research

The impact of bivalent HPV vaccine in Scotland

ORIGINAL RESEARCH Retrospective population study

Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland

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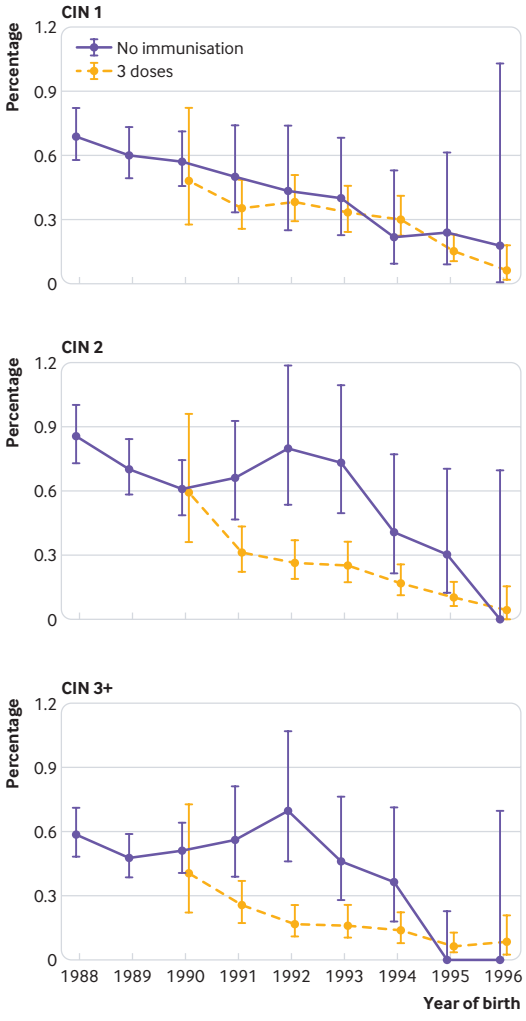
Study question What has been the impact of routine vaccination of girls aged 12-13 years with the bivalent human papillomavirus (HPV) vaccine on disease in the first year of screening at age 20 in Scotland?

Methods A retrospective analysis of screening outcomes (cytology result, referral for colposcopy and histologically confirmed cervical intraepithelial neoplasia (CIN)) was performed in women born between 1 January 1988 and 5 June 1996. Anonymised routinely collected screening data, including immunisation status, were extracted in September 2017. Women born between January 1988 and December 1990 were not eligible for vaccination, women born between January 1991 and December 1994 had catch-up vaccination, and women born after January 1995 had routine vaccination. Multinomial logistic regression was used to relate the outcomes to age at vaccination and immunisation status, using women not eligible for vaccination as the comparator. Herd protection was investigated by comparing the apparent vaccine effectiveness in unvaccinated women with women not eligible for vaccination.

Study answer and limitations 138 692 records were retrieved. Younger age at immunisation was associated with increasing vaccine effectiveness: 86% (75% to 92%) for CIN grade 3 or worse for women vaccinated at age 12-13 compared with 51% (28% to 66%) for women vaccinated at age 17. Evidence of herd protection against CIN grade 2 or worse was found in unvaccinated girls in the 1995 and 1996 cohorts. The analysis was restricted to data from the first year of screening, and attendance at age 20 was 51% for vaccinated women and 23% for unvaccinated women, possibly leading to over-estimation of vaccine effectiveness. Women born in 1995 and 1996 have shorter follow-up, possibly leading to lower estimates for vaccine effectiveness. Changes to management of low grade disease might have affected the robustness of the data relating to CIN grade 1 only.

What this study adds Routine vaccination of girls aged 12-13 years with the bivalent HPV vaccine in Scotland has led to a dramatic reduction in preinvasive cervical disease. Evidence of clinically relevant herd protection is apparent in unvaccinated women.

Funding, competing interests, and data sharing Health Protection Scotland funds the surveillance of immunisation with the bivalent HPV vaccine in Scotland. The authors have no conflicts of interest likely to affect the study findings. No additional data available.



