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HPV vaccination—reaping the rewards of the appliance of science

National programmes could virtually eliminate certain diseases and substantially reduce costs

Simon Barton clinical director, Department of Sexual Health and HIV, Chelsea and Westminster Foundation Trust, London SW10 9TH, UK
simon.barton@chelwest.nhs.uk
Colm O'Mahony consultant in sexual health and HIV, Countess of Chester NHS Trust, Chester, UK

The optimism generated by scientific breakthroughs often turns to disappointment when applied to the real world of clinical care. It is therefore worth celebrating the extraordinary success of Australia's national human papillomavirus (HPV) vaccination programme, which was implemented five years ago. In a linked paper, Ali and colleagues analyse data on 85 770 new patients from six Australian sexual health clinics revealing a remarkable reduction in the proportion of women under 21 years of age presenting with genital warts—from 11.5% in 2007 to 0.85% in 2011 (P<0.001).[1] Only 13 cases of genital warts were diagnosed in women under the age of 21 across all six health clinics in 2011. Such a reduction in this distressing disease caused by a sexually transmitted virus is a major public health achievement. The near eradication of genital warts in young Australian women will probably have a major impact on the costs of sexual healthcare.

In 2007, Australia became one of the first countries to implement a nationally funded HPV vaccination programme for girls and young women with the quadrivalent vaccine. It started with the vaccination of girls aged 12 years in schools and a catch-up programme for girls and women aged 13-26 years. Quadrivalent vaccine protects against HPV types 6 and 11, which cause more than 90% of genital warts, in addition to HPV types 16 and 18, which cause cervical cancer. Vaccination coverage rates were exemplary, averaging almost 80% for all three doses.

Ali and colleagues also found a significant decline in the proportion of women aged 21-30 years presenting with genital warts—from 11.3% in 2007 to 3.1% in 2011 (P<0.001). As might be expected, the rate of diagnoses of genital warts in women over 30 did not drop. The proportion of men under 21 years presenting with genital warts also decreased sharply, from 12.1% in 2007 to 2.2% in 2011 (P<0.001). From 2007 to 2011, there was no significant decrease in the prevalence of genital warts in heterosexual men over 21 years or in men who have sex with men.

DR P MARAZZI/SPL

Australia achieved good vaccine coverage

In the United Kingdom, policy makers chose a bivalent HPV vaccine (effective against HPV types 16 and 18) for the national vaccination programme. This was judged the best option on economic grounds—economic analyses during the tendering process found that the bivalent vaccine was substantially cheaper than the quadrivalent one. At the time, there was much debate about whether the benefits of preventing genital warts had been properly assessed, given the current high rate of new and recurrent genital warts—more than 150 000 cases a year—in the UK, which cost more than £50m (€59m; $76m) to manage.[2] This seemingly short sighted policy decision caused consternation among experts in sexual health services.[3 4] However, in September 2012, the UK national programme began to use the quadrivalent vaccine. Given Ali and colleagues' findings, the number of young women presenting with genital warts to sexual health services should drop substantially in five to nine years' time, reducing the workload in sexual health clinics.

What about including boys in the national vaccination programme in the UK? In 2013 the Australian government began a publicly funded HPV vaccination programme for 12-13 year old boys, with a catch-up for 14-15 year old boys. This decision was prompted by two important considerations. The first was the increasing incidence of HPV related oropharyngeal cancers in men.[5] The second was the realisation that young men who have sex with men, who would not benefit from heterosexual herd immunity, would be unfairly discriminated against under a vaccination programme targeted only at girls. Ali and colleagues state that, in addition to helping prevent genital warts and anal, penile, and oropharyngeal cancers in men, "the vaccination programme is expected to increase herd immunity and provide further indirect protection to unvaccinated women." They comment that this may lead to control, if not elimination, of the target HPV types in Australia.[1]

Throughout Europe, there has been regional tendering to use quadrivalent or bivalent vaccines in young women only. Doctors in sexual health would obviously favour the quadrivalent vaccine because new and recurrent genital warts are the most common sexually transmitted diseases managed in clinics.

