Human papillomavirus vaccination in the UK
Is projected to be beneficial and cost effective

This September, the Department of Health in the United Kingdom will begin a national programme of routine human papillomavirus immunisation of 12-13 year old schoolgirls, coupled with a two year catch-up campaign for those up to the age of 18 in 2009. The selected bivalent vaccine, Cervarix, protects against two of the most common human papillomavirus types that cause cervical cancer (types 16 and 18), whereas an available quadrivalent vaccine, Gardasil, also protects against two non-oncogenic types that cause genital warts (types 6 and 11). The linked study by Jit and colleagues from the Health Protection Agency describes the mathematical modelling approach and results used to inform the Department of Health’s decision.

Mathematical models are used to synthesise multiple data sources, to extrapolate short term clinical findings into long term outcomes of population level benefits and cost effectiveness, and to investigate the influence of uncertainties about data and alternative scenarios. The authors develop a dynamic model that reflects the sexual transmission of human papillomavirus infections (types 6, 11, 16, 18, and other high risk types). The model captures the direct benefits to girls who receive the vaccine and the indirect benefits to those who are not vaccinated, as a result of the reduced prevalence of human papillomavirus in the population—so called herd immunity. Unlike most other model based studies of human papillomavirus and cervical cancer, the authors analyse thousands of scenarios in which epidemiological and economic dimensions are varied simultaneously, which allows them to evaluate the uncertainty more comprehensively.

The model projects the effect of human papillomavirus vaccination on cervical dysplasia, squamous cell carcinoma and adenocarcinoma, as well as genital warts in men and women. Because of the uncertainty about the efficacy of the vaccine for other health conditions, the effect on non-cervical cancers associated with human papillomavirus is estimated separately and included in a secondary analysis.

Assuming a willingness to pay threshold of £30 000 (€37 000; $59 600) per quality adjusted life year (QALY) gained, Jit and colleagues find that vaccinating 12 year old girls against human papillomavirus is cost effective in the context of current screening practice in the UK, when vaccine uptake is high (≥80%) and as long as protection lasts longer than 10 years. This result is consistent with most other model based analyses under similar assumptions of vaccine efficacy, longevity, and coverage in settings with organised screening programmes. Not surprisingly, the probability of this strategy being cost effective increases under optimistic scenarios of vaccine duration, efficacy against non-cervical cancers, and cross protective effects.

Their results also indicate that a two year catch-up campaign for females up to age 18 would be cost effective. Because sexual activity—and therefore risk of previous exposure to vaccine targeted human papillomavirus infections—increases with age, studies have found that the health benefits of vaccination past the age of 18 are marginal; however, the optimal upper age limit for a catch-up programme has varied from 18 to 25. Jit and colleagues also conclude that including 12 year old boys in the immunisation programme is unlikely to be cost effective when compared with vaccinating girls only. Conflicting results of including boys have been reported previously, with cost effectiveness ratios ranging from £45 100 to £442 000 per QALY gained. Because data on vaccine efficacy in boys are not yet available, all studies have relied on assumptions that will need to be revisited when empirical data become available from trials. Model attributes and assumptions that may contribute to variations in results across different studies are discussed in several reviews.

One of the study’s unique contributions is a cost threshold analysis that compares the bivalent and quadrivalent vaccines. Because the quadrivalent vaccine protects against genital warts caused by human papillomavirus types 6 and 11, to be equally cost effective the bivalent vaccine must be less expensive—the authors estimate that the bivalent vaccine must be £13 to £21 less expensive per dose than the current price of the quadrivalent vaccine. Assuming 80% coverage of current 12 year old girls in the UK with the full three dose vaccine series, this price differential translates to savings of £11.5m to £18.6m from the vaccine price alone in the first year of the programme, compared with adopting the quadrivalent vaccine. The decision to select the bivalent vaccine implies that the Department of Health is willing to accept forgone health benefits (and additional cost savings) from averting cases of genital warts for the reduced financial outlay, which may be allocated to other priority investments in health.

Despite the study’s findings, several important questions need to be considered. For example, the authors assume that coverage of 80% is achievable and vary this value within a limited range only. Although a study in the BMJ reported encouraging uptake rates of first and second doses of vaccine in schoolgirls, the uptake rate...
for the full three dose series is unknown, and this will affect the magnitude of direct and indirect benefits. Also, an important finding from that study was that uptake was lower in girls from minority groups and from less affluent backgrounds. The extent to which these girls receive less screening in adulthood—and consequently face a higher incidence of cervical cancer—will influence the overall success of the vaccination programme and may widen disparities in the risk of developing cervical cancer among socioeconomic groups. Although Jit and colleagues include a small subgroup of women who are unscreened, their model does not accommodate further heterogeneities in screening behaviour in women to explore this matter more thoroughly. Other analyses have reported that the cost effectiveness of human papillomavirus vaccination is compromised when vaccination uptake is higher in women who are screened frequently in adulthood, suggesting that equitable access to the vaccine should be a priority.10 11

