The proposed change to primary HPV screening in New Zealand: reasons for caution

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It is likely that the National Screening Unit (NSU) will recommend to the Minister of Health that the screening test for cervical cancer should be changed from liquid-based cytology (LBC) to a molecular based human papillomavirus (HPV) test in 2018. However, New Zealand's pathway to primary HPV screening has been very different to countries with similar highly successful cytology-based cervical cancer screening programs. The lack of wide consultation and haste in which this major change in policy is to be introduced is cause for disquiet.

We believe that while primary HPV screening shows promise, particularly in de novo screening programs, implementation in New Zealand in 2018 is premature and wrong. This decision could reduce the current level of cervical cancer protection and increase unnecessary referrals for assessment and treatment. The potential physical and psychological cost to women is unknown. Financial projections suggesting savings for the government are optimistic and the proposed change may cost more. The public sector colposcopy services are currently stressed and unlikely to meet future demand without considerable extra resourcing. All of this uncertainty and transition risk is unnecessary and could be avoided by co-testing with cytology and HPV.

Since 2008, the collection of cervical screening samples in New Zealand has been into a vial of proprietary preservative fluid. This liquid-based solution is suitable for both cytology and molecular (HPV) analysis. Cytology is currently done on all samples. A subset of women with low-grade cytology have HPV testing. Primary HPV screening reverses the sequence with all women having HPV testing and a subset with high-risk virus having additional cytology. Co-testing is when cytology and HPV testing are done together as the screening test.

The UK's NHS has the most similar cytology-based screening program to New Zealand. The NHS has, over a period of many years, kept its stakeholders closely informed about possible changes to cervical screening. In New Zealand, the proposed changes to primary screening were first made publicly known in September 2015 and a public consultation document was produced by the NSU in October 2015.[1] The document favoured primary HPV screening, the authors were not stated, and it contained a number of errors, suggesting that it had been hastily drafted. Stakeholders were given 3 weeks to respond using a template of directed specific questions. The NSU hosted public meetings in October, but the short notice and limited circulation meant overall attendance was poor. The NSU gave no indication as to how stakeholder feedback would be evaluated.

This process marks a significant change from earlier consultation on the development of the screening program in New Zealand, which was extensive, wide-ranging and considered.

Given the inadequate consultation, it is likely that the recommendations forwarded to the Minister of Health will be little changed from the 2015 consultation document.[1] The move to primary HPV testing, as proposed by the NSU, is not merely a simple change of the primary laboratory test, but requires multiple changes to most aspects of cervical screening.

While the recommendation to change to Primary HPV testing is based on a large body of international clinical trial evidence and population-based modelling,[2-8] no data is yet available on primary HPV screening performance in national cervical screening programs. In the UK, large multi-centre pilot studies were set up in 2013 in order to: compare the results of primary HPV screening with liquid-based cervical cytology; assess the safety of proposed follow-up protocols for women testing positive for high-risk HPV; determine whether extending the screening interval to 5-yearly HPV testing is safe; review the change in logistics required to successfully implement primary HPV testing; and check the acceptability of HPV screening to different ethnic groups.[10]

This data is essential to ensure correct decisions are made about if and when to change from a highly successful primary cytology screening program to a primary HPV screening program. In New Zealand, there have been no pilot studies to guide this decision. The NSU "Technical appendix to the public consultation paper" simply noted that:

> *Rather than 'reinventing the wheel', the National Screening Unit is using the considerable knowledge that has been built internationally, and is working closely with the Australian renewal program.*[1]

However, Australia is not the same as New Zealand. Conventional cytology, not semi-automated LBC is the publicly funded screening test.

Simulation models of policy change use trial data and various assumptions about the natural history of the disease detected, test performance outside of the trials, and patient acceptability to estimate the possible outcomes and service demands of changes in screening policy. The population simulated must include all those who are currently being screened and not just a screening naïve group. Simulation models are a poor substitute for actual observations of the effects of screening in practice. Where practicable, health service observations of the effects of potential changes in screening policy are strongly advised.

Despite the large body of research data presented on the topic in the New Zealand consultation document, the safety of HPV testing at extended screening intervals is not certain.[11,12] The clinical trials used to model the safety of primary HPV screening are all largely dependent on CIN3 as an end point to justify screening performance and clinical safety. However, CIN3 only progresses in a subset of patients and is therefore only a surrogate for invasive cancer.[12-14] Therefore, there is great interest in the performance of primary HPV screening to prevent invasive cancers.[15]

The available results are not reassuring. Four large European clinical trials provide much of the data used for modelling primary HPV screening. In these clinical trials, 8 of 19 invasive carcinomas tested were negative for HPV 2.5–8 years prior to the diagnosis of invasive carcinoma—a false negative rate for invasive carcinoma of 42%.[8] Three of the 4 European studies used conventional cytology not LBC, and so their cytology performance is not applicable to New Zealand, where LBC has been the standard since 2008.

