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Challenges Ahead for Cervical Cancer Screening

The introduction of vaccination programmes against human papillomaviruses (HPV) will precipitate widespread changes to cervical cancer screening programmes, say Icelandic researchers. The vaccine protects against type 16/18 HPV and is expected to prevent the majority of cases of cervical cancer, but its impact will be far from straightforward, and have wider implications for the cost, organisation, and technology used in screening programmes.

In an interview with *EJC News*, Dr. Kristján Sigurðsson (Icelandic Cancer Society, Reykjavik, Iceland) stressed that vaccination will not remove the need for cytology screening, because some invasive cancers are not linked to types 16/18 HPV. The overall costs of vaccination and screening will inevitably increase, and it will take 10–20 years before the decrease in prevalence begins to be felt. Furthermore, the cost of the vaccine itself is likely to stay constant for the foreseeable future since new vaccines which protect against more strains of HPV are likely to replace those becoming available now.

Vaccination programmes targeting girls of about 12 years old are expected to be set up, as the vaccines are most effective if given before girls become sexually active. But politicians will need to be convinced of future benefits. Dr. Sigurðsson said, "It's a very good opportunity for cost-effectiveness analyses to show politicians what will happen."

At the recent HPV Masterclass Europe (Madrid 30–31 January 2007), it was reported that German insurance companies, which cover the bulk of healthcare costs in the country, are willing to pay for vaccination, not only of these very young girls, but also for a catch-up programme for those up to 16 years or even older. "The reasoning was that, in time, this will decrease the cost of treatment. It's an interesting point of view from private companies," Dr. Sigurðsson said.

In the US, enthusiasm is so great that Michigan senate passed a bill in September 2006 to make HPV vaccination of 11–12 year old girls mandatory. The move was applauded in the UK by *The Lancet*, which urged EU member states to do the same, and, further, said that trials in boys are urgently needed (*Editorial* 2006;**368**:1212).

"RUSHED INTRODUCTION OF VACCINATION WILL LEAVE WOMEN LESS PROTECTED THAN NOW"

The view is not universally accepted. Dr. Sigurðsson said, "HPV 16/18 vaccines will undoubtedly be a blessing in countries unable to accomplish an effective cytological screening program but health authorities in countries with well established organized screening programs or planning to start such screening should carefully evaluate implications of future vaccination programs with HPV 16/18 vaccines". A letter in response to the Lancet editorial (*Lancet* 2007;**369**:367–8) went further. "Countries with high mortality and no screening can achieve major gain from vaccination. But rushed introduction in Europe will worsen HPV-related illness by undermining existing screening and leaving women less protected than now," it stated.

If large scale vaccination programmes are to be implemented, the coverage achieved will be crucial for success. Initial fears that parents may object – on the grounds that vaccination could encourage promiscuous behaviour – may be unfounded. A recent study by Cancer Research UK (*doi:10.1016/j.vaccine.2007.01.059*) found that three-quarters of mothers said they would probably or definitely accept the HPV vaccine for their daughter.

"This suggests that a school-based programme of vaccination is likely to find approval among parents", said lead author Professor Jane Wardle, adding that "The study showed no evidence that parents from less affluent backgrounds were any less enthusiastic about the vaccine."

The clinical impact of the vaccine will remain unknown in advance of large-scale vaccination programmes. Dr. Sigurðsson: "The pharmaceutical companies have said that the vaccines will decrease the incidence of invasive disease by 70–75%, but we can't conclude that. We can say that vaccination will decrease invasive disease by 60%, because types 16/18 are found as a single HPV infection in 60% of cases. But we don't know what will happen in multi-infection cases when types 16/18 are eradicated. Studies suggest that replacement by other types is unlikely, but only time will show whether this is true."

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Challenges Ahead for Cervical Cancer Screening (*Continued*)

The decrease in invasive disease and pre-invasive lesions is clearly welcome from a clinical point of view, but it poses a problem for existing screening programmes. A reduction in the prevalence of the disease will decrease the predictive value of cytological screening. There will be more false positives and negatives and it may become necessary to revamp screening programmes – with further cost implications. In a recent EJC paper (*doi.10.1016/ejca. 2006.11. 017*), Dr. Sigurðsson said, "The decreased prevalence of abnormal smears may decrease the alertness of the cytoscreeners, thus stimulating the incorporation of more expensive screening techniques. This will decrease the cost effectiveness of the screening and press decision makers to change the age limits and lengthen the screening intervals."

