Sargent, A; Bailey, A; Almonte, M; Turner, A; Thomson, C; Peto, J; Desai, M; Mather, J; Moss, S; Roberts, C; +2 more... Kitchener, HC; ARTISTIC Study Group; (2008) Prevalence of type-specific HPV infection by age and grade of cervical cytology: data from the ARTISTIC trial. British journal of cancer, 98 (10). pp. 1704-1709. ISSN 0007-0920 DOI: https://doi.org/10.1038/sj.bjc.6604324

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Prevalence of type-specific HPV infection by age and grade of cervical cytology: data from the ARTISTIC trial

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Human papillomavirus (HPV) infection causes cervical cancer and premalignant dysplasia. Type-specific HPV prevalence data provide a basis for assessing the impact of HPV vaccination programmes on cervical cytology. We report high-risk HPV (HR-HPV) type-specific prevalence data in relation to cervical cytology for 24,510 women (age range: 20–64; mean age 40.2 years) recruited into the ARTISTIC trial, which is being conducted within the routine NHS Cervical Screening Programme in Greater Manchester. The most common HR-HPV types were HPV16, 18, 31, 51 and 52, which accounted for 60% of all HR-HPV types detected. There was a marked decline in the prevalence of HR-HPV infection with age, but the proportion due to each HPV type did not vary greatly with age. Multiple infections were common below the age of 30 years but less so between age 30 and 64 years. Catch-up vaccination of this sexually active cohort would be expected to reduce the number of women with moderate or worse cytology by 45%, but the number with borderline or mild cytology would fall by only 7%, giving an overall reduction of 12% in the number of women with abnormal cytology and 27% in the number with any HR-HPV infection. In the absence of broader cross-protection, the large majority of low-grade and many high-grade abnormalities may still occur in sexually active vaccinated women.

British Journal of Cancer (2008) 98, 1704–1709. doi:10.1038/sj.bjc.6604324 www.bjcancer.com

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Keywords: cervical screening; HPV typing; HPV vaccination

Human papillomavirus (HPV) infection has a central role in the aetiology of cervical cancer (Walboomers et al, 1999). More than 100 HPV types have been described (de Villiers et al, 2004) and 40 can infect the anogenital tract. Genital HPV types are categorised according to their association with cervical cancer (Munoz et al, 2003). About 20 are classified as high-risk (HR) types and are associated with cervical cancer and precancerous lesions, as well as low-grade cervical pathology. Worldwide, HPV types 16 and 18 cause approximately 70% of cervical cancers; HPV types 31, 33, 35, 45, 52 and 58 account for an additional approximately 20% of cases, although there is substantial geographical variation in the relative frequency of different HR types (Clifford et al, 2005). Low-risk HPV types, including HPV6 and 11, cause low-grade cervical lesions, genital warts and recurrent respiratory papillomatosis.

In 2006, a quadrivalent prophylactic vaccine against HPV types 6, 11, 16 and 18 was licensed in the United States (FDA, 2006) and Europe (EMEA, 2006). More recently, the bivalent vaccine against HPV types 16 and 18 has been approved in Europe (EMEA, 2007). Prophylactic HPV vaccination of young female adolescents has been approved as a public health policy in the United Kingdom and other countries, and data on the type-specific prevalence of HPV infection are relevant in assessing its potential impact on cervical pathology and screening.

A Randomised Trial in Screening to Improve Cytology (ARTISTIC) is being conducted within the routine NHS Cervical Screening Programme in Greater Manchester to evaluate the effectiveness of HPV testing in primary cervical screening. The randomised comparison will determine whether combining HPV testing with liquid-based cytology offers added sensitivity over cytology alone and, if so, whether this would be cost-effective. Our first report described the baseline prevalence of HPV16, 18 and all other HR-HPV types in relation to age, cytology and histology (Kitchener et al, 2006). We now report type-specific prevalence data for all HR-HPV types in relation to cervical cytology and age.

MATERIALS AND METHODS

High-risk HPV detection

After processing for cytology, residual ThinPrep® liquid-based cytology samples were sent to the Virology Laboratory at Manchester Royal Infirmary. High-risk HPV detection was carried
out using the Digene Hybrid Capture 2™ (hc2) test according to the manufacturer’s instructions, as described previously (Kitchener et al., 2006). A positive hc2 result was defined as an RLU/Co value of ≥1, according to the manufacturer’s criteria at the start of the study. Residual cells from all liquid-based cytology samples were pelleted and stored at −70°C.

