
HPV testing in the NHS CSP

Dr Karin Denton

North Bristol NHS Trust/ SW QARC

North Bristol NHS Trust/Avon Cervical
screening programme

Sentinel Sites Study Group

R Albrow	<u>H Kitchener (Chair)</u>	J Patnick
A Bailey	T Levine	J Rimmer
H Cubie	R Lonsdale	A Sargent
K Denton	J Marshall	J Smith
M Desai	J Mather	J Tidy
K Ellis	C Moore	P Walker
C Evans	S Moss	R Winder
V Frew	P Muir	M Young
R Kelly		

Analysis: R Kelly and S Moss (Institute of Cancer Research)

NHSCSP: J Patrick, J Rimmer, R Winder

HPV as a biomarker of risk

- Normal cytology 12% positive
- Borderline 40% positive
- Mild dyskaryosis 80% positive
- Moderate 90% positive

HPV has an NPV of over 99%

Sentinel Sites

- Manchester
 - Liverpool
 - Sheffield
 - Northwich Park
 - Norwich
 - Bristol
- 10% population
 - Pilot of implementation

Protocol for Triage

- First borderline or mild dyskaryosis
- HPV negative – routine recall
- HPV positive – colposcopy referral
 - Colp negative - return to recall
 - CIN2/3(\pm 1) - treatment/6 month FU
 - Untreated CIN1, local protocol

Protocol for Test of Cure

- Cytology at 6 months
 - Abnormal - refer to colposcopy
 - Negative - HPV test
 - If HPV negative, routine recall
 - If HPV positive, colposcopy

Results

- Study took place between 1 Jan 2008 and 1 April 2009
- Data collected until September 2009
- Analysis conducted independently at Cancer Screening Evaluation Unit, Institute of Cancer Research
- Over 90% of women attended colposcopy

HPV positive rates by age group and initial cytology result

Age Grp	Borderline		Mild		Total	
	No of women	HPV + n (%)	No of women	HPV + n (%)	No of women	HPV + n (%)
25-34	3121	2144 (68.7)	2203	1964 (89.2)	5324	4108 (77.2)
35-49	2783	1165 (41.9)	1129	869 (77.0)	3912	2034 (52.0)
50-64	603	187 (31.0)	212	141 (66.5)	815	328 (40.2)
Total	6507	3496 (53.7)	3544	2974 (83.9)	10051	6470 (64.4)

SSS Results from different centres

HPV positive rate by site and initial cytology 1

Site	Borderline		Mild			Total	
	n	HPV +ve (%)	n	HPV +ve (%)	n	HPV +ve (%)	
A	1263	866 (68.6)	404	370 (91.6)	1667	1236 (74.1)	
B	643	224 (34.8)	523	384 (73.4)	1116	608 (52.1)	
C	2557	1111 (43.4)	1507	1232 (81.8)	4064	2343 (57.7)	
D	789	455 (57.7)	420	372 (88.6)	1209	827 (68.4)	
E	663	406 (61.2)	557	500 (89.8)	1220	906 (74.3)	
F	592	434 (73.3)	133	116 (87.2)	7255	550 (75.9)	

SSS Results from different centres

HPV positive rate by site and initial cytology 2

Site	Borderline		Mild		Total	
	n	HPV +ve (%)	n	HPV +ve (%)	n	HPV +ve (%)
Centre C (Thinprep® LBC)	1188	543 (47.7)	798	669 (83.8)	1986	1236 (61.0)
Centre C (BD Surepath™ LBC)	426	216 (50.7)	241	204 (84.6)	667	420 (63.0)
Total (Thinprep® LBC)	3903	2270 (58.2)	2179	1911 (87.7)	6082	4181 (68.7)
Total (BD Surepath™ LBC)	1661	874 (52.6)	897	704 (78.5)	2558	1578 (61.7)

