herd protection with a substantial reduction in HPV16/18 prevalence in the unvaccinated in the 1993, 1994 and 1995 birth cohorts. Examining the change in prevalence in the unvaccinated individuals (Table 3) indicates that those born in 1995 have a substantially reduced odds of HPV16/18 infection compared to those in 1988 (adjusted OR=0.13; 95% CI: 0.06-0.28). In the unvaccinated, there is evidence of a reduction in HPV31/33/45 (Figure 1B) with a significant reduction in the odds of infection observed in the 1995 cohort compared to the 1988 cohort (OR=0.45, 95% CI: 0.23-0.89), for the first time demonstrating herd protection against cross-protective HPV types. Sensitivity analysis focusing on the unvaccinated who were eligible for vaccination (those born after 1st September 1990) shows similar results (Supplementary Table 4).

Discussion

Population-based data from the Scottish HPV immunisation programme clearly demonstrates that the bivalent vaccine is associated with a significant reduction in the prevalence of HPV 16/18 and each of the cross protective types 31, 33 and 45 in those attending for routine cervical screening. The magnitude of this effect increases with successive birth cohorts. Moreover, we can demonstrate that cross-protection remains high at age 20 for girls vaccinated at age 12-13, differing from an earlier meta-analysis of clinical trial data[8] which postulated that there may be waning of cross-protection over time.

The implications of these findings are significant. According to global meta-analyses HPV 16,18,31,33 and 45 are implicated in 84% of invasive cervical cancers[25] and in Scotland these 5 HPV types account for 90% of cancers[11]. For all 5 types, vaccine effectiveness in those vaccinated at age 12-13 exceeded 79%. This differs from recent meta-analysis[7] which found evidence for HPV 31 cross-protection but little evidence for reductions of HPV 33 or 45. This meta-analysis was potentially influenced by inclusion of results for both the bivalent and quadrivalent vaccines as the latter has previously been shown to have lower levels of cross-protection[8], by stratification by vaccine availability period (pre and post) rather than known vaccination status, and by the inclusion of studies with low population vaccine uptake. Our results suggest that the high levels cross-protection associated with the bivalent vaccine may have been underestimated in the baseline assumptions of cost-effectiveness models. Recalibration of such models may impact future vaccine choice with a recent review[26] highlighting that “the 9-valent was not cost-effective (vs 2-valent), under assumptions of maximum cross-protection for the 2-valent vaccine”.

We have demonstrated that partial vaccination conveys protection against HPV16/18 albeit at a lower level (2 dose VE=39%, 1 dose VE=27.6%). However, it is important to emphasise that the majority of those receiving partial vaccination were vaccinated as part of the catch-up cohorts at age 16 and over. Comparable 3 dose VE was 75.9% in those vaccinated at age 16, 58.1% at age 17 and 28.9% at age 18. It should also be noted that the 2 dose schedule was generally delivered as planned within a 3 dose regime i.e. at 0 and 1 month rather than at the current 2 dose recommended scheduling of 0 and 6 months, where higher VE would be expected. Partial vaccination in older women shown to be HPV-negative, as suggested by the HPV Faster protocol[27] for accelerated reduction of cervical cancer incidence, may also have a higher VE. Given the age range of women considered for HPV Faster, they are likely to be largely unaffected by genital warts and there may be merit in offering bivalent vaccine to these women.

Encouragingly, there was no significant increase in non-16/18/31/33/45 HR-HPV types even though 16/18 prevalence has reduced by 6-fold (28.9% to 4.8%). There is therefore no evidence of "type replacement", at least in the shorter term. However, for this to be addressed robustly further longitudinal studies which relate infecting HPV type to the future risk of disease in immunised populations are required and ongoing in the Scottish population.

Retesting the 59 samples in the 1995 cohort that were positive for 16/18 according to the epidemiologically orientated assay with a clinically validated assay (with a cut off set for the detection of CIN2+)[24], showed that only 7 (4 vaccinated) were HPV 16 positive and none were HPV 18 positive. This suggest that the majority of HPV 16 infection in routinely immunised women may be at thresholds that are clinically irrelevant. Analytically sensitive assays are also more likely to detect HPV associated with recent acquisition rather than actual intra-cellular infection which has the capacity to persist. Follow up studies to determine the clinical significance of residual infection in vaccinated women are underway to examine this more specifically.

