



Testing times



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WHAT WILL THE NEW HPV VACCINE MEAN FOR THE FUTURE OF CYTOLOGY? KATE WOODS REPORTS.

There is no denying it. The advent of the prophylactic human papillomavirus (HPV) vaccine has been one of the most exciting recent developments in medicine.

It promises to prevent more than 90% of genital warts, eliminate at least 70% of cervical cancers and save the lives of up to 300 Australian women each year.

And with the vaccine now part of the National Immunisation Program Schedule and therefore more affordable for a significant number of women, these predictions could become reality before too long.

But while there are undoubted national advantages to an HPV vaccine, it's not all good news for cytology. If the mood among cytopathologists is a little more reserved, it's because this latest development has thrown up some tricky issues regarding the future of their discipline.

The Pap smear process of course involves the role of scientists working as cytology screeners, as well as cytopathologists trained in anatomical pathology.

When a sample is taken from the cervix and placed on a slide, the cells are viewed by cytology screeners, who detect any abnormalities and refer them on to the cytopathologist for review and a final diagnosis.

An existing shortage of cytopathologists however, could be compounded in this new landscape, according to one of the vaccine's developers Professor Ian Frazer.

A weakening of expertise among established cytopathologists and cytology screeners and the potential for laboratory performance measures to become outdated once the vaccine's impact starts to be felt, are other hurdles to be cleared, he says.

Same work, just different

"The vaccine won't alter the screening program for cervical cancer because firstly, most of the people vaccinated will be young women and the screening program is aimed at women aged over 20 years," Professor Frazer says.

"Secondly, the vaccine only protects against 70% of the strains that cause cervical cancer, so even in a vaccinated population, screening will still be needed."

But while the workload will remain constant – the same number of Pap smears will still cross the desk – Professor Frazer says that the chances a smear will be abnormal will be significantly reduced.

In fact, he predicts that over the next 8–10 years there will be a 75% drop in the number of abnormal smears, and 50% of these will be high-grade abnormalities.

As a consequence, the National Pathology Accreditation Advisory Council's performance measures – which outline the number of abnormalities laboratories and pathologists are required to see over a set period of time – will need to be revised, he says.

Dr Marion Saville, director of the Victorian Cytology Service, agrees. She says full-time screeners currently see about 200 Pap tests each week, of which one is generally a high-grade abnormality. But if the prevalence of high-grade abnormalities falls by 50%, she says this figure would drop to one a fortnight.

"There will also be a reduction in the positive predictive value of these high-



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grade reports purely on the basis of reduced prevalence,” she adds.

Dr Gabriele Medley, head of cytopathology at Melbourne Pathology

and a member of the RCPA Cytopathology Advisory Committee, says whether the standards need to be revised will depend on whether there are eventually fewer labs

around the country performing gynaecological cytopathology.

“If we end up having fewer laboratories doing more smears because of the cost of the machines and the shortage of cytopathologists and cytoscreeners, the current [NPAAC measures] would be fine,” she says.

“But if the current laboratory structure is to persist then yes, they may need to be revised.”

Dr Saville warns a drop in abnormalities could lead to further workforce shortages, with lecturers already seeing some reluctance from science students to choose cytology as a major area of study.

“Informally we believe this is due to the publicity about the vaccine and students’ belief that this skill will not be relevant for the entirety of their working lives.”

As a result, it’s possible we could see a decline in the capacity to report Pap tests before there is a decline in demand.

To further complicate matters, anatomical pathologist Dr Nick Mulvany believes it will become increasingly difficult for established anatomical pathologists to maintain their expertise in cytopathology over the coming years.

“People need to see a certain volume of material to become and stay good at diagnosing abnormalities. With fewer abnormal cases coming through, I strongly

Prophylactic vaccines: a profile

Up to three-quarters of all sexually active people acquire the human papillomavirus (HPV) at least once during their life, making it the most common sexually transmitted viral infection in the world.

But with two HPV prophylactic vaccines – one already approved for use, the other on its way – experts are hoping this could soon change.

The first vaccine, Gardasil, is a quadrivalent vaccine made up of highly purified ‘virus-like’ particles based on the recombinant capsid protein L1. These particles induce a strong humoral immune response to protect people against HPV types 16 and 18 – which cause 70% of cervical cancers – and types 6 and 11, which account for about 90% of genital warts.