Furthermore, because nearly a third of cases of cervical cancer are attributable to non-vaccine human papillomavirus types, cervical screening will continue to be a vital component of cancer prevention efforts in the UK. Several analyses have shown that human papillomavirus vaccination is more cost effective when followed by less frequent screening, starting at later ages and with newer screening technology, such as testing for human papillomavirus DNA.10 11 Although the current model cannot look at changes in screening practice, alternative policies that efficiently synergise vaccination with screening should be considered and evaluated carefully. Policy decisions that are being made now will continue to benefit from model based analyses that aim to synthesise the best available data, as long as model inputs and assumptions are iteratively revised as new information becomes available. It may be decades before we see the true effect of human papillomavirus vaccination on cervical cancer, even though most studies indicate that vaccinating adolescent girls will provide benefit and be cost effective; Jit and colleagues’ study shows that this is likely to be the case even in the context of current screening practice in the UK. Better data on the natural history of human papillomavirus and the properties of the vaccine are needed to generate a similar consensus on other policy questions involving catch-up age limits and including boys in the immunisation programme.


Open access to research
Increases readership but not citations

This week the BMJ publishes a paper that has nothing directly to do with medicine or health care.1 It does, however, have everything to do with access to research results, a topic that should interest authors and readers in any field. The paper asks whether open access (free full text online publication) increases the chances of an article being read and cited compared with subscription access publication (where articles are accessible only to individuals or institutions who pay to subscribe).

It is a question that many have asked and tried to answer since academics first challenged the subscription based publishing model over 10 years ago. Open access offered an end to what they saw as profit-seeking by publishers at the expense of the academic community. It restored a public good. If it could also offer higher usage and citation rates, this was icing on the cake. Authors who submitted their work to open access journals might be rewarded with greater visibility, and publishers who launched open access titles or converted existing ones to open access might see their usage figures and impact factors rise.

Studies in various disciplines have explored this possibility.2 Most have found a correlation between usage and citation rates, as well as a citation advantage from open access. However, all of these have been retrospective observational studies. In what is, to the best of our knowledge, the first randomised trial of open access, Davis and colleagues sampled papers due for publication in a group of physiology journals and randomly allocated them to either open access or subscription access publication. They found significantly...
higher online usage of open access articles, but no significant difference in citation rates between the two groups in the first year after publication.\(^1\)

The study suggests that previous findings of a citation advantage from open access may have been the result of self selection, with more highly citable articles being more likely to be published in open access journals. Indeed, a previous study of medical journals found that the higher the impact factor of the journal in which an article was published, the more likely it was that the article would be available on a non-publisher website.\(^2\) Davis and colleagues’ finding that open access provided no citation advantage, despite increased readership, may be explained by the fact that journal readers who generate citations already have subscription access to journals.

The study confirms that open access articles reach audiences that subscription based access does not reach. Interestingly, it also found that abstracts were downloaded less often when the full text was freely available. Of course, we don’t know whether this means that people are more likely to read the full text rather than just the abstract, but it raises the potential for an additional scientific advantage of open access—that readers and authors are able, should they wish, to build their ideas on a whole article rather than just the summary.

Can these findings be generalised to medicine? It is hard to see why not. However, one difference between medicine and physiology is the wider press coverage given to medical research. We know that press coverage increases citations.\(^3\) If open access increases press coverage, as some have suggested because of the convenience to journalists of being able to access the full text, it is possible that open access could lead to an increase in citations to medical research.

The BMJ’s own experiment with free or open access publishing of research is now 10 years old and going strong, although as with all experiments it remains under evaluation. In 1998, the BMJ was the first major general medical journal to provide free full text online access to its articles from the moment of publication, to deposit the full text in PubMed Central, and to allow authors of research articles to retain copyright. Access controls were introduced for non-research content in 2006 to protect subscription revenue and to allow us to continue providing the research content free. Since then, the BMJ Group has extended its open access experiment by introducing BMJ Unlock (http://adc.bmj.com/info/unlocked.dil), which allows authors submitting research to any of the group’s 19 specialist research journals to pay an author fee in order to make their work open access. (The BMJ itself does not charge author fees.) We have also now made changes to our copyright licence and the information we include in the research articles so that they can be formally listed as open access articles in PubMed Central and other repositories.

