A cluster randomised trial of strategies to increase cervical screening uptake at first invitation (STRATEGIC)

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Background

Cervical screening depends on high coverage to achieve its aim of preventing cancer and deaths from cancer. In recent years, uptake among young women has fallen despite public concern expressed over the decision to raise the age threshold for cervical screening in England from 20 to 25 years. In Manchester, for example, uptake of cervical screening among women aged 25 years receiving their first invitation to screening has been around 30% at 6 months after their invitation, compared with an aimed for coverage of 80%, in line with national coverage across the screening age range. Women do have a choice regarding participation in cervical screening, but some women may not fully understand the benefits of cervical screening, and, for others, day-to-day challenges mean that screening is not one of their priorities. A systematic review suggested that there are different reasons for non-participation among women. Although reminders, which are already built into the screening process, have been shown to be effective, our hypothesis was that overcoming barriers to screening young women would require different types of interventions to be explored in order to address these different factors. These should address issues such as anxiety, convenience, dislike of a gynaecological procedure, indifference and not feeling at risk of cervical cancer. It was also felt that the transtheoretical model was relevant, whereby women could be persuaded to progress from pre-contemplation to action. There has been concern that the level of protection from human papillomavirus (HPV) prophylactic vaccination could induce a sense of immunity from cervical cancer in young women, making them less likely to participate in cervical screening and we wished to study this in a Scottish cohort where screening of vaccinated females began in 2010.

Objectives

1. To evaluate the clinical effectiveness of a range of interventions in:
   i. all women receiving their first invitation for cervical screening
   ii. those who had not attended by 6 months.
2. To evaluate the cost-effectiveness of these interventions.
3. To study preferences for cervical screening among non-attenders.

Methods

Uptake of screening

This study involved two sets of interventions that were offered to two cohorts of women who were to receive their first invitation to cervical screening. The first cohort comprised all such women in Manchester, Salford and Trafford primary care trusts (PCTs) (now redesignated Clinical Commissioning Groups) in Greater Manchester, north-west England, between April 2012 and June 2014 who were approaching their 25th birthday. The second cohort comprised women who had just reached their 20th birthday and who were receiving their first screening invitation in the Grampian region of north-east Scotland, between October 2012 and December 2014. Around 65–70% of the Grampian women had been HPV vaccinated in the national catch-up vaccination campaign of 2008–10. The study had a complex design based on cluster randomisation of general practices, and involved two phases:

1. In phase 1, all women who were eligible for cervical screening were, in parallel with a control group, cluster randomised to receive a specially designed pre-invitation leaflet 4–6 weeks prior to receiving their initial routine invitation. Women in the Manchester PCT were also cluster randomised to an offer of online booking using a factorial design to balance pre-leaflet groups. A feasibility pilot study was
performed during phase 1 on a prior cohort of non-attenders to assess the feasibility and uptake of several novel interventions to be used in phase 2. These included self-sampling offered and kits sent unsolicited, a nurse navigator (NN) to advise and support women, timed appointments and a choice of the last two.

2. In phase 2, all non-attenders in the cohort were offered the piloted interventions at 7.5 months after the standard invitation, again in a general practice cluster randomised trial with a factorial design to balance the phase 1 interventions. In phase 2 there was, again, a set of control practices with no study intervention.

All of the interventions were offered initially by mail from the screening agency in Greater Manchester and by the study team in Grampian. The pre-leaflet had been designed on the basis of issues raised by young women in focus groups. The online booking could be made available only to women in the Manchester PCT, through the community sexual health clinics. The study research nurse acted as the NN, who could be contacted by telephone. Self-sampling, whether by request or unsolicited, involved a vaginal sample that was returned dry and then tested using the Cobas 4800 assay (Roche Diagnostics, Pleasanton, CA, USA). Timed appointments were offered by almost all of the randomly allocated general practices and were booked at the women’s request.

Data on uptake were obtained from the screening agency (Lancashire and South Cumbria Agency) in Greater Manchester and from the research team in Grampian. The primary outcome in phase 1 was uptake of screening 3 months following the standard invitation and in phase 2, it was uptake 12 months following the standard invitation. Data analysis was performed using a generalised estimating equation in the form of a population average model to adjust for practice size and pre-study coverage.