The new screening techniques would include HPV testing in place of the smear test, with the smear reserved for those testing positive for HPV. This approach is considered too expensive at present in Iceland and many other countries.

Any doubts about the efficacy of screening come at a difficult time for the programme as young women appear increasingly reluctant to participate. Figures from the UK's National Health Service (NHS) Cancer Screening Programme, show that the number of 25–29 year old women who attended for screening in 2005–6 was 69%; down from 79% in 1995–6. The same trend was seen among those aged 30–34: in 2005–6, 78% took up the offer of a test compared with 84% ten years earlier.

The introduction of HPV vaccination could further reduce participation. "It will be very important to educate individuals about the fact that it is not a complete vaccine," Dr. Sigurðsson said. "It is very important that vaccinated women continue to attend screening as before."

The age at which screening starts is also being debated. International guidelines recommend that screening should start at age 25 with 3–5 year intervals. The cost effectiveness of screening women under 25 has been criticised due to the high prevalence of low-grade smears at that age, most of which will regress spontaneously. But Dr. Sigurðsson argues that it is rational to start screening at age 20, as has been the practice in Iceland in 1988.

These women are often difficult to reach due to pregnancy, travel and so on. It takes time to reach optimal attendance levels and it is better to start at age 20 so that these levels can be reached by age 25.

"The contraindications of over-diagnosis and over-treatment can be counterbalanced by observing lower grade lesions to see whether they regress."

Others agree that screening should start before age 25. A letter to the *British Medical Journal* (*BMJ* 2007;**334**:273) notes that in the UK, screening has reduced cervical cancer incidence and mortality by more than 40% since it was centrally organised in 1988, despite increased risk of disease.

The letter states: "The new policy [not to screen women aged 20–24] will add more than 3000 women with untreated CIN3 (carcinoma in situ) to the larger numbers failing to accept their invitations later on." Any degree of CIN may regress, but invasive cervical cancer "can develop within a couple of years of missed high-grade cytology, failure to investigate cytological abnormalities, or incomplete treatment, emphasising the importance of treating high-grade CIN when it is found."

Key questions need to be answered before changes are made to the screening programme as a response to HPV vaccination, Dr. Sigurðsson said. Researchers in countries with national cancer and screening registries need to combine descriptive data on trends in invasive and pre-invasive diseases in the pre-vaccine era, with data on the age-specific distribution of HPV types in these lesions (types 16/18 versus other types). They need to look at the cumulative frequency of cases caused by different HPV types after the last normal smear.

"This information will help us to decide whether we can change the lower age limit and lengthen the screening interval after implementation of the HPV 16/18 vaccines," he said.

EU Law on Medicines for Children

An EU ruling which should improve children's access to cancer treatments has come into force. The paediatric regulation (EC no 1901/2006) obliges companies to explore the potential use of new drugs in children.

Pharmaceutical research involving children has often been overlooked by companies because of the small market, the challenges of undertaking trials in children and the high development costs. The new legislation offers incentives in the form of patent extensions to companies that undertake this research.

The move was welcomed by Dr. Bruce Morland, head of the Children's Cancer and Leukaemia Group (CCLG), and chair of the Innovative Therapies for Children with Cancer (ITCC), a network of research laboratories and clinical centres across Europe. "This news is very encouraging for children with cancer across Europe."

"These children will now have earlier access to many more potential treatments. The new law enables new medicines to be tested in pan-European large-scale clinical trials across Europe to find out which treatments are best, and make improvements in childhood cancer survival rates," he said.

At present, children are given scaled-down doses of medication designed for adults – doses that may not have gone through full clinical trials. Scientists now will be able to test potential new medicines on experimental models of children's cancers; clinicians and pharmaceutical companies will be able to design appropriate clinical trials in an effort to improve treatments.

''CHILDREN WILL HAVE EARLIER ACCESS TO MORE TREATMENTS''

Dr. Sally Burtles, director of Cancer Research UK's drug development office said, "Childhood cancers are very different from adult tumours so specialist knowledge from groups such as the ITCC and CCLG is crucial in order for advances to be made. This new law presents a massive boost to drug discovery programmes across Europe and will encourage further collaboration between pharmaceutical companies and childhood cancer experts."

