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A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: Extended follow up in the ARTISTIC trial

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ABSTRACT

Background: The additional sensitivity of HPV testing compared with cytology could permit extended cervical screening intervals. We wished to determine, through a further (third) round of screening in the ARTISTIC trial, the protection provided by a negative baseline HPV screen compared with that of cytology over a 6 year period.

Methods: Cumulative rates of CIN2 or worse (CIN2+) and CIN3 or worse (CIN3+) were correlated with baseline HPV status and cytology. HPV was detected using the Hybrid Capture 2 (Qiagen) assay for high risk types and genotyped using the Linear Array (Roche) and Papillocheck (Greiner) assays. LBC was performed using ThinPrep (Hologic).

Findings: Round 3 included 8,873 women of whom 6,337 had been screened in both rounds 1 and 2 and 2,536 had not been screened since round 1. The median duration of follow-up was 72.7 months. The cumulative rate of CIN2+ over three rounds was 3.88% (95%CI 3.59%, 4.17%) overall; 2.39% in round 1, 0.78% in round 2 and 0.74% in round 3. Cumulative rates by baseline status were 20.53% (95%CI 19.04%, 22.08%) for abnormal cytology, 20.12% (95%CI 18.68%, 21.61%) for HPV detection, 1.41% (95%CI 1.19%, 1.65%) for negative cytology and 0.87% (95%CI 0.70%, 1.06%) for a negative HPV test. In HPV negative women aged over 50 the cumulative rate was 0.16% (95%CI 0.07%, 0.34%). Women who were HPV positive/cytology negative at entry had a cumulative CIN2+ rate of 7.73% (95%CI 6.29%, 9.36%) over 6 years, twice the overall rate.

Interpretation: A negative HPV test was significantly more protective than normal cytology over three rounds. The findings of this extension of ARTISTIC suggest that the screening interval could be extended to 6 years if HPV testing replaced cytology as the primary screening test.

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1. Introduction

Screening with cervical cytology at regular intervals has formed the basis for cervical cancer prevention worldwide. In the United Kingdom, the introduction of the national cervical screening programme in 1988 resulted in a marked reduction in cervical cancer deaths.[1] Liquid based cytology (LBC) was implemented between 2003 and 2008 and this has facilitated reflex HPV testing to triage low grade cytology which has undergone limited implementation.

Primary cervical screening using HPV DNA testing instead of cytology has been advocated on the basis of greater sensitivity for detection of cervical neoplasia. Randomised trials comparing HPV testing combined with conventional cytology against cytology alone have shown substantially increased detection of high grade cervical intraepithelial neoplasia (CIN2+) in a single screening round.[2–4] In the ARTISTIC trial, which used LBC instead of conventional cytology, a smaller proportion of CIN2+ cases diagnosed in the initial round were in HPV positive women with negative cytology.[5] These trials all showed a reduced incidence of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) in the subsequent screening round, but no difference when the results of two successive screening rounds were summed. Thus both regular cytology and HPV testing identify underlying cervical lesions, but a positive HPV test sometimes leads to earlier diagnosis and also predicts increased risk upto ten years later.[6] The ARTISTIC trial also revealed a very high negative predictive value for HPV testing with fewer than 0.1% of women who were initially HPV negative (HPV–ve) being found to have CIN3+ over two screening rounds.[5] These observations suggest that a negative HPV test confers greater protection over a longer period than negative cytology.

We have extended follow up in the ARTISTIC study over a further (third) screening round with two objectives. The first was to compare baseline cytology and HPV testing and typing in terms of detection of CIN2 or worse (CIN2+) over a 6 year period. The second was to use HPV genotyping results on round 1 samples to estimate the potential impact of HPV vaccination on the incidence of abnormal cytology and high grade CIN over three rounds of screening.

