The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds

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Scientific summary

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Background

The ARTISTIC (A Randomised Trial In Screening To Improve Cytology) trial, published in 2009, randomised women undergoing cervical screening with liquid-based cytology (LBC) to either human papillomavirus (HPV) testing, which was revealed and acted upon if cytology was negative, or concealed at entry and at the next screening round 3 years later. The study demonstrated that LBC and HPV testing combined was not superior to LBC alone, over either the initial or two consecutive rounds of cervical screening. Other trials of HPV testing, which demonstrated that HPV testing was more sensitive than cytology in an initial prevalence round, used conventional cytology and not LBC. Data from ARTISTIC confirm the very high negative predictive value of HPV status, and an economic analysis suggested that initial screening for HPV triaged by cytology would be less costly than cytology-based screening, which relies on repeat cytology for low-grade abnormalities. One of the key attributes of HPV testing could be prolongation of screening intervals, as suggested by data from other studies. A particular strength of the ARTISTIC study was an extensive programme of HPV genotyping in rounds 1 and 2. This extension of the ARTISTIC study to a third round of screening was performed under two broad headings: the clinical effectiveness and cost-effectiveness of HPV primary screening.

Clinical effectiveness

1. The cumulative cervical intraepithelial neoplasia (CIN) grade 2 or worse (2+) rates over three screening rounds.
2. The cumulative rates of CIN2+ in women who were HPV negative at baseline and cytology negative at baseline.
3. The potential for HPV testing to extend the screening interval.
4. The influence of genotyping on cumulative CIN2+.
5. The potential benefit of using a Hybrid Capture 2 (HC2) cut-off value of 2 rather than 1 relative light unit (RLU) in maintaining sensitivity but increasing specificity of HPV testing.
6. The potential impact of the UK national HPV vaccination programme on the results of cervical screening.

Cost-effectiveness

1. To use clinical results from the ARTISTIC trial to inform an evaluation of the cost-effectiveness of various options for primary HPV screening in England compared with current practice with cervical cytological screening. The predicted long-term outcomes following the implementation of strategies involving primary HPV screening were compared with those associated with current screening using cervical cytology.

Methods

Clinical study

This study comprised an extension of follow-up of the ARTISTIC study cohort into a third screening round, 3 years following round 2. All women were screened with LBC, and HC2 testing for HPV was performed on LBC residues. HPV genotyping was performed on HC2-positive samples. In round 3, colposcopy was performed on all women with HPV-positive results and borderline or mild dyskaryosis, and women with

moderate dyskaryosis or worse. Women with negative cytology, or HPV negative and borderline or mild dyskaryosis, were returned to routine recall in line with the so-called NHS Sentinel Site protocol for HPV triage. Colposcopic-guided biopsy was performed in the presence of a colposcopic abnormality and if CIN2+ was detected the transformation zone was excised by loop excision. In screening round 3, there was no difference in the management of screening results between the original arms of the trial.

Economic study

The economic analysis utilised a pre-existing, pre-calibrated and validated modelling platform that has been previously used to evaluate outcomes in Australia, New Zealand, the UK and China. This platform was then further validated against clinical results from the ARTISTIC trial, after setting up a simulation of the ARTISTIC cohort at trial entry which reflected the observed age and test outcome distribution in the cohort. The model was then used to perform a larger simulation of HPV transmission, the natural history of CIN and cancer, and cervical screening and HPV vaccination in England. Cervical screening, HPV triage, diagnosis and HPV test-of-cure were modelled using compliance data from registries and NHS HPV Sentinel Sites. A range of assumptions for HPV and cytology characteristics were used. HPV transmission was simulated using the second National Survey of Sexual Attitudes and Lifestyles (NATSAL II) survey of sexual behaviour, and vaccination coverage data since 2008 was incorporated (84% coverage in 12- to 13-year-olds). Extensive validation was performed against a number of observational data sets. This model was then used to simulate lifetime outcomes after the introduction of primary HPV screening on a population-wide basis in England, in unvaccinated cohorts and in cohorts offered vaccination. Several potential triaging strategies were considered for HPV-positive women: (strategy 1) reflex cytology with triage-negative women followed in 12 (or 24) months with HPV testing; (strategy 2) as for strategy 1 but women followed up at 12 or 24 months have a HPV test with partial genotyping, and women positive for types 16/18 are referred to colposcopy; (strategy 3) HPV 16/18 referred to colposcopy at primary screening; and (strategy 4) HPV and cytology performed adjunctively or 'co-testing'. In addition, a range of variants on each strategy were considered, which included consideration of different recommended screening intervals and follow-up times for triage-negative women. We evaluated the cost-effectiveness of these screening strategies, and their variants, against a comparator of current screening practice, incorporating detailed data-driven modelling of compliance to current recommendations. Cross-sectional outcomes, including estimated rates and case numbers of cervical cancer cases and deaths, biopsies, detected high-grade abnormalities, colposcopies, and numbers of screening tests, were predicted, after incorporating information on the population age structure. Detailed sensitivity analyses using one-way and probabilistic sensitivity analysis were performed on a wide range of input parameters used in the model.

