Economic evaluation of human papillomavirus vaccination in the United Kingdom

Mark Jit, Yoon Hong Choi, W John Edmunds

ABSTRACT

Objective To assess the cost effectiveness of routine vaccination of 12 year old schoolgirls against human papillomavirus infection in the United Kingdom.

Design Economic evaluation.

Setting UK.

Population Schoolgirls aged 12 or older.

Main outcome measures Costs, quality adjusted life years (QALYs), and incremental cost effectiveness ratios for a range of vaccination options.

Results Vaccinating 12 year old schoolgirls with a quadrivalent vaccine at 80% coverage is likely to be cost effective at a willingness to pay threshold of £30 000 (€37 700; $59 163) per QALY gained, if the average duration of protection from the vaccine is more than 10 years. Implementing a catch-up campaign of girls up to age 18 is likely to be cost effective. Vaccination of boys is unlikely to be cost effective. A bivalent vaccine with the same efficacy against human papillomavirus types 16 and 18 costing £13-£21 less per dose (depending on the duration of vaccine protection) may be as cost effective as the quadrivalent vaccine although less effective in terms of health benefits.

Conclusions Routine vaccination of 12 year old schoolgirls combined with an initial catch-up campaign up to age 18 is likely to be cost effective in the UK. The results are robust to uncertainty in many parameters and processes. A key influential variable is the duration of vaccine protection.

INTRODUCTION

Two prophylactic vaccines against human papillomavirus (a bivalent vaccine against types 16 and 18 and a quadrivalent vaccine including types 6 and 11) have been shown to be efficacious against cervical infection and associated disease and anogenital warts for up to five years. The results from clinical trials suggest that both vaccines may offer partial protection against oncogenic human papillomavirus types not in the vaccine.

In the UK the Department of Health has announced a human papillomavirus immunisation programme using the bivalent vaccine from September 2008 for schoolgirls aged 12 or 13, with a two year catch-up programme for girls up to age 18. The decision to vaccinate, the age groups to target, and the choice of vaccine were informed by cost effectiveness modelling. We describe the model and consider the impact of vaccination on several outcomes.

METHODS

We used a transmission dynamic model (see details on bmj.com) to predict the burden of human papillomavirus related disease in a screened population for the number of cervical screens, treatments for precancerous abnormalities of the cervix, and cases of cancer and anogenital warts expected before and after vaccination. In separate scenarios we considered the additional benefit of vaccinating the unscreened population, possible vaccine protection against non-cervical cancers, and possible vaccine protection (with 27% efficacy) against non-vaccine type cervical infection.

We constructed a total of 2700 possible scenarios for high risk human papillomavirus types and 900 scenarios for low risk types from combinations of assumptions on the epidemiology of human papillomavirus, clinical course of infection, accuracy of cervical screening, and rates of sexual partnership. Of these we chose outcomes from 72% of scenarios for the economic analysis on the basis of their goodness of fit to prevalence data on human papillomavirus. We then generated distributions of likely parameter values for cost and utility weights (see bmj.com). By sampling from different combinations of epidemiological and economic assumptions we constructed a total of 50 000 meta-scenarios.

We followed the population in the transmission model for 100 years after the onset of vaccination. We measured health utilities in quality adjusted life years (QALYs), discounted costs and benefits at 3.5% per year in the base case, and adopted a healthcare provider perspective on costs.

We analysed the cost effectiveness of a range of vaccination strategies. The base case assumption was vaccination of girls aged 12 years using a school based programme, with 80% vaccine coverage for the full three doses. Alternative scenarios were vaccinating boys and girls at age 12 and a catch-up campaign in the first year of vaccination to vaccinate females from age 12 to ages 14, 16, 18, or 25.

We analysed the cost effectiveness of a bivalent vaccine against virus types 6, 11, 16, and 18, and a quadrivalent vaccine against types 16 and 18. All base
case analyses used the quadrivalent vaccine. We varied the cost for a dose of the quadrivalent vaccine between £60 (price of Gardasil in the United States) and £80.50 (price of Gardasil available privately in the UK). For the base case scenario we determined the estimated price differential between equally cost effective bivalent and quadrivalent vaccines, calculated by dividing the net present value of the additional benefits of a quadrivalent vaccination programme for preventing anogenital warts (cost savings to the health service and quality of life gains) by the number of doses of vaccine required to achieve the benefits. The net present value was calculated on the basis of a willingness to pay threshold of £30 000 per QALY gained.

RESULTS

The median cost per QALY gained of the base case scenario (vaccinating girls aged 12 at 80% coverage with a quadrivalent vaccine) with vaccine protection for an average of 20 years is £22 500 (95% range £13 800–£32 900). The median net discounted cost of the programme over 100 years is £1.8bn (95% range £1.5bn–£2.2bn). The epidemiological impact of this base case scenario has been shown to reduce the incidence of cervical cancer by 24–93% and anogenital warts by 22–100% by 100 years after an ongoing vaccination programme. Catch-up campaigns reduce incidence in the first 30 years but have little effect beyond that. Extending vaccination to boys provides only a small additional reduction in incidence of cervical cancer and anogenital warts.

Cost effectiveness

The vaccination programme with base case assumptions is expected to generate cost savings to the health service from reduced treatment. These are, however, outweighed by the yearly cost of the programme itself (£77m, 95% range £68m–£88m). Hence vaccination is unlikely to be cost saving (see bmj.com). QALYs are gained through a reduction in the detection and treatment of cervical dysplasia, anogenital warts, and cervical cancer.

Partial protection against infection by non-vaccine human papillomavirus types has the greatest potential for cost savings, as these types account for a large portion of positive smear results requiring expensive follow-up (see bmj.com). The QALY gains from preventing these infections are smaller because these virus types account for only about 30% of cervical cancers in the UK.

