HPV Prevalence and Herd Immunity after Introduction of Vaccination Program in Scotland

Kate Cuschieri

Scottish HPV Reference Laboratory (SHPVRL)

http://www.hps.scot.nhs.uk/reflab/VirLabDetail.aspx?id=26

Functions of SHPVRL

1. HPV testing for **Epidemiology and Surveillance** for the HPV immunisation programme

2. HPV screening / genotyping in individual **clinical cases** where knowledge of HPV status will inform clinical management

3. Provision of **quality assurance and assessment** materials for UK-wide HPV testing laboratories and beyond

4. Commitment to a **research and development programme Teaching and training** of medical, scientific and technical staff

5. Advice and testing services for the **Scottish Cervical Screening Programme**

6. Consolidation of **HPV sample archives** to facilitate research, quality assurance, test development, audit and teaching.

Scotland's Cervical Screening Programme

- Scotland 5.3 million people (2011 census)
- National, organised call/recall cervical screening programme.
- Liquid based cytology (PreservCyt)
- Age range 20 -60 years. **To change** to 25-65 year olds June 2016. 3 yearly screening up to age 50 then 5-yearly
- ~70% uptake
- Centralised IT system. This captures - cytology, call recall, histology, colposcopy, HPV and immunisation status

- HPV testing performed as a test of cure of treatment (not as triage)
- Business case for primary HPV testing to be submitted in 2016

Scottish HPV immunisation programme and associated surveillance

- HPV immunisation initiated in September 2008 - schools based programme
- **12-13 year olds girls = routine/ "target" cohort**
- **Three year "Catch-up" ran for girls ≤18 years**
- Bivalent vaccine until September 2012, changed to quadrivalent
- Three dose schedule- changed to two dose in 2014
- **Partner programme of longitudinal surveillance to determine impact**

Scottish HPV immunisation surveillance (initiated 2008)

- **Facilitated through**
  - Unique person identifier "CHI number"
  - Existing national databases for cervical screening, colposcopy, immunisation and cancer; linkage between them possible through CHI.
  - Funding for a specific programme through National Services Division
  - National pathology networks, reference laboratory facility[1], Scottish HPV Investigators Network[2], National HPV Sample Archive.[3]
  - Age at cervical screening initiation =20 years, **so…women immunised as part of catch up (ie born after 1st Sept 1990) have been entering the programme since 2011/12**

1. http://www.hps.scot.nhs.uk/reflab/

2. http://www.shine.mvm.ed.ac.uk/

3. http://www.shine.mvm.ed.ac.uk/archive.shtml

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Scottish HPV immunisation surveillance

- **Programme includes**
  - Baseline assessments (pre-immunised population)[1,2,3]
  - Monitoring impact of immunisation on disease outcomes over time (histological[4], cytological[5], colposcopic[6])
  - Monitoring impact of immunisation on HPV infection
    - In women attending for first smear (yearly) – residual LBC[7]
    - In women 20-25 diagnosed with CIN2/3 -residual biopsy
    - Assessment of < 3 doses of vaccine

1: O'Leary et al HPV type-specific prevalence using a urine assay in unvaccinated male and female 11- to 18-year olds in Scotland. Br J Cancer.2011 Mar 29;104(7):1221-6.
2:Cuschieri et al. Distribution of HPV types associated with cervical cancers in Scotland and implications for the impact of HPV vaccines. Br J Cancer.2010 Mar 2;102(5):930-2
3: Kavanagh K et al. Estimation of HPV prevalence in young women in Scotland; monitoring of future vaccine impact. BMC Infect Dis. 2013 Nov 5;13:519.
4: Pollock KG, et al. . Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. Br J Cancer. 2014 Oct 28;111(9):1824-30.
5: Palmer, T. J., et al. Effect of HR-HPV immunisation on the performance of cervical cytology, presented at EUROGIN 2015 *OC12, p206*
6: Cruickshank M et al "Implications of HPV immunisation on colposcopy services and practice" Submitted -
7: Kavanagh K, Pollock KG, Potts A, Love J, Cuschieri K, Cubie H, Robertson C, Donaghy M. 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. Br J Cancer. 2014 May 27;110(11):2804-11.
8. Cuschieri et al. Impact of partial bivalent HPV vaccination on vaccine-type infection: a population-based analysis. Br j Cancer 2016. May 24;114(11):1261-4