In the UK-based ARTISTIC (A Randomised Trial In Screening To Improve Cytology) study, the cytology protection from invasive carcinoma was significantly superior to primary HPV screening. All 5 of the women who developed invasive carcinoma had negative HPV tests at baseline. There were no women with invasive carcinoma in the cytology arm.[8]

Real life performance of HPV screening protection from invasive cancer using extended screening intervals is now beginning to emerge.[16] Baseline HPV test negative rates of up to 40% in invasive carcinoma should raise concerns about the safety of extended screening intervals. There are multiple possible reasons for this lower than expected HPV screening performance, but a significant factor is that even when the complete tumour is available for examination, more than 10 percent cannot be shown to have detectable HPV by current technology.[17-20] The proportion is higher for adenocarcinoma of the cervix.

Questions should also be raised about the low cytology performance in some of the influential clinical trials which conclude HPV is the more accurate screening test. Where LBC cytology is done to high standard, there is no significant difference

between HPV and cytology test sensitivity. The orthodoxy is that HPV must be more sensitive than cytology. This is not true.[21] It depends on the quality of the cytology. The detection of a sexually transmitted infection rather than a significant cytological abnormality is a major change in the aim of screening. This may reduce screening participation. Any reduction in screening coverage will reduce protection from cervical cancer.

Primary HPV screening may harm women through excessive referral to colposcopy and consequent over treatment. HPV screening will detect high-grade squamous intraepithelial lesions (HSIL) earlier, but this will not necessarily reduce overall invasive cancer, as persistent HSIL would have been detected later by cytology before it became invasive.[22] Because the HPV test is less specific than cytology, more women without any identifiable cervical cancer precursor must be sent to colposcopy to find each HSIL. The likelihood of over treatment will be highest in women less than 30 years of age.[23]

Most HPV positive women will have no abnormality on either colposcopy or histology.[23] This will create a new category of HPV positive, but colposcopy negative, women. The risk of developing cervical cancer in these women is low, as most of these HPV-positive tests will represent either transient infections or small non-progressing squamous intra epithelial lesions. Managing these abnormal, but low risk, test results will be difficult for both clinicians and women. Inevitably at some point persisting HPV infection may generate a recommendation to treat the cervix by excision.

There is no debate about whether or not there will be extra colposcopy referral, diagnostic biopsies and treatments as a result of primary HPV compared to current cytology screening. The debate is only around how much extra and whether the New Zealand health service can cope with the increased demand for these services. Without a considerable increase in already stressed colposcopy resources, waiting times for colposcopy are likely to increase considerably when HPV testing is introduced. Because of this, we believe it is possible the primary HPV new screening algorithm may cost the New Zealand Government more than it currently spends on cervical screening.

So how can we do better? First, acknowledge that primary HPV screening creates risk for our well-established, high-quality screening program. Second, recognise that co-testing can safely provide the New Zealand data necessary to address any uncertainty with respect to primary HPV screening cancer protection (sensitivity) and over treatment (specificity). The need to model screening scenarios from overseas clinical trials would no longer exist. The feasibility and acceptability of primary HPV screening for New Zealand women would be established, or not, in a staged process that would allow for full and equal stakeholder participation.

The current haste by the NSU to implement primary HPV screening is difficult to understand. The semi-automated LBC cervical screening test is designed to continue to provide a high level of test accuracy for years to come despite unconvincing suggestions that incomplete national vaccination will undermine test performance in the short term. While the test is robust, the highly skilled workforce required to maintain the cytology service is fragile as a result of the poorly managed NSU change process. Co-testing would stabilise the work force through a well-defined transition period and reduce the risk of early loss of cytology capacity.

We believe, on the evidence available, that co-testing with LBC and HPV is the best way of assessing the contribution of HPV testing to cervical screening in New Zealand and to evaluate its implementation. Recent New Zealand experience with HPV vaccination provides a good example of poor implementation of Ministry of Health policy. The undue haste with which the NSU seeks to introduce primary HPV screening in New Zealand places women at unnecessary risk and may produce a deterioration in the effectiveness of the screening program for the unvaccinated (vast majority) or women with infection with non-vaccination oncogenic HPV types.

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