ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening

HC Kitchener,¹* M Almonte,² C Gilham,² R Dowie,³ B Stoykova,³ A Sargent,¹ C Roberts,⁴ M Desai⁵ and J Peto²,⁶ on behalf of the ARTISTIC Trial Study Group

¹School of Cancer and Imaging Sciences, University of Manchester, St Mary’s Hospital, Manchester, UK
²Non-Communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, UK
³Health Economics Research Group, Brunel University, Uxbridge, UK
⁴Biostatistics Group, University of Manchester, Manchester, UK
⁵Department of Cytology, Central Manchester and Manchester Children’s University Hospitals NHS Trust, Manchester, UK
⁶Institute of Cancer Research, Sutton, UK

*Corresponding author

Executive summary

Health Technology Assessment 2009; Vol. 13: No. 51
DOI: 10.3310/hta13510
Executive summary

Objectives

Primary cervical screening is currently based on using cervical cytology to detect cancer precursor lesions. Human papillomavirus (HPV) testing could add sensitivity to the detection of these lesions [cervical intraepithelial neoplasia stage 3 or beyond (CIN3+)] either as an adjunct to cytology, or as a first test with cytology reserved for women who are HPV positive. We aimed to answer the following principal questions:

• Do cytology and HPV testing combined achieve a reduction in incident CIN3+ by detecting significantly more prevalent disease?
• Is the use of HPV testing cost-effective in primary cervical screening?
• Is HPV testing in primary cervical screening associated with adverse psychosocial or psychosexual effects?
• How would HPV perform as an initial screening test followed by cytology for HPV positivity?

Interventions

HPV testing was performed on the liquid-based cytology (LBC) sample obtained at screening. Women were randomised in a ratio of 3:1 either to have the HPV test result revealed and acted upon if persistently positive in cytology-negative cases, or concealed from the woman, her doctor and the investigators. In addition, a detailed health economic evaluation and a psychosocial and psychosexual assessment were performed.

Main outcome measures

The primary outcome was CIN3+ in round 2. Secondary outcomes included an economic assessment and psychosocial effects. We have also conducted a large HPV genotyping study.

Results

In round 1 there were a total of 313 CIN3+ lesions representing a prevalence in the revealed and concealed arms of 1.27% and 1.31% respectively ($p = 0.81$). Round 2 involved 14,230 women (58.1%) of those screened in round 1. In round 2, (50–48 months) only 31 CIN3+ were detected and although the CIN3 rate was lower in the revealed arm (0.18% revealed versus 0.34% concealed; $p = 0.09$), this was not statistically significant. A less restrictive definition of round 2, (26–54 months) increased the CIN3+ numbers in round 2 from 31 to 45, with a statistically significant reduction in CIN3+ incidence in the revealed arm (0.24% revealed versus 0.41% concealed; $p = 0.05$). There was no difference in CIN3+ between the arms when round 1 and 2 were combined (1.45% revealed versus 1.65% concealed; $p > 0.1$). Among 2226 women who screened as cytology negative and HPV positive in round 1, 32 CIN2+ lesions were detected among the 1657 women in the revealed arm as a consequence of adjunctive HPV testing. This resulted in a lower CIN2+ rate in the revealed arm in round 2 (30–48 months; 1.92% versus 3.99%; $p = 0.06$), which just failed to reach significance.
The prevalence of high-risk types was highly age-dependent: 27.9% in women aged 25–29 years compared with 6.5% at age 50–64 years. The overall prevalence of HPV type 16 and/or type 18 in borderline, mild, moderate and severe dyskaryosis was 10.0%, 22.0%, 46.8% and 62.4% respectively. Type-specific viral persistence rates declined from over 80% after 6 months to 20–25% after 48 months.

Mean (SD) costs per woman (covering screening and colposcopy-related events) in round 1 were £72 (£175), [95% confidence interval (95% CI), £70 to £75] for the revealed arm and £56 (£178), (95% CI, £52 to £60) for the concealed arm (p < 0.001). Costs were age-dependent, so an age-adjustment based on the age profile for the national screening programme reduced the mean costs to £65 and £52 respectively. The incremental cost-effectiveness ratio for detecting an additional CIN3+ by the addition of HPV testing to LBC screening in round 1 was £38,771. The experiences of revealed women in round 1 informed the development of alternative screening policies with simplified management protocols. An age-adjusted mean cost for LBC primary screening with HPV triage was £39 compared with £48 for HPV primary screening with LBC triage, the main influence on the costs being the rates of referral for colposcopy.

HPV testing did not appear to cause significant psychosocial distress.

**Conclusions**

Routine HPV testing did not add significantly to the effectiveness of LBC in this study. The use of LBC was associated with an unexpectedly low number of CIN3+ lesions in round 2, suggesting an increase in sensitivity compared to conventional cytology. No significant adverse psychosocial effects were detected, which is reassuring for the wider use of HPV testing. It is clear that it would not be cost-effective to screen with cytology and HPV combined but there was evidence that HPV testing, either as a triage or as an initial test triaged by cytology, would be cheaper than the current use of cytology without HPV testing.

The introduction of HPV vaccination against types 16/18 for 12- to 13-year-old girls in 2008 will reduce the risk of the most severe abnormalities in vaccinees by 65% but only 10–20% of low-grade cytological abnormalities will be prevented.

The ARTISTIC findings suggest that LBC, which has been implemented countrywide, would not benefit from combined testing with HPV. While LBC is highly effective as primary screening, HPV testing has the twin advantages of a high negative predictive value, which should allow longer screening intervals, and automated platforms enabling high throughput. HPV primary screening would have a major impact on the volume of cytology, which would require major contraction and reconfiguration of laboratory services.

**Further research**

There is a need to confirm from other UK laboratories, the finding in the ARTISTIC cohort of a very low incidence of CIN3+ in subsequent screening rounds of women previously screened with LBC. This would suggest that LBC in the quality-assured setting of the NHS can indeed achieve a greater degree of sensitivity than hitherto recognised.

The ARTISTIC trial is continuing to follow up women while maintaining the randomised concealment of HPV testing results for a further 3-year round of screening. This will allow evaluation of the risk of developing cytological abnormalities in type-specific HPV-positive and HPV-negative women over a 6-year interval, which will be important in developing screening protocols for the post-vaccination era, when the case for initial HPV testing with cytology triage will become stronger. The 6-year follow-up will also provide data on the relative protection of a negative cytology and negative hybrid capture 2 over 6 years in different age ranges.

**Publication**

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series Health Technology Assessment.

**Criteria for inclusion in the HTA journal series**

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 98/04/64. The contractual start date was in June 2001. The draft report began editorial review in February 2008 and was accepted for publication in March 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

**Editor-in-Chief:** Professor Tom Walley CBE

**Series Editors:** Dr Aileen Clarke, Professor Chris Hyde, Dr John Powell, Dr Rob Riemsmma and Professor Ken Stein

---

**Criteria for inclusion in the HTA journal series**

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 98/04/64. The contractual start date was in June 2001. The draft report began editorial review in February 2008 and was accepted for publication in March 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

**Editor-in-Chief:** Professor Tom Walley CBE

**Series Editors:** Dr Aileen Clarke, Professor Chris Hyde, Dr John Powell, Dr Rob Riemsmma and Professor Ken Stein

---

ISSN 1366-5278

© 2009 Queen’s Printer and Controller of HMSO

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.