2. Methods

2.1. *The protocols for rounds 1, 2 and 3 are summarised in Fig. 1*

Rounds 1 and 2: The ARTISTIC trial methods and design have been reported for rounds 1 and 2.[5,7] Briefly, women aged 20–64 undergoing routine cervical screening between 2001 and 2003 underwent liquid based cytology and HPV testing, and were randomly allocated in a ratio of 3:1 to have the HPV result revealed and acted upon, or concealed and further management based on cytology alone. Management of women with abnormal cytology was identical on both arms, to the national guidance for the English Cervical Screening Programme,[8] with the exception in round 2 of referral to colposcopy after two rather than three borderline cytology results. Women in the revealed arm with negative cytology who tested HPV positive were invited for repeat HPV testing at 12 months and if still positive could choose between immediate colposcopy or a repeat HPV test at 24 months and colposcopy if still positive. Prior to the study extension to round 3, the protocol was amended to offer exit colposcopy to women in the revealed arm who were cytology negative and persistently HPV positive after the round 2 test, providing information on detection of high grade disease by HPV testing over two screening rounds. The proportion in the revealed arm who reattended at least once within 24 months was 62.6% (1048/1675) in women who were cytology negative and HPV positive in round 1, and 57.3% (339/592) in women who had been cytology negative in round 1 and were cytology negative and HPV positive in round 2. The corresponding proportions in the concealed arm were 3.4% (19/551) in round 1 and 3.2% (6/187) in round 2. Under the original protocol the trial endpoint was high grade disease detected by round 2 cytology.

Round 3: The cohort has now been followed beyond the original protocol for a third screening round. During this study extension, the ethics committee required that HPV results were linked to anonymised data, so women on both randomised arms were managed on the basis of cytology according to national guidelines. HPV results in round 3 were ignored until March 2008, when the Manchester Cytology Centre became one of six Sentinel Sites for HPV triage in England. The aim of the Sentinel Sites project was to evaluate the roll-out of HPV triage of low grade cytological abnormalities. Therefore, women with borderline and mild dyskaryosis cytology who tested HPV positive were referred to colposcopy, whilst those who were negative were returned to routine recall.

Cytology was performed with ThinPrep (Hologic, Crawley, UK) LBC and HPV testing with Hybrid Capture 2 (Qiagen, Crawley, UK). The HPV result was based on a cut-off of RLU/Co of 1 pg/μl. Three HPV typing assays were used to genotype HC2 positive samples. All HC2 positive LBC samples accrued during rounds 1 and 2 were genotyped using the prototype Roche Line Blot Assay (LBA) as previously described.[5] In order to compare typing assays, two thirds of HC2 positive round 1 archived samples were also tested by the Greiner Bio-one PapilloCheck assay and in round 2 one third of archived HC2 positive samples were tested by the Roche Linear Array (LA). The prototype LBA was replaced with the commercially available LA assay during the extension period of this study, so only 34% of HC2 positive samples in round 3 were tested by the LBA. The remainder were tested using PapilloCheck only (23%), LA only (15%) or both PapilloCheck and LA (28%). In all three rounds, any HPV type detected by any of the assays was included in the analysis.

2.2. *Statistical analysis*

Women were eligible if they were aged 20–64 when they provided a round 1 sample, which was defined as the first cytologically adequate sample after randomisation at entry that gave a satisfactory HPV result. Many women attended for their next routine screen earlier or later than the scheduled