The economic evaluation of primary HPV screening in England took a health services perspective, taking into account the health services costs associated with population-based screening, management, diagnosis, and follow-up and treatment of CIN and invasive cancer. A discount rate of 3.5% was used for costs and effects. Life-years was considered as the primary outcome of the analysis, as supplementary analysis for quality-adjusted life-years (QALYs) outcomes found substantial variations in outcomes when alternate health utility weight sets (QALY weights) were considered.

Results

Clinical results

Between January 2006 and June 2009, eligible samples were collected from 8873 women, of whom 71% had been screened in round 2 and 29% had not been screened since round 1. The median duration of follow-up was 72.7 months. The proportion with cytological abnormalities was around 5% in round 3, similar to round 2. The HPV-positive rate, which was 16% in round 1, had fallen to 11% in round 3.

1. The CIN2+ rate in round 3 was 0.74% compared with 2.39% in round 1 and 0.78% in round 2. The cumulative rate of CIN2+ over three screening rounds was 3.9% [95% confidence interval (CI) 3.6% to 4.3%] in the revealed arm and 3.7% (95% CI 3.2% to 4.3%) in the concealed arm.

   – The cumulative CIN2+ rate for women who were HPV negative at baseline was 0.87% (95% CI 0.70% to 1.06%) after three rounds of screening. This was significantly lower than that for women with negative cytology: 1.41% (95% CI 1.19% to 1.65%).
   – Women who were cytology negative and HPV positive at round 1 continued to develop CIN2+ over rounds 2 and 3 (3.67% and 2.77%, respectively) at rates twice those of the cohort overall and had a cumulative CIN2+ rate at 6 years of 7.7%, significantly higher than women who were cytology positive/HPV negative (3.2%).
   – Women who had not been screened in round 2 had a higher CIN2+ rate than those who had been screened (1.34% and 0.50%, respectively).

2. For women who were HPV positive at baseline, the cumulative CIN2+ rate was 20.1%. The cumulative rate of CIN2+ over three rounds and 6 years of follow-up in HPV-negative women (0.87%) was similar to that for women with negative baseline cytology after round 2 and 3 years (0.78%), clearly demonstrating an extended period of protection by a negative HPV result compared with a negative cytology report.
3. The influence of different genotype groups in terms of cumulative CIN2+ after three rounds is clearly shown by significant differences between 16 alone, 16/18, 31/33/45/52/58, and other high-risk types. Women who were HPV-type 16 positive at entry had a cumulative CIN2+ rate over three rounds of 43.6%, compared with 20.1% for all HPV-positive tests. Repeat detection of a specific genotype, that is to say true persistence, was associated with a higher CIN2+ rates than HC2-positive persistence with different type-specific infection in different rounds.
4. If screening were HPV-based [HC2 relative light unit/mean control (RLU/Co 1)] with cytology triage, 4.9% would be referred for borderline+ based on ARTISTIC data. If women with negative cytology were referred based on reflex typing for 16, 18, 31, 33, 45, 52, 58, then 87% of CIN2+ would be detected but the colposcopy referral rate would almost double.
5. Using a HC2 cut-off of RLU/Co ≥ 2 would maintain acceptable sensitivity and result in 16% fewer HPV-positive results.
6. By combining data from the published randomised trial of Cervarix™, the vaccine used in the UK vaccination programme (until 2012), with genotyping data from ARTISTIC, it can be estimated that 70% of CIN2+ would be prevented in vaccinated women and this is seen in all three rounds. At current rates of vaccination coverage (~80%) in 12- to 13-year-olds, there would be a reduction in CIN2+ of about 55%. A far smaller proportion of low-grade cytological abnormalities would be prevented by vaccination, as these are associated with lower rates of underlying HPV 16/18.

Economic results

Most of the primary HPV screening strategies examined were cost saving in both unvaccinated and vaccinated cohorts, and many of the strategies also resulted in an increase in predicted life-years saved in the population. Overall, the cost savings compared with current practice were predicted to be slightly higher in vaccinated cohorts, varying from 9% (strategy 4) to 22% (strategy 1) in vaccinated cohorts and from 7% (strategy 4) to 18% (strategy 1) in unvaccinated cohorts. The most effective strategy involving HPV as the sole primary screening test incorporated partial genotyping for HPV 16/18 at the primary screening step, and direct referral of women positive for these types to colposcopy (strategy 3). In unvaccinated cohorts, the genotyping strategy is predicted to result in a 20% increase in the number of colposcopies performed in England due to the immediate referral of HPV-16/18 women at the primary screening step, but in vaccinated cohorts the number of colposcopy referrals is predicted to be lower than current practice. The increase in colposcopies in unvaccinated cohorts for the partial genotyping strategy S3 suggests that using cytology as a reflex triage test for oncogenic HPV positive women may be, in practice, more feasible in England.