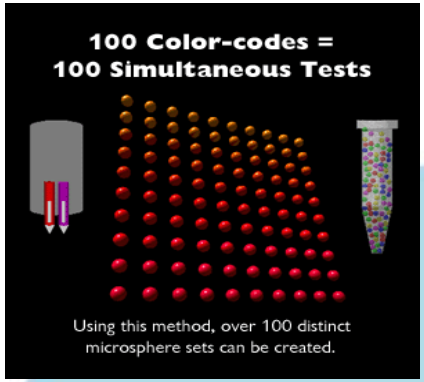
Baseline Studies in Pre-immunised populations

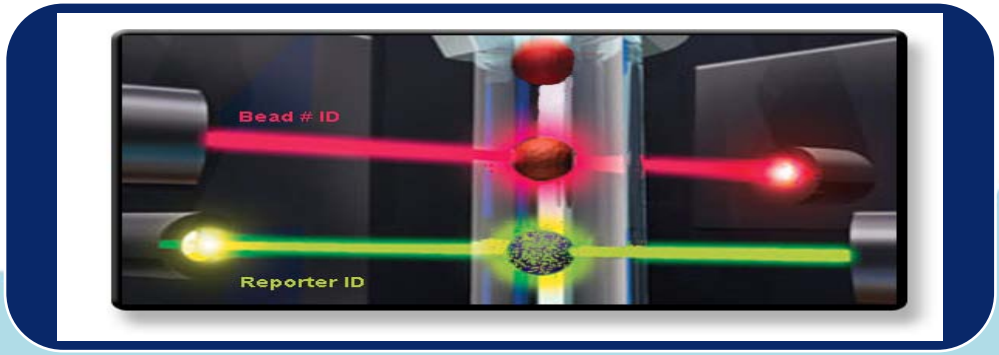
- Assessment of HPV prevalence in
  - **Young people (11-18)**
  - **Women attending for first smear aged 20**
  - **Women who defaulted from first smear**
  - **CIN2/3**
  - **Cancers**

- Technical validation of
  - HPV Assays that can be used for non-invasive samples and formalin fixed paraffin embedded materials

Technical validation (1) – validate genotyping technology for diverse biospecimens

- Luminex based detection
- Validations for **self taken samples**, **LBC** and **Formalin Fixed Paraffin embedded material**
- High risk or putative high-risk types: **16,18**,26,**31,33,35,39,45,51,52**,53,**56,58,59**,66,**68**,70, 73,82
- Low risk types: **6,11**,42,43,44





Red laser reads the bead, i.e. the target

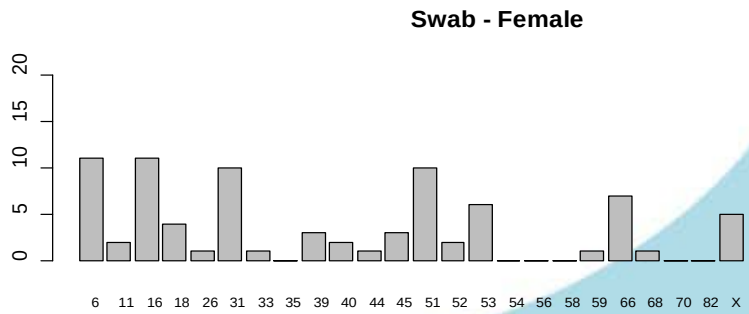
Green laser detects the amount of the target

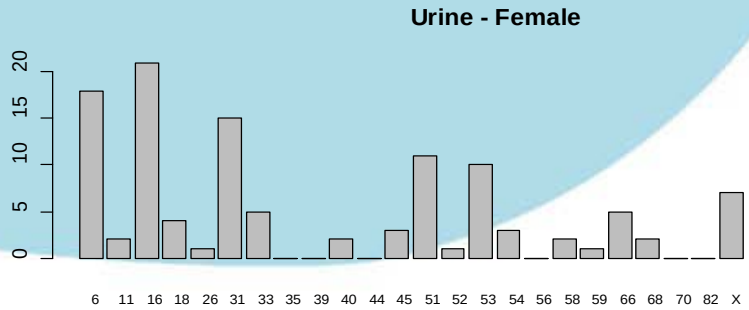
Technical validation (2) Assess the suitability of urine as a bio-specimen for HPV surveillance