EUROFILE

Drug Costs: How Much is Too Much?

With prices of cancer medicines reaching record heights, how can society decide what is value for money and what is not? At a time when healthcare budgets are limited, making an expensive drug freely available to patients inevitably means cutting back in other areas. But who should make the choice of what to allow and what not? These were among the questions posed at a recent conference in Brussels organised by Cancer World magazine (Saving Lives in Cancer, 21–22 November, 2006).

Philippe Swennen represented the International Association of Mutual Benefit Societies (AIM), Brussels, Belgium – a federation of social health insurers in EU member states and Switzerland. He said that it was time for a sea change in drug pricing policies. More effort is needed to reduce the major differences in access to healthcare and cancer services at national and even at regional level within European countries, and one of the major problems is the lack of transparency on drug prices by pharmaceutical companies, he said.

Drug pricing is a heavily veiled secret at present. Although companies seem happy to tell the world how expensive developing a new medicine is, they frequently include marketing and other expenditure on top of the money spent on research, development and production. It appears that companies can charge what they want for new products, leaving no-one any the wiser as to their profit margin.

''IT IS TIME TO TACKLE EXORBITANT PRICES''

Given the increase in the number of new drugs coming on to the market, said Swennen, it was time to tackle their 'exorbitant' prices. "A new cancer drug should be really innovative, giving additional therapeutic value in comparison with existing treatments, and also be cost effective", he said. "The high prices are no longer sustainable. Medicines are not just ordinary goods; there are questions of ethics and fairness in access to medicines. The only way we can reach a win-win situation for all is to revise prices."

But how can this be done? Pharmaceutical companies are bound to be resistant to suggestions of change to a system which has seen them become among the most profitable of all industry sectors. Patients will not accept governments telling them that there just isn't enough money to pay for new treatments. Doctors will feel frustrated reading about therapies that they are not allowed to prescribe.

And at what price do you save a life? One of the problems with new drugs is that, early on at least, it is often hard to find out just how effective they are compared with existing treatments. The only way to deal with this conundrum is through a major rethink of the system, says Swennen. "We all accept that patients should get the best possible treatment, but too often these days they are asking for new drugs on the basis of less than objective information. Pharmaceutical companies are putting more and more money into marketing their products, and it's only normal that people, having heard about product X which is claimed to be 100% better than product Y, should want to have it. But there is little independent drug information available to those who need it the most." In addition, he said, the pharmaceutical industry should disclose all information on clinical trials and pharmacovigilance.

The AIM is pushing for an EU logo, which would give the stamp of approval to objective and independent information on medicines. "At the moment there is too much confusion between public health and commercial interests", he says. "We believe that the European Parliament and Council took the right decision in 2004 when they rejected a proposal that would have allowed the pharmaceutical industry to provide information directly to patients, as is the situation in the US." The proposal for an EU 'trust mark' for independent drug information, should hopefully be discussed at the June 2007 meeting of the steering committee of the European Commission's pharmaceutical forum, composed by health ministers and other representatives, and its acceptance would be a valuable asset to both healthcare providers and patients, says the AIM.

But even if this comes into being, it will not help the drug pricing problem. Price should be related to value for money; in other words the therapeutic benefit of the medicine and its cost effectiveness. Relative effectiveness of a product should be assessed to ensure that patients get good value compared with other possible treatments. Non-inferiority trials with the best standard therapy as the reference product should be carried out. "Only in this way can we really establish the innovative character of new medicines", says Swennen. "We need to look at finding new ways of rewarding pharmaceutical innovation. This could be a medical innovation prize fund, for example."

''WE NEED INDEPENDENT, UNBIASED AND OBJECTIVE INFORMATION''

This is clearly a difficult political debate in which a wide range of players need to be involved. If budgets are limited and new drugs are allowed within a healthcare system, which older ones should be disallowed in order for this to be able to happen? "This needs a transparent debate, open to civil society, and not just to governments and pharmaceutical companies", says Swennen. "At the end of the day we need full transparency and the availability of independent, unbiased and objective information about new drugs in order to allow us to make such decisions, and currently this is not always available in the time required."