If vaccine induced immunity is short lived (10 years) then it is unlikely that vaccination of girls aged 12 would be acceptable on the grounds of cost effectiveness. If the vaccine induces lifelong protection, however, then more than 80% of scenarios suggest

<table>
<thead>
<tr>
<th>Programme</th>
<th>Average cost effectiveness ratio* (£)</th>
<th>Incremental cost effectiveness ratio† (£)</th>
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<tr>
<td></td>
<td>Median</td>
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<tr>
<td>10 years' vaccine protection:</td>
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<td>Girls aged 12</td>
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<td>33 296</td>
<td>18 464</td>
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<td>Catch-up aged 12-16</td>
<td>32 244</td>
<td>17 978</td>
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<td>Catch-up aged 12-18</td>
<td>31 132</td>
<td>17 447</td>
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<td>Catch-up aged 12-25</td>
<td>39 096</td>
<td>21 785</td>
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<td>Girls+boys aged 12</td>
<td>53 099</td>
<td>31 696</td>
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<td>20 years' vaccine protection:</td>
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<td>Girls aged 12</td>
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<td>22 210</td>
<td>13 636</td>
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<td>13 420</td>
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<td>Catch-up aged 12-18</td>
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<td>Catch-up aged 12-25</td>
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<tr>
<td>Girls+boys aged 12</td>
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<td>28 011</td>
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<td>Lifetime vaccine protection:</td>
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<td></td>
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<tr>
<td>Girls aged 12</td>
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<td>10 093</td>
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<tr>
<td>Catch-up aged 12-14</td>
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<td>Catch-up aged 12-25</td>
<td>19 476</td>
<td>13 443</td>
</tr>
<tr>
<td>Girls+boys aged 12</td>
<td>33 281</td>
<td>23 814</td>
</tr>
</tbody>
</table>

*Cost effectiveness of particular option compared with no vaccination option.
†Ratio of additional costs and benefits of particular vaccination programme compared with previous option. Options being compared with are no vaccination when considering routine vaccination of girls aged 12, routine vaccination of girls aged 12 when considering routine vaccination of both sexes aged 12, and programme listed immediately before for each of catch-up campaign options.
that vaccination would be regarded as cost effective (below £80 000-£30 000 per QALY gained). If vaccine induced immunity lasts on average around 20 years then about 25-85% of scenarios suggest that the vaccination programme is cost effective (see bmj.com). Assuming that vaccine uptake is 80% in girls who do not subsequently attend screening is not sufficient to make a vaccine with 10 years’ protection cost effective. If this assumption is used and the vaccine is also assumed to be efficacious against non-cervical cancers and partially efficacious against infection by non-vaccine human papillomavirus types, then vaccination may be cost effective even if vaccine induced immunity lasts only 10 years (see bmj.com).

Vaccination of boys
Vaccination of boys at age 12 years in addition to girls is unlikely to be cost effective, even if vaccination results in lifelong protection (table 1). This is because at 80% coverage most cervical cancers due to human papillomavirus types 16 and 18 will be prevented, along with many cases of anogenital warts in both sexes.

Catch-up campaigns
A catch-up campaign in girls up to age 18 may be cost effective, but extending the campaign to age 25 is highly unlikely to be cost effective (table 1). Campaigns up to age 18 are more likely to be cost effective than the base case programme, because vaccinating at a slightly older age is more cost effective than vaccinating at age 12. This implies that if the base case programme is viewed favourably, then vaccinating girls up to age 18 in an initial catch-up campaign should also be adopted. Above this age an increasing proportion of females have previous evidence of human papillomavirus infection, and the delivery costs increase because it is assumed that vaccination in females older than 16 would be offered through their doctors rather than through a school based programme.

Price differential for quadrivalent and bivalent vaccines
A bivalent vaccine would have to be around £13-£21 less expensive per dose for it to be as cost effective as an equivalent quadrivalent vaccine in a vaccination programme directed at girls aged 12 (table 2). The price differential is greatest if the vaccines both give lifelong protection. If the programme was extended with a catch-up programme for girls up to age 18, then the bivalent vaccine would have to be around £15-£23 less expensive per dose. Catch-up campaigns make the quadrivalent vaccine slightly more cost effective than the bivalent vaccine if the duration of vaccine protection is not life long, because they enable a larger portion of the burden of anogenital warts to be prevented.

The most important determinants of the cost effectiveness of the programme are the average duration of vaccine protection and of natural immunity (see bmj.com). Vaccination has the greatest impact if the duration of protection is long and the duration of natural immunity short. The cost effectiveness ratio is highly sensitive to the discount rate for benefits because most of the QALY gains from preventing cervical cancers occur decades after the vaccination programme begins (see bmj.com).

DISCUSSION
Our economic analysis indicates that vaccinating 12 year old girls through a school based programme with a quadrivalent human papillomavirus vaccine priced at around £60-£80 per dose is likely to be cost effective at a threshold of £20 000-£30 000 per QALY gained as long as protection lasts more than 10 years. If the duration of protection is only 10 years then the programme may still be cost effective if high vaccine uptake can be achieved among girls who do not subsequently attend screening, if the vaccine is highly efficacious against non-cervical cancers caused by human papillomavirus types 16 and 18, and if it is partially efficacious against cervical cancers not caused by human papillomavirus types 16 and 18. The duration of vaccine protection and the duration of natural immunity after infection had a strong influence on the costs and health gains from vaccination. The models also suggest that a catch-up campaign of girls up to age 18 is likely to be cost effective, but vaccination of boys is unlikely to be cost effective.

Table 2: Estimated price differential between equally cost effective bivalent and quadrivalent human papillomavirus vaccines (vaccination of girls aged 12 years, 80% effective vaccine coverage, 100 year time horizon, and 3.5% discount rate for costs and benefits)

<table>
<thead>
<tr>
<th>Age at vaccination and catch-up</th>
<th>Duration of vaccine protection</th>
<th>10 years</th>
<th>20 years</th>
<th>Life long</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (£)</td>
<td>12.96</td>
<td>17.27</td>
<td>20.94</td>
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</tr>
<tr>
<td>95% centile (£)</td>
<td>22.06</td>
<td>26.59</td>
<td>30.30</td>
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</tr>
<tr>
<td>5% centile (£)</td>
<td>6.26</td>
<td>9.37</td>
<td>12.95</td>
<td></td>
</tr>
<tr>
<td><strong>Girls aged 12 with catch-up to age 18:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (£)</td>
<td>15.54</td>
<td>20.28</td>
<td>23.21</td>
<td></td>
</tr>
<tr>
<td>95% centile (£)</td>
<td>25.26</td>
<td>29.91</td>
<td>32.79</td>
<td></td>
</tr>
<tr>
<td>5% centile (£)</td>
<td>8.58</td>
<td>12.28</td>
<td>14.98</td>
<td></td>
</tr>
</tbody>
</table>

£1.00 (£1.26, £1.98).
Results are based on 50 000 meta-scenarios representing uncertainty in epidemiological and economic parameters.
The range of models we have presented represent uncertainty in natural immunity to human papillomavirus infection; the sensitivity of the screening test; progression and regression between precancerous states; the prevalence of human papillomavirus types by age; the rates of sexual partnerships in the UK population; and the impact of vaccination on other high risk types, the unscreened population, and non-cervical cancers. Many other features of the biology of human papillomavirus are uncertain but were not varied as part of our uncertainty analysis.