- Group of young males and females <25 attending drop in sexual health services

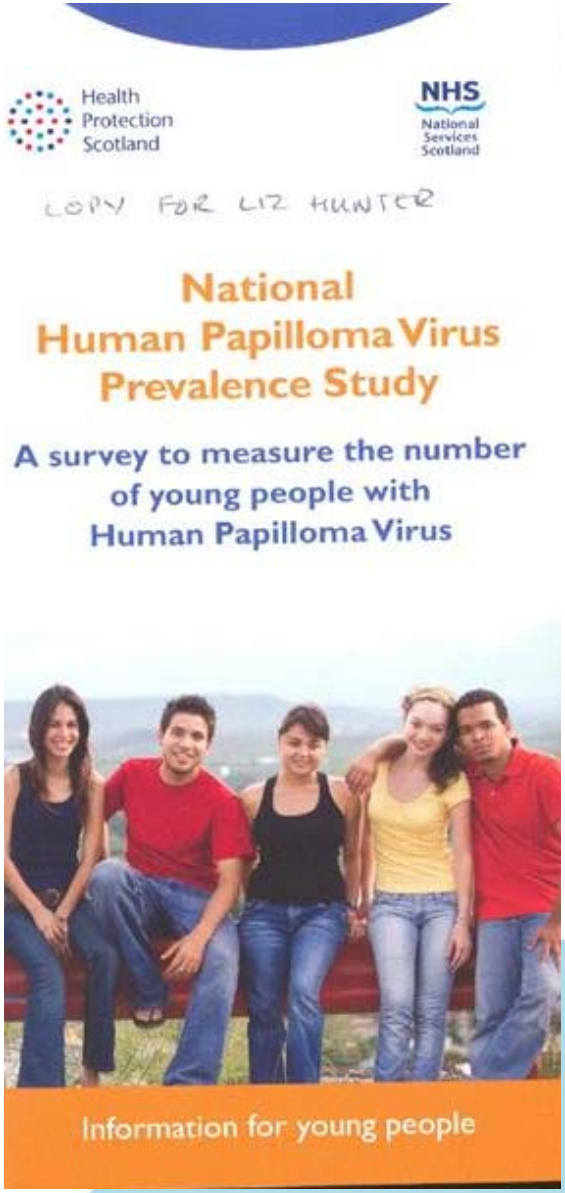
HPV positivity/concordance in urine vs gold standard measured

Urine testing as a surveillance tool to monitor the impact of HPV surveillance programmes. Cuschieri K(1), Nandwani R, McGough P, Cook F, Hogg L, Robertson C, Cubie H. J Med Virol. 2011 Nov;83(11):1983-7

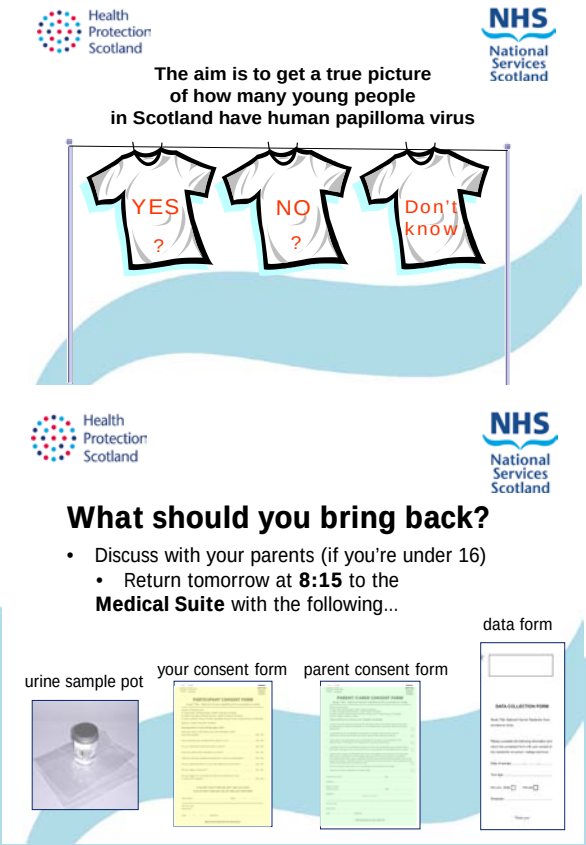




Baseline HPV Prevalence Study in 11-18 year olds through school population



Information leaflet



School presentations -

School Presentations

2447 urine's…

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Self-collected testing for Human Papilloma Virus (HPV)

Will I get my test results?