Histological abnormality (% of women screened) by year of birth and immunisation status. Whiskers represent 95% confidence intervals. CIN=cervical intraepithelial neoplasia; 1988-90=pre-immunisation programme cohort; 1991-94=catch-up cohort; 1995-96=routinely vaccinated cohort

COMMENTARY New analyses show substantial cross protection and herd immunity

It was initially believed that prophylactic human papillomavirus (HPV) vaccines were probably type specific and provided protection only against infection with, and disease due to, the types of HPV the vaccines were targeted against. Given the predominance of the two most oncogenic HPV types (16 and 18) across all HPV related cancers, the two first generation vaccines (a bivalent vaccine targeting types 16 and 18 and a quadrivalent vaccine targeting types 6, 11, 16, and 18) offered important potential for meaningful cancer prevention even with no cross-protection.[1]

Initial findings from the bivalent HPV vaccine trial, suggesting substantial cross-protection against related HPV types, were therefore met with some scepticism.[2 3] In a linked paper, Palmer and colleagues report unequivocal findings from Scotland showing high vaccine effectiveness in young women against high grade cervical disease regardless of causal HPV type.[4]

Although Scotland changed to the quadrivalent vaccine in September 2012, the vaccinated women in the study all received the bivalent vaccine. The authors identified cervical disease using both cytology and histopathology outcomes and conducted two analyses: one comparing disease rates in vaccinated cohorts with pre-vaccine cohorts, and a second comparing vaccinated and unvaccinated women within each birth cohort. Estimates of vaccine effectiveness were adjusted for deprivation and rurality—both important predictors of cervical disease in Scotland.

We must work towards a world in which all girls and their families are offered, and the majority accept, HPV vaccination

Unequivocal results

The findings are dramatic and document a considerable reduction in high grade cervical disease over time. The authors estimate a vaccine effectiveness of 86% (95% confidence interval 75% to 92%) for the most severe outcome of cervical intraepithelial neoplasia (CIN) grade 3 or worse in women fully vaccinated at ages 12-13 compared with the unvaccinated cohort. Notably, they report a large reduction in CIN grade 3 or worse in the most recent cohort of women compared with the pre-vaccination cohort, whether they were vaccinated or not, suggesting that interruption of HPV transmission in Scotland has created substantial herd protection.

Although HPV types 16 and 18 are known to predominate in cervical lesions among young women,[5] a reduction of over 85% against CIN grade 3 or worse caused by all HPV types clearly indicates that the cross-protection documented previously in Scotland against related HPV types 31, 33, and 45[6] is translating directly into disease prevention.

This study also highlights the value of integrated registries that can systematically collect and use high quality data from screening and vaccination programmes. In its prepublication review of the paper, the charity Jo's Trust, also emphasised the importance of information technology infrastructure to optimise programmes.

All countries must now consider how best to implement and evaluate vaccination, screening, and treatment programmes that support WHO's call for elimination of cervical cancer as a public health problem.[7] Scotland has shown that integrated registry systems

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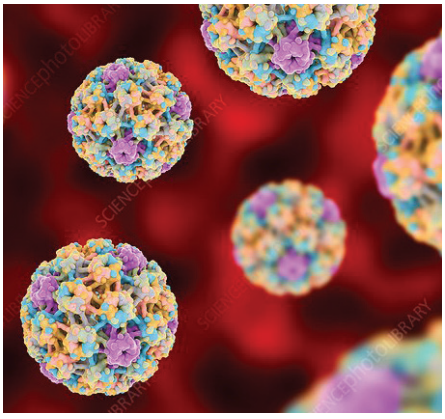
AUTHOR PERSPECTIVE Tim Palmer

Cervical cancer is a major morbidity worldwide. Most cancers are preventable by effective screening, and cervical cancer screening, arguably, best meets the Wilson criteria for a screening programme. Understanding the biology of the disease underpins and informs effective screening, and this understanding has advanced greatly since I first was involved in the UK programme in 1989. Most importantly, understanding the obligate role of persistent infection by high risk human papillomavirus (hr-HPV), particularly HPV type 16, in the genesis of most cervical cancers has led to the introduction of HPV testing for screening and to the production and delivery of vaccines against clinically relevant hr-HPV.

The protective effect of hr-HPV immunisation was shown in clinical trials using the bivalent and quadrivalent vaccines. The bivalent vaccine is directed against HPV 16 and 18, the most important high risk types. The quadrivalent vaccine also generates immunity against two low risk types (HPV 6 and 11) that cause genital warts. Real life data from Australia (quadrivalent vaccine) and Scotland (bivalent vaccine), have shown that both vaccines are highly effective in preventing HPV infection and its consequences: preinvasive cervical disease and genital warts. Furthermore, herd protection is unequivocal, as HPV infection, genital warts, and cervical disease have also decreased in women and men who have not had the vaccine. No evidence has been found for HPV "fighting back" by either type replacement (other hr-HPV becoming more prevalent in important disease) or mutation (HPV has a low mutation rate). Finally, the data show that the bivalent vaccine is associated with significant cross protective immunity against three other important hr-HPV types—31, 33, and 45—that are related to HPV 16 and 18, making it effectively a pentavalent vaccine. UK epidemiological data have shown that HPV 16, 18, 31, 33, and 45 alone are associated with 90% of cervical cancers.