Only the 72% of model structures that best fit prevalence data for human papillomavirus were used in the analysis, but care should be taken when interpreting model results not to assume that each of the remaining model structures is equally plausible. Fortunately, in many cases most of the scenarios lie on one side of the £20 000-£30 000 per QALY gained threshold, indicating that reliable conclusions can be drawn about the cost effectiveness of a programme even if the more likely scenarios may be unequally distributed within the range of outputs.

Model predictions about the cost effectiveness ratio assuming lifelong protection are broadly in line with base case results from other published models of human papillomavirus vaccination in developed countries. Existing UK models are limited as they do not take full account of the many biological, epidemiological, and economic uncertainties surrounding human papillomavirus vaccination. Such models have assumed a base case structure and performed sensitivity analysis around the parameter values one or two at a time. For the case of human papillomavirus it is difficult to justify a choice of base case because of the uncertainty around many key parameters, and indeed the structure of the model itself. Only two published cost effectiveness models on human papillomavirus (Canada and Brazil) have performed multivariate sensitivity analyses on model structure. Neither of these are transmission dynamic models.

Although we have included the estimated impact of cervical screening in the model and tried to account for the accuracy of screening in our results, the heterogeneity of the screened population is difficult to properly implement in the current model structure. Since vaccination could act to either increase or decrease health inequalities depending on the uptake rates for screening and vaccination by socioeconomic groups and the level of herd protection generated, future modelling and surveillance work should deal with these aspects. Furthermore, our model assumes that the screening programme will continue unchanged, which is likely in the short term, particularly as current vaccines against human papillomavirus cannot provide full protection against all oncogenic human papillomavirus types. If the prevalence of human papillomavirus infection is, however, significantly reduced as a result of universal vaccination, as our model predicts, then it may be possible to extend the interval between routine screens or to increase the age at which screening is first offered, as suggested in other cost effectiveness studies. Such analyses would also need to take account of possible changes to the cervical screening programme, such as the introduction of DNA testing for human papillomavirus, as changes in the prevalence of infection after vaccination would be expected to alter the attractiveness of screening tests with improved sensitivity.

Models are simplifications of reality and the strengths of the conclusions drawn from modelling studies depend on the reasonableness of the assumptions and parameters that make up the model. By adopting a range of assumptions and parameter estimates the approach taken here should generate more robust conclusions than can be derived from studies in which a single model structure is chosen and sensitivity analysis done on the parameter values one or two at a time. Although considerable uncertainty remains, the study also highlights the areas of research that could be taken to reduce this uncertainty. With the adoption of human papillomavirus vaccination in the UK and other countries, some of the other aspects of the clinical course of human papillomavirus should become apparent. High quality surveillance combined with mathematical models will, however, be needed to help disentangle the complex epidemiological patterns that are likely to emerge after immunisation.

We thank Ruby Siddiqui for information on the literature about cost and quality of life implications of human papillomavirus associated infections, Sue Westlake and the Office for National Statistics for providing incidence data on cervical cancer, Zia Sadique for statistical advice, the panel of referees who commented on an earlier version of this work, and Kate Saldan, Nigel Gay, and Elizabeth Miller for helpful discussions.

Contributors: See bmj.com.

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Interventions before consultations to help patients address their information needs by encouraging question asking: systematic review

Paul Kinnserley,1 Adrian Edwards,1 Kerry Hood,1 Rebecca Ryan,2 Hayley Prout,1 Naomi Cadbury,1 Fergus MacBeth,3 Phyllis Butow,4 Christopher Butler1

EDITORIAL by Murray

Neuadd Merionedd, School of Medicine, Cardiff University, Cardiff CF14 4XN
3Cochrane Consumers and Communication Review Group, Australian Institute of Primary Care, LaTrobe University, Victoria, Australia
1Clinical Effectiveness Support Unit (Wales) Roseway, Llandough Hospital, Penarth
3School of Psychology, University of Sydney, Australia
Correspondence to: P Kinnserley kinnserley@cf.ac.uk

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ABSTRACT

Objective To assess the effects on patients, clinicians, and the healthcare system of interventions before consultations to help patients or their representatives gather information in consultations by question asking.

Design Systematic review with meta-analysis.

Data sources Electronic literature searches of seven databases and hand searching of one journal and bibliographies of relevant articles.

Review methods Inclusion criteria included randomised controlled trials.

Main outcome measures Primary outcomes were question asking; patients’ anxiety, knowledge, and satisfaction; and length of consultation.

Results 33 randomised trials of variable quality involving 8244 patients were identified. A few studies showed positive effects. Meta-analyses showed small and statistically significant increases in question asking (standardised mean difference 0.27, 95% confidence interval 0.19 to 0.36) and patients’ satisfaction (0.09, 0.03 to 0.16). Non-statistically significant changes occurred in patients’ anxiety before consultations (weighted mean difference −1.56, −7.10 to 3.97), patients’ anxiety after consultations (standardised mean difference −0.08, −0.22 to 0.06), patients’ knowledge (−0.34, −0.94 to 0.25), and length of consultation (0.10, −0.05 to 0.25). Interventions comprising written materials had similar effects on question asking, consultation length, and patients’ satisfaction as those comprising the coaching of patients. Interventions with additional training of clinicians had little further effect than those targeted at patients alone for patients’ satisfaction and consultation length.

Conclusions Interventions for patients before consultations produce small benefits for patients. This may be because patients and clinicians have established behaviours in consultations that are difficult to change. Alternatively small increases in question asking may not be sufficient to make notable changes to other outcomes.

INTRODUCTION

Providing information is a key part of clinical care, which influences patients’ satisfaction, compliance, and understanding.1-3 Failure to give information or providing unwanted information can cause harm.4 We undertook a systematic review to assess the effects on patients and clinicians of interventions delivered before consultations to help patients address their information needs within consultations.5

METHODS

We considered peer reviewed randomised controlled trials that involved interventions directed at patients of any age (or their representatives) consulting with doctors or nurses delivered before the consultation to encourage question asking (see bmj.com for search

REFERENCES


3 Brown D. HPV type 6/11/16/18 vaccine: first analysis of cross-protection against persistent infection, cervical intraepithelial neoplasia (CIN), and adenocarcinoma in situ (AIS) caused by oncogenic HPV types in addition to 16/18. 47th annual Intercencence Conference on Antiinmunol Agents and Chemotherapy, Chicago, USA 2007.