We previously showed preliminary evidence, based on small numbers, of herd protection in the unvaccinated population for the vaccine types[4]. Scotland has benefitted from high uptake rates of vaccine of around 90% in the routine cohort since initiation of the programme. The growing evidence of herd protection extending to the cross-protective types serves as a positive, reinforcing message for future and existing programmes in their drive to achieve and maintain high uptake levels.

Reduced HPV 16/18/31/33/45 infection will naturally have implications for screening, as current modalities have been calibrated to pre-vaccination era levels of disease. The positive predictive value (PPV) of a screening test will reduce as the prevalence of target disease reduces[28]. Data derived from the population vaccinated as part of catch-up in Scotland has already shown a significant reduction in the PPV of cytology for CIN2+ in immunised women[21]. While it is argued that HPV primary screening using objective molecular assays may mitigate the issues of cytology screening, it is subject to the same influences as cytology and is not a panacea. The randomised controlled trials which provided evidence for its introduction have been based solely on unvaccinated women[29].

Compared to other high-risk types, HPV 16/18 have been shown to confer a significantly higher risk of disease[30], particularly HPV 16 and particularly when CIN3 or worse is used as an outcome. Consequently, residual HR-HPV infection in immunised women will be clinically less significant. In line with this, preliminary data on the clinical performance of HPV testing for primary screening in Scotland indicated that the positive predictive value for CIN2+ was significantly lower in vaccinated women compared to unvaccinated women[31]. Therefore,

robust “triage” for primary HPV testing becomes increasingly relevant for immunised populations. The choice of optimal triage is a fertile area of research and extended genotyping, methylation and cytology with adjunctive biomarker staining represent some of the many options under consideration[32]. Furthermore, an ecological study which assessed national colposcopy data in Scotland before and after the introduction of vaccination, showed that the PPV of colposcopy for CIN2+ decreased from 79% in 2008/9 to 67% in 2013/14 - close to the UK key performance indicator threshold of 65%[33] .

There are limitations to this study. The sample collection and testing strategy necessarily involved only those women who attended screening who represent only 50% of their age group[34]. In our study vaccine uptake figures are the same as in the general population. There is therefore no substantial bias in who comes to screening with respect to vaccine receipt. This coupled with the equity of vaccine uptake[18] in the routinely vaccinated cohorts in Scotland, and the similarity in HPV positivity levels in 2009/10 between screening attenders and non-attenders[20], should mitigate any differential vaccine effect in non-attenders who were vaccinated at younger ages. In those vaccinated as part of the catch-up cohorts who had lower overall uptake, our previous work[18] has shown lowest uptake of vaccination in the most deprived, a group disproportionately affected by cervical malignancy. Our results show that there remains a deprivation effect in HPV positivity and, whilst this effect may be driven by inequitable vaccine uptake in the catch-up cohorts, perhaps in addition to differences in sexual behaviour and smoking status (which we cannot ascertain in our study), they reinforce the need for appropriate delivery and uptake of cervical screening.

With the change to quadrivalent vaccination in 2012, future work to examine vaccine impact, both in terms of herd protection and direct protection, will be confounded by the inevitable sexual mixing of the two vaccination cohorts. In this study however, the 4-year gap between the 12/13 year olds vaccinated in 2008/9 and the first quadrivalent cohort in 2012/13, coupled with examining HPV prevalence at age 20/21 and the final collection year being 2015, reassures that any impact attributable to quadrivalent vaccine in the cohorts examined is likely to be minimal. We are committed to ongoing surveillance to assess the impact of the change to quadrivalent vaccine.

To conclude, HPV 16, 18, 31, 33, and 45 have reduced substantially following a population-based vaccination programme which has achieved high uptake of bivalent vaccine. Levels of cross-protective immunity endure for at least 7 years and further follow-up will provide important information as to their ultimate longevity. The massive reductions in the most carcinogenic types of HPV have clear implications for cervical screening and disease management and there may be a time when the current cervical screening programme is no

longer cost-effective. Primary screening with HPV testing already allows extended screening intervals compare to cytology, and immunisation will permit even longer intervals and possibly a rise in the age at which screening starts in developed countries[35]. The levels of sustained cross protection observed with bivalent vaccine may also have implications for future vaccine choice, which needs to be matched to the prevalence of HPV types in the target population. Indeed, if the cross protection observed translates to fewer HPV related cancer cases in a population, then there are likely to be implications for the cost effectiveness of the bivalent vaccine relative to alternative HPV vaccines. It is therefore imperative that data such as those described above are incorporated into models which can inform optimal strategies for future cervical disease screening and cost-effectiveness calculations for vaccine choice.