In general, strategies for which HPV is used as the sole primary screening test were found to be both cost and life-years saving, if attention was paid to the optimal combination of screening interval (5- or 6-yearly) and follow-up interval (12 or 24 months) for HPV-positive, cytology-negative ('intermediate risk') women. For all strategies in which HPV is used as the sole primary screening test, decreasing the follow-up interval for HPV-positive/cytology-negative risk women from 24 to 12 months increased the overall effectiveness of primary HPV screening. If 24-month follow-up is retained, the (relative) loss of effectiveness can be partly compensated for by decreasing the screening interval from 6-yearly to 5-yearly, although this was generally a less effective approach than optimising the follow-up of intermediate risk women by decreasing the follow-up interval. Having a recommended follow-up of 12 months in intermediate risk women resulted in between 73–113 and 37–41 additional life-years saved per 100,000 women in unvaccinated and vaccinated cohorts, respectively, when compared with the corresponding strategy with 24-month follow-up. Having a recommended routine screening interval of 5 years was the next most effective variation, and resulted in 40–45 and 20–21 additional life-years saved per 100,000 women in unvaccinated and vaccinated cohorts, respectively, when compared with the corresponding strategy with 6-yearly screening.

In exploratory analysis, strategies for which cytology screening was retained until either age 30 or 35 years, and for which a switch to primary HPV screening was implemented in older women, were predicted to be of somewhat higher costs and intermediate effectiveness than those associated with full implementation of primary HPV screening from age 25 years, even for unvaccinated cohorts. This exploratory finding suggests that implementation from age 25 years of the appropriate strategy for primary HPV screening has the potential to optimise cost and life-year savings in England. However, this finding should be interpreted with caution as it depends on assumptions made about screening behaviour and compliance with recommendations at the 'switch over' point, particularly in relation to management of women already undergoing follow-up at the time of the 'switch'. Further analysis, using detailed protocols for the proposed recommendations underpinning such 'switching', would be required to confirm this finding.

The most influential factors in sensitivity analysis were test characteristics and compliance with follow-up for HPV-positive, cytology-triage-negative ('intermediate risk') women.

Probabilistic sensitivity analysis for the range of potential costs of screening, diagnosis and treatment was conducted. In vaccinated cohorts, strategies 1–3 (but not strategy 4) were cost saving under all sets of cost assumptions and strategy variants considered; in unvaccinated cohorts, strategy 1 and strategy 2 were cost saving under most sets of assumptions but strategy 3 (and strategy 4), with 12 months' follow-up of HPV-positive, triage-negative women, were more costly than current practice under some, but not all, sets of cost assumptions. In supplementary analysis, calculated QALYs were widely divergent depending on the health-state utility weight set used, but under some conditions these weights modified the calculated effectiveness (in terms of quality-adjusted life-years saved) of HPV screening.

Conclusions

The extended ARTISTIC study has provided valuable insights into several key areas. The first is the longer interval of protection by a HPV-negative result than that of a cytology-negative result (6 rather than 3 years), as evidenced by the lower cumulative rate of CIN2+. The data also provide evidence that HPV-negative women aged 50 years could be safely rescreened after 10 years rather than 5. This is an important consideration in relation to HPV testing as a replacement for cytology as the initial screening test. The risk of cumulative CIN2+ following a HPV-positive/cytology-negative result means that optimal strategies will balance the need for surveillance with the potential benefit of immediate intervention. The genotyping data are also relevant to the possible use of HPV typing to select women, for example HPV 16/18 positive, for colposcopic assessment followed by return to routine recall if colposcopy negative. A HC2 cut-off of 2RLU/Co instead of the manufacturer's recommended cut-off of 1 would be clinically beneficial in terms of an optimal balance between sensitivity and specificity.

The extended ARTISTIC data indicate that HPV vaccination with Cervarix™ at the current rates of vaccination in 12- to 13-year-olds could be expected to prevent the majority of CIN2+ lesions resulting in an eventual two-thirds reduction in CIN2+.

Modelled analysis predicts that primary HPV screening would be both more effective and cost saving compared with current practice with cervical cytology for a number of potential strategies in both unvaccinated and vaccinated cohorts. Compliance with surveillance and optimal management of HPV-positive/cytology-negative women after primary HPV screening is of key importance. This study and the economic evaluation lend support to convert from cytology to HPV-based screening, piloting of which commenced in the English programme in the second quarter of 2013.

Study registration

This trial is registered as ISRCTN25417821.

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