Health economic study
The economic analysis complied with methodological guidelines issued by the National Institute for Health and Care Excellence and followed the reporting standards of the Consolidated Health Economic Evaluation Reporting Standards statement. For each intervention, the cost per attendance was calculated together with the unit costs of the screening tests. Other screening-related costs, such as colposcopy and treatment, were estimated. A literature review was conducted to obtain information about costs of lifetime quality-adjusted life-years (QALYs) of women who have attended cervical screening and those who have not. A meta-analysis was performed to pool the lifetime costs and outcomes reported in the selected studies, using a specified random-effects model. Costs were inflated from each study price reference year to 2014, and life expectancy adjusted to the UK context. A decision model was constructed to determine cost-effectiveness and cost–utility analyses. Incremental cost-effectiveness ratios (ICERs) were expressed as incremental costs per attendee and incremental costs per QALY. Uncertainty and scenario analyses were also performed, using probabilistic sensitivity analysis, and the results plotted in cost-effectiveness planes.

Discrete choice experiment
In order to gauge the importance that young women attached to cervical screening, as well as the elements of the screening that they valued, a discrete choice experiment (DCE) was undertaken. This involved an initial set of interviews with non-attenders to determine the relevant attributes included in the scenarios presented to women in a subsequent much larger postal survey. The design and statistical analysis used in the DCE were informed by recent guidance on the conduct of stated preference exercises.

Results

Phase 1
Between April 2012 and December 2013, a total of 20,879 women in 276 practices (193 in Greater Manchester and 83 in Grampian) were cluster randomised, in phase 1, to either pre-leaflet or no pre-leaflet. In the Manchester PCT, 9734 women in 102 practices were cluster randomised to the offer of online booking or not. At the 3-month time point, 18.8% of the pre-leaflet arm had been screened, compared with 19.2% of the controls [odds ratio (OR) 0.96, 95% confidence interval (CI) 0.88 to 1.06;
At 6 months, the equivalent uptake was 31.1% and 30.6%, respectively (OR 1.01, 95% CI 0.93 to 1.10; $p = 0.747$). These data show that the pre-leaflet had no effect. Online booking also showed no impact on uptake. After 3 months, uptake was 17.8% in the group offered online booking, compared with 17.2% in those not offered online booking (OR 1.02, 95% CI 0.87 to 1.20; $p = 0.802$). At 6 months, the equivalent data were 28.8% versus 26.6% (OR 1.09, 95% CI 0.94 to 1.28; $p = 0.242$). There was no interaction between these two interventions. Among the Grampian population, however, there was evidence of increased uptake among previously vaccinated women compared with unvaccinated women: 23.7% versus 11.0% at 3 months (OR 2.07, 95% CI 1.69 to 2.53; $p < 0.001$) and 40.1% versus 18.2% at 6 months (OR 2.57, 95% CI 2.2 to 2.9; $p < 0.001$).

**Phase 2**

During phase 1, 6454 women were screened, 2330 were excluded from the study cohort because of a delay in operationalising the interventions and 1969 were excluded resulting from a change of address. Therefore, between April 2013 and December 2014, a total of 10,126 non-attenders were cluster randomised in phase 2 to the interventions, and 30 practices served as a control. At the primary time point of 12 months following the standard invitations, uptake was 16.2% among the controls, compared with 21.3%, 16.2%, 14.5%, 19.8% and 18.8% for self-sample sent, self-sample offered, NN, timed appointment and choice, respectively. Self-sampling kits (SSKs) sent and timed appointments showed a significant increment in uptake, with an OR of 1.51 (95% CI 1.20 to 1.91) and 1.4 (95% CI 1.14 to 1.74), respectively. At the secondary time point of 18 months following the standard invitation, uptake in the control group was 27.1% and the SSK sent group was 30%, with an OR of 1.29 (95% CI 1.06 to 1.57), but timed appointments was no longer significantly different (OR 1.19, 95% CI 0.97 to 1.46).