Conflicts of interest

KP received travel monies for attendance at IPV, 2015 from Sanofi.

RB received speaker honoraria and travel expenses from Abbott molecular.

CM and KC reports grants Cepheid, Becton Dickinson, GeneFirst, EuroImmun, Self Screen and non-financial support from Hologic.

HC reports grants from GSK and personal fees from Abbott Diagnostics.

All other authors declare no conflicts of interest.

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Authors' contributions

All authors contributed to the text of the manuscript and commented on drafts. Kimberley Kavanagh lead on the drafting of the manuscript with large contributions from Kevin G Pollock and Kate Cuschieri. Kevin G Pollock managed the national surveillance system with the support of Ross L Cameron. Cameron Watt managed the data submission and provided extracts. Ramya Bhatia, Catherine Moore and Kate Cuschieri conducted and managed the HPV testing and sample curation at the HPV reference laboratory. Kimberley Kavanagh lead on the statistical analysis with oversight from Chris Robertson. Maggie Cruickshank, Chris Robertson, Tim Palmer and Heather Cubie provided strategic oversight for the programme of work and were responsible for setting up the original protocol for this surveillance scheme.

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			HPV 16/18				HPV 31/33/45			
Variable	**Level**	**Number tested**	**Number positive**	**Percentage Positive (95% CI)**	**Unadjusted OR (95% CI)**	**p-value***	**Number positive**	**Percentage Positive (95% CI)**	**Unadjusted OR (95% CI)**	**p-value***
Birth cohort	1988	838	251	30.0 (26.9,33.1)	1.00 (-,-)	<0.0001	119	14.2 (12.0,16.7)	1.00 (-,-)	<0.0001
	1989	1180	345	29.2 (26.7,31.9)	0.97 (0.80,1.17)		140	11.9 (10.1,13.8)	0.81 (0.63,1.06)	
	1990	1255	367	29.2 (26.8,31.8)	0.97 (0.80,1.17)		162	12.9 (11.2,14.9)	0.90 (0.70,1.16)	
	1991	940	187	19.9 (17.5,22.6)	0.58 (0.47,0.72)		87	9.3 (7.6,11.3)	0.62 (0.46,0.83)	
	1992	1324	186	14.0 (12.3,16.0)	0.38 (0.31,0.47)		98	7.4 (6.1,8.9)	0.48 (0.36,0.64)	
	1993	1022	116	11.4 (9.5,13.4)	0.30 (0.23,0.38)		73	7.1 (5.7,8.9)	0.47 (0.34,0.63)	
	1994	708	51	7.2 (5.5,9.3)	0.18 (0.13,0.25)		30	4.2 (3.0,6.0)	0.27 (0.17,0.40)	