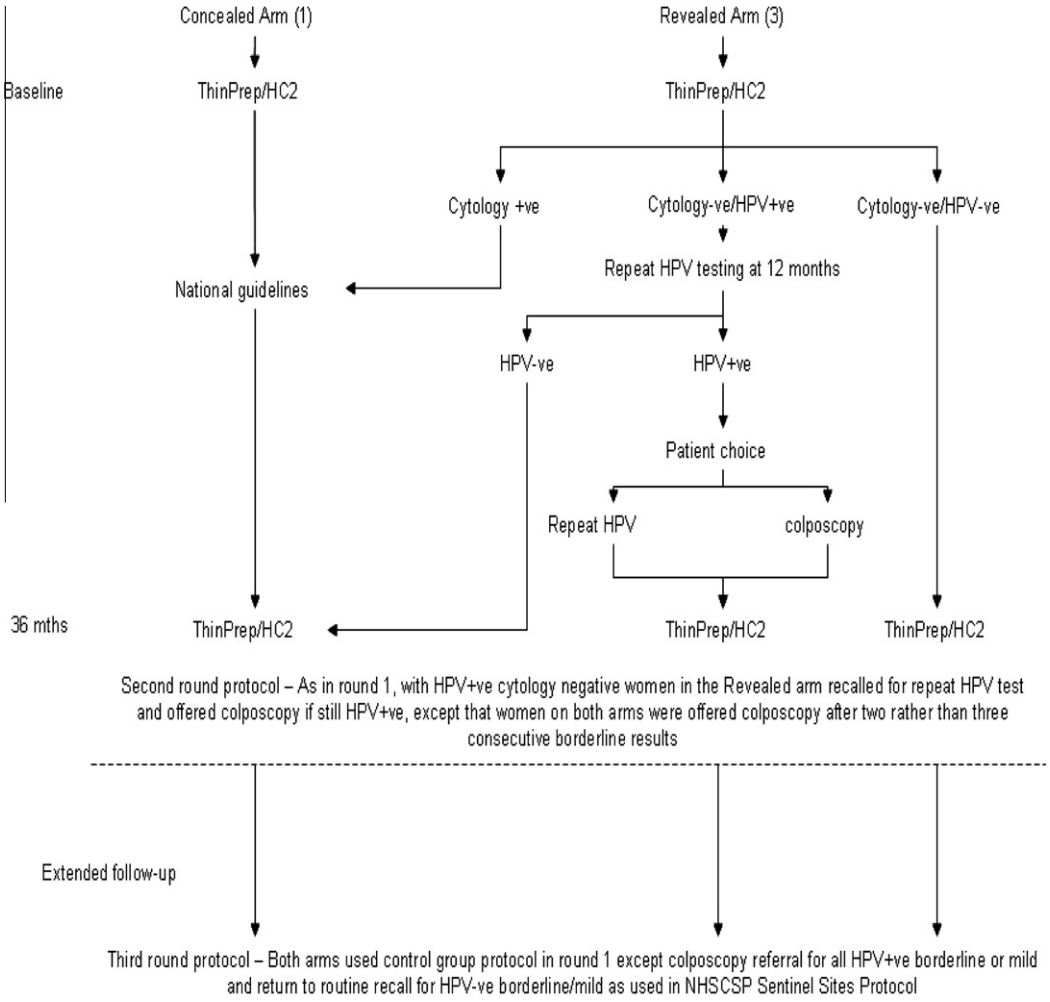

Fig. 1 – Original ARTISTIC protocol over two rounds of cervical screening plus extended follow-up to a third round.

three year recall. To minimise exclusions, the round 2 sample was, therefore, defined as the first cytologically adequate sample taken between 26 and 54 months after the date of the round 1 entry sample. The round 3 sample was defined as the first cytologically adequate sample at least 54 months after the round 1 sample, and at least 24 months after the round 2 sample (if there was one). Women were classified histologically at round 1, round 2 and round 3 on the basis of the highest grade of histology within 30 months of the round 1, round 2 or round 3 cytology. Women with CIN2 histology or worse (CIN2+) were excluded from subsequent rounds. The flow of women through three screening rounds is shown in a CONSORT diagram (Fig. 2).

Women were followed for cytology until the end of June 2009 and for histology to October 2009. Follow-up was based on cytology and histology reports received by the labs in Manchester and Stockport. Cytology and histology taken outside these areas were not available.

HPV prevalence, cytological abnormality and CIN2+ proportions were tabulated by combinations of round, randomisation arm and HPV status at entry or round. HPV status was split further by main HPV type identified: (1) HPV 16 or 18, (2) HPV 31,33,45,52 and 58, (3) other HPV+ve results, including HC2 positive samples where none of the 13 high risk HPV types was identified. These groupings allow reference to the published data for efficacy of the Cervarix HPV 16/18 vaccine which is used in the UK vaccination programme.[9]

Cumulative CIN2+ and CIN3 or worse (CIN3+) rates were estimated as $P = 1–(1–P_1)(1–P_2)(1–P_3)$ where P_i denotes the proportion with disease (D_i/N_i) in round i. Confidence intervals were calculated from Greenwood's formula for the standard error $\sqrt{(1–P)^2\Sigma_i(D_i/(N_i(N_i–D_i)))}$.[10] All analyses were programmed in STATA 11.[11]

2.3. *Role of the funding source*

The funding source reviewed and approved the study design. The data collection, analysis, interpretation and write-up were conducted independently by the authors.

3. Results

Of the 24,510 eligible women randomised in round 1, 15,790 (64.42%), and 8873 (36.20%) were screened in rounds 2 and 3, respectively, and 6337/8873 (71.42%) of round 3 women were also screened in round 2. The median time to round 3 was 72.7 months after round 1. The proportions of women with CIN2, CIN3 and CIN2+ by round and randomisation arm are