As this study is anonymous, women who take part in this study will not get their results back and neither will their GP. It is not possible to get an HPV test within the NHS at the moment.

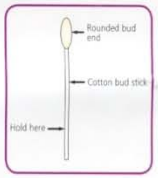
What if I have my period or I might be pregnant?

If you are in any doubt as to whether you are pregnant we would recommend that you do not take part in the study. It is best to take part when you do not have your period.

What do I need to do to take part?

Testing for HPV is easy. Just unpack the kit you received with this leaflet and follow these 10 steps:

1. Find a position most comfortable for you to insert the cotton bud into your vagina, perhaps sitting on a chair or toilet seat with your knees apart, or stand with your foot resting on the toilet seat/chair. If you use tampons, you may want to use the same position you would use to insert a tampon.



2. Remove one of the long cotton buds form the packaging (only use the second one if you make a mistake, otherwise dispose of it).

3. Hold the cottonbud about 3/4 way down the stick. Use your other hand to fold back the skin that covers the opening to your vagina. Point the rounded end of the cotton bud to your vaginal opening and gently insert it into the vagina.

mple by 30 April 2009

Assessment of HPV prevalence in women who defaulted from 1st Smear

Dispatch of self sampling kits - Option to provide swab or urine

5000 sent out…

~712 returned. ~14%

Baseline HPV results – unvaccinated population

Sample Type	Population	Age (collection period)	Sample Size	HPV +ve (%)	HPV 16/18 (%)
Biopsy Cancer *	Clinical/case ♀	All (2005-2000)	370	88	82
Biopsy CIN2+	Clinical/case ♀	21-25 (2005)	514	88.7	69
Residual Cervical LBC	1st time Screening ♀	20-21 (2009)	1995	49.4	23.2
Self taken Urine	Non-attendees ♀	0 6.5	380	31.6	9.5
Self Taken Swab	Non-attendees ♀	20-21 (2009)	332	39.2	16
Self Taken Urine	School and FEC ♂	11-14 15-18	*Total =724*	1.4 3.9	0.7 0.7
	♀	11-14 15-18 (2008)	*Total =1121*	1.1 15.2	0 6.5

Vaccine uptake is high in Scotland

Table 1: Annual HPV immunisation uptake rates for the S2 routine cohort by the end of the school year and one year later; school years 2008/09 to 2013/14[1]

School Year	% Uptake Dose 1		% Uptake Dose 2		% Uptake Dose 3	
	End of school year	1 year later	End of school year	1 year later	End of school year	1 year later
2008/09	93.7	94.5	92.7	93.8	89.4	92.4
2009/10	92.6	93.6	91.1	92.5	86.9	90.9
2010/11	91.8	92.9	90.2	92.0	81.0	90.1
2011/12	93.1	94.2	91.7	93.4	82.8	91.4
2012/13	93.5	94.4	91.8	93.4	82.0	91.4
2013/14	93.6	..	91.7	..	81.4	..

Source: CHSP School (May 2009 to 2014)/SIRS (August 2009 to 2014)

1. The uptake rates relate to the cohort of girls recorded on CHSP School in class year S2 during the school year indicated. These girls were in the second year of secondary school and were around 12 to 13 years of age.
.. These figures will be published in September 2015.

~90% uptake in target population ~65% uptake in catch up population

http://www.isdscotland.org/Health-Topics/Child-Health/publications/data-tables.asp?id=1300#1300

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Longitudinal assessments - as a consequence of vaccination, do we see impact on…

- HPV infection in women attending for first smear?
- The types of HPV infection associated with CIN2+?
- Overall rates of CIN?
- Overall rates of cytological abnormalities?
- Performance of cytology?
- Uptake at first cervical smear?
- Herd Immunity?
- *Colposcopy performance*