	1995	1317	59	4.5 (3.5,5.7)	0.11 (0.08,0.15)		34	2.6 (1.9,3.6)	0.16 (0.11,0.23)	
Number doses	0	4008	1116	27.8 (26.5,29.3)	1.00 (-,-)	<0.0001	504	12.6 (11.6,13.6)	1.00 (-,-)	<0.0001
	1	223	50	22.4 (17.4,28.3)	0.75 (0.54,1.03)		30	13.5 (9.6,18.6)	1.08 (0.71,1.58)	
	2	391	76	19.4 (15.8,23.6)	0.63 (0.48,0.81)		32	8.2 (5.9,11.3)	0.62 (0.42,0.89)	
	3	3962	320	8.1 (7.3,9.0)	0.23 (0.20,0.26)		177	4.5 (3.9,5.2)	0.33 (0.27,0.39)	
SIMD quintile	1: Most deprived	1976	412	20.9 (19.1,22.7)	1.00 (-,-)	<0.0001	195	9.9 (8.6,11.3)	1.00 (-,-)	<0.0001
	2	1739	324	18.6 (16.9,20.5)	0.87 (0.74,1.02)		179	10.3 (9.0,11.8)	1.05 (0.85,1.30)	
	3	1630	291	17.9 (16.1,19.8)	0.83 (0.70,0.97)		146	9.0 (7.7,10.4)	0.90 (0.72,1.13)	
	4	1519	282	18.6 (16.7,20.6)	0.87 (0.73,1.02)		110	7.2 (6.0,8.7)	0.71 (0.56,0.91)	
	5: Least deprived	1720	253	14.7 (13.1,16.5)	0.66 (0.55,0.78)		113	6.6 (5.5,7.8)	0.64 (0.50,0.82)	
Collection year	9	1656	478	28.9 (26.7,31.1)	1.00 (-,-)	<0.0001	215	13.0 (11.4,14.7)	1.00 (-,-)	<0.0001
	10	1101	344	31.2 (28.6,34.0)	1.12 (0.95,1.32)		148	13.4 (11.6,15.6)	1.04 (0.83,1.30)	
	11	1074	251	23.4 (20.9,26.0)	0.75 (0.63,0.90)		110	10.2 (8.6,12.2)	0.77 (0.60,0.97)	
	12	1051	179	17.0 (14.9,19.4)	0.51 (0.42,0.61)		90	8.6 (7.0,10.4)	0.63 (0.48,0.81)	
	13	1073	116	10.8 (9.1,12.8)	0.30 (0.24,0.37)		70	6.5 (5.2,8.2)	0.47 (0.35,0.62)	
	14	1019	117	11.5 (9.7,13.6)	0.32 (0.26,0.40)		61	6.0 (4.7,7.6)	0.43 (0.32,0.57)	
	15	1610	77	4.8 (3.8,5.9)	0.12 (0.10,0.16)		49	3.0 (2.3,4.0)	0.21 (0.15,0.29)	
Age at vaccination	12-13	976	39	4.0 (2.9,5.4)	1.00 (-,-)	<0.0001	20	2.0 (1.3,3.1)	1.00 (-,-)	<0.0001
	14	283	15	5.3 (3.2,8.6)	1.35 (0.71,2.43)		9	3.2 (1.7,5.9)	1.57 (0.67,3.39)	
	15	986	74	7.5 (6.0,9.3)	1.95 (1.32,2.93)		45	4.6 (3.4,6.1)	2.29 (1.36,3.98)	
	16	1319	123	9.3 (7.9,11.0)	2.47 (1.72,3.62)		85	6.4 (5.2,7.9)	3.29 (2.05,5.54)	
	17	571	96	16.8 (14.0,20.1)	4.86 (3.32,7.23)		39	6.8 (5.0,9.2)	3.50 (2.05,6.18)	
	18	359	70	19.5 (15.7,23.9)	5.82 (3.87,8.87)		30	8.4 (5.9,11.7)	4.36 (2.46,7.89)	
	Over 18	82	29	35.4 (25.9,46.2)	13.15 (7.53,22.90)		11	13.4 (7.7,22.4)	7.41 (3.31,15.81)	
	Unvaccinated	4008	1116	27.8 (26.5,29.3)	9.27 (6.78,13.07)		504	12.6 (11.6,13.6)	6.88 (4.50,11.17)	