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strategy. We included studies providing training for clinicians if it was additional to interventions for patients.

Our main outcomes were question asking, satisfaction, anxiety, knowledge, and consultation length. Anxiety was measured before and after consultations (see bmj.com).

When studies used combined interventions, we used data on the effects for the main outcomes. We assessed adequacy of randomisation, particularly concealment of allocation. Intention to treat analyses were used when available.

We carried out a narrative synthesis of the included trials, then pooled data across studies and did meta-analyses for the main outcomes. We calculated summary estimates of the intervention effects. Weighted mean differences were used for similar methods and units, or standardised mean differences for differing methods. We used fixed effect models for homogeneity across studies, and random effect models for heterogeneity. We examined potentially important effect modifiers on the outcomes, particularly type of intervention and whether additional training for clinicians produced benefits. We undertook sensitivity analyses for studies without adequate concealment of allocation or that did not account for clustering in their design.

### RESULTS

All 33 included studies were in English (see bmj.com). Thirty-three reported on patients consulting doctors, two on patients consulting doctors or nurses, and one on patients consulting family planning care nurses. Twenty-five trials used question prompt sheets. In six of these, additional coaching was provided. Five trials used coaching alone. In two trials brief instructions were used. One trial combined coaching with a computer program and another with video and written materials. One study accessed patients’ medical records of previous consultations and another used audiotapes of the previous consultation.

In five trials clinicians also received training.

#### Methodological quality of included trials

Randomisation was by patient in 30 trials, by clinician in two, and site of delivery of a community based intervention in one. Only six trials provided sample size calculations.

Four trials provided evidence of adequate concealment of allocation; four were judged unclear and five inadequate.

#### Effect sizes of interventions to encourage patients to ask questions in consultations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of studies</th>
<th>No of patients</th>
<th>Standardised mean difference (95% CI)</th>
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</thead>
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</tr>
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<td>Question asking*</td>
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<td>2020</td>
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<tr>
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<tr>
<td>No clinicians’ training</td>
<td>12</td>
<td>2798</td>
<td>0.17 (0.10 to 0.24)</td>
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</table>

*Two assumptions were made about data from study by Roter—that number analysed in intervention and control groups for outcomes of question asking and patients’ satisfaction were equal and that means for patients’ satisfaction in the two groups were 1.46 and 1.37 and not 146 and 1.37 as stated in text.

†Weighted mean difference.

‡In two studies intervention for control group could increase patients’ knowledge. Analysis was repeated with remaining three studies and a small and not statistically significant increase in knowledge was found (0.17, −0.09 to 0.43).
In the 18 trials that used audiotapes or videotapes to gather data, seven used assessors blind to allocation group. Eight trials used double rated tapes to check reliability. Only two trials used intention to treat analyses.

Quantitative data synthesis

**Question asking**

Seventeen studies measured question asking. Six found statistically significant increases and the remainder found no effects. Meta-analysis of 14 studies with extractable data showed a small and statistically significant overall effect (standardised mean difference 0.27, 0.19 to 0.36; table and bmj.com).

**Patients’ anxiety**

Anxiety before consultations was measured in four studies; two found a reduction, one an increase, and one no effect. Meta-analysis of three studies with extractable data showed a large but non-statistically significant decrease in patients’ anxiety (weighted mean difference −1.56, −7.10 to 3.97; table and bmj.com). In nine studies anxiety was measured after the consultation, with two reporting a reduction, one an increase, and six no effect. Meta-analysis of six studies with extractable data showed a small and non-statistically significant decrease (standardised mean difference −0.08, −0.22 to 0.06; table and bmj.com).

**Patients’ knowledge**

Reductions in knowledge were found in two studies and no change in three. Meta-analysis of these studies found a small and non-statistically significant decrease (−0.34, −0.94 to 0.25; table and bmj.com). This result was not substantially altered when two studies showing a decrease—a potential influence from the intervention in the control group—were removed (−0.26, −0.52 to 0.01).

**Patients’ satisfaction**

In 14 studies no changes were found and in five satisfaction increased. In two additional studies increases occurred only for depth of relationship and interpersonal satisfaction. Meta-analysis of 17 studies with extractable data showed a small and statistically significant increase in patients’ satisfaction (0.09, 0.03 to 0.16; see bmj.com).

**Length of consultations**

Seventeen studies measured the length of consultations; three found statistically significant increases and 13 no effect. Meta-analysis of 13 studies with extractable data found a small and non-statistically significant increase (0.10, −0.05 to 0.25; see bmj.com).

Recalculating effects and confidence intervals without the five trials with inadequate concealment and the three that used randomisation by clinician resulted in small changes.

**Effect modifiers**

Similar small to moderate and statistically significant increases were found in question asking for written materials (0.42, 0.26 to 0.59) and coaching (0.36, 0.16 to 0.56). Written materials led to a small and statistically significant increase in length of consultations (0.13, 0.05 to 0.21), and coaching produced a smaller, non-significant change (0.07, −0.07 to 0.20). Written materials produced a small increase in patients’ satisfaction of borderline statistical significance (0.08, 0.00 to 0.16) and for coaching the effect was a small but statistically significant increase (0.23, 0.08 to 0.38).

Three studies considered the addition of training clinicians and had extractable data on the effects of combined interventions (patients and clinicians) on consultation length and patients’ satisfaction. Training had little impact on consultation length compared with patient only interventions (combined 0.17, 0.01 to 0.32 vs patient only 0.17, 0.10 to 0.24); the corresponding values for patients’ satisfaction were 0.08 (−0.06 to 0.22) and 0.13 (0.05 to 0.21).

Two studies assessed the impact of interventions directed at patients in the context of all clinicians receiving training. In one study the intervention produced a small non-statistically significant decrease in consultation length and no effect on patients’ satisfaction (consultation length −0.49, −0.88 to −0.10, satisfaction 0.00, −0.39 to 0.39). The other study showed a small increase in consultation length (0.24, −0.05 to 0.43) and little effect on satisfaction (0.03, −0.16 to 0.22).

**DISCUSSION**

Thirty three randomised trials of interventions to help patients ask questions and gather information in consultations were identified. Meta-analyses showed that the interventions resulted in small but statistically significant increases in question asking and patients’ satisfaction, a large but not statistically significant decrease in anxiety before consultations, and small but not statistically significant effects on anxiety after consultations and length of consultations.

We identified a large number of trials that aimed to improve the information patients obtain during consultations. Our search strategy identified more trials than other related reviews of broader designs. Other reviews are broadly supportive of interventions to promote information gathering by patients, identifying a range of benefits. Our meta-analyses suggest that the evidence of benefits is less compelling.