HPV polymerase chain reaction and genotyping

Genotyping of all hc2-positive samples was carried out using the prototype Roche Line Blot Assay (LBA). Polymerase chain reaction (PCR) amplification and product detection for 37 genotypic types were essentially performed as described previously (Peyton et al., 2001). Following DNA extraction from a 50 μl volume of the stored, pelleted sample using the Roche MagNA Pure automated system, a 50 μl volume of extracted DNA was added to an equal volume of reaction mixture containing 10 mM Tris-HCl (pH 8.5), 50 mM KCl, 4 mM MgCl₂, 500 μM each of biotinylated HPV primers PGMY09 and PGMY11, 25 μM each of biotinylated human beta-globin primers PC04 and GH20, 200 μM each of nucleotides dATP, dCTP, dGTP, and dUTP, 600 μM of nucleotide dUTP and 7.5 U of Amplitaq Gold. Following heating at 95°C to activate the Amplitaq Gold polymerase enzyme and render the native DNA single stranded, nucleic acid was amplified by 40 cycles of 95°C/1 min to allow strand denaturation, 55°C/1 min for primer annealing and 72°C/1 min for primer extension. This cycling program was followed by an elongated primer extension period of 56 min at 72°C. Amplified product was stored at 4°C. Following denaturation, amplified product was hybridised to oligonucleotide-coated genotyping strips before colour development and interpretation using the template provided.

Due to the unexpectedly large number of hc2-positive LBA-negative samples, a subset (n = 102) of these samples was examined using GP5+/6+ PCR (de Roda Husman et al., 1995). The PCR product was visualised after electrophoresis through a 2% agarose gel and ethidium bromide staining.

Cytology

All cytology was read independently of the HPV results. Slides were read according to the routine laboratory protocol and reported as such. There was no attempt to reach consensus for any of the smear grades. There has been no post hoc review of cytology. National guidelines were adhered to, which meant that high-grade abnormalities, that is, moderate and severe dyskaryosis, were referred for colposcopy and biopsy. In women with low-grade abnormalities, that is, borderline and mild dyskaryosis, cytology was repeated at 6 months with referral to colposcopy if the abnormality persisted.

RESULTS

A total of 24 510 eligible women had satisfactory cytology and HPV results by hc2 at entry. Samples from 3813 women (15.6% of all eligible women) were HPV-positive by hc2, but 40 (1.0%) of these either gave negative results for beta-globin gene amplification and were reported as inhibitory or were of insufficient volume for further testing. These 40 were excluded, and all the results were based on the remaining 24 470 women. Crossreactivity with low-risk or HR types not included in the hc2 probe mix was observed in 417 (11.1%) hc2-positive samples. A broad range of HPV type crossreactivity occurred. This was particularly noticeable for HPV types 53, 66 and 70, which were frequently detected. A further 772 (20.5%) hc2-positive samples did not hybridise to any of the LBA probes. These 1189 samples were classified as hc2 positive but HR-HPV negative. The remaining 2584 hc2-positive samples (68.5%) were positive by LBA for one or more of the 13 HR types included in the hc2 HR probe mix. Of those hc2-positive samples giving a low RLU/Co value between 1 and 3, 26.7% contained an hc2 HR type; 16.2% crossreacted with other types and 57.1% failed to type. The corresponding figures of those hc2-positive samples giving a high RLU/Co value of ≥100 were 91.9, 4.8 and 3.3%. In total, 50% of hc2-positive LBA-negative samples had an RLU/Co value between 1 and 2.11. On testing a subset of 102 hc2-positive LBA-negative samples by GP5+/6+ PCR, 39.2% were found to be HPV positive. Multiple HR-HPV types were detected in 680 (18.0% of hc2-positive samples) and infection with a single HR-HPV type was detected in 1904 (50.5%) samples.

Prevalence rates for each HR-HPV type are shown in Table 1, both overall and by age group. The most common genotype at all ages was HPV16 (overall prevalence 3.3%), followed by HPV types 52 (1.5%), 18 and 31 (both 1.3%), 51 (1.2%) and 39 (1.1%). There was a marked decline in the prevalence of HR-HPV with age, both overall (27.3% below age 30 years and 6.1% at age 30 years or above) and for each HPV type, but less so for hc2-positive samples in which no HR-HPV was detected (6.4% of women aged below 30 years and 4.5% aged 30–64 years).