Table 1: Positivity for HPV 16/18 and HPV31/33/45 by birth cohort, number of vaccine doses, SIMD quintile, collection year and age at vaccination. *p-value evaluated as a test of linear trend by including the variable as an ordered factor in a logistic regression model

			HPV 16/18		HPV31/33/45		Other HR HPV		Any HPV	
			Adjusted OR (95% CI)		**Adjusted OR (95% CI)**		**Adjusted OR (95% CI)**		**Adjusted OR (95% CI)**	
Birth cohort	1988		1.00 (-,-)		1.00 (-,-)		1.00 (-,-)		1.00 (-,-)	
	1989		0.96 (0.79,1.17)		0.81 (0.62,1.06)		1.19 (0.98,1.44)		1.11 (0.93,1.33)	
	1990		1.06 (0.88,1.29)		0.99 (0.77,1.28)		1.38 (1.14,1.68)		1.11 (0.93,1.33)	
	1991		0.92 (0.73,1.18)		0.92 (0.67,1.27)		1.34 (1.07,1.68)		1.29 (1.04,1.59)	
	1992		0.70 (0.54,0.89)		0.81 (0.58,1.12)		1.40 (1.13,1.74)		1.17 (0.95,1.43)	
	1993		0.54 (0.41,0.70)		0.77 (0.55,1.09)		1.35 (1.08,1.69)		1.10 (0.89,1.36)	
	1994		0.37 (0.26,0.51)		0.49 (0.31,0.77)		1.42 (1.11,1.81)		1.17 (0.93,1.48)	
	1995		0.24 (0.17,0.33)		0.31 (0.20,0.48)		1.20 (0.96,1.50)		0.86 (0.69,1.06)	
Number doses	Unvaccinated		1.00 (-,-)		1.00 (-,-)		1.00 (-,-)		1.00 (-,-)	
	1 dose		0.89 (0.63,1.25)		1.10 (0.71,1.65)		1.06 (0.79,1.42)		1.10 (0.82,1.47)	
	2 dose		0.75 (0.57,0.99)		0.64 (0.42,0.93)		1.11 (0.88,1.40)		1.06 (0.84,1.33)	
	3 dose		0.40 (0.33,0.48)		0.46 (0.36,0.58)		0.96 (0.83,1.10)		0.79 (0.69,0.90)	
SIMD	1: Most deprived		1.00 (-,-)		1.00 (-,-)		1.00 (-,-)		1.00 (-,-)	
	2		0.85 (0.72,1.01)		1.05 (0.85,1.31)		1.03 (0.90,1.18)		0.95 (0.84,1.09)	
	3		0.83 (0.70,0.99)		0.92 (0.73,1.15)		0.98 (0.85,1.12)		0.87 (0.76,1.00)	
	4		0.91 (0.76,1.08)		0.75 (0.58,0.95)		0.99 (0.86,1.14)		0.91 (0.80,1.04)	
	5: least deprived		0.72 (0.60,0.86)		0.70 (0.55,0.89)		0.86 (0.75,0.99)		0.77 (0.68,0.88)	
Vaccine effectiveness		**N tested**	**N positive**	**Adjusted† VE (95% CI)**	**N positive**	**Adjusted† VE (95% CI)**	**N positive**	**Adjusted† VE (95% CI)**	**N positive**	**Adjusted† VE (95% CI)**
12-13	3 doses	971	39	89.1 (85.1, 92.3)	20	85.1 (77.3, 90.9)	296	7.8 (-7.3, 20.9)	456	38.1 (28.7, 46.3)

14	3 doses	269	12	87.7 (78.9, 93.5)	6	83.6 (66.2, 93.6)	86	0.2 (-29.6, 23.8)	134	29.6 (9.8, 45.1)
15	3 doses	880	56	82.3 (76.8, 86.7)	37	69.2 (57.2, 78.5)	293	-4.8 (-22.3, 10.3)	465	21.7 (9.3, 32.4)
16	3 doses	1156	97	75.9 (70.2, 80.8)	66	56.8 (44, 67.1)	412	-17.1 (-34.3, -2)	640	12.5 (0.1, 23.4)
17	3 doses	422	59	58.1 (44.8, 68.8)	24	57.9 (37.2, 73.1)	141	-4.9 (-29.5, 15.4)	234	13.8 (-5.6, 29.6)
18 and over	3 doses	264	57	28.9 (4.5, 47.8)	24	29.5 (-6.2, 55.3)	75	16.9 (-9.0, 37.2)	144	16.5 (-7.4, 35.0)
All ages‡	2 doses	391	76	39 (21.3, 53.3)	32	40.3 (14.5, 59.7)	146	-23.1 (-52.5, 1)	244	-12.5 (-39.7, 9.1)
All ages§	1 dose	223	50	27.6 (0.7, 48)	30	-3.6 (-51.7, 31.6)	81	-17.3 (-54.9, 11.8)	141	-15.9 (-53.8, 12.2)
All ages	Unvaccinated	4008	1116	-	504	-	1297	-	2366	-

Table 2: Adjusted odds of HPV positivity for each HPV grouping by birth cohort, number of doses received and SIMD quintile.

*HR HPV not 16/18/31/33/45

† Vaccine Effectiveness (VE) adjusted for SIMD quintile. All VE calculated at baseline level of SIMD (SIMD quintile 1: most deprived). VE is calculated relative to those unvaccinated across all study years.

‡2 doses age split: 5 age 12-13, 8 age 14, 71 age 15, 102 age 16, 95 age 17, 87 age 18, 23 over 18. On average (median) those in receipt of 2 doses were administered at 49 days apart.