Academic publishing is going through interesting times. We don’t know which model will prevail, or indeed whether there will ultimately be one or several coexisting models. Three things may precipitate a move towards greater openness of access—the demand from funding agencies, such as the US National Institutes of Health and the Wellcome Trust, that grant recipients must self archive or publish in open access journals;\(^3\) the new Food and Drug Administration (FDA) Amendment Act, which requires trialists seeking FDA approval to deposit their main results in clinicaltrials.gov within 12 months of recruiting the last participant;\(^5\) and the rapidly expanding and unpredictable influence of web 2.0 on the way we all communicate.

If greater openness is the future, as it almost certainly is, the academic and publishing communities have some decisions to make. What sort of quality control do we want in the 21st century and how do we fund it? Do we need the current level of peer review and technical editing before dissemination or could medicine move to the physics archive model—dissemination followed by selection for peer reviewed publication (http://arxiv.org/)? How would such a model play in a world in which the media are hungry for new medical breakthroughs, and where manipulation of data and overinterpretation of results is rife? Should quality control continue to be funded largely through subscriptions or can author charges take the strain, either alone as at BioMed Central or with the help of charitable support, as at the Public Library of Science? If funders and institutions support greater access to research results, should they also fund the quality control? Where then would people look for independent verification? Should peer review be centralised and professionalised rather than run by individual journals?

These are questions that reach to the very heart of the way in which scientists and clinicians communicate. Much will depend in the short to medium term on whether publishers are able to make online usage profitable through advertising rather than subscriptions, whether author charges prove to be a sustainable model, how much pressure is brought to bear by funders and institutions for greater access, and whether the FDA Amendment Act leads to legislation in other countries and beyond randomised trials. These questions also reach to the heart of how academics are acknowledged and rewarded. Hit rates and online profile may soon become as or more important than citations. Whatever the mix of communication models that emerges over the next few years, we need to make sure that science and health care are well served.

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Providing information for patients
Is insufficient on its own to improve clinical outcomes

Patients consistently report wanting more, and better, information about their health, health care, and treatment options. Providing this information is challenging. One approach is coaching patients to ask questions during consultations. In the linked study, Kinnersley and colleagues report a systematic review which shows that this approach has relatively little effect.¹ So what is the underlying rationale for improving health information for patients, and what interventions are likely to work?

Some people argue that improving patient information and educating patients about their health problems is ethically essential and needs no further justification.² Others point to the benefits of patient education, in terms of improved self care,³ enhanced patient satisfaction,⁴ improved health status,⁵ and reduced healthcare expenditure.⁶ Improving clinical outcomes, however, needs more than just information—it requires a partnership between patients and their health professionals, with the patient actively engaged in self care.

People living with long term conditions face three challenges: medical management, emotional management, and role management.⁷ Most health professionals focus on medical management, which includes monitoring symptoms, changing health behaviours (such as eating a healthier diet, taking more exercise, taking drugs regularly), and working with health professionals. For the patient, emotional management—dealing with the emotional consequences of having a long term condition, which include anger, guilt, despair, and frustration—can be equally challenging and equally important for quality of life. Role management—coming to terms with a change in life role (for example, from “healthy” to “sick” or from “provider” to “cared for,” with the connotation of “burden”) is also a substantial challenge.⁷

Information is a prerequisite for dealing with these challenges, but it is not enough to overcome them. Changes in behaviour, emotional and social support, and help in making decisions are also needed. Clinicians, commissioners, and policy makers who want to help patients engage in self care face two challenges: firstly, how to provide patients with accurate, up to date, comprehensible information at a time and place that meets their needs; and secondly, how to meet these other needs which are equally important, and, if anything, even harder to deliver. The complexity of these needs may go some way to explaining why simple interventions, such as leaflets or coaching, seem to have little effect.¹ ⁸

What does work? The English Department of Health has invested considerable effort in investigating and promoting self care.⁹ One of the best known initiatives is the expert patient programme, based on the chronic disease self management programme designed in Stanford. The expert patient programme consists of six group sessions, facilitated by a lay leader, and aims to enhance the self efficacy (a person’s belief in their own ability to manage their health problem) of participants in managing their health. This, and other similar programmes, have a positive effect on participants’ self efficacy, but with a disappointingly small effect on health outcomes, quality of life, and healthcare use.¹⁰ Moreover, programmes that require attendance at groups will inevitably exclude people who have difficulty attending, such as those who work, have caring commitments, or have mobility problems.

An alternative may be internet delivered health interventions. Such interventions can present almost unlimited health information in an accessible and comprehensible format, by using video clips and visual images. They can combine high quality evidence based health information with interactive services such as support for changing behaviour, decision support, emotional support, and computerised cognitive behavioural therapy.

For people with home internet access, internet delivered treatments are convenient and accessible. Moreover, with the rapid convergence of digital technology, such interventions will be available from mobile phones and digital television, which between them have almost universal population coverage in the developed world. Emotional support can be provided through online electronic support groups or by provision of “personal stories” or illness narratives (for example, DIPEX; www.dipex.org).