Sentinel Site Study

Results at colposcopy 1

		Inadequate/ unknown/ other		Negative		Positive Cytology	
		n	(%)	n	(%)	n	(%)
BL	25-34	64	(3.3)	1091	(56.6)	45	(2.3)
	35-49	30	(2.8)	679	(64.0)	26	(2.5)
	50-64	8	(4.7)	124	(72.5)	3	(1.8)
	Total	102	(3.2)	1894	(59.9)	74	(2.3)
Mild	25-34	71	(4.1)	821	(46.9)	62	(3.5)
	35-49	27	(3.4)	392	(49.2)	25	(3.1)
	50-64	3	(2.3)	80	(61.5)	5	(3.8)
	Total	101	(3.8)	1293	(48.3)	92	(3.4)
Total		203	(3.5)	3187	(54.6)	166	(2.8)

Sentinel Site Study

Results at colposcopy 2

		CIN 1		CIN2		CIN3+	
		n	(%)	n	(%)	n	(%)
BL	25-34	394	(20.4)	193	(10.0)	142*	(7.4)
	35-49	173	(16.3)	88	(8.3)	65	(6.1)
	50-64	27	(15.8)	4	(2.3)	5	(2.9)
	Total	594	(18.8)	285	(9.0)	212	(6.7)
Mild	25-34	468	(26.7)	217	(12.4)	111	(6.3)
	35-49	236	(29.6)	87	(10.9)	30	(3.8)
	50-64	31	(23.8)	8	(6.2)	3	(2.3)
	Total	735	(27.5)	312	(11.7)	144	(5.4)
Total		1239	(22.8)	597	(10.2)	356	(6.1)

*Includes 3 invasive cancers

Sentinel Site Study

PPV of colposcopy by site 1

Site	Borderline			Mild		
	No attending colposcopy	PPV CIN2+	PPV CIN3+	No attending colposcopy	PPV CIN2+	PPV CIN3+
A	803	21.5	7.8	350	25.4	7.1
B	178	11.2	6.2	317	9.1	3.5
C	978	11.6	5.0	1104	15.9	4.8
D	430	16.5	7.4	354	21.8	7.6
E	355	9.3	2.5	440	10.9	2.5
F	417	20.9	11.5	112	30.0	15.2

Sentinel Site Study

PPV of colposcopy by site 2

Site	Total		
	No attending colposcopy	PPV CIN2+	PPV CIN3+
A	1153	22.7	7.6
B	495	9.9	4.4
C	2082	13.9	4.9
D	784	18.9	7.5
E	795	10.2	2.5
F	529	23.4	12.3

Sentinel Sites Study

Rate of disease at 1, 2 3 and >3 years after negative colposcopy in 956 women with long term follow-up

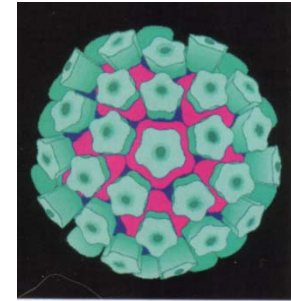
Time since negative colposcopy	Abnormal cytology		CIN1		CIN2		CIN3	
	No.	%	No.	%	No.	%.	No.	%
1 year	10	1.0	18	1.9	6	0.6	10	1.0
2 years	19	2.0	33	3.5	16	1.7	19	2.0
3 years	25	2.6	38	4.0	19	2.0	23	2.4
>3 years	30	3.1	49	5.1	23	2.4	28	2.9

Test of Cure

- Preliminary data only in un-triaged women
- 3203 women had test of cure
- Failed test of cure by 18.3%
 - 6.2% by abnormal cytology
 - 12.1% by HPV +ve with normal cytology
- Increased 'failure' rates with lower CIN grade
- Persistent CIN2+ in 7%
 - 3% in HPV +ve
 - 13% in cytology +ve