Despite our efforts to search comprehensively we may have missed some studies. Although we contacted authors we only included published trials. As unpublished studies would more likely have shown...
null results our findings may overestimate the effects of interventions. Furthermore, an English language bias may exist because of the databases searched. We restricted the review to studies of patients consulting doctors or nurses but it is possible that interventions have been tested in other health professionals. However, doctors and nurses are considered by patients to be their main source of information. In our meta-analyses we combined the effects of interventions across varied settings. Individual interventions may perform better in particular settings and the process of combining studies may lose an element of specificity.

The increase in question asking we found shows a direct effect of the interventions and that simple interventions can influence the clinical dialogue. The small increase in patients’ satisfaction is consistent with other reports of benefits from patient centred interventions. A possible explanation for the limited effects is that many clinicians and patients adopt ritualised styles of consulting on the basis of previous experience. These may not be readily changed by interventions, particularly if delivered only once, immediately before the consultation, as part of research projects, and targeted at only one participant in the consultation. Data on the possibility of interventions reducing patients’ anxiety before consultations are inconclusive. Patients attending consultations may feel uncertain about getting an opportunity to express their concerns. Enabling them to organise their thoughts might reduce anxiety. One study that involved patients with cancer showed an increase in anxiety. Anxiety may not improve and may even increase if clinicians do not respond appropriately to patients’ questions. Secondly, anxiety may increase if the information given is worrying. We expected that the interventions in this review would foster a sense of control because patients would have identified and possibly practised asking questions. This preparation may have disturbed the balance of authority in the consultation, however, and generated difficulties for patients so that they moved back to their usual mode of consulting. More intense interventions such as coaching had few additional benefits over simpler written interventions that required little clinic time. It has been suggested that interventions would be more effective if supported by training of clinicians. We found no consistent evidence for this from the small number of studies.

Although evidence is lacking of an increase in consultation length as a result of the interventions, the data could be considered to indicate a trend to longer consultations. Data analysed from 17 studies, however, showed that interventions do not lead to sizeable increases in length of consultations.

Some patients might find the interventions more helpful than others. Many of the studies were set in oncology clinics. Two studies explored the impact of the interventions on different patient groups.

Conclusions
Successful consultations require that patients and clinicians agree on the nature of the problem and what should be done. Decision making must be shared and clinicians need to be sufficiently flexible to respond to the preferences for information and involvement of different patients or of the same patient in different circumstances.

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Competing interests: PK directs a university unit that generates income by delivering training in communication skills to clinicians.

Ethical approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

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ABSTRACT

Objective To examine the protective efficacy of measles vaccination in infants in a low income country before 9 months of age.

Design Randomised clinical trial.

Participants 1333 infants aged 4.5 months: 441 in treatment group and 892 in control group.

Setting Area in Guinea-Bissau.

Intervention Measles vaccination using standard titre Edmonston-Zagreb vaccine at 4.5 months of age.

Main outcome measures Vaccine efficacy against measles infection, admission to hospital for measles, and measles mortality before standard vaccination at 9 months of age.

Results 28% of the children tested at 4.5 months of age had protective levels of maternal antibodies against measles at enrolment. After early vaccination against measles 92% had measles antibodies at 9 months of age. A measles outbreak offered a unique situation for testing the efficacy of early measles vaccination. During the outbreak, 96 children developed measles; 19% of unvaccinated children had measles before 9 months of age. The monthly incidence of measles among the 441 children enrolled in the treatment arm was 0.7% and among the 892 enrolled in the control arm was 3.1%. Early vaccination with the Edmonston-Zagreb measles vaccine prevented infection; vaccine efficacy for children with serologically confirmed measles and definite clinical measles was 94% (95% confidence interval 77% to 99%), for admissions to hospital for measles was 100% (66% to 100%), and for measles mortality was 100% (~42% to 100%). The number needed to treat to prevent one case of measles between ages 4.5 months and 9 months during the epidemic was 7.2 (6.8 to 9.2). The treatment group tended to have lower overall mortality (mortality rate ratio 0.18, 0.02 to 1.36) although this was not significant.

Conclusions In low income countries, maternal antibody levels against measles may be low and severe outbreaks of measles can occur in infants before the recommended age of vaccination at 9 months. Outbreaks of measles may be curtailed by measles vaccination using the Edmonston-Zagreb vaccine as early as 4.5 months of age.

Trial registration Clinical Trials NCT00168558 [ClinicalTrials.gov].

INTRODUCTION

As a result of the first measles vaccination programme in Guinea-Bissau in 1979,1 many mothers have not had natural measles infection. We previously found that immunised mothers in Guinea-Bissau and Senegal transferred only half the concentration of maternal antibodies.5,6 Children born to immunised mothers may lose protection by 3-5 months of age.

In 2003 we started a trial of two doses of Edmonston-Zagreb measles vaccine in infants aged 4.5 and 9 months in urban Guinea-Bissau. Shortly after the trial started an outbreak occurred in the study area and provided a unique situation for testing the efficacy of early vaccination.

METHODS

The trial was carried out in the study area of the Bandim Health Project, which covers five districts4 and has three health centres. Children are visited every three months until age 3 years. About 20% of the mothers are

EDITORIAL by Broutin and Miller

Bandim Health Project, Indepth Network, Bissau, Guinea-Bissau

Bandim Health Project, Danish Epidemicology Science Centre, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark

MRC Laboratory, Fàjara, Gambia

Department of Pathology, Herlev University Hospital, Denmark

Correspondence to: P Aaby
p.aaby@bandim.org

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Protective efficacy of standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a randomised clinical trial

Cesário L Martins,1 May-Lill Garly,1,2 Carlito Balé,1 Amabelia Rodrigues,1 Henrik Ravn,1,2 Hilton C Whittle,3 Ida M Lisse,4 Peter Aaby1,2


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travelling at any given time and a large proportion of the children may have late vaccinations.

We planned to compare vaccination strategies using the two main strains of measles vaccine, Edmonston-Zagreb and Schwarz. The trial design included three arms: two dose measles vaccination with Edmonston-Zagreb vaccine at 4.5 and 9 months of age and Schwarz vaccine or Edmonston-Zagreb vaccine at 9 months. The primary end point was survival to 3 years. The children were enrolled at 4.5 months of age and randomised to one of the three groups.

Studies have suggested that diphtheria, tetanus, and pertussis given with or after measles vaccine may be associated with increased mortality compared with measles vaccine given alone. 