While the vaccine has been shown to be almost 100% effective, duration of protection beyond five years is still unknown.

The second is a bivalent vaccine known as Cervarix. It has not yet been approved for use but manufacturer GlaxoSmithKline says it is hoping for some positive news soon.

While the two vaccines work in a similar manner, Cervarix’s L1 capsid protein was produced using a recombinant baculovirus propagated in insect cells, while Gardasil’s was produced using transgenic yeast.

Cervarix targets HPV types 16 and 18, but may also protect against HPV types 31 and 45, which are responsible for up to 10% of all cervical cancers. If approved, GSK is hoping it will be indicated for women aged 10–55 years.

A number of therapeutic vaccines have also been developed, but most are still undergoing early-phase trials.

suspect it will become more difficult for cytologists to pick them up.”

Then there is the issue of training. “This is a highly subjective field – it’s more subjective than histology and certainly more difficult and more subtle in its interpretations,” says Dr Mulvany, senior anatomical specialist pathologist at the Austin and Mercy Hospital in Melbourne.

“Trying to get consistency from one institution to another is and will become an increasing problem.”

Technological boost

Dr Mulvany suggests the solution may be to introduce liquid-based cytology and automated screening.

ThinPrep and SurePath are the two liquid-based cytology devices currently available in Australia.

Compared to the Pap smear, these tests are easier and quicker to examine because they produce slides containing cells that are evenly distributed in a concentrated area, without obscuring agents such as blood and mucus.

A computer-assisted primary screening system has also been produced for use in association with the tests. Currently being trialled in a number of Australian laboratories, this system locates and displays potential abnormal cells for cytologists to view.

Dr Paul Shield, chief scientist at Sullivan Nicolaides Pathology, says preliminary trial results suggest the automated device provides at least an equivalent level of sensitivity to manual screening, but higher productivity.

If it does prove successful, it could help reduce the problems associated with maintaining expertise and staff shortages.

“This would be a good way to use the technology – use the machines to do the searching and the trained scientists or pathologists to do the interpretation.”

Dr Medley says liquid-based cytology has the added advantage of being able to be used for high-risk (HR) HPV DNA testing.

Unlike the Pap smear (designed to pick up abnormal cell changes in a woman’s cervix), HR HPV DNA testing



looks for evidence of the viruses that cause the abnormal changes.

The federal government’s Medical Services Advisory Committee is expected to review a proposal to fund liquid-based cytology in combination with DNA testing later this year.

Vaccine not the whole answer

While it’s still uncertain whether these tests will become standard practice, Dr Medley says the assumption that cervical cancer – and therefore cervical screening – will disappear with the vaccine is a very simplistic view of the situation.

The vaccine’s duration of protection remains uncertain, and the community has not yet fully accepted the need to immunise all children, she says.

Also, many unvaccinated women remain at risk of developing cervical cancer.

However, if we do move to a system in which cells are assessed using HR HPV DNA testing and are then prescreened by automated technology, there will need to

be financial ‘trade-offs’ because these additions won’t be cheap.

“It may well be that we will need to have a two-tiered screening system where those who have been vaccinated are screened every five years and those who haven’t are screened every three years,” Dr Medley suggests.

“There are many pieces that need to be fitted into this complex jigsaw, and I cannot stress too strongly the importance of dealing with the Cervical Cancer Screening Program as a whole, and not in a piecemeal way.”

In contrast, Dr Saville believes it will be far too complex to introduce two different screening programs.

Instead, she suggests it may be worthwhile moving the age at which all women commence cervical screening to age 25 – after vaccination – and then using the HPV test as the primary screening tool and cytology as a follow-up for those who are HPV positive.

This method is currently being trialled overseas. “The main drawback of this strategy in the current environment is that at 25 years of age about 20% of women can be expected to test positive for high-risk HPV.

“However, if almost all women had been vaccinated, then the proportion of women testing positive to high-risk HPV could be expected to dramatically decline. This will improve the specificity of HPV as a primary screening test.”

Whatever happens though, with a number of new technologies available at a time when vaccination is also to be introduced, all decisions must be evidence-based, Dr Saville argues.

“We should be anticipating the evidence that would be needed to support change and be proactive about trying to get the evidence if it is not already available.”

Dr Medley agrees all changes and introductions need to be evidence based, but says good evidence favouring the new technology is available.

“So far, the reason it has not been taken up is because of the costs, not evidence.” 📌