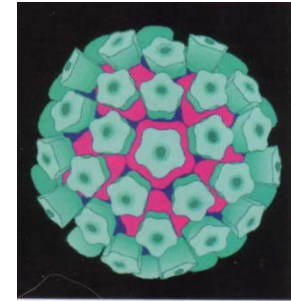
Our experience

- As a programme
- As a hub site for HPV testing

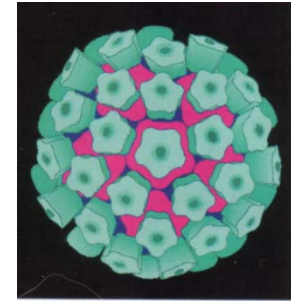


Programme experience

- Sample taker training
- Lean/14 day TAT
- Colposcopy



Sample taker training

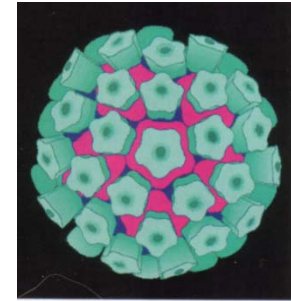


- Bristol was an original LBC/HPV pilot site
- Extensive HPV testing from 2001-2003
- Relatively stable population of well trained sample takers
- Sample taker register and universal update training
- Decision made to offer electronic /written update training only on implementation
- Worked reasonably well but colposcopy report women arriving have a lot of questions

-
- Sample taker training is vital

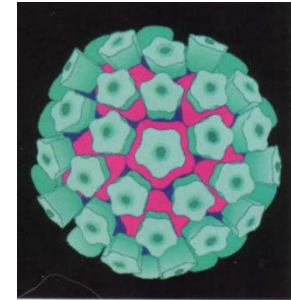


14 day TAT/lean

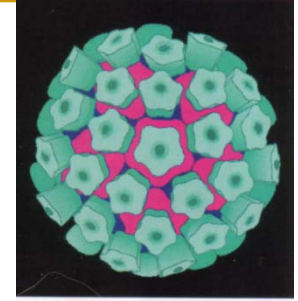


- Bristol meets the vital signs target
- Has required careful management
- 2 additional staff appointed “senior MLA”
- Do most of the HPV testing (under BMS supervision)
- Chase results
- Careful monitoring of specimens about to breach

Lean

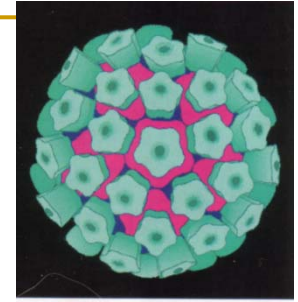


- Sample screened and checked
- To consultant/AP before 11 am
- Consultant/AP opinion before 11 am
- “Test” code entered on computer
- At 11, an electronic extract of all cases for testing is run
- DNA extraction day 1
- Analysis day 2
- Results available day 2 lunch time

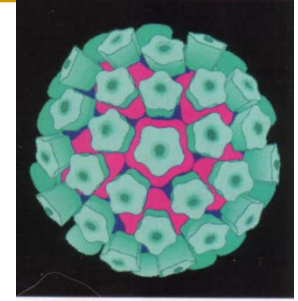


- Results entered by consultant/AP if available but any consultant/AP or trained senior BMS staff can enter final result
- Daily download to PCSA at 7 am
- No problem attaining 14 days with 1 HPV test
- (Currently doing 4 which has been a bit more challenging)

Colposcopy



- Implementation of Sentinel sites coincided with other changes
 - Change in screening interval
 - Jade Goody
 - Organised change to community follow up after treatment-early discharge



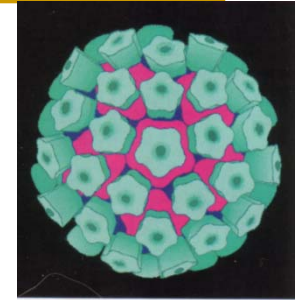
- However no doubt that there was an increase in colposcopy referrals due to sentinel sites
- At peak 5 additional clinics running / week
 - Additional consultant clinics

Colposcopy after 3 years



- New referrals up around 10% on baseline
- Probably accounted for by early discharge ie total number of new and follow up appointments has not increased