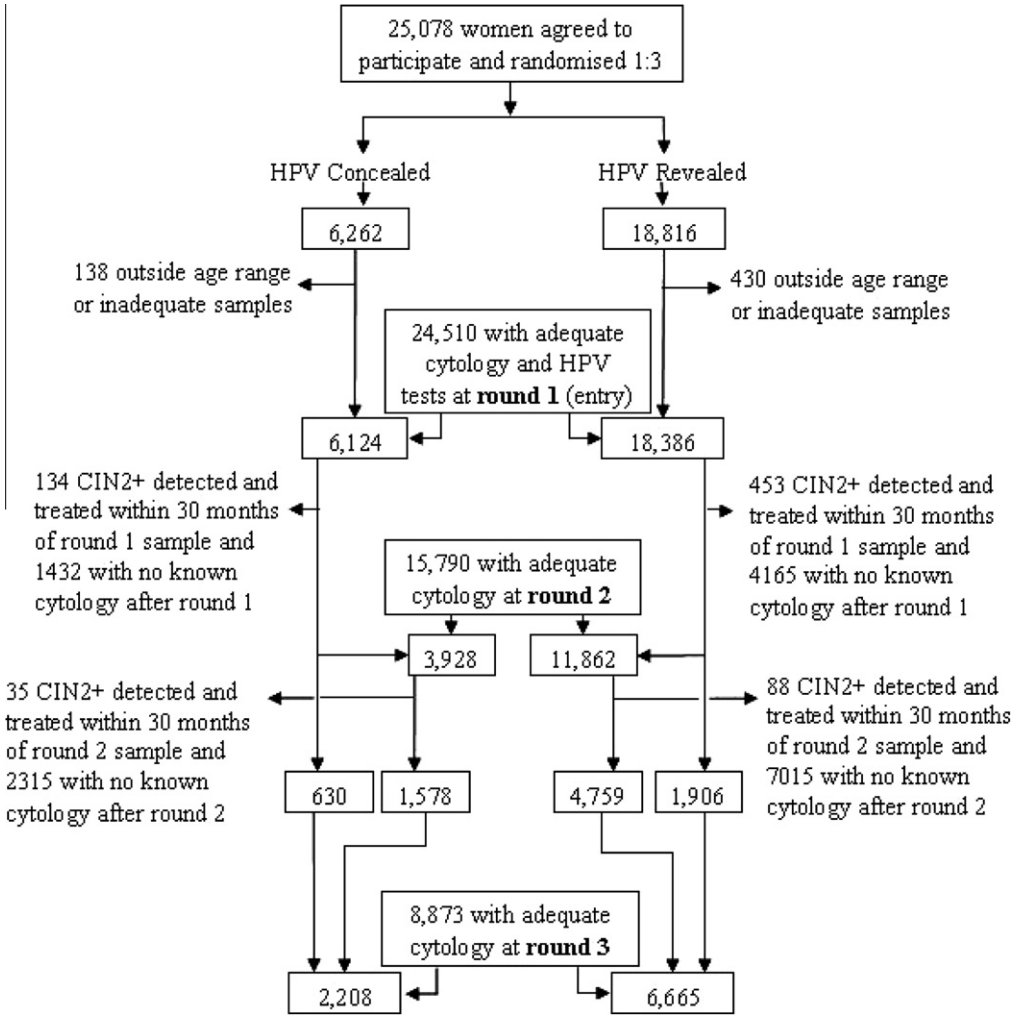

Fig. 2 – Consolidated Standards of Reporting Trials (CONSORT) diagram showing the flow of participants through the study. The majority of participants were screened in round 2 (15790, 64.4%), a minority missed the round but were screened in round 3 (2536, 10.3%) and the remaining were censored (587, 2.4%) or lost to follow-up (5597, 22.8%). Women who were treated for CIN2+ were excluded from subsequent rounds.

shown in Table 1. As previously reported,[7] there was a marked fall in the detection rate of high-grade disease between rounds 1 and 2, but no significant change between rounds 2 and 3. The cumulative detection of CIN2+ over three rounds was 3.9% (95%CI 3.6%, 4.3%) in the revealed arm and 3.7% (95%CI 3.2%, 4.3%) in the concealed arm (OR = 0.94, 95%CI 0.78, 1.13, $p > 0.1$).

The cumulative detection rate of CIN2+ and CIN3+ amongst the entire study cohort over three rounds (median follow-up 6 years) according to baseline cytology, HPV status and age at entry is shown in Tables 2 and 3, respectively. The cumulative CIN2+ rate for women who were both cytology–ve and HPV–ve at round 1 was 0.67% (95%CI 0.51%, 0.87%), compared with 7.73% (95%CI 6.29%, 9.36%) for those who were cytology–ve/HPV+ve at round 1. Amongst women who were cytology +ve and HPV+ve at baseline, the cumulative rate was 37.44% (95%CI 34.91%, 40.04%) compared with 3.24% (95%CI 2.32%, 4.38%) for those who were cytology+ve/HPV–ve. Whether baseline cytology was negative or positive, baseline HPV detection thus increased the CIN2+ risk more than 10-fold.