And also an impact of…

- **Less than 3 doses of vaccine?**

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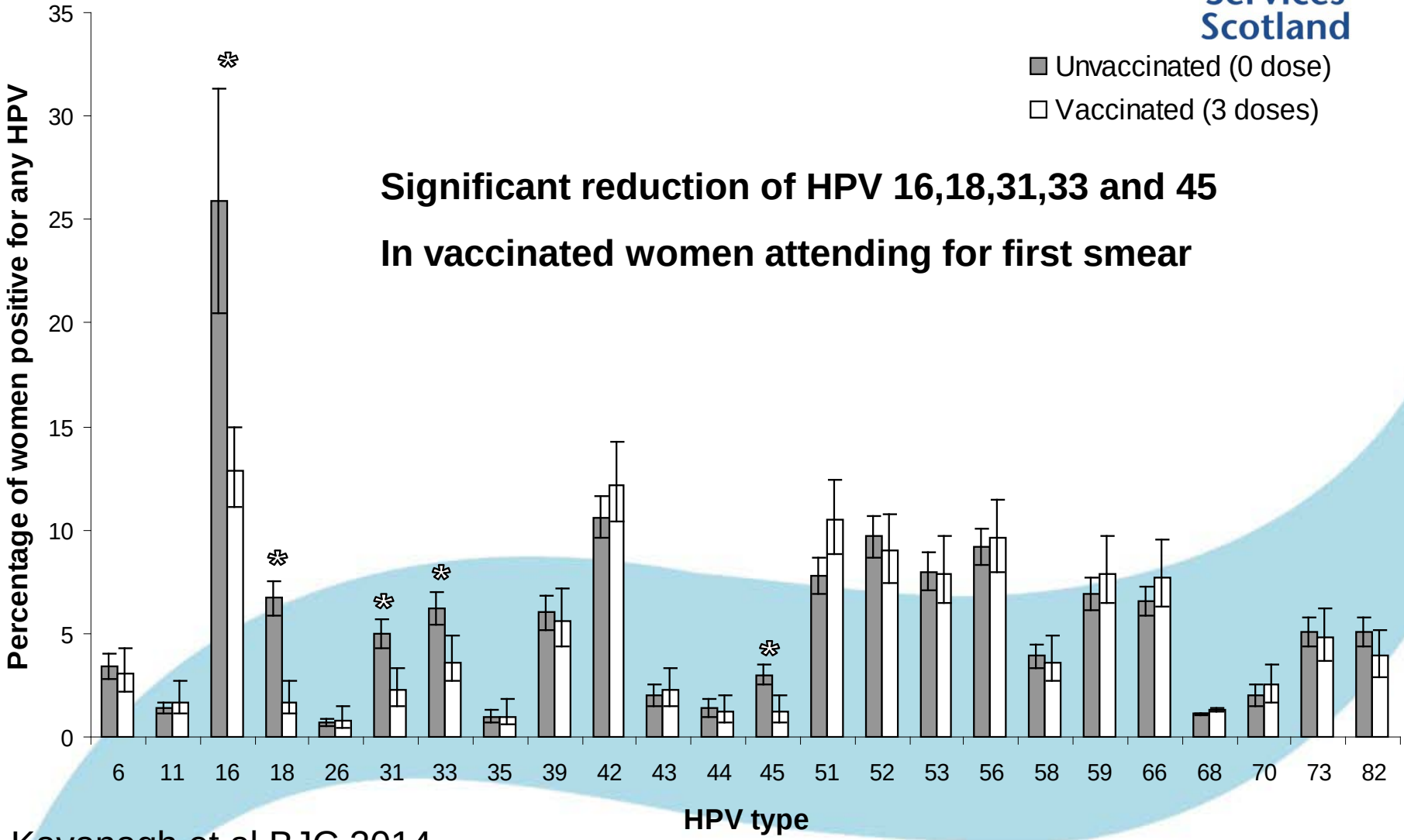
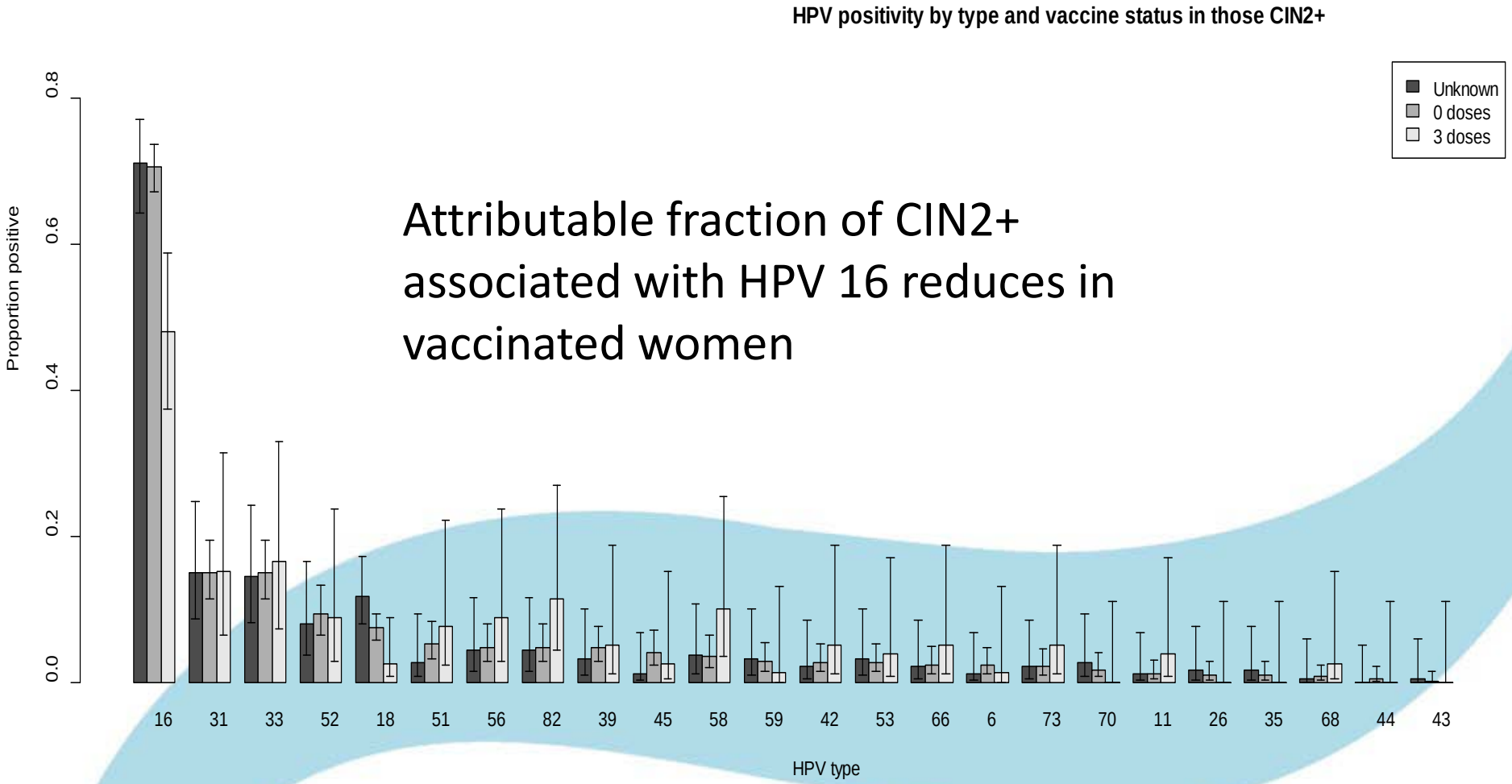