The HPV prevalence rates by age group and cytology are shown in Table 2 for HPV16, HPV18 without HPV16 and for other HR-HPVs combined. Below age 30 years, a high proportion of infected women carried two or more different HR-HPV types (44% of women with HPV16, 50% with HPV18 but not HPV16 and 24% of all women with other HR-HPVs). Multiple infections were less common at age 30–64 years (23% of women with HPV16, 20% with HPV18 and 14% of women with other HR-HPVs). The proportion with moderate dyskaryosis or worse was 15.3% (396 out of 2584) in women with any HR-HPV infection, 1.2% for hc2 positives with no HR-HPVs and 0.22% for hc2-negative women. The risk of moderate or worse cytology was highest in women infected with HPV16 irrespective of the presence of other HPVs (26.2% for HPV16 alone, 25.3% together with other HR-HPVs).

Cytology by HPV status is shown in Table 3 for women aged 20–29 years, 30–64 years and overall. Summing up the number of different HR-HPV types detected in each woman for the denominator, the proportion of all detected infections that were due to each HPV type did not vary greatly with age. Below age 30 years, 24.9% (499 out of 2077) of HR-HPV infections were due to HPV16, compared with 21.3% (306 out of 1435) at age 30–64 years (P = 0.06). The corresponding proportions were 6.3 and 3.7% for HPV33 (P = 0.001), 2.4 and 4.1% for HPV35 (P = 0.003) and 4.5 and 6.7% for HPV45 (P = 0.005). No other type showed significant variation with age. The proportion of women with a single HR-HPV type who had moderate or worse cytology (Table 3; middle column) was 26% for HPV16, between 12 and 19% for HPV types 18, 31, 33 and 58, 7–9% for types 35, 45, 51 and 52, and less than 5% for types 39, 56, 59 and 68. The proportion with borderline or mild cytology was much less variable, ranging from 23 to 42%. The proportion of different grades of cytology positive for HPV types 16, 18, 31, 45 and 52 are shown in Figure 1. This graphically demonstrates the increasing prevalence with cytology grade.

Of the CIN2+ lesions found before the exit round, 108 out of 329 (33%) and 83 out of 225 (37%), respectively, were identified in high- and low-grade cytological abnormalities, which were HR-HPV positive but types 16/18 negative.

DISCUSSION

The ARTISTIC trial cohort (see Appendix for ARTISTIC Trial Study Group) is the first large population of women in the United Kingdom to have undergone HPV testing and genotyping. Although from a limited geographic area, the setting in primary
The failure of the LBA to confirm that 31.5% of the hc2-positive samples contain hc2 HR-HPV types is a cause of concern, especially if this assay was to be used as a frontline screening specimen collection and storage methods employed in the earlier study. Alternatively or additionally, changes in the prevalence of genital HPVs as suggested by increased UK diagnosis of genital warts between 1972 and 2005 (Health Protection Report, 2007) may be relevant. However, changes in clinical practices in the diagnosis and reporting of genital warts may further complicate the picture. The difference in prevalence between young and older women is less marked in most other countries (Franceschi et al, 2006). Most HR-HPV types show a similar age distribution, with relatively minor differences in the type distribution above and below the age of 30 years. The most marked difference was shown by HPV33, being detected in 9.3% of women 20–29 years 30–39 years 40–49 years 50–64 years All ages