The risk of CIN2+ detection over 6 years was significantly less if the initial screen was HPV negative (0.87%; 95%CI 0.70%, 1.06%) rather than cytology negative (1.41%; 95%CI 1.19%, 1.65%), as shown in Table 2. The same effect was seen for CIN3+ (Table 3), the risk following a negative HPV test (0.28%; 95%CI 0.18%, 0.40%) being less than half that following negative cytology (0.63%; 95%CI 0.48%, 0.80%). There was no significant difference ($p > 0.1$) in cumulative CIN2+ rate over the three rounds between women who were HPV+ve or cytology+ve at entry. The influence of age and HPV status at round 1 on 6 year cumulative detection of CIN2+ is also shown in Table 2. Among women who were HPV+ve at baseline, the cumulative detection of CIN2+ was 23.53% at age 20–24, 24.30% at 25–34, 15.92% at 35–49 and 6.40% above age 50. Amongst women who were HPV–ve at baseline the cumulative incidence of CIN2+ over 6 years was much lower and fell sharply with age, from 3.04% at age 20–24 to 1.44% in the

Table 1 – CIN2 and CIN3 by randomisation arm and round.

	Concealed		Revealed		Total	
	n	%	*n*	%	*n*	%
Round 1 (entry)						
CIN2	53		220		273	
CIN3+	81		233		314	
CIN2+	**134**	**2.19%**	**453**	**2.46%**	**587**	**2.39%**
Total women	6124		18386		24510	
Round 2						
CIN2	18		52		70	
CIN3+	17		36		53	
CIN2+	**35**	**0.89%**	**88**	**0.74%**	**123**	**0.78%**
Total women	3928		11862		15790	
Round 3						
CIN2	7		28		35	
CIN3+	8		23		31	
CIN2+	**15**	**0.69%**	**51**	**0.77%**	**66**	**0.74%**
Total women	2208		6665		8873	

Table 2 – Cumulative CIN2+ rate by cytology, HPV status and age at entry.

Status at entry		Round 1			Round 2			Round 3			Cumulative CIN2+ rate% (95%CI)
		n	CIN2+	%	*n*	CIN2+	%	*n*	CIN2+	%	
Cytology:											
	Normal	21380	33	0.15%	13930	81	0.58%	7799	53	0.68%	1.41% (1.19%, 1.65%)
	Abnormal	3130	554	17.70%	1860	42	2.26%	1074	13	1.21%	20.53% (19.04%, 22.08%)
HPV:											
	–	20697	36	0.17%	13720	37	0.27%	7552	32	0.42%	0.87% (0.70%, 1.06%)
	+	3813	551	14.45%	2070	86	4.15%	1321	34	2.57%	20.12% (18.68%, 21.61%)
Cytology and HPV:											
Normal	–	19154	0		12595	32	0.25%	6932	29	0.42%	0.67% (0.51%, 0.87%)
Abnormal	–	1543	36	2.33%	1125	5	0.44%	620	3	0.48%	3.24% (2.32%, 4.38%)
Normal	+	2226	33	1.48%	1335	49	3.67%	867	24	2.77%	7.73% (6.29%, 9.36%)
Abnormal	+	1587	518	32.64%	735	37	5.03%	454	10	2.20%	37.44% (34.91%, 40.04%)
Age and HPV:											
20–24	–	1564	8	0.51%	790	9	1.14%	636	9	1.42%	3.04% (1.94%, 4.45%)
25–34	–	4875	11	0.23%	2843	16	0.56%	2264	15	0.66%	1.44% (1.03%, 1.97%)
35–49	–	9032	14	0.16%	6338	8	0.13%	3953	8	0.20%	0.48% (0.32%, 0.71%)
50–64	–	5226	3	0.06%	3749	4	0.11%	699	0		0.16% (0.07%, 0.34%)
20–24	+	1036	156	15.06%	502	31	6.18%	370	15	4.05%	23.53% (20.53%, 26.77%)
25–34	+	1401	252	17.99%	736	40	5.43%	502	12	2.29%	24.30% (21.82%, 26.90%)
35–49	+	1010	127	12.57%	601	14	2.33%	390	6	1.54%	15.92% (13.53%, 18.55%)
50–64	+	366	16	4.37%	231	1	0.43%	59	1	1.69%	6.40% (3.12%, 11.47%)
All women		24510	587	2.39%	15790	123	0.78%	8873	66	0.74%	3.88% (3.59%, 4.17%)

25–34, 0.48% at 35–49 and only 0.16% in women aged over 50 years. The 6 year cumulative incidence of CIN3+ in this group of HPV–ve women aged over 50 years was only 0.05% (95%CI 0.01%, 0.19%).