Children in the present trial had to have received three doses of the diphtheria, tetanus, and pertussis vaccine before enrolment.

Interim analysis

A large outbreak of measles occurred between November 2003 and May 2004, shortly after the trial started. We decided to report immediately the efficacy of early measles vaccination. In contrast to the three groups specified in the protocol, this interim analysis directly compared two groups: children receiving the Edmonston-Zagreb vaccine at age 4.5 months and the combined group of children to receive the Schwarz or Edmonston-Zagreb vaccines at 9 months. The primary outcomes in the interim analysis were incidence of measles, admissions to hospital for measles, and measles mortality. Hence the interim study reports the efficacy of early vaccination with the Edmonston-Zagreb vaccine in an outbreak situation. The study includes all children enrolled in the trial between the start of the study and the end of May 2004, when the measles epidemic ended.

Randomisation

Children randomised to Zagreb-Edmonston vaccination at 4.5 months of age received a standard titre. Mothers of children in the control group were told that their children would not receive measles vaccine at enrolment but that they should be vaccinated at 9 months of age.

Outcomes

We collected blood samples to assess the levels of maternal antibody levels against the measles virus. We collected samples at 4.5, 9, and 24 months of age from the treatment group and at 9, 18, and 24 months of age from the control groups. The samples at 4.5 and 9 months of age in the treatment group were used to document the degree of seroconversion after early vaccination.

A measles outbreak built up during 2003 and lasted until May 2004. Children with measles seen at the study health centres were identified. When fieldworkers visited their houses as part of routine activities they attempted to identify additional cases of measles.

Two special surveys to obtain information on measles infection or exposure to measles infection were carried out for children in the present trial, in the early phase in January 2004 and at the end of the outbreak, in June or July 2004. These surveys were carried out by fieldworkers who were not involved in the enrolment of children.

Children were considered to have definite clinical measles if they had Koplik’s spots or a measles rash or a history of measles with desquamation simultaneous with less specific symptoms. Children reported with measles but not seen in the acute phase were considered to have probable measles if the family reported symptoms of rash, desquamation, cough, and conjunctivitis, and contacts with known infected children. We included both definite and probable cases in the analysis of measles incidence.

We collected blood samples from children in the acute phase of measles and one month later. For children seen only in the second month after measles infection a blood sample was collected for possible confirmation with an IgM antibody test.

During the most intensive months of the outbreak (December 2003 to March 2004) the study doctors were overwhelmed and many cases not seeking care were not seen in the acute phase but identified later through surveillance.

Overall, 905 children were admitted to hospital with measles in Bissau during the outbreak. We obtained sufficient information from the vaccination card to identify study children. Children with measles were followed to ascertain deaths in the acute phase.

The fieldworkers carrying out the surveys were unaware of the vaccination status of the children. The doctor carrying out the clinical examination of suspected cases was asked to avoid looking at the vaccination card before making a diagnosis. At the paediatric ward, the doctors would not look at the vaccination card.

We excluded from the main analysis children with measles within 21 days of enrolment. Likewise, we followed up children to 21 days after the measles vaccination at 9 months of age as this vaccination is unlikely to have prevented infection within that period. We estimated the incidence rate ratio between treated and control children using a Cox proportional hazards model, with time since enrolment as the time variable.

RESULTS

Overall, 1333 children were included in the analysis of the protective effect of early measles vaccination using the Edmonston-Zagreb vaccine; 441 in the group treated at 4.5 months (treatment group) and 892 in the two control groups due to receive the first dose of vaccine at 9 months (see bmj.com).

Baseline characteristics of the children in both arms were similar (see bmj.com). Of the 188 children in the treatment arm tested for maternal antibodies at enrolment, 61% (n=114) had detectable levels but only 28% (n=52) had protective levels. At 9 months
only 5% (21/405) of the control children had protective levels.

Among treated children, 92% (128/139) had a measurable antibody titre compared with 9% (38/405) among control children (relative risk 9.81, 95% confidence interval 7.2 to 13.3); 77% and 5%, respectively, had protective levels (14.9, 9.7 to 22.7).

Overall, 103 children were reported as having measles between enrolment and within three weeks of vaccination at 9 months. After exclusions, 96 children had a diagnosis of measles on the basis of clinical or serological data; 48 (50%) were seen in the acute phase and considered to have definite clinical measles and the remaining 48 had probable measles.

Sixty nine children (72%) had serologically confirmed measles, with a fourfold increase in antibody levels or a positive response with the IgM test. Of the remaining 27 children, eight control children had high IgG antibody levels but were sampled too late to be IgM positive and no adequate sample was collected from 19 children, mainly because of death, admission to hospital, travel, or being seen only after vaccination at age 9 months. Eight of the children with no adequate blood sample had been considered to have clinically definite measles. Hence, 77 children (80%) had a serologically confirmed diagnosis or a clinically definite diagnosis.

The incidence of measles was high; 4.2% (58/1391) of the children had measles before enrolment of whom 33 had serologically confirmed measles. These children were excluded from further analysis (see bmj.com). Among the children in the control group 86 contracted measles (figure). The monthly incidence was 3.1% (95% confidence interval 2.5% to 3.8%) and for children remaining unvaccinated the cumulative incidence reached 14.4% (11.7% to 17.7%) before age 9 months and 19.4% (14.1% to 26.4%) before age 12 months. Ten children in the treatment arm contracted measles (figure). The monthly incidence was 0.7% (0.4% to 1.3%) and the cumulative incidence was 3.1% (1.5% to 6.2%) before 9 months and 6.7% (2.6% to 16.4%) before 12 months. The case fatality for all cases was 8.3% (8/96).

The vaccine efficacy for serologically confirmed cases was 94% (74% to 98%) and for clinically definite cases was 91% (62% to 98%; see bmj.com). When serologically confirmed and clinically definite cases were combined vaccine efficacy was 94% (77% to 99%).

All admissions to hospital were among children in the control arm; vaccine efficacy against admission was 100% (46% to 100%; see bmj.com). Twenty one children in the control arm and eight in the treatment arm were admitted for reasons other than measles.

The seven deaths from measles more than 21 days after enrolment were in the control arm; vaccine efficacy against death was 100% (42% to 100%). From the start of the trial to the end of the measles outbreak, overall mortality was lower in the treatment arm (see bmj.com) although the mortality rate ratio of 0.18 (0.02 to 1.36) was not statistically significant. The treatment group had no more non-measles related deaths than the control group.