Experience as an HPV testing Hub

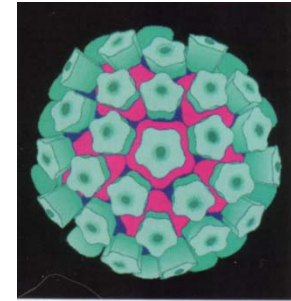


Frequency of HPV tests



- Started x2/week
- Moved to x5 in 2 weeks
- Moved to daily
- 3 large labs (combined approx 200 000 samples/year screened)
- Triage and TOC
- About right for 1 plate/day

Conclusions on HCII



- Not difficult but skilled
- Best results with dedicated technical operators
- Careful BMS review of results
- Space requirement
- Daily runs
- Good communication with spoke sites essential

What next?

- DOH requirement to roll out

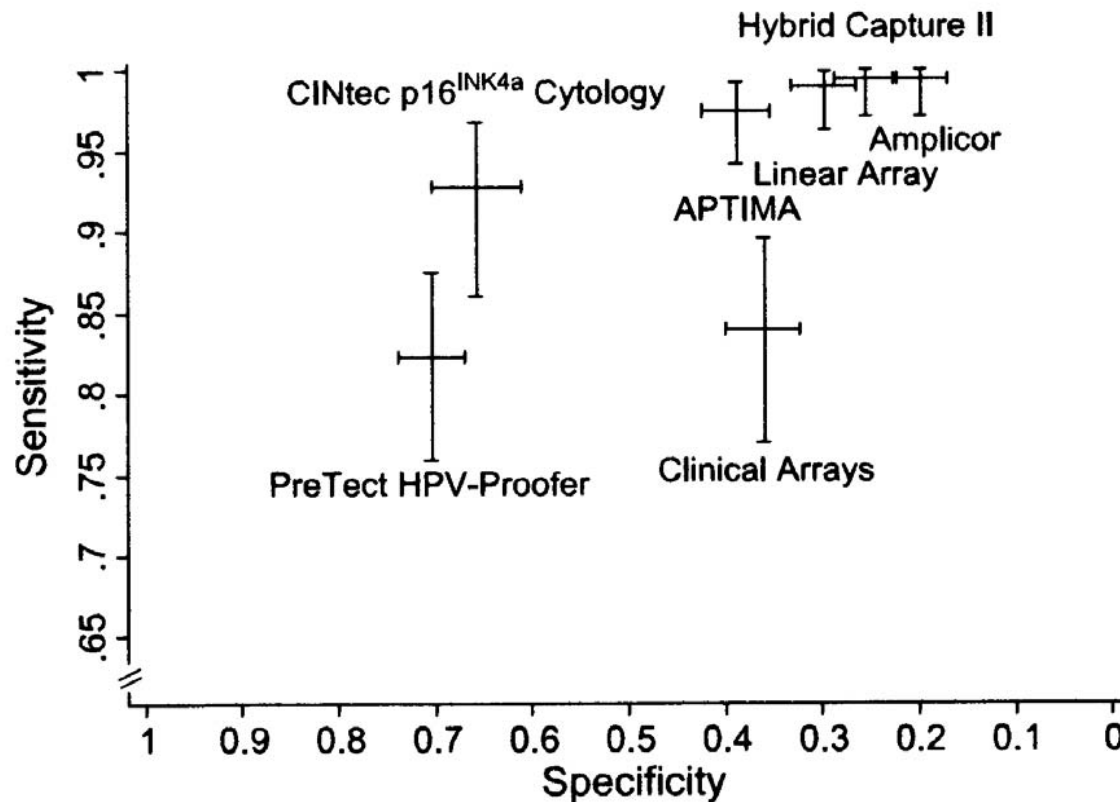
What are the issues?

- Which test?
- Where should the test be done?
- 14 day TAT
- Practical aspects of roll out

Which test?