The influence of baseline HPV genotype at round 1 on cumulative CIN2+ over three rounds is shown in Table 4. The dominant effect of type 16 or 16/18 combined is clearly evident, particularly for CIN3+ with a 3-fold greater rate for type 16 (30.35%) compared with types 31, 33, 45, 52 and 58 combined (10.68%). There were 524 women with a new HR-HPV infection in round 2 (i.e. a type which was not present at round 1) and 241 women with a type-specific persistent infection in round 2 (i.e. same type present in both rounds 1 and 2). The corresponding numbers in round 3 with new and persistent HR-HPV infections were 409 and 96, respectively. Among these women, the CIN2+ rates were much lower in women with a new infection (6.9% in round 2 and 8.3% in round 3) than in those with a persistent infection (22.0% in round 2 and 16.7% in round 3).

Since 2008, there has been a UK national programme of vaccinating teenage girls with the bivalent Cervarix (GSK) vaccine. The potential impact of HPV vaccination of 12/13 year old girls (almost all of whom are expected to be HPV–ve) on the subsequent incidence of cervical cytology abnormalities can be calculated from Table 5, which shows cytology and HPV typing results at each round. Reported data on Cervarix

Table 3 – Cumulative CIN3+ rate by cytology, HPV status and age at entry.

Status at entry		Round 1			Round 2			Round 3			Cumulative CIN3+ rate% (95%CI)
		n	CIN3+	%	*n*	CIN3+	%	*n*	CIN3+	%	
Cytology:											
	Normal	21380	11	0.05%	13930	36	0.26%	7799	25	0.32%	0.63% (0.48%, 0.80%)
	Abnormal	3130	303	9.68%	1860	17	0.91%	1074	6	0.56%	11.01% (9.87%, 12.23%)
HPV:											
	–	20697	9	0.04%	13720	12	0.09%	7552	11	0.15%	0.28% (0.18%, 0.40%)
	+	3813	305	8.00%	2070	41	1.98%	1321	20	1.51%	11.19% (10.05%, 12.40%)
Cytology and HPV:											
Normal	–	19154	0		12595	11	0.09%	6932	10	0.14%	0.23% (0.14%, 0.36%)
Abnormal	–	1543	9	0.58%	1125	1	0.09%	620	1	0.16%	0.83% (0.40%, 1.52%)
Normal	+	2226	11	0.49%	1335	25	1.87%	867	15	1.73%	4.05% (2.98%, 5.36%)
Abnormal	+	1587	294	18.53%	735	16	2.18%	454	5	1.10%	21.18% (19.03%, 23.45%)
Age and HPV:											
20–24	–	1564	2	0.13%	790	1	0.13%	636	2	0.31%	0.57% (0.16%, 1.45%)
25–34	–	4875	3	0.06%	2843	7	0.25%	2264	5	0.22%	0.53% (0.29%, 0.88%)
35–49	–	9032	4	0.04%	6338	2	0.03%	3953	4	0.10%	0.18% (0.08%, 0.34%)
50–64	–	5226	0		3749	2	0.05%	699	0		0.05% (0.01%, 0.19%)
20–24	+	1036	82	7.92%	502	14	2.79%	370	10	2.70%	12.90% (10.49%, 15.63%)
25–34	+	1401	140	9.99%	736	20	2.72%	502	8	1.59%	13.83% (11.83%, 16.04%)
35–49	+	1010	74	7.33%	601	6	1.00%	390	2	0.51%	8.72% (6.94%, 10.78%)
50–64	+	366	9	2.46%	231	1	0.43%	59	0		2.88% (1.39%, 5.24%)
All women		24510	314	1.28%	15790	53	0.34%	8873	31	0.35%	1.96% (1.76%, 2.17%)

Table 4 – Cumulative CIN2+ and CIN3+ rate by HPV type at entry.