It remains to be seen whether we will see similar dramatic reductions in HPV-16 and HPV-18 associated diseases, such as cervical cancer, vulval cancer, other anogenital cancers, and head and neck tumours as a result of national vaccination programmes. This is likely given the reported evidence for the efficacy of the vaccines. It is hoped that future vaccines will protect against other HPV types, such as types 31 and 45, which are also involved in the genesis of genital cancer. Countries should carefully explore whether it is economically feasible to vaccinate young men.

Do HPV vaccines have a role to play in treatment? It is scientifically plausible that they do, because wart virus infection and recurrence are caused by failure of immune recognition. The immunity induced by vaccination is four or five times greater than that induced by natural infection. Recent treatment studies indicate benefit.[6 7]

These are exciting times in the science of HPV and the world can confidently look forward to the virtual elimination of genital warts, recurrent laryngeal papilloma, most genital cancers, and some 60% of head and neck cancers. The interruption of transmission of a major sexually transmitted infection through a public health initiative offers the prospect of substantial cost savings. Countries should consider these data seriously and act decisively.

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RESEARCH, p 10

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Research: Evaluation of the national Cleanyourhands campaign to reduce *Staphylococcus aureus* bacteraemia and *Clostridium difficile* infection in hospitals in England and Wales by improved hand hygiene (*BMJ* 2012;344:e3005)

Keeping hand hygiene high on the patient safety agenda

WHO's call to action reminds us that "patients have a voice too"

Sheldon Stone senior lecturer, Royal Free Campus, University College London Medical School, London NW3 2PF, UK s.stone@medsch.ucl.ac.uk
Graziella Kontowski founder of *Clostridium difficile* support group , Clostridium Difficile Support Group, London, UK www.cdiff-support.co.uk
Rose Gallagher nurse adviser, infection prevention and control, Royal College of Nursing, London, UK
Julie Storr president, Infection Prevention Society, Bathgate, UK
Louise Teare consultant microbiologist and infection control doctor, Broomfield Hospital, Chelmsford, UK

The World Health Organization's annual global hand hygiene day was on 5 May (www.who.int/gpsc/5may/en). The day offered participating hospitals tools to improve hand hygiene and supported WHO's first global patient safety challenge, launched in 2005 to reduce the global burden of healthcare associated infection through sustained improvements in hand hygiene. By 5 May last year, 130 countries had registered with WHO's "save lives: clean your hands" initiative (www.who.int/gpsc/5may/background/en). This year the number is 170. WHO's call to action for 5 May 2013 asked hospitals to "continue to focus on hand hygiene monitoring and feedback" and reminded them that "patients have a voice too." This reminder has particular resonance for the English NHS in light of recent events where patient safety had low priority, even though England and Wales were the first, in December 2004, to roll out a national Cleanyourhands campaign.[1]

Research published in the *BMJ* a year ago showed that the Cleanyourhands campaign, coordinated by the National Patient Safety Agency, was highly successful.[2] The study found strong independent associations between procurement of alcohol hand rub and soap and declining rates of meticillin resistant *Staphylococcus aureus* and *Clostridium difficile*. The hand hygiene intervention now offered to countries through the WHO save lives initiative is similar.

The campaign's external reference group advised the National Patient Safety Agency that the Cleanyourhands campaign should continue but change focus to concentrate on techniques of hand hygiene audit and feedback, in a prescient echo of the current call to action by WHO. However, the government closed the campaign in December 2010. Worried that the gains from the campaign might be lost, members of the reference group formed the Independent Alliance of Patients and Health Care Workers for Hand Hygiene (www.idrn.org/alliance.php).[3] The alliance aims to ensure that a high standard of hand hygiene, based on the best available evidence, continues to be observed by all healthcare workers. It plans to achieve this through working with the agencies that emerge in the newly configured NHS for commissioning, regulation, and education. Responding to a letter from WHO expressing concern at the campaign's closure, the then health minister wrote: "Hand hygiene is now an established part of clinical care." The alliance does not agree. Although audits by ward staff regularly report compliance levels of 90% or more, independent audits conducted by infection control teams commonly show compliance rates of 30-40%.