DISCUSSION

Standard titre Edmonston-Zagreb measles vaccination at 4.5 months of age in Guinea-Bissau was protective against measles infection and admission to hospital for measles. For children with definite measles, protection was more than 90%. Most of the cases were serologically verified and, even including self reported cases, vaccine efficacy was 80%. The study was too small to document significant protection against measles mortality. Such protection is, however, likely as admission to hospital is a reliable indicator of the severity of infection. Furthermore, overall mortality may have been lower in the treatment group than control group although this was not statistically significant.

The present analysis is an interim report from a large randomised trial so conclusions should be interpreted with caution. It is unlikely that further cases of measles that may modify the estimate of vaccine efficacy will occur before the trial ends.

The most important limitations of the study may relate to lack of blinding of vaccination status among possible cases and to the impossibility of seeing all children in the acute phase of infection. Firstly, surveys to identify cases in the community and the detection of cases at the health centres and the hospital were carried out without reference to the vaccination status. Project doctors were instructed not to look at the vaccination card before diagnosis but we cannot be certain they never looked. Nearly all diagnoses were confirmed in the independent blinded serological analyses. The selection of children from whom blood samples were collected could have been biased. We think this is unlikely as Guinean doctors have often observed measles infection in vaccinated children and are
Mothers immunised against measles transmit low levels of measles antibodies to their offspring
Measles vaccination using standard titre Edmonston-Zagreb vaccine might immunise children before 9 months of age even in the presence of maternal antibodies

In this interim analysis standard titre Edmonston-Zagreb measles vaccination at 4.5 months of age provided more than 90% protection against infection and 100% protection against admission to hospital

Therefore unlikely to be influenced by assumptions. At the paediatric ward, the doctors who admitted the children would not inspect the vaccination card. The hospital data clearly showed good protection from Edmonston-Zagreb measles vaccination at 4.5 months of age. Had the decision to admit a child with possible measles to hospital been biased, we should have seen in the treated group relatively more admissions to hospital for non-measles related reasons and deaths not related to measles. If anything, fewer children in the treated group were admitted to hospital for non-measles related reasons and died.

Secondly, not all children with measles could be seen, partly because infected children may have been travelling. More importantly, the workload during the epidemic made it impossible for clinicians to search out children with mild infection. This could have meant that we identified too few cases, particularly children with milder disease. During the epidemic fieldworkers blinded to randomisation status of the children carried out surveys to identify children with measles. Most of the children with probable measles were identified. We think it unlikely that many cases remained undetected. The incidence of measles was high, with 4.2% of the children having measles before enrolment and an additional 14.4% before 9 months of age in the control arm.

Only 28% of the children had protective antibody levels at enrolment, and the Edmonston-Zagreb vaccine may be able to immunise in the presence of maternal antibodies.11-13 Nearly all of the children vaccine may be able to immunise in the presence of levels at enrolment, and the Edmonston-Zagreb could be used to immunise young household contacts who may have some maternal antibodies but not enough to prevent them from becoming infected when exposed at home.17

Changing antibody profiles of mothers, high birth rates, and rapid urbanisation mean that African cities will be open to major outbreaks of measles should there be problems in maintaining a high vaccination coverage. A reduction in the age of routine measles immunisation and possibly a two dose strategy should be considered.

Given the strongly beneficial effect of the vaccination strategy we tested, it should be possible to recommend the first dose of Edmonston-Zagreb measles vaccine at 4.5 months of age in situations with a high risk of infection before 9 months of age. When control of outbreaks is needed the Edmonston-Zagreb vaccine could be used to immunise young household contacts who may have some maternal antibodies but not enough to prevent them from becoming infected when exposed at home.17

Changing antibody profiles of mothers, high birth rates, and rapid urbanisation mean that African cities will be open to major outbreaks of measles should there be problems in maintaining a high vaccination coverage. A reduction in the age of routine measles immunisation and possibly a two dose strategy should be considered.

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Competing interests: None declared.

Ethical approval: The protocol was approved by the Danish central ethical committee, the Gambia/Medical Research Council scientific and ethics committees, and the Guinean Ministry of Health's research coordination committee. Participants had access to free consultations at the local health centres and to essential drugs free of charge.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Open access publishing, article downloads, and citations: randomised controlled trial

Philip M Davis,1 Bruce V Lewenstein,1 Daniel H Simon,2 James G Booth,3 Mathew J L Connolly4

ABSTRACT
Objective To measure the effect of free access to the scientific literature on article downloads and citations.

Design Randomised controlled trial.

Setting 11 journals published by the American Physiological Society.

Participants 1619 research articles and reviews.

Main outcome measures Article readership (measured as downloads of full text, PDFs, and abstracts) and number of unique visitors (internet protocol addresses). Citations to articles were gathered from the Institute for Scientific Information after one year.

Interventions Random assignment on online publication of articles published in 11 scientific journals to open access (treatment) or subscription access (control).

Results Articles assigned to open access were associated with 89% more full text downloads (95% confidence interval 76% to 103%), 42% more PDF downloads (32% to 52%), and 23% more unique visitors (16% to 30%), but 24% fewer abstract downloads (~29% to ~19%) than subscription access articles in the first six months after publication. Open access articles were no more likely to be cited than subscription access articles in the first year after publication. Fifty nine per cent of open access articles (146 of 247) were cited nine to 12 months after publication compared with 63% (859 of 1372) of subscription access articles. Logistic and negative binomial regression analysis of article citation counts confirmed no citation advantage for open access articles.

Conclusions Open access publishing may reach more readers than subscription access publishing. No evidence was found of a citation advantage for open access articles in the first year after publication. The citation advantage from open access reported widely in the literature may be an artefact of other causes.

INTRODUCTION
In 2001 it was first reported that freely available online science proceedings garnered more than three times the average number of citations received by print articles.1 This “citation advantage” has since been validated in other disciplines. The primary explanation for this advantage is that freely available articles are cited more because they are read more than articles available by subscription only.

Some argue that open access articles are cited more because authors selectively choose articles to promote freely, or because highly cited authors disproportionately choose open access.2-5 This has been termed the self selection postulate.6 Self archiving an accepted manuscript in a subject based digital repository may provide additional time for these articles to be cited.6,5 A study of medical journals reported that the probability of an article being found on a non-publisher website was correlated with the impact factor of the journal.6 We carried out a randomised controlled experiment to measure the effect of free access to the scientific literature on article downloads and article citations from a journal publisher’s websites.

METHODS
From January to April 2007 we randomly assigned 247 research articles and reviews published in 11 journals of the American Physiological Society to open access status upon online publication (see bmj.com). The control group (1372 articles) was composed of subscription only articles.

