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Optimising future cervical screening strategies

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A B S T R A C T

The switch from primary cytology to primary high risk papillomavirus (HR-HPV) testing for cervical screening is now being implemented in a number of countries. The advantages of this are to increase screening sensitivity which will save lives, and at the same time to extend screening intervals. The challenge with HR-HPV testing is its relatively poor specificity which means identifying a large number of women who are HR-HPV positive with negative cytology. One way of tackling this is to use early recall, in order to select referral to colposcopy to those women who do not clear the virus over a period of 1-2 years, as done in the recently published English Pilot Study. Another challenge in optimising screening is to recognise that wide coverage with prophylactic vaccination will require fewer screens over the lifetime of vaccinated women to maintain cost-effectiveness. HR-HPV testing allows self sampling which could both encourage more women to be screened and be more convenient for those who do wish to be screened. Cervical cancer prevention which combines vaccination and screening now offers a future in which cervical cancer could become a rarity, but efficient strategies need to be implemented.

1. Introduction

Since the 1960's, exfoliative cervical cytology has been used to screen for underlying cervical intraepithelial neoplasia, and has been universally regarded as a cost-effective means of reducing both the incidence and death rate of cervical cancer. Two pivotal scientific advances, namely prophylactic HPV vaccination and the use of high risk human papillomavirus (HR-HPV) as a biomarker, offer a strategy which combining primary and secondary prevention, could be capable of a future virtually free of the scourge of cervical cancer. Investment in both of these interventions does present challenges to screening, in terms of achieving optimal, cost effective outcomes. In many developed economies, this discussion is an issue for now and the near future and over the next 5–10 years. The 'elephant in the room' of course is the excessive burden of cervical cancer in the countries economically least equipped to treat this disease, and where resources for secondary prevention through screening have been lacking. HPV vaccination does offer a more straightforward means to at least reduce cervical cancer for the next generation.

The increased sensitivity of HR-HPV testing to detect underlying cervical intraepithelial neoplasia and increase cancer prevention, when compared with exfoliative cytology, has been proven in high quality clinical trials. What is also universally accepted is that testing negative for HR-HPV allows screening intervals to be extended over those used hitherto for cytology. Furthermore, the introduction of HPV vaccination means a far higher proportion of women entering screening will be HR-HPV negative, particularly HPV 16, the most oncogenic type. This combination of HPV vaccination and increased sensitivity of HR-HPV testing, therefore make a compelling case for implementing the latter in place of cytology as the primary screen. Optimising future screening strategies is therefore about how best to implement HR-HPV primary screening and to determine how to maintain the cost effectiveness of cervical screening given the anticipated impact of vaccination.

The price of added sensitivity is of course reduced specificity, due in large part to the prevalence of HR-HPV infection, particularly in younger women. This requires triage using liquid based cytology to achieve sufficient specificity to guide referral to colposcopy. Indeed, some authorities in the field advocate not using HR-HPV testing in women under the age of 30, however this denies women aged 25–29 access to a more sensitive screen. Whatever regimen is used, a significant proportion of women will screen HR-HPV positive/cytology negative, and this new class of screened woman represents the difference when using primary HR-HPV screening. In the recently reported English Pilot study [1], only one third of screen positives had abnormal cytology, prompting immediate referral to colposcopy (Fig. 1). So what is the optimal strategy for the remainder, who are at twice the risk of developing CIN2+ over the following six years? [2]. To refer all to colposcopy would be associated with a low positive predictive value (PPV). An alternative which has been adopted in the US and in Australia [3] is to refer those women with type 16/18 infection and negative cytology. In the ATHENA trial [4] the PPV for CIN2+ was 11% which is well below that seen in colposcopy referral when HPV is used to triage cytology. The third approach, and that used in the English Pilot and the new Dutch national screening programme [5], is to institute early recall for these women, in order to exploit natural viral clearance which can be expected to be 40% and 50–60% over the initial 12 and 24 months respectively. In the English Pilot model, subsequent referral is based on persistent infection and abnormal cytology at 12

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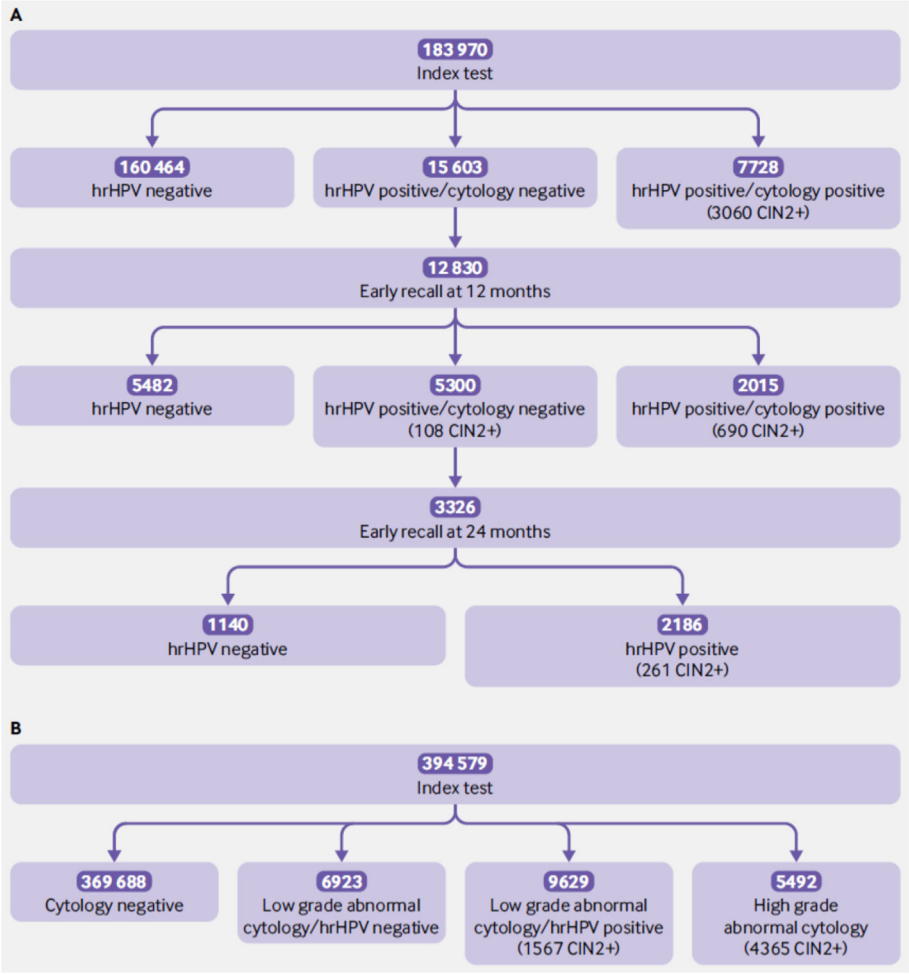