§1 dose age split: 0 age 12-13, 6 age 14, 35 age 15, 61 age 16, 54 age 17, 43 age 18, 24 over 18

	Birth cohort	Number tested	Number positive	% Positive (95% CI)	Unadjusted OR (95% CI)	Adjusted OR** (95% CI)
HPV 16/18	1988	836	250	29.9 (26.9,33.1)	1.00 (-,-)	1.00 (-,-)
	1989	1176	342	29.1 (26.6,31.7)	0.96 (0.79,1.17)	0.96 (0.79,1.16)
	1990	1014	308	30.4 (27.6,33.3)	1.02 (0.84,1.25)	1.01 (0.83,1.24)
	1991	282	85	30.1 (25.1,35.7)	1.01 (0.75,1.36)	1.00 (0.74,1.34)
	1992	252	64	25.4 (20.4,31.1)	0.80 (0.58,1.10)	0.79 (0.57,1.09)
	1993	197	44	22.3 (17.1,28.6)	0.67 (0.47,0.97)	0.66 (0.46,0.95)
	1994	99	15	15.2 (9.4,23.5)	0.42 (0.24,0.74)	0.42 (0.24,0.74)
	1995	152	8	5.3 (2.7,10)	0.13 (0.06,0.27)	0.13 (0.06,0.28)
HPV31/33/45	1988	836	118	14.1 (11.9,16.6)	1.00 (-,-)	1.00 (-,-)
	1989	1176	139	11.8 (10.1,13.8)	0.82 (0.63,1.06)	0.81 (0.62,1.06)
	1990	1014	146	14.4 (12.4,16.7)	1.02 (0.79,1.33)	1.04 (0.80,1.35)
	1991	282	36	12.8 (9.4,17.2)	0.89 (0.60,1.33)	0.87 (0.58,1.30)
	1992	252	25	9.9 (6.8,14.2)	0.67 (0.42,1.06)	0.67 (0.42,1.06)
	1993	197	22	11.2 (7.5,16.3)	0.77 (0.47,1.24)	0.75 (0.46,1.22)
	1994	99	8	8.1 (4.2,15.1)	0.54 (0.25,1.13)	0.53 (0.25,1.12)
	1995	152	10	6.6 (3.6,11.7)	0.43 (0.22,0.84)	0.45 (0.23,0.89)
Other HR*	1988	836	234	28 (25.1,31.1)	1.00 (-,-)	1.00 (-,-)
	1989	1176	370	31.5 (28.9,34.2)	1.18 (0.97,1.44)	1.18 (0.97,1.43)
	1990	1014	365	36 (33.1,39)	1.45 (1.19,1.76)	1.45 (1.19,1.77)
	1991	282	97	34.4 (29.1,40.1)	1.35 (1.01,1.80)	1.34 (1.01,1.79)
	1992	252	90	35.7 (30.1,41.8)	1.43 (1.06,1.93)	1.45 (1.07,1.95)
	1993	197	59	29.9 (24,36.7)	1.10 (0.78,1.55)	1.11 (0.79,1.55)
	1994	99	32	32.3 (23.9,42)	1.23 (0.79,1.92)	1.23 (0.78,1.92)
	1995	152	50	32.9 (25.9,40.7)	1.26 (0.87,1.83)	1.28 (0.88,1.86)
Any HPV	1988	836	475	56.8 (53.4,60.1)	1.00 (-,-)	1.00 (-,-)
	1989	1176	699	59.4 (56.6,62.2)	1.11 (0.93,1.33)	1.11 (0.93,1.33)
	1990	1014	608	60 (56.9,62.9)	1.14 (0.95,1.37)	1.14 (0.95,1.38)
	1991	282	188	66.7 (61,71.9)	1.52 (1.15,2.02)	1.50 (1.13,1.99)
	1992	252	158	62.7 (56.6,68.4)	1.28 (0.96,1.71)	1.29 (0.96,1.72)
	1993	197	110	55.8 (48.9,62.6)	0.96 (0.70,1.31)	0.95 (0.69,1.30)
	1994	99	53	53.5 (43.8,63)	0.88 (0.58,1.33)	0.88 (0.58,1.33)
	1995	152	75	49.3 (41.5,57.2)	0.74 (0.52,1.05)	0.77 (0.54,1.09)

Table 3: HPV positivity in those unvaccinated in each birth cohort *HR HPV not 16/18/31/33/45 **Adjusted for SIMD

Figure 1: Impact of vaccination on HPV prevalence by birth cohort 1988-1995 for (A) HPV 16 or 18 (B) HPV 31 or 33 or 45 (C) Other high risk HPV (not HPV 16/18/31/33/45) (D) Any HPV