**Health economic study**

The meta-analysis revealed a lifetime quality-adjusted life expectancy gain from participating in screening of 0.0947 QALYs per woman attending, and a lifetime additional cost of £566. In phase 1, the pre-leaflet intervention was less costly but less effective than controls. Although online booking was more effective and more costly, with a cost-effectiveness ratio of £8344 per QALY gained, there was low certainty of cost-effectiveness. In phase 2, HPV self-sampling on request was more costly but more effective than controls, with an ICER of £6784 per QALY gained. SSKs sent unsolicited was also more costly but more effective at an ICER of £8434 per QALY. NNs were less costly but less effective. Timed appointments were more costly but more effective than controls, at an ICER of £7593 per QALY. Offering a choice between a NN and the offer of a HPV self-sample sent was also more costly but more effective at an ICER of £7382 per QALY. The probabilistic sensitivity analyses demonstrate, however, that only timed appointments and SSKs sent unsolicited has a high likelihood of cost-effectiveness at a ceiling ratio of £20,000 per QALY gained.

**Discrete choice experiment**

A questionnaire was sent to 4000 non-attenders outside the STRATEGIC trial cohort with a response rate of 5.5%. Questionnaire responses showed that women who were non-attenders at 6 months following the standard invitation understood the value of cervical screening. It also demonstrated preferences for the screening process where minimal personal action is required for the screening test, where the test is performed privately at home and where a nurse is available for discussion. It also demonstrated that women valued testing that was cheaper for the NHS. Some of these characteristics are in line with self-sampling, especially if the kit is sent unsolicited.

**Discussion**

**Phase 1**

The pre-invitation leaflet, which had been designed with the transtheoretical framework in mind, proved ineffective in persuading more young women to attend for screening. We had hypothesised that it would prepare women ahead of receiving their invitation to be more likely to move from thinking about screening to deciding to attend. The leaflet contained messages that young women had highlighted as relevant to them at prior focus group meetings, but clearly this approach did not work. We do not know...
whether or not women actually read the leaflet as it was simply mailed to them by the screening agency. Online booking was taken up by around 6% of women offered. Many did not actually attend the booked appointment and, in absolute terms, the uptake at 3 months was very similar to controls. Although a 2% higher uptake than that seen in the control group after 6 months of follow-up was observed, this did not achieve statistical significance. One important observation made in phase 1 was that among the Grampian women, prior vaccination was associated with a significantly increased uptake, and that overall uptake among unvaccinated women was < 20% after 6 months. This minority who are unvaccinated and unscreened remain at a higher risk of cervical cancer.

**Phase 2**
All of the interventions were successfully implemented. Compared with controls, a SSK sent and timed appointment were associated with a statistically significantly increased uptake at 12 months following the standard invitation with an increased uplift over controls in absolute terms of 5.1% and 3.7%, respectively. By 18 months, however, participation by controls rose from 16.2% to 27.1%, and only SSKs sent continued to show a significant increase in uptake. Although these interventions were aimed at specific barriers, accessing the interventions did not always directly result in uptake, but appeared to ‘nudge’ women into action. It seemed that a significant number of women who had not attended promptly for screening, did understand its importance and got round to it over time. This concept is supported by the DCE in which women who had not attended promptly indicated that they thought cervical screening was important.

It was clear from the ORs of the interventions that unrequested SSKs sent had the largest effect, followed by timed appointments, and this was reflected in the cost-effectiveness results. Other phase 2 interventions were thought to carry lower certainty of cost-effectiveness, and neither of the phase 1 interventions was effective. Offering timed appointments and unsolicited SSKs to a national cohort of women aged 25 years, and across the entire lifetime of screening would cost £13.4M and £18.37M, respectively, with cost-effectiveness ratios of £7593 and £8437 and a 94% probability of being below the £20,000 ceiling. It may be more cost-effective to offer all invited women a timed appointment and reserve SSKs for non-attenders. The DCE confirmed that the attributes valued by women who had not yet attended are inherent in the strategy of sending SSKs.

**Conclusions**
Women receiving their initial invitation to cervical screening do not attend promptly but continue to do so during the interval prior to the next screening round. Approximately 30% had been screened by 6 months and another 20% over the following year. Previously vaccinated women had a higher uptake than unvaccinated women. The pre-invitation leaflet and online booking were not effective in increasing uptake, but the latter would be convenient for many young women. Among non-attenders at 6 months, both SSKs sent to women and timed appointments resulted in a 10% increase in uptake. These interventions were also shown to have a high likelihood of being cost-effective in the NHS. A DCE revealed that women who had not attended valued privacy and convenience, both of which are inherent in self-sampling. Future work should focus on optimising self-sampling in terms of age range, timing of offer for non-attenders and the use of urine testing instead of vaginal samples.

**Trial registration**
This trial is registered as ISRCTN52303479.

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