Kavanagh et al BJC 2014

HPV positivity by type and vaccine status in those with CIN2+ (data aggregated from 2011 & 13)



Attributable fraction of CIN2+ associated with HPV 16 reduces in vaccinated women

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Adjusted odds of infection with HPV 16 or 18 compared to an unvaccinated individual with CIN2 in 2011 –

	HPV 16 or 18	
	Adjusted OR	95% CI
Vaccine status		
Unvaccinated	1	-
1	0.65	(0.19, 2.25)
2	0.39	(0.14, 1.13)
3	**0.35**	**(0.21, 0.56)**
Unknown	0.88	(0.57, 1.37)
Year		
2011	1	-
2013	**0.67**	**(0.49,0.93)**
Histology		
CIN2	1	
CIN3	**2.23**	**(1.67, 2.97)**

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Vaccination reduces the amount of CIN

- CIN 1 (RR 0.71, 95% CI 0.58 to 0.87, p=0.0008)
- CIN 2 (RR 0.5, 95% CI 0.4, 0.63, p<0.0001) and
- CIN 3 (RR 0.45, 95% CI 0.35 to 0.58, p< 0.0001)

for women who received 3 doses of vaccine compared with unvaccinated women – adjusting for deprivation and age women received vaccine

Pollock et al BJC 2014

Vaccination reduces the amount of cytological abnormalities

- When compared with fully vaccinated women, unvaccinated women had odds ratio of

- 2.95 (95% CI 2.17–4.02), for severe dyskaryosis
- 2.43 (95% CI 1.94–3.05) for moderate dyskaryosis
- 1.38 (95% CI 1.26–1.51) for low-grade dyskaryosis
- 1.27 (95% CI 1.19–1.35) for borderline changes