ARNO MASSEE/SPL

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The evidence base regarding what works in terms of monitoring, audit, feedback, and improvement of hand hygiene compliance has grown considerably in the past few years. WHO has made a big contribution through its "five moments tool," its technical guides for hand hygiene observation,[4] and its multimodal hand hygiene intervention, as has the six year programme of research funded in the United Kingdom by the now defunct Patient Safety Research Programme. Hand hygiene observation tools are now robustly standardised,[5] we know how long an observer should observe for,[6] and evidence from a randomised controlled trial shows that coupling audit and feedback to a repeating cycle of personalised action planning improves hand hygiene significantly.[7] We also know that hospitals use different hand hygiene observation tools, few of which are standardised or have detailed standard operating procedures, and that hand hygiene deteriorates if gloves are worn.[8]

The technique of hand hygiene observation has to be taught. This was recognised by the Cleanyourhands campaign's expert reference group, which suggested that observation of technique should form the focus of a renewed campaign. Correct observation requires several hours training, as does the technique of effective feedback (www.idrn.org/nosec.php).[7] However, bedside observation is labour intensive and does not record compliance at all times. Electronic alternatives such as video recording and direct feedback are available and require exploration alongside technical means to overcome problems of privacy, dignity, and data protection.[9]

Hand hygiene is the most basic of all patient safety interventions. Three years after closure of the Cleanyourhands campaign we still need to ensure that hand hygiene really is "an established part of clinical care." On 8 May the hand hygiene alliance will meet NHS England, the Care Quality Commission, National Institute for Health and Care Excellence, and other agencies responsible for patient safety in the NHS to explore future partnerships, using hand hygiene as an exemplar of how to work together to achieve a common vision of patient safety. One patient representative says of hand hygiene, "It's such an easy thing to do, why isn't it done?" The answer is that it is not as easy as it seems. Initiatives like the annual global hand hygiene day keep hand hygiene high on the patient safety agenda and enable its advocates, including patients, to make their voices heard.

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A core group has worked with a large number of outside organisations to look carefully at the Helsinki Declaration and to restructure and rewrite it

Editorial: Fresh thinking about the Declaration of Helsinki (*BMJ* 2008;337:a2128)

Revising the Declaration of Helsinki

Your chance to influence research governance

Vivienne Nathanson director of professional activities, BMA, London WC1H 9JP, UK, VNathanson@bma.org.uk

In the middle of the 20th century, the Nuremberg trials laid bare the abuse of medical knowledge and techniques used in human experimentation, with perhaps the most famous offender being Joseph Mengele. The outcomes of the trials included the Nuremberg Code—a legal document intended to stop such abuses—and the establishment of the World Medical Association (WMA). Both were intended to ensure that doctors never again performed such inhuman experiments.

Over the next two decades the newly formed WMA began to put together a core set of policies, designed to reflect ethical thinking, to which doctors were expected to conform. The Declaration of Helsinki, published in 1964,[1] set out rules and limits for human experimentation based on the findings of the Nuremberg trials and an unshakeable conviction that human experimental subjects have fundamental rights that drive a series of duties for the experimenter. Key to its development and adoption was that it was essentially written by doctors for doctors.

Since then, the declaration has been incorporated into national laws in several countries and has been a touchstone for researchers. It has not remained static; changes have been made on eight occasions. Another revision is now under way, and a draft document is currently open for comments for the next month.[2]

The WMA committees, council, and member associations have often struggled to find clear, simple ways to express complex concepts, including the need for balancing rights and duties. An example is finding an ethical solution to what happens to a research subject who benefits from a new drug when a trial is over.

For the past two years a core group has worked with a large number of outside organisations to look carefully at the Helsinki Declaration and to restructure and rewrite it. The aim is to make it clearer, to remove elements seen as mutually contradictory, and to cover some areas previously left undiscussed.

Seven key elements have emerged from discussions. They are: the structure of the declaration, vulnerable groups, post-study arrangements for study participants, research ethics committees, compensation for research subjects, biobanks, and how often the declaration should be amended in the future.

Debate on a revised version of the declaration took place at the recent WMA council, and this has now been published for comments by interested parties. Comments will be taken into account and a revised version considered at an assembly meeting in October.

Most usefully, an annotated version of the draft revision is available for review on the WMA website.[2] It explains what the authors hope their changes have achieved. Some—such as the addition of the words "and wellbeing" to doctors' duties—are intended to reflect the broader emphasis of modern medicine and the essentially holistic nature of "doctoring." Throughout, the use of the words "must" and "should" has been carefully considered; the first is an absolute and the second a strong steer that recognises the existence of exceptions. The text is, for the first time, divided by a series of subheadings clarifying the focus of different sections.