No serious adverse effects

The most recent population based data from Scotland reinforce the message that the vaccine is having a considerable and sustained effect, showing that women who were immunised at age 12-13 have virtually no high grade disease eight years later. One of the implications of this work is that considerably fewer women will have to live with the physical and psychological implications, including pregnancy loss, of colposcopy and treatment. Globally, millions of doses of HPV vaccine have been given to women and, increasingly, men. In Scotland, as elsewhere, no serious adverse effects have

are highly effective tools in achieving and evaluating high vaccine uptake,[8] and in assessing subsequent outcomes,[4] including screening performance.[9]

A good choice

As we manage supply problems (including shortages) with HPV vaccines,[10] and consider whether the nonavalent HPV vaccine (which protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58) [11] will ever be affordable for low income countries, these data highlight that the bivalent HPV vaccine is still a good choice for prevention.

We must not forget, however, the girls who were not vaccinated and the women who do not currently screen. We must work towards a world in which all girls and their families are offered, and the majority accept, HPV vaccination, wherever they live. We must also actively develop, resource, and scale-up more effective, feasible, and culturally acceptable strategies for cervical screening, such as self-collection of specimens,[12] if we are ever to effectively reduce the global burden of cervical cancer effectively.

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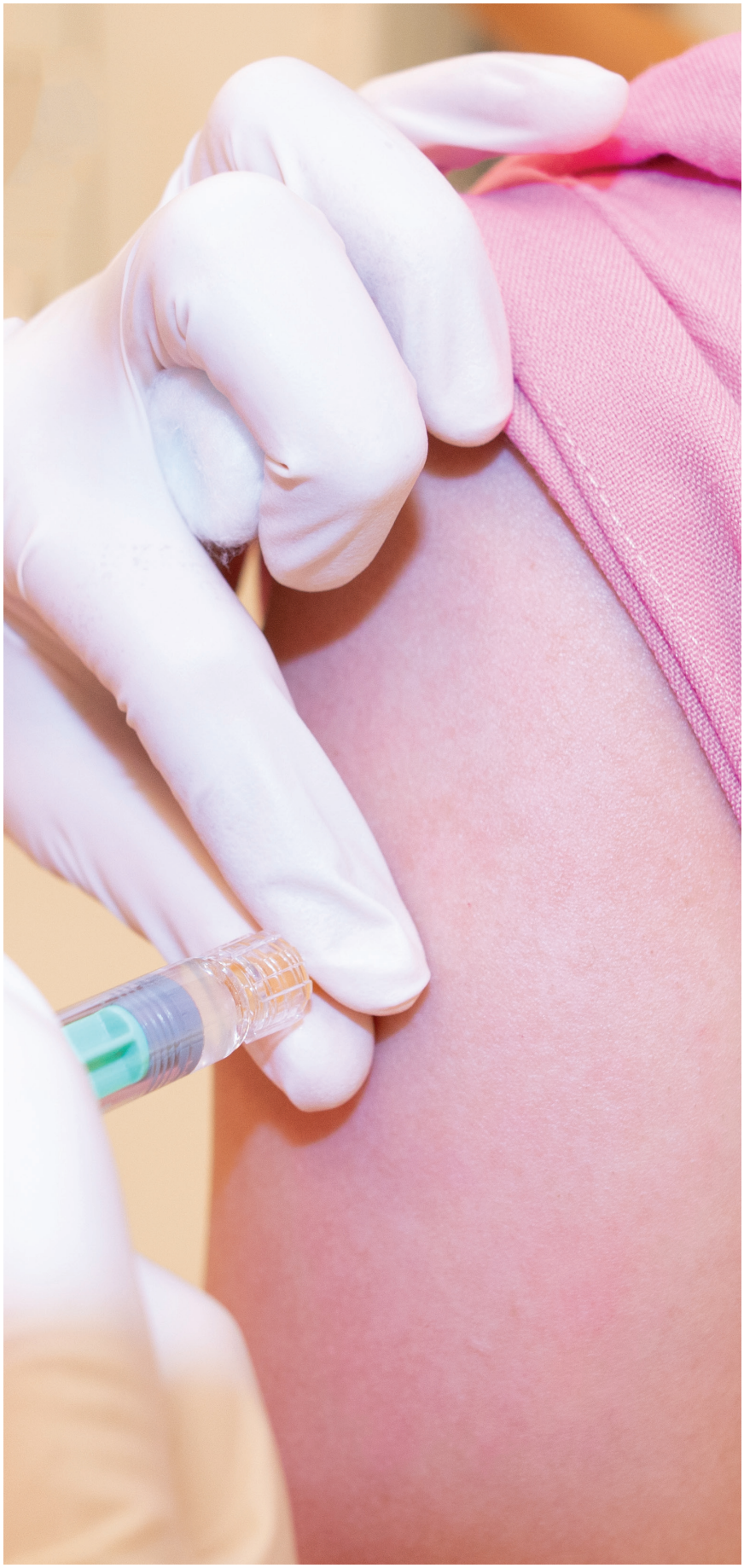