HPV at entry	Round 1			Round 2			Round 3			Cumulative CIN2+ rate% (95%CI) [10]	Cumulative CIN3+ rate% (95%CI) [10]
	N	CIN2+%	CIN3+%	*N*	CIN2+%	CIN3+%	*N*	CIN2+%	CIN3+%		
–	20697	36	9	13720	37	12	7552	32	11	0.87%	0.28%
		0.17%	0.04%		0.27%	0.09%		0.42%	0.15%	(0.70%, 1.06%)	(0.18%, 0.40%)
16	827	287	191	339	33	20	213	9	8	43.55%	30.35%
		34.70%	23.10%		9.73%	5.90%		4.23%	3.76%	(39.75%, 47.45%)	(26.70%, 34.24%)
16/18	1098	331	213	487	38	23	312	14	11	38.49%	25.91%
		30.15%	19.40%		7.80%	4.72%		4·49%	3.53%	(34.25%, 41.81%)	(22.90%, 29.09%)
31/33/45/52/58	895	152	67	480	24	11	338	12	4	23.93%	10.68%
		16.98%	7.49%		5.00%	2.29%		3.55%	1.18%	(20.82%, 27.26%)	(8.46%, 13.23%)
Other	1820	68	25	1103	24	7	671	8	5	6.95%	2.73%
		3.74%	1.37%		2.18%	0.63%		1.19%	0.75%	(5.61%, 8.50%)	(1.86%, 3.85%)

vaccine efficacy in women who were HPV DNA negative, indicated 98% efficacy against CIN2+ associated with types 16/18, and cross protection conferring 70% efficacy against CIN2+ associated with types 31/33/45/52/58.[9] These results, together with the ARTISTIC data correlating HPV types with grades of cytological abnormality shown in Table 5, suggest that Cervarix would prevent about 68% of cytology graded moderate or worse (HSIL) and 22% of borderline/mild (ASCUS/LSIL) cytology. Of the 757 women with a known HPV result and confirmed CIN2+ over three rounds, 401 (53%) were associated with HPV16 or HPV18 and 197 (26%) with types 31, 33, 45, 52, or 58, suggesting that 70% of CIN2+ cases in ARTISTIC could have been prevented by vaccination. The proportion of CIN2+ cases attributed to these HR-HPV types decreases with age; we estimate that approximately 78% of CIN2+ cases in women aged 20–34 and 65% of CIN2+ cases in women aged 35–49 would be prevented by vaccination.

4. Discussion

This extended follow-up of the ARTISTIC cohort to a median of 6 years has focussed on three issues: cumulative CIN2+ rates based on HPV and cytology results at the initial screening round, the influence of different HPV genotypes, and the predicted impact of the national HPV vaccination programme on screening abnormalities. The strengths of the study are (a) long follow-up, (b) the use of LBC and HC2 throughout, both of which are widely used and quality assured products

Table 5 – Cytological abnormality and HPV status in rounds 1, 2 and 3.

Round	Cytology	HPV									
		–ve		16/18		31/33/45/52/58		Other HC2+ve		Total	
1	Negative	19154	89.6%	473	2.2%	476	2.2%	1277	6.0%	21380	100%
	Borderline	1232	68.9%	179	10.0%	160	8.9%	218	12.2%	1789	100%
	Mild	265	30.2%	197	22.4%	148	16.9%	268	30.5%	878	100%
	Moderate	38	14.0%	130	48.0%	66	24.4%	37	13.7%	271	100%
	Severe+	8	4.2%	119	62.0%	45	23.4%	20	10.4%	192	100%
Total		20697	84.4%	1098	4.5%	895	3.7%	1820	7.4%	24510	100%
2	Negative	12647	93.2%	164	1.2%	208	1.5%	549	4.0%	13568	100%
	Borderline	265	64.3%	43	10.4%	33	8.0%	71	17.2%	412	100%
	Mild	47	23.7%	50	25.3%	33	16.7%	68	34.3%	198	100%
	Moderate	1	3.1%	14	43.8%	8	25.0%	9	28.1%	32	100%
	Severe+	4	18.2%	13	59.1%	4	18.2%	1	4.5%	22	100%
Total		12964	91.1%	284	2.0%	286	2.0%	698	4.9%	14232	100%
3	Negative	7398	92.0%	109	1.4%	109	1.4%	425	5.3%	8041	100%
	Borderline	114	56.7%	14	7.0%	22	10.9%	51	25.4%	201	100%
	Mild	21	15.1%	31	22.3%	32	23.0%	55	39.6%	139	100%
	Moderate	2	9.1%	9	40.9%	7	31.8%	4	18.2%	22	100%
	Severe+	2	8.0%	10	40.0%	6	24.0%	7	28.0%	25	100%
Total		7537	89.4%	173	2.0%	176	2.1%	542	6.6%	8428	100%