The report's approach to vulnerable populations, a historically sensitive area, is worthy of mention. Specific groups are not mentioned as they were in previous documents. Instead, the current draft leaves readers to consider the circumstances that might make a group particularly vulnerable and the special protection that should apply. It goes on to emphasise that research on vulnerable people should be carried out only if the same answers cannot be obtained another way, and that the vulnerable group should stand to benefit from the research.

The working group has also suggested substantial changes to the section on research ethics committees, recognising that such committees vary in calibre. The group recommends that these committees must receive a report from the researchers containing a summary of the study's findings and conclusions. What should happen to that report? Should it become part of the transparency processes now seen as essential in medical research? And what should or must the committee do if such a report does not arrive?

Changes to a single paragraph on biobanks make it clear that research on materials or on routinely collected data also requires consent except in exceptional situations or when this would be impossible or impracticable. For some, who call for specific informed consent by all subjects in all cases, this will seem too weak. Others will think that consent is not needed in these circumstances and the placing of material or data in a research repository or biobank is, in itself, sufficient to allow its use for ethical research.

The use of placebos has long been a contentious area. The revised draft tries to clarify when they may be used, while keeping as the central point the need to protect the health and wellbeing of the research subject.

Some items remain unchanged, such as a paragraph stating that doctors who both treat and carry out research on patients must have good reason to believe that participation in the research will not adversely affect their patients' health. But no researcher can know all the risks before doing the research. They cannot know if the research protocol will be beneficial or harmful—if they do, then the research is unnecessary and hence unethical. Some patients might benefit, whereas others may do less well than on a standard treatment. Some patients may be harmed, or even killed. Certainly, researchers must do everything possible to consider the likelihood of benefit and harm, but they cannot know for sure until the research is carried out.

The final version of the new revision of the Helsinki Declaration will depend on the final analysis of the committees, council, and assembly of the WMA. They will take into account all comments submitted by all interested parties—be they researchers, research subjects, lay groups, or healthcare practitioners. Comments should be submitted by 15 June 2013.

Competing interests: I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: I have represented the BMA at the WMA. However, although I have accompanied the current BMA representative to WMA meetings on occasion, I have not been involved in the working group that has debated the revision of the Declaration of Helsinki.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 World Medical Association. WMA Declaration of Helsinki—ethical principles for medical research involving human subjects. www.wma.net/en/30publications/10policies/b3/index.html.
2 World Medical Association. DoH public consultation 2013. www.wma.net/en/20activities/10ethics/10helsinki/15publicconsult/index.html.

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The European Medicines Agency's plans for sharing data from clinical trials

The agency must press on, despite legal challenge

Trish Groves deputy editor, *BMJ*, London WC1H 9JR, UK
tgroves@bmj.com
Fiona Godlee editor in chief, *BMJ*, London WC1H 9JR, UK

A bold plan by the European Medicines Agency (EMA) to prospectively release anonymised clinical trial data on drugs has suffered a potentially serious setback. Cases brought by biopharmaceutical companies AbbVie and InterMune have led to an interim ruling from the General Court of the European Union ordering the agency not to release relevant documents on request until final judgment has been made.[1 2] It is not yet clear whether this interim ruling will derail the agency's much wider plan to publicly release the anonymised patient level trial data on all drugs it approves from January 2014.[3] If the final judgment does block this plan, a great opportunity to complete the evidence base on drugs and to improve human health will have been lost.[4] The risk to the public interest and to patients has prompted the *BMJ* and the BMA to join forces in support of the EMA. The two organisations are requesting leave from the court to intervene in the case brought by AbbVie.

Getting full access to data from trials of drugs and medical devices is not, as some who oppose the move suggest, primarily about trying to uncover misconduct or encourage patients to seek recompense for harms, although these actions may sometimes be necessary and valuable. Nor are calls for open clinical trial data simply academic. The main reasons for sharing full clinical trial data are scientific and ethical, with the interests of prescribers and patients at their heart.[5] Alex Lomas is a patient taking Humira (adalimumab), the drug that AbbVie doesn't want scrutinised through data access requests to the EMA. In a personal view in the *BMJ*, he says "With such a new drug, it is vital that all data, whether it's good news or bad, are made available so that I, my consultant, and the care commissioning group can make informed decisions about the efficacy and cost effectiveness of treatments . . . This decision by AbbVie is a backwards step and is offensive to trial participants, patients, and the wider public who ultimately pick up the tab."[6]

The wider debate . . . has moved on from "shall we support data sharing?" to "how shall we do it?"