| Age | No. of women | HPV16 | HPV18 not 16 | HPV16 and/or 18 | hc2 positive |
|-----|-------------|-------|--------------|-----------------|-------------|
|     |         | Single | Multiple | Single | Multiple | No other | Other | HR-HPV | not 16/18 | HR-HPV | No HR | hc2 negative |
|     |         | HR-HPV | HR-HPV | HR-HPV | HR-HPV | HR-HPV | HR-HPV | HR-HPV | HR-HPV | HR-HPV | HR-HPV |
| 20–29 | 5150 | 280 (5.4) | 240 (4.7) | 219 (4.3) | 77 (1.5) | 78 (1.5) | 374 (7.3) | 280 (5.4) | 750 (14.6) | 1404 (27.3) | 329 (6.4) | 3417 (66.3) |
| 30–39 | 7599 | 158 (2.1) | 116 (1.5) | 49 (0.6) | 65 (0.9) | 117 (0.2) | 225 (3.0) | 64 (0.8) | 490 (6.5) | 779 (10.3) | 368 (4.8) | 6452 (84.9) |
| 40–49 | 6111 | 51 (0.8) | 11 (0.2) | 15 (0.2) | 3 (0.1) | 3 (0.1) | 48 (1.1) | 12 (0.2) | 179 (2.9) | 259 (4.2) | 270 (4.4) | 5582 (91.3) |
| 50–64 | 5610 | 27 (0.5) | 10 (0.2) | 14 (0.2) | 3 (0.05) | 43 (0.8) | 11 (0.2) | 88 (1.6) | 142 (2.5) | 222 (4.0) | 5246 (93.5) |

Table 1 Prevalence of HR-HPVs overall and as a proportion of HR-HPV-positive women by age group

| Type | % of all women | % of HR-HPV+ women | % of all women | % of HR-HPV+ women | % of all women | % of HR-HPV+ women | % of all women | % of HR-HPV+ women | % of all women | % of HR-HPV+ women | % of all women | % of HR-HPV+ women |
|------|---------------|------------------|---------------|------------------|---------------|------------------|---------------|------------------|---------------|------------------|---------------|------------------|
| 16   | 499.9         | 35.5             | 207.2         | 26.6             | 62             | 23.9             | 37             | 26.1             | 805.3         | 31.2             |
| 18   | 191.3         | 13.6             | 89.2          | 11.4             | 20             | 10.4             | 19             | 13.4             | 319.1         | 12.3             |
| 31   | 185.3         | 13.2             | 102.1         | 13.1             | 27             | 10.4             | 12             | 8.5              | 326.1         | 12.3             |
| 33   | 130.2         | 9.3              | 41.0          | 5.3              | 10             | 3.9              | 2              | 1.4              | 183.7         | 7.1              |
| 35   | 49.1          | 3.5              | 39.0          | 5.0              | 17             | 3.6              | 3              | 1.1              | 108.4         | 4.2              |
| 39   | 159.3         | 11.3             | 75.1          | 9.6              | 17             | 3.6              | 15             | 3.0              | 266.1         | 10.3             |
| 45   | 94.8          | 6.7              | 58.0          | 7.4              | 20             | 3.7              | 18             | 3.3              | 190.8         | 7.6              |
| 51   | 189.3         | 13.5             | 73.0          | 9.4              | 26             | 4.0              | 17             | 3.2              | 305.1         | 11.8             |
| 52   | 211.1         | 15.0             | 106.1         | 13.6             | 39             | 5.1              | 11             | 2.8              | 367.1         | 14.2             |
| 56   | 98.1          | 7.0              | 58.0          | 7.4              | 13             | 5.0              | 13             | 7.0              | 182.7         | 7.0              |
| 59   | 97.1          | 6.9              | 46.0          | 5.9              | 18             | 3.7              | 7              | 0.9              | 168.7         | 6.5              |
| 68   | 125.4         | 8.9              | 40.0          | 5.1              | 23             | 3.6              | 11             | 3.2              | 199.8         | 7.7              |

Table 2 Prevalence of single and multiple infections with HPV16, 18 and other HR-HPV types by age group and cytology result

HR-HPV = high-risk human papillomavirus.

B/M = borderline/mild dyskaryosis; HR-HPV = high-risk human papillomavirus; Mod+ = moderate dyskaryosis or worse.
This is due, in part, to the demonstrated crossreaction of the hc2 test with other putative HR as well as low-risk types. However, the fact that 20.5% failed to yield any detectable HPV type is more problematic. As the whole of the PGMY-amplified product generated during LBA testing was denatured, further analysis by gel electrophoresis was not possible. Further work using another well-documented primer system (GP5+/6+ PCR) followed by gel electrophoresis suggested that 39.2% of these hc2-positive LBA-negative samples might in fact contain HPV. Confirmation of this observation would require further analysis on a larger number of samples. The 13% originally selected merely provides an insight into the true HPV status of these samples. The use of the improved, commercially available linear array assay (Coutlee et al., 2006) to confirm these hc2-positive samples should improve the confirmatory rate. There would still remain a substantial number of samples that do not appear to contain a demonstrable HPV genotype. Approximately half of these samples give an hc2 RLU value between 1 and 2 providing further evidence that it may be

test.