Mary Rice
Brussels

New Head of Cancer Research UK

Mr. Harpal Kumar

Mr. Harpal Kumar has been appointed to succeed Professor Alex Markham as Cancer Research UK's new chief executive. Professor Markham stepped down late in 2006 in order to return to full-time academic and clinical work at the University of Leeds, UK.

Mr. Kumar was chief operating officer of Cancer Research UK and chief executive of the charity's subsidiary Cancer Research Technology.

''I'M PASSIONATE ABOUT OUR VISION TO BEAT CANCER''

He was previously chief executive of the disability charity, The Papworth Trust, and of the Nexan Group, a venture capital-backed medical devices company.

He holds a degree in chemical engineering from University of Cambridge, UK, and an MBA from Harvard Business School, USA. He worked for 4 years as a management consultant.

Mr. Kumar said, "I'm delighted and honoured to be appointed chief executive of Cancer Research UK. I'm passionate about our vision to beat cancer and the ambitious goals we are setting ourselves for the future. This is perhaps the most exciting period in the last fifty years in terms of our rapidly improving understanding of cancer and the progress we are making in beating it."

Workplace Smoking 'May Double Lung Cancer Risk'

A meta-analysis from the International Agency for Research on Cancer (IARC) has shown, for the first time, a clear dose-response between exposure to co-workers' smoke, and risk of lung cancer. Highly exposed workers had a two-fold increased risk.

The review included 22 studies and 4305 cases of lung cancer in various work settings. It strengthens the previous IARC Monograph (Tobacco smoke and involuntary smoking), published in 2004, which classed involuntary exposure to tobacco as a group 1 carcinogen.

The meta-analysis is published as a smoking ban is introduced in France. The ban covers public places including workplaces unless measures such as specific smoking rooms are in place. Restaurants, bars, tobacconists, casinos and nightclubs have until January 1, 2008, to implement the ban.

"For many years, authorities have been following a policy of identifying occupational exposures which increase the risk of human cancer and taking legislative action to eliminate or reduce such exposures to a minimum," said Dr. Paolo Boffetta, a senior epidemiologist at IARC. "Environmental tobacco smoke is an occupational hazard and exposure to workers can, and should, be eliminated."

Launch of Obesity Charter

The European Charter on Counteracting Obesity was launched in Copenhagen on 20th February, 2007. The Charter was officially adopted by Member States of the World Health Organization (WHO) European Region in November 2006, at the European Ministerial Conference in Istanbul, turkey (*see EJC News, EJC* 2007 **43**:1).

The Charter states that: "Visible progress, especially relating to children and adolescents, should be achievable in most countries in the next 4–5 years and it should be possible to reverse the trend by 2015 at the latest."

Key areas of action include reducing marketing pressure, particularly towards children; promoting breast feeding; reducing free sugars, fat and salt in manufactured products; adequate labelling of foods; promoting cycling and walking through better urban design and transport policies.

Speaking at the launch, Crown Princess Mary of Denmark, Patron of the WHO Regional Office for Europe, said, "I hope that the action it produces will serve as a turning point to adapt the environment we live in and ultimately enable everyone in the WHO European Region to make healthy choices."

More information about the charter can be found at www.euro.who.int/obesity.

My Doctor Right or Wrong?

A group of oncologists 20 years ago foresaw the improvements in cancer outcomes – but were wide of the mark in pinpointing which treatments would be responsible.

A study commissioned by Bristol-Myers in 1986 asked 227 clinical scientists to predict the state of medicine in the early 21st century. They estimated that the average cure rate for all types of cancer was about 50% at the time. Their estimates for the year 2000 ranged from no change to 90%, with a median of 65%. Currently the US' Centers for Disease Control estimated that the overall 5 year survival rate for adults with cancer is 65%.

They distinguished between tumours for which survival would improve (haematological malignancies and breast, prostate and ovarian cancers), and those for which it would not (lung, liver, stomach, pancreas, brain). "The only big improvement they missed was in colorectal cancer", the article stated (BMJ 2006;**333**:1311–13).