Fig. 1. Flow diagram for prevalence episodes that started by 31 December 2014 including outcomes from per protocol follow-up until 31 May 2017 for women screened with high risk human papillomavirus (hrHPV) testing (A) and liquid based cytology (LBC) (B). CIN2+ = cervical intraepithelial neoplasia grade 2 or worse. From Rebolj M, Rimmer J, Denton K et al. Primary cervical screening with high risk human papillomavirus testing: observational study. *BMJ (Clinical research ed)* 2019; 364: l240.

months, and persistent infection irrespective of cytology at 24 months. In the English Pilot, early recall over 24 months contributed 25% of the total detection of CIN2+ (Fig. 1). Compared with liquid based cytology, primary HPV testing achieved an overall increased detection of CIN3+ and cancer of 40% and 50% respectively. The incidence of CIN3+ at the subsequent screening round after 3 years, was only 0.1% compared with 0.5%; adjusted odd ratio 0.14 (0.09–0.23), confirming the safety of extending the screening interval. There remains the issue of 'exiting' women aged 60–70 who have had their final screen but remain HR-HPV positive, and whether to continue testing annually, or whether to manage purely on the results of cytology. The latter is probably preferable to indefinite surveillance, though another strategy could be to offer suitable women a loop excision in cases of type 16 infection.

Whatever strategy is used, the prize is uplift in the detection of CIN2+ and CIN3+, and the safety of extending screening intervals to at least five years, and potentially to ten years for women over the age of 50 years. Despite the need for additional colposcopy in the prevalence round, this strategy is likely to achieve the sought after double of increased effectiveness and reduced costs. An important mitigating factor for the issue of reduced specificity is the expected impact of vaccination where this has achieved high coverage. In both Scotland and Australia where the impact has been measurable due to the vaccinated cohort reaching screening aged 20, there has been a dramatic fall in HR-HPV prevalence, particularly types 16/18, along with a consequent fall in reported prevalence of CIN.

The establishment of prophylactic HPV vaccination in many countries will have significant implications for screening, not simply in terms of less prevalent disease, but in terms of maintaining cost effective screening in a population at reduced risk. These effects of vaccination will not be profound initially, but within 10 years, the combination of the vaccinated cohort reaching the age of 30–35, and the impact of two rounds of HR-HPV primary screening will mean far lower disease prevalence and incidence going forward. Several modelling studies have estimated that depending on vaccination status, between 2-4 lifetime screens will be required in settings with fully established HPV based primary and secondary prevention [6,7].

Another strategy that has been studied is that of self sampling, which could induce some women who are reluctant to be screened to engage, and could be viewed by many women as a more 'friendly' and convenient means of being screened than attending a clinical setting. Studies to date have indicated that there is a modest response amongst non attenders, with good compliance if cytology triage and subsequent colposcopy are required. It is likely that self testing will gain traction not only for non attenders, but as a convenient means of screening women with busy lives and a dislike of speculum examination. The frequently debated issue of screening older women, beyond the age range of most national programmes, has been invigorated by the use of self testing which can avoid the need for potentially difficult speculum examination. The problem remains however, that the small proportion

who test HR-HPV positive, would require cytology. Not only can procedures requiring full cervical exposure be very uncomfortable or even impossible in older women, but colposcopy is frequently indecisive and treatment more difficult with a greater risk of morbidity.

A further strategy that may emerge in the next 5–10 years is a 'therapeutic' vaccine capable of clearing a HR-HPV infection. This could be an attractive option for women with persistent infection in the absence of abnormal cytology and a useful adjunct to a primary HPV screening programme.

In conclusion, primary screening based on HR-HPV testing represents the future, but requires proven strategies to mitigate the poor specificity of HPV as a biomarker, and recognition of the need for less frequent screening, which will become more urgent as the full impact of prophylactic vaccination begins to be felt.

Conflicts of interest

The author is Chair of the Advisory Committee for Cervical Screening (Public Health England) and the thoughts expressed are those of the author and do not reflect the thoughts of PHE. Henry Kitchener has acted as a consultant for GSK.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pvr.2019.04.001.

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