### Table 3 Cytology by HPV status

| HPV type | 20–29 years | 30–64 years | All ages | 1904 women with a single HPV infection |
|----------|-------------|-------------|----------|----------------------------------------|
|          | Negative B/M* | Mod+* | Negative B/M | Mod+ | Total | Negative | B/M | Mod+ |
| 16       | 184         | 202        | 113       | 136  | 75  | 95       | 320  | 277 | 308 | 208  | 258  | 805  | (100%) |
| 18       | 93          | 74         | 24        | 67   | 41  | 20       | 160  | 115 | 155 | 84   | 122  | 326  | (100%) |
| 31       | 83          | 67         | 35        | 62   | 46  | 33       | 145  | 113 | 176 | 68   | 209  | 326  | (100%) |
| 33       | 45          | 58         | 27        | 21   | 22  | 10       | 66   | 80  | 110 | 37   | 120  | 183  | (100%) |
| 35       | 23          | 20         | 6         | 28   | 25  | 6        | 51   | 45  | 115 | 41   | 117  | 168  | (100%) |
| 39       | 67          | 71         | 21        | 56   | 38  | 13       | 123  | 109 | 232 | 64   | 126  | 266  | (100%) |
| 45       | 47          | 33         | 14        | 58   | 28  | 10       | 105  | 61  | 166 | 32   | 124  | 190  | (100%) |
| 51       | 70          | 99         | 20        | 63   | 40  | 13       | 133  | 139 | 252 | 72   | 194  | 305  | (100%) |
| 52       | 96          | 88         | 27        | 82   | 57  | 17       | 178  | 145 | 323 | 44   | 129  | 367  | (100%) |
| 56       | 43          | 46         | 9         | 40   | 38  | 6        | 83   | 84  | 167 | 15   | 89   | 182  | (100%) |
| 58       | 40          | 45         | 12        | 32   | 24  | 15       | 72   | 69  | 141 | 27   | 66   | 168  | (100%) |
| 59       | 69          | 44         | 12        | 46   | 20  | 8        | 115  | 64  | 179 | 32   | 66   | 199  | (100%) |
| 68       | 27          | 19         | 4         | 27   | 13  | 4        | 54   | 32  | 86  | 8    | 40   | 94   | (100%) |
| 16 and/or 18 | 265       | 260        | 129       | 198  | 111 | 114      | 463  | 371 | 834 | 243  | 426  | 1077 | (100%) |
| Any HR-HPV | 651        | 556        | 197       | 619  | 362 | 199      | 1270 | 918 | 2188| 44   | 129  | 2584 | (100%) |
| hc2+ No HR-HPV | 236      | 88         | 5         | 704  | 147 | 9        | 940  | 235 | 1179| 14   | 12   | 1189 | (100%) |
| All women | 4006              | 930        | 214       | 17358 | 1720 | 242      | 21364 | 2650 | 4560| 574  | 1605 | 24470 | (100%) |
| No. of HR-HPVs detected | 887 | 866 | 324 | 718 | 467 | 250 | 1605 | 1333 | 574 | 3512 | 1021 | 613 | 270 |

B/M = borderline/mild dyskaryosis; HR-HPV = high-risk human papillomavirus; Mod+ = moderate dyskaryosis or worse. Results by age (20–29, 30–64 years), overall, and in 1904 women with a single HPV type.

![Figure 1](image-url) Prevalence rates for four of the commonest five types and HPV45 by cytological grade.

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Box 1: Preventing cervical cancer through vaccination

- Vaccination can prevent cervical cancer by targeting HR-HPV types associated with high-grade abnormalities.
- Cross-protection against non-vaccine types is possible, reducing the overall risk.
- The benefit-risk balance of vaccination is improved with time as the proportion of high-grade abnormalities decreases.

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ACKNOWLEDGEMENTS

The ARTISTIC trial is funded by the UK Health Technology Assessment Programme. The Line Blot Assays were kindly provided by Roche.

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APPENDIX

**ARTISTIC Trial Study Group:** HC Kitchener (principal investigator), C Thomson (trial coordinator); *Epidemiology/Statistics:*

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**Type-specific prevalence: ARTISTIC trial data**

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