NB An additional 1558 women in round 2 and 445 women in round 3 had cytology without an HPV test.

and (c) the conduct of the study within the routine national screening programme. As previously discussed,[7] the reduction from round 1 to round 2 in both abnormal cytology and high-grade histology rates reflected enhanced detection of prevalent disease following the introduction of LBC and retraining of cytology laboratory staff.

The change of protocol in round 3 to use HPV triage for low grade cytological abnormality will have reduced the likelihood of CIN remaining undetected within the timeframe of the study. The rate of follow-up from round 1 to round 2 was 64%, similar to the overall rate of adherence of around 65% in consecutive screening rounds in Greater Manchester in the routine programme. Many women who were recruited aged 58 and over at enrolment will have exited screening having reached aged 64 before round 3.

The most significant finding of the study is the longer duration of protection provided by initial HPV testing when compared with liquid based cytology, with the cumulative CIN2+ rate over three rounds (about 6 years) following a HPV–ve baseline test (0.87%) being similar to that after two rounds (about 3 years) following a cytology –ve baseline test (0.73%). This was also seen in several European cohorts,[12] and suggests that if HPV testing were the initial screen, screening intervals could be extended from 3 to 6 years without reducing the current level of sensitivity provided by regular cervical cytology. In women aged 50 and over, the interval could perhaps be increased from the current 5 year interval to 10 years given the very small cumulative risk of CIN2+ (0.16%) and CIN3+ (0.05%) for HPV–ve women aged 50–64 years.

Women who were HPV+ve/cytology–ve had a 7.73% rate of CIN2+ over 6 years, twice the overall rate for all screened women (3.9%). If primary screening began with HPV testing followed by cytology triage for HPV+ve women, those who were HPV+ve/cytology–ve would require either further triage to identify a higher risk group for referral to colposcopy, or repeat HPV testing after a shorter interval than HPV–ve women. One triage strategy would be to select women with HPV types 16 or 18, which confer a significantly higher risk than other HPV types. Newer HPV tests are offering 16/18 restricted typing.[13] Triage tests using various biomarkers are also being evaluated. In one study,[13] which compared the ability of different tests to identify high grade CIN (albeit in a referral population), CINtec $p16^{INK4a}$ and HPV RNA for types 16,18,31,33 and 45 (HPV-Proofer, NorChip) achieved far higher specificity than high risk HPV tests and offer potential in this setting. Restricting HPV based primary screening to women aged 30 years and older has been recommended,[14] but such a two tier national programme would create complexity and the prevalence of HPV in young women can be expected to fall following the introduction of teenage HPV vaccination.

The analysis of cytological abnormality rates by HPV genotype shows that vaccination would considerably reduce high grade cytology. This has implications for primary cervical screening, which could not maintain current levels of positive predictive value with greatly reduced rates of high grade cytology. One recent modelling study of British women aged 20–29 estimated the HPV vaccination against HPV 16/18 would achieve a 63% reduction in cervical cancer, 51% reduction in CIN3 and a 27% reduction in cytological abnormalities. Even this young age group, however, the impact would not be seen until 2025.[15] Another study estimated a 76% reduction in lifetime risk of cervical cancer for 12 year old girls vaccinated in the UK against HPV 16/18.[16]

In conclusion, these ARTISTIC follow-up results, together with other published data showing the high negative predictive value of HPV testing, suggest that changing primary screening from cytology to HPV testing would offer advantages in terms of increased screening intervals and increased sensitivity.

Conflict of interest statement

HCK is Chair of the Advisory Committee in Cervical Screening (ACCS). The views expressed in this report are those of the

author(s) and in no way represent views of the ACCS or the Department of Health.

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Contributors

HCK, JP, SM, MD and CR all contributed to the study design. HCK, JP and CG contributed to drafting. JP, CG and CR contributed to the statistical analysis. AS, AB and AT did the virological analyses. MD and JM supervised and co-ordinated the cytological activity. HCK acted as chief investigator. RA acted as trial co-ordinator. All authors contributed to revision of the manuscript.

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