Cognitive behavioural therapy delivered through the internet is effective in helping patients manage several long term physical and mental health problems, such as pain, headache, tinnitus, depression, and anxiety.¹¹ Support for behavioural change—with formal self assessment exercises, goal setting, self monitoring, and feedback—may help with adopting healthier dietary and exercise behaviours. Although considerably more research is needed on how such interventions work, who they work for, and for what conditions, preliminary data suggest they can be effective under some conditions.¹¹

Finally, given that the balance of power in the doctor-patient relationship lies firmly with the doctor, perhaps we should be looking at ways to enhance patient centred medicine. Although Kinnersley and colleagues found no additional effect of interventions—including training clinicians to answer patient’s questions—some data suggest that making consultations more patient centred can improve patient satisfaction and possibly health outcomes.¹² Whether current moves towards polyclinics, with the potential loss of continuity of care and disruption of an ongoing doctor-patient relationship in general practice, will promote or impede patient centredness remains to be seen.
Early vaccination against measles in developing countries

May improve control of measles but cannot replace doses given at 9-15 months

Before vaccination, measles was ubiquitous and caused many deaths in children under 5 years. Routine vaccination in high-income countries since the 1960s has successfully controlled measles. In low-income countries, measles vaccination was included in the World Health Organization’s expanded immunization programme since 1974. Interruption of measles transmission has been documented in most countries of the Americas, and the recent increase in vaccination coverage in Africa has been followed by an estimated 75% decline in annual mortality over the past decade. However, the disease remains an important and unacceptable cause of death in Africa and South Asia.

In the linked randomised controlled trial, Martins and colleagues assess the protective efficacy of vaccination at 4.5 months in infants during an outbreak in Guinea-Bissau. In most nations, vaccination strategies are based on the provision of a first dose at age 9–15 months and either a second scheduled dose or a subsequent dose administrated through mass campaigns. Susceptible infants may also be protected indirectly from 6–15 months. The duration of protection depends on several factors. Maternal antibodies also neutralise vaccine virus, contributing to this protection. Moreover, as measles virus is immunosuppressive, it is imperative to ensure that antibodies developed from other concurrently administered vaccines are not suppressed.

The current goal to achieve high vaccine coverage should not be separated from the need for more timely vaccination, especially in developing countries. In developing countries, earlier vaccination strategies could be considered—but may mean that a higher proportion of children fail to respond initially. To minimise...
Doctors’ complicity with torture
It is time for sanctions

Steven H Miles

It is an arresting thought. More doctors abet torture than treat the millions of victims. More than 100 countries condone the use of torture. A third to a half of torture survivors report that a doctor oversaw the abuse.1 Many prisoners never see the doctors who refined the techniques to minimise evidential scars, prolong pain, or cause psychological destruction.2 Estimates of the numbers of torture victims do not include people whose murders disappear when a doctor writes “natural causes” on a death certificate.

The medical profession ought to dissociate itself from torture—a practice that destroys institutions of civil society; that is used against colleagues of conscience, and that has far reaching adverse mental, physical, and social consequences. Instead, medical societies and licensing boards offer lofty condemnation, which is most ardently aimed at offenders abroad rather than accomplices at home.

Doctors who abet torture rarely face professional risks. Governments will not punish a doctor for helping them carry out their crimes. Few medical societies or licensing boards have the courage and constancy of vision to investigate or censure colleagues who carry out the law of the land. In principle, medical societies support ethics codes like the World Medical Association’s Declaration of Tokyo, which bars doctors from complying with torture. In practice, they sustain the policy of impunity.3

The exceptions are instructive. The Nuremberg trial of Nazi doctors for war crimes was the birth of bioethics. That admirable court was convened by victors over defendants from a vanquished nation. But it is the wrong place to look for solutions to the common problem of doctors complying with torture. The problem today is to their harm or injustice, I will protect them.” Governments will use regimens for the benefit of the ill but from what of vigilance in the Hippocratic oath acknowledges that medical staff. A civilian medical community that acquiesces to torture by its military members cannot credibly protest against foreign doctors who carry out torture. Such a community can hardly support doctors who are endangered for their resistance against torture. The prestige and values of medicine make it a crucial part of the campaign to abolish torture.

“I will guard my art and my life.” That pivotal promise of vigilance in the Hippocratic oath acknowledges that medical professionalism is not an easy virtue. Diverse enticements lure doctors from the core of medicine: “I will use regimens for the benefit of the ill but from what is to their harm or injustice, I will protect them.” Governments that practice torture need doctors. The medical accomplices of torture must not rest in the confidence that they can violate civil society and the ethics of medicine with impunity.

All references are on bmj.com

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