Performance of cytology reduces in women immunised as part of catch up– particularly low grade cytology

	CIN2+			CIN3+		
	All	Unvacc	3 doses	All	Unvacc	3 doses
PPV	74.69	76.73	69.30	37.06^{NS}	37.97^{NS}	34.32^{NS}
APV	23.62	29.58	16.44	6.77	9.43	3.72
RV	2.168	1.942	2.679	4.950	4.353	6.333

PPV =positive predictive value - for high grade cytology to detect CIN
APV=abnormal predictive value for low grade cytology to detect CIN
RV= Referral value - how many cytologically abnormal cases need to be referred to colposcopy to detect one case of CIN

Palmer et al –Br J Cancer 2015

FULL PAPER

BJC

British Journal of Cancer (2016), 1–6 | doi: 10.1038/bjc.2015.473

Keywords: cervical cancer screening; screening uptake; HPV immunisation

HPV immunisation and increased uptake of cervical screening in Scottish women; observational study of routinely collected national data

T J Palmer*[,1], M McFadden[2], K G J Pollock[3], K Kavanagh[4], K Cuschieri[5], M Cruickshank[6], S Nicoll[7] and C Robertson[3,4,8]

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Background: To measure the uptake of first invitation to cervical screening by vaccine status in a population-based cohort offered HPV immunisation in a national catch-up campaign.

Methods: A retrospective observational study of routinely collected data from the Scottish Cervical Screening Programme. Data were extracted and linked from the Scottish Cervical Call Recall System, the Scottish Population Register and the Scottish Index of Multiple Deprivation. Records from 201 023 women born between 1 January 1988 and 30 September 1993 were assessed. Women born in or after 1990 were eligible for the national catch-up programme of HPV immunisation. Attendance for screening was within 12 months of the first invitation at age 20 years.

Results: There was a significant decline in overall attendance from the 1988 cohort to the 1993 cohort with the adjusted attendance ratio of the 1988 cohort being 1.49 times (95% CI 1.46–1.52) that of the 1993 cohort. Immunisation compensated for this decrease in uptake with unvaccinated individuals having a reduced ratio of attendance compared with those fully vaccinated (RR = 0.65, 95% CI 0.64–0.65). Not taking up the opportunity for HPV immunisation was associated with an attendance for screening below the trend line for all women before the availability of HPV immunisation.

Conclusions: HPV immunisation is not associated with the reduced attendance for screening that had been feared. Immunised women in the catch-up cohorts appear to be more motivated to attend than unimmunised women, but this may be a result of a greater awareness of health issues. These results, while reassuring, may not be reproduced in routinely immunised women. Continued monitoring of attendance for the first smear and subsequent routine smears is needed.

Countries with organised cytology-based cervical screening programmes have shown a considerable decrease in the incidence of cervical cancer. Data from the United Kingdom and the Republic of Ireland demonstrate the temporal relationship between the central organisation of cervical screening in 1988 and the subsequent decrease in the incidence of invasive cervical carcinoma (Comber and Gavin, 2004). In Scotland, women are currently screened between the ages of 20 and 60 years. Uptake over 5.5

Screening uptake in women eligible for catch up vaccine (born after Sept 1990) compared to those not eligible

Unvaccinated individuals had a reduced ratio of attendance compared with fully vaccinated women (RR= 0.65, 95% CI 0.64–0.65).

Will we see something similar in those women who were vaccinated aged 12-13?

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Table 6. Prevalence and odds of infection with HPV types 16 or 18 and for HPV cross-protective types among nonvaccinated women, by study year, Scotland, 2009–2013*

Study year	No. women	HPV 16 or 18			Cross-protective HPV types†		
		No. pos	% Pos (95% CI)	OR (95% CI)	No. pos	% Pos (95% CI)	OR (95% CI)
2009	1,652	468	28.3 (26.2–30.6)	1 (reference)	211	12.8 (11.2–14.5)	1 (reference)
2010	1,012	310	30.6 (27.9–33.5)	1.13 (0.95–1.34)	139	13.7 (11.8–16.0)	1.10 (0.87–1.38)
2011	557	164	29.4 (25.8–33.4)	1.05 (0.85–1.29)	71	12.7 (10.2–15.8)	0.99 (0.74–1.32)
2012	245	78	31.8 (26.3–37.9)	1.18 (0.88–1.57)	28	11.4 (8.0–16.0)	0.88 (0.58–1.33)
2013	198	42	21.2 (16.1–27.4)	0.67 (0.47–0.96)	19	9.6 (6.2–14.5)	0.71 (0.44–1.17)

*HPV, human papillomavirus; OR, odds ratio; pos, positive.
†HPV 31, 33, or 45.