We measured four different proxies for article readership: abstract downloads, full text downloads, PDF downloads, and unique internet protocol addresses. We also tested the effect of publisher defined open access on article citations (odds of being cited in year after publication and number of citations for each article).

Each month after publication we gathered usage statistics from the publisher’s websites. HighWire Press, the online host for the American Physiological Society’s journals, was able to provide reports on article downloads including and excluding internet robots. Article metadata (attributes of the article) and
citations were provided by the Institute for Scientific Information’s Web of Science database. We carried out a search algorithm to identify as many instances of self archiving on the internet as possible.

**Statistical analysis**

We used linear regression to estimate the effect of open access on article downloads and unique visitors. Our outcome measures were downloads of abstracts, full text, and PDFs, and the number of unique internet protocol addresses (number of visitors). We log transformed these variables because of known skewness. Our principal explanatory variable was open access. We controlled for three influences on downloads: self archiving, being featured on a front cover, and being press released by the journal. We also controlled for article type, number of authors, authors based in the United States, number of references, length of article (pages), and journal impact factor. As articles are published within issues we nested the issue variable within the journal variable.

On 2 January 2008 we retrieved the number of article citations from the Web of Science. As our trial included articles published at different times (January to April 2007), we used a numerical indicator for each issue.

We estimated the effect of open access on citation counts using a negative binomial regression model with the same set of explanatory variables as described. This model is appropriate for count data and can work with over-dispersion in data.

Finally, we used a logistic regression model to estimate the effect of open access on the odds of being cited, with the same set of explanatory variables employed in the download and negative binomial regression citation model.

**RESULTS**

The figure shows the effect of open access on article downloads and unique visitors in the first six months after publication. Full text downloads were 89% higher (95% confidence interval 76% to 103%), PDF downloads 42% higher (32% to 52%), and unique visitors 23% higher (16% to 30%) for open access articles than for subscription access articles. Viewing of abstracts was 24% lower (−29% to −19%, P<0.001 for all) for open access articles.

For open access articles, known internet robots could account for an additional 83% full text downloads, 5% additional PDF downloads, 4% additional unique visitors, and a 12% reduction of abstract downloads.

Regression analysis showed that several characteristics of articles had as much, or more, of an effect on article downloads as free access (see bmj.com). Having an article press released by the publisher increased PDF downloads by 65% (7% to 156%), and having an article featured on the front cover increased PDF downloads by 64% (21% to 121%). Longer articles, articles with more references, and those published in journals with higher impact factors had significantly more downloads.

Twenty instances of self archiving were identified—18 were final copies from the publisher and two were final manuscripts. The estimated effect of self archiving was positive on PDF downloads although non-significant (6%, −6% to 19%; P=0.36) and essentially zero for full text downloads (−1%, −23% to 27%; P=0.95).

Of the 247 articles randomly assigned to open access status, 59% (n=146) were cited after 9-12 months compared with 63% (859 of 1372) of subscription access articles.

The negative binomial regression model estimated that open access reduced expected citation counts by 5% (incident rate ratio 0.95, 95% confidence interval 0.81 to 1.10; P=0.484), and that self archiving reduced expected counts by 10% (0.90, 0.53 to 1.55; P=0.716, see bmj.com).

A supplementary logistic regression analysis based on the same set of variables estimated that open access publishing reduced the expected odds of being cited by about 13% (odds ratio 0.87, 95% confidence interval 0.66 to 1.17; P=0.36, see http://hdl.handle.net/1813/11049), although this effect was not statistically significant.

**DISCUSSION**

Strong evidence suggests that open access increases the readership of articles but has no effect on the number of citations in the first year after publication. These findings were based on a randomised controlled trial of 11 journals published by the American Physiological Society.

Although we missed citation activity that occurred after these initial months, we believe that our timeframe was sufficient to detect a citation advantage, if one exists.

Previous studies have relied on retrospective and uncontrolled methods to study the effects of open access. As a result they may have confused causes and
WHAT IS ALREADY KNOWN ON THIS TOPIC

Studies suggest that open access articles are cited more often than subscription access ones. These claims have not been validated in a randomised controlled trial.

WHAT THIS STUDY ADDS

Open access articles received more downloads but exhibited no increase in citations in the year after publication. Open access publishing may reach more readers than subscription access publishing. The citation advantage of open access may be an artefact of other causes.

effects or been unable to control for unmeasured variables.

Our finding that open access does not result in more citations suggests that the citation advantage may be an artefact of other explanations such as self selection.

To contribute meaningfully to the scientific literature access to resources as well as to the relevant literature are needed. These two requirements are highly associated and concentrated among the elite research institutions worldwide. That we observed an increase in readership and visitors to open access articles but no citation advantage suggests that the increase in readership is taking place outside the community of core authors.

The increase in full text downloads for open access articles in the first six months after publication (figure) suggests that the primary benefit to the non-subscriber community is in browsing, as opposed to printing or saving, which would have been indicated by a commensurate increase in PDF downloads. The fact that internet robots were responsible for much of the initial increase in full text downloads (83%) compared with PDF downloads (5%) implies that internet search engines are helping to direct non-subscribers to free journal content.

The discussion over access and its effects on citation behaviour assumes that articles are read before they are cited. Studies on the propagation of citation errors suggest that many citations are merely copied from other articles. Given the common behaviour of citing from the abstract (normally available for free), the act of citation does not necessarily depend on access to the article. Secondly, the rhetorical dichotomy of “open” access compared with “closed” access does not recognise the degree of sharing that takes place among an informal network of authors, libraries, and readers.

Our citation counts are limited to those journals indexed by Web of Science. Because this database focuses on the core journals in a particular discipline, we missed citations in articles published in peripheral journals.

We measured the number of unique internet protocol addresses as a proxy for the number of visitors to an article. We implied that the difference in number of visitors between open access and subscription based articles represents the size of the non-subscriber population. A more direct method of calculating access by non-subscribers would be to analyse the transaction logs of the publisher and to compare the internet protocol addresses from subscribing institutions with the total list of addresses. Because of confidentiality issues we did not have access to the transaction logs.

Open access articles on the American Physiological Society’s journals website are indicated by an open green lock on the table of contents page. These may signal something about the quality of the article to potential readers and therefore created a positive bias on download counts.

Finally, we do not understand whether providing open access to articles had any effect on the behaviour of authors as they promoted their work. We are carrying out similar randomised experiments with other journals where authors and readers are unaware of the access status of articles.

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1 Lawrence S. Free online availability substantially increases a paper’s impact. Nature 2001;411:521.

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