Sentinel Site Study

Sensitivity & specificity for the detection of CIN3+ (with 95% CI)



-
- Hybrid capture II currently the only approved test
 - Roche, Genprobe, Abbott, Cervista being evaluated, published results by September 2011
 - HC II used in Sentinel sites
 - Testing done in Manchester Virology and Bristol Cytology

Experience of HC II

- Not difficult
- Much of the work done by Band 4's under BMS supervision
- Space requirement
- Some dexterity required – pipetting
- Careful attention to QA – initially some runs had to be repeated.

Is HC II the best test

- Almost certainly not!

Where should the test be done?

- Cytology or virology
- Configuration...

14 day TAT/lean

- Achieving 14 day TAT with HPV test is possible
- Both hub and spoke sites have achieved
- Adds at least 1 day on to pathway
- Careful leaning of all processes

Practical issues

R Winder 9.3.11

- Roll out fully funded
- Funds held by NHS CSP
- Bidding process from 1.4.11
- NHS CSP will contract with labs. Expect sub contracts with other parts of the programme

Participation criteria

- Lab size > 35 000
- Colposcopy capacity identified
- 14 day TAT can continue to be met
- HPV testing meets quality criteria
- Pathway manager identified and empowered
- QA and PCT to sign off

Funding

- 100 k per 50 000 eligible samples
- Year 1 £2/sample , Year 2 £1/sample

HPV tests

- Roche, Abbott, Genprobe and Horlogic undergoing evaluation. Due Sept 11
- NHS Supply in process of forming a framework agreement
- HC2 is approved clinically but cannot be purchased until framework agreement is in place
- Unable to go live before September 2011

Next Steps

National

- Evaluation report to be published
- Advise to the NHS – May
- Implementation guidance
- Primary care pack
- Letters and leaflets
- Revisions to guidance
 - ABC
 - Colposcopy
 - Histology

Local

- Develop bid
- Which HPV test (price unknown)
- Colp capacity
- Local protocols
- National template letters
- Sample taker training
- Identify pathway manager
- Amend lab IT systems

Role of PCT/SHA/QA

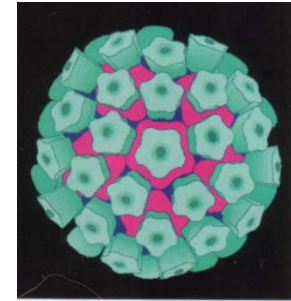
- PCT's still have lead role
 - ? Will they be able to proceed with reconfigurations?
- Looking into whether SHA may contribute strategically
- Specialised commissioning team?

- QA role is to advise on quality of proposals

Patient experience



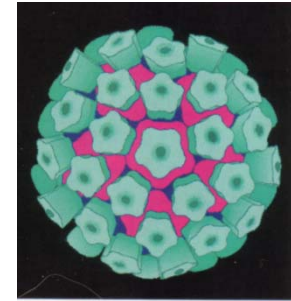
Case 1



- Routine screen
- BC HPV+
- Colp at 8 weeks from date of test
- CIN3 on biopsy
- LLETZ
- TOC at 6 months, negative
- Routine recall
- Time for whole episode 9 months

- Routine screen
- BC
- Repeat at 6 months, BC
- Repeat at 6 months BC
- Colp 14 -18 months from date of test
- CIN 3 LLETZ
- Annual follow up for 10 years
- Time for whole episode 12 years

Case 2



- Routine recall
 - Borderline HPV+
 - Colp SCC 1A1
 - LLETZ
 - 10 years annual follow up
 - Normal fertility and life expectancy
- Routine recall
 - Borderline
 - Repeat at 6 months
 - Colp referral delayed for 6-12 months
 - SCC 1B+
 - Radical treatment
 - Fertility and mortality affected

Conclusion



- Evidence for clinical and cost effectiveness of HPV triage and Test of cure is robust
- Implementation in England is mandatory and is funded
- There is a lot of work to do to design and specify the new service
- Actual start date likely to be Sept 11