Initial evidence of herd immunity for HPV 16 or 18 in unimmunised women?

Cameron et al Emerging Infectious Diseases 2015

Even one dose of vaccine may be efficacious for HPV 16/18 infection

	No. of Doses	Unadjusted VE [%, (95 CI's)]	P value	Adjusted VE: [%, (95 CI's)]	P value
HPV 16/18					
	1	25.1 (-5.7,48.0)	0.1093	**48.2** (16.8,68.9)	0.0075
	2	36 (15.3, 52.3)	0.0023	**54.8** (30.7, 70.8)	<0.0001
	3	70.2 (65.0, 74.7)	<0.0001	**72.8** (63.8, 80.3)	<0.0001
HPV 31/33/45					
	1	-15.9 (-74.6, 25.9)	0.4978	-1.62 (-85.1, 45.3)	0.9588
	2	41.4 (12.1, 62.8)	0.0143	**48.3** (7.6, 71.8)	0.0287
	3	55.5 (45.1, 64.1)	<0.0001	**55.2** (32.6, 70.2)	<0.0001

Cuschieri et al BJC 2016

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As a consequence of vaccination, do we see impact on…

- HPV infection in women attending for first smear?
- The types of HPV infection associated with CIN2+?
- Overall rates of CIN?
- Overall rates of cytological abnormalities?
- Performance of cytology?
- Uptake at first cervical smear?
- Herd Immunity?
- *Colposcopy performance*

And also an impact of…

- **Less than 3 doses of vaccine?**

……*YES…!*

- Impact of vaccination is being observed at the population level
- Pattern of infection and disease is changing – particularly that relating to HPV 16/18
- These changes are likely to be more profound as the routinely immunised girls enter the screening programme (from 2015)
- The prediction that morphology based screening tests may be negatively affected by immunisation is bearing out in population based data sets
- How do we best manage residual infection/associated disease in those both eligible and not eligible for vaccination?

The UK NSC recommendation on Cervical Cancer screening in women

Recommendation	Systematic population screening programme recommended
Last review completed	January 2016
Next review due in	2018/19
Key downloads	• Recommendation statement • Last external review - Cost-effectiveness of primary HPV screening - summary of evidence • Last external review - Evaluation of HPV Primary Screening Pilots

- Key phrase: "UK Cervical Cancer Screeing Programme should adopt the test for HPV as a primary screening test"

Evidence to support continuati
this is currently being revised,
due course. Each programme
more about cervical cancer sc

UK Cervical Cancer Screenin
The programmes should contin
evidence should be presented to the UK NSC on a regular basis to allow for consistent UK practice outside formal research. Major modifications should be brought formally to the UK NSC.

The UK NSC recommended in November 2012 that the age of first invitation for cervical screening should be raised to 25 in Wales and Scotland on the basis that there is evidence of a large number of women screened and treated with relatively little

Building capacity for relevant research – The Scottish HPV Archive

NHS National Services Scotland

- Started in 2009
- Archive of largely cervical samples from women in Scotland
- Data linkage to immunisation/screening records possible
- Can be used for HPV related research
- Over 30,000 and counting…. Multiple aliquots

INTERESTED IN USING THE ARCHIVE? Get in touch –
HPVarchive@ed.ac.uk
0131 242 6625 – Dr Ramya Bhatia - archive manager

The Scottish HPV Investigators Network (SHINe, est 2008)

NHS National Services Scotland

Purpose

The purpose of SHINe is to act as a multi-disciplinary forum for discussion on HPV and HPV-related diseases, identify emerging research and clinical questions, and implement a series of research programmes/projects relevant to HPV disease prevention and management in the future.

SHINe

http://www.shine.mvm.ed.ac.uk

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Thanks to

- HPV Surveillance Team at HPS past a present – including but not confined to Kevin Pollock, Kim Kavanagh, Chris Robertson, John Love, Ross Cameron, Alison Potts, Katy Sinka, Maureen O Leary.
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- Scottish HPV Investigators Network
- GISCifor the opportunity to allow me to present