been demonstrably linked to the vaccine. The ratio of benefit to possible harm therefore strongly supports immunisation.

In the context of a professional life in which cervical screening has been a major part, this is remarkable news. The anxiety caused by the inherent subjectivity of reading a cervical smear, and therefore the follow-up of abnormalities of uncertain significance, has been a major concern. Even the move to HPV testing as the primary screening test does not get around these problems. Neither method of screening is feasible in low and middle income countries, which shoulder the greatest burden of cervical cancer.

HPV immunisation therefore offers the only feasible solution to preventing a cancer the cause of which is well established—hr-HPV infection—in those areas of the world where the burden of the disease is greatest. It is also the most cost effective method in developed countries. This a veritable triumph for medicine.

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ORIGINAL RESEARCH Population based nested case-control study

Cervical screening and risk of adenosquamous and rare histological types of invasive cervical carcinoma

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Study question Does cervical screening lead to reduced risk of adenosquamous and rare histological types of invasive cervical carcinoma?

Methods This was a nationwide, population based, nested case-control study including all invasive cases of cervical carcinoma in Sweden during 2002-11 (4254 confirmed cases after clinical and histopathological review). Cases that were neither squamous cell carcinoma nor adenocarcinoma (n=338) comprised 164 cases of adenosquamous cell carcinoma (ASC) and 174 rare types of invasive cervical carcinoma (RICC) (glassy cell carcinoma, clear cell carcinoma, small cell carcinoma, neuroendocrine cell carcinoma, large cell carcinoma, and undifferentiated carcinoma). 30 birth year matched controls from the general Swedish population were matched to each case by applying incidence density sampling. The risk of ASC and RICC was estimated in relation to screening status and screening history, with adjustment for education.

Study answer and limitations Women with two screening tests in the previous two recommended screening intervals had a lower risk of ASC (incidence rate ratio 0.22, 95% confidence interval 0.14 to 0.34) and RICC (0.34, 0.21 to 0.55), compared with women without any test. The small number of cases resulted in reduced precision in subgroup analyses, and adjustment for lifestyle factors was not possible.

What this study adds Women who attended screening according to routinely recommended intervals had a significantly reduced risk of ASC and RICC. The magnitude of risk reduction in relation to cervical screening was less for RICC than for ASC.

Incidence rate ratio (IRR) of adenosquamous cell carcinoma and rare types of invasive cervical carcinoma by screening status in previous two screening intervals in women aged 30 and older

Screening status	Cases—No (%)	Controls—No (%)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
Adenosquamous cell carcinoma (n=155)				
No test	65 (42)	954 (21.5)	Reference	Reference
One test	44 (28)	1290 (29.0)	0.40 (0.26 to 0.60)	0.39 (0.26 to 0.59)
Two tests	46 (30)	2197 (49.5)	0.22 (0.15 to 0.34)	0.22 (0.14 to 0.34)
Rare types of invasive cervical carcinoma† (n=152)				
No test	70 (46)	1461 (33.8)	Reference	Reference
One test	47 (31)	1169 (27.1)	0.64 (0.42 to 0.99)	0.69 (0.45 to 1.06)
Two tests	35 (23)	1691 (39.1)	0.31 (0.19 to 0.49)	0.34 (0.21 to 0.55)

*Adjusted for educational level and age.
†Includes glassy cell carcinoma, clear cell carcinoma, and other rare types.

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