The scientists anticipated that improvements would come from biological response modifiers, monoclonal antibodies, "magic bullet" drug-antibody conjugates, cytokines, and anti-angiogenic agents. However, improvements in the main have been for more prosaic reasons: earlier diagnosis, better surgery and radiotherapy, hormonal and cytotoxic chemotherapy, and better supportive care.

The article concludes: "In short, oncologists in 1986 were remarkably accurate in predicting improvements in overall and tumour-specific survival, but for entirely the wrong reasons."

PODIUM

Coordination, Not Harmonisation

Evert-Ben van Veen

Evert-Ben van Veen specialises in medical law and drew up the legal framework for the Tubafrost project, which involves the exchange of tissue and data across borders. He devised the "coordinating rule" – a fast and simple alternative to harmonisation – for Tubafrost as a solution to the problems caused by the variation in regulations in the countries involved. (See EJC 2006;42:2914–23).

What is the coordinating rule?

It states that investigators must operate by the rules in force in the country where the sample was taken, and where the patient lives. This applies even if the investigator is working in a country with different regulations. It means that all patients are protected by the laws in place in their own country.

So an innovative project required innovative law?

This approach has already been tried in European law. In many treaties and negotiations we accept each other's rules in this way. But it is a relatively new approach in medical research. In this field, everyone has assumed we need to harmonise the rules of different countries, but if you step back and think, you may decide that perhaps we don't need harmonisation at all, but rather, respect for one another's rules.

Are there specific features of Tubafrost which make this approach appropriate?

It is similar to other research projects involving cross-border collaboration; the difference is in its budget. Tubafrost was originally funded within the EU's 5th Framework Programme, and later taken up by the Organisation of European Cancer Institutes (OECI) with a limited budget. We had to find the most pragmatic solution. I came up with the coordinating rule, which is much faster and simpler than harmonisation.

So necessity was the mother of invention?

This pragmatic solution presupposes that participating countries have organised systems in which basic human rights are respected. It would not work otherwise. But in Europe, the rules in each country do not differ too much, nor do they in the US, Canada or Australia, for example and research collaborations could use the coordinating rule. But if the tissue came from a country where unethical practices were commonplace, so that tissue might be taken from prisoners, for example, the system could not work.

What are the advantages and disadvantages of harmonisation?

There are only disadvantages, it doesn't work in ethics. If you try to harmonise ethics, differences between countries remain. Furthermore, if you do this using nonbinding Codes of Conduct or recommendations, the resulting 'harmonised' pseudo-legislation is usually a compilation of the most restrictive practices in the countries involved. National systems are not challenged and the strictest legislation comes into force. This is the only way harmonisation can work because otherwise researchers in the country with the strictest system would be unable to be involved; they could not follow harmonised rules that were less strict than the law in their own country. This tendency to level up can be seen in various international projects at present. Many large projects at the moment have large ethical and legal schemes, which reinvent the wheel. Their so-called "new" rules on 'ownership' of tissue or data protection already exist in most countries. The tendency is not to be pragmatic. I believe we should not invent new rules. We have got enough already.

Does the coordinating rule entail any new rules?

Tubafrost has strict privacy rules, which researchers must adhere to, along with a code of conduct. But each country has privacy legislation so the extra Tubafrost rules are fairly basic and merely outline good research conduct.

The coordinating rule makes research much more straightforward for the clinicians involved as they are only subject to the rules where they and their patients are based. They don't have to learn rules specific to this project. Each country is responsible for its own researchers' proper conduct. It's a bottom-up approach, with no central authority.

Are there wider implications within the medical research field?

I believe so. Elsewhere in cancer research, a project proposed by ESTRO is using the coordinating rule, but this has a different set up from Tubafrost: a central database, and central control of research projects. A surveillance network for infectious diseases is also using the coordinating rule.

But we proposed the coordinating rule for research with residual tissue of patients, a fairly limited subject within the range of possibilities of tissue research. Where certain countries prohibit certain activities, like the use of foetal tissue for research, the coordinating rule does not apply.

How has the coordinating rule been received?

We have only recently published it and, thus far, comments have been encouraging. I've heard no objections which may be a good sign in that everybody is happy, or conversely, a bad sign meaning that nobody is taking it seriously.

The main question is whether national supervisory authorities will accept it. Within Tubafrost, it has been accepted without problem, but we will only know for sure once people are working with it.