AbbVie's legal challenge, arguing that the patient level data requested "did not meaningfully contribute to the scientific review or evaluation of our products," may reflect the prevailing view across industry, despite worthy words about supporting greater transparency. But some companies are breaking ranks. Medtronic has allowed complete and unconditional release of individual patient level data relating to one of its recombinant bone morphogenetic protein-2 products, and the results of an independent analysis by academics at Yale University will be published next month.[7]

Furthermore, GSK says it will go ahead and share data despite the court ruling.[8] The company says it will post detailed clinical study reports on its open clinical trial register (www.gsk-clinicalstudyregister.com/) for all of its future drugs "once they have been approved or discontinued from development and the results have been published." It will also gradually release such reports for all its global studies back to 2000 when GSK formed. In addition, it is setting up a secure platform and an "independent review panel" to allow access to patient level data and study documents on request: vital details that will be redacted from the clinical study reports. The full details of the plan, including the members of the panel, will be released shortly.[9] Sceptics point out that, so far, drug companies have not delivered the transparency that they have promised. For example, negotiations over access to the data on GSK's antiviral drug zanamivir (Relenza) are continuing but, over the past four years, the company has yielded no more analysable data than have been delivered by the much maligned Roche for its drug oseltamivir (Tamiflu) (www.bmj.com/open-data).

However slow the progress with industry is, and whatever the EU court's final ruling, there's still room for optimism, given the head of steam that is now driving data sharing. The wider debate among governments, research funders and investigators, systematic reviewers and other academics, some parts of the drug industry, and—most importantly, many patients' groups—has moved on from "shall we support data sharing?" to "how shall we do it?"[10] Much of the credit for this has to go to the AllTrials campaign—its petition calling for all clinical trials to be registered and all results reported (through release of clinical study reports and anonymised patient level data) has garnered more than 50 000 signatures in less than six months.[11] More than 250 organisations have signed up too, including more than 100 patient advocacy groups, although only one drug company, GSK, has signed and as yet no industry representative body has done so. Last month the Geisel School of Medicine at Dartmouth College in the United States joined the campaign and pledged to lead efforts to enlist all US medical schools and patient groups to add their support to the AllTrials campaign. And the Institute of Medicine has announced that it will take up the challenge of working out how data should be shared.[12]

The *BMJ* was one of the cofounders of AllTrials. This was a natural extension of our work in publishing original research and investigative journalism exposing the extent and implications of selectively reporting and withholding clinical trial data (www.bmj.com/open-data). We will continue to build the case, to campaign for access to data, and to provide evidence to the UK government and the European Parliament on the need for such open science.[13 14] Meanwhile, we will explore the "how" of data sharing at a high level seminar hosted by the *BMJ* on 14 June.

We already encourage authors of all *BMJ* papers to share their datasets publicly through Dryad (http://datadryad.org) or other online repositories, and we specifically require authors reporting drug and devices trials in the journal to commit to sharing anonymised patient level data (whether publicly or not) on reasonable request.[15] But researchers need to know that they are sharing the data in the most ethical, useful, and valid ways. Over the next few months the *BMJ* will explore the practicalities and challenges of data sharing, not least by scrutinising the newly published recommendations of the EMA's advisory groups on five key concerns. These concerns are: protecting patients' privacy, formatting clinical trial data to facilitate sharing and reuse, rules of engagement between the agency and those accessing the data, good practice in secondary analysis of the data, and legal considerations.[16]

Most importantly, the EMA will consider appealing against the court's interim ruling. And meanwhile it will press on with examining the advisory group's recommendations and formulating and consulting on its policy by the end of November 2013. It will continue to consider single requests for access to data, through which it has released more than 1.9 million pages since November 2010, though not into the public domain. And it will make internal changes that recognise that "the EMA is increasingly a central data and knowledge hub for the European medicines network as a whole" and which reinforce that "data held by the agency will be increasingly shared with partners and stakeholders."[17] We urge *BMJ* readers, where appropriate, to respond to and support the EMA's plans, and to join the AllTrials campaign.

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