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Implementation considerations using HPV self-collection to reach women under-screened for cervical cancer in high-income settings

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PARADIGM SHIFT TOWARDS HPV SCREENING GLOBALLY

The success of cytology (Pap screening) programs is undeniable and has drastically reduced cervical cancer rates in high-income settings where it has been implemented[1]. However, cytology for primary cervical cancer screening has a number of limitations including poor sensitivity, a taxing demand on human and operational infrastructure, high health system costs, and limited uptake rates, leading researchers and policy-makers to question whether further gains in public health are possible using this approach[2]. Persistent infection with high-risk genotypes of human papillomavirus (HPV) is well established as the necessary cause for development of cervical cancer[3]. Research has shown a 30% improvement in sensitivity in detecting high-grade lesions, cervical squamous intraepithelial neoplasia (CIN) grade 2 or greater (CIN2+), can be achieved with high-risk HPV DNA testing compared with cytology[4]. A negative HPV test confers two-fold greater reassurance against the development of cervical cancer over three years compared with a negative cytology test[2,5]. The Netherlands has recently transitioned from cytology to HPV testing for primary cervical cancer screening in their National program. Many organized screening programs intend to implement primary HPV screening[6-9], including Australia, which will begin implementation in December 2017.

A consistent barrier to cytology-based cervical cancer screening is non-attendance, which can be addressed through HPV testing using self-collected samples. Primary cervical cancer screening with HPV DNA testing allows for the opportunity of self-collected samples, which is not possible with cytology. In HPV self-collection the sample is obtained vaginally by the woman herself, using a device such as a swab or brush. The swab is subsequently tested for high-risk strains of HPV in a laboratory. With this approach to screening, programs can mail self-collection kits directly to women who are overdue for screening as an alternative to a clinic-based visit. Self-collected cervical samples receiving HPV testing show comparable CIN2+ sensitivity compared with clinician-collected samples tested with cytology and with HPV[10-12]. Self-collection has proven to be highly acceptable among women[13].

Human papillomavirus self-collection has the potential to overcome many of the personal and system-level barriers to screening that exist for cytology or other clinic-based screening methods. Some women, particularly those who have experienced abuse[14] or are otherwise marginalized, may find self-sampling preferable because of such things as cultural/religious embarrassment or discomfort associated with a pelvic exam[13,15-17]. Time, transportation, inconvenient clinic hours, or not having a regular practitioner are also relevant factors associated with under-screening that can be mitigated through HPV self-collection using mailed samples[13,16,17]. However, there are psychosocial barriers to HPV screening, including women's lack of awareness and fears around HPV and cervical cancer screening, which cannot be addressed through self-collection-based screening alone[17,18].

USING HPV SELF-COLLECTION TO REACH UNDER-SCREENED WOMEN

Globally, it is women who do not attend cervical cancer screening that are at highest risk for severe cervical dysplasia and cervical cancer[19]. In countries with publicly funded cervical cancer screening programs, irregular attendance or non-attendance to screening is one of the key barriers to further reducing cervical cancer rates[19,20]. Lower screening rates have been reported in specific populations, such as immigrant women, women of low socio-economic status, and Indigenous women[21,22]. The acceptability and feasibility of screening using HPV self-collection to reach under-served women has been demonstrated in street-involved or otherwise marginalized women [23], rural communities[24], and Indigenous communities in Canada[25]; however, these evaluations were conducted as smaller research projects and did not consider the implications for scaling up to a program level.

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At a population level, HPV self-collection has been used in large-scale randomized controlled trials to reach under-screened women in settings where further gains in screening coverage with cytology have plateaued[26-28]. A recent systematic review and meta-analysis reported that HPV self-screening with home kits significantly improved pooled participation in cervical cancer screening by double, compared with invitations to attend cytology[29]. By shifting screening to a non-clinical setting, self-collection can improve access to screening[10] among women who face barriers to clinic-based screening, and it offers a patient-centred approach that may improve engagement with screening[30]. Despite generally high acceptability of self-collection, some women expressed concerns of sampling accuracy and a lack of confidence in collecting the sample correctly[30]. Perceptions of low self-efficacy to perform the test can negatively impact women's attitudes towards using self-sampling[31], underscoring the need for health education as part of an implementation plan. Additional studies conducted in Australia[28], Denmark[26], Sweden[32], and Norway[33] largely recommend the use of self-collected HPV screening to increase participation in screening among under-screened populations. What is less clear is how best to operationalize this approach into existing health care systems.

CONSIDERATIONS FOR IMPLEMENTATION

There are different approaches to offering self-collection-based screening to non-attenders that have been tested in various countries[29]. The HPV-based screening program in the Netherlands is attempting to reach a higher number of non-attenders by using an opt-out approach in which self-collection kits are directly mailed to under-screened women, often after a reminder letter. Modelling has shown that this method will improve the effectiveness of a primary HPV screening-based program in a cost-effective manner, provided that sensitivity remains high and the program can sufficiently reach under-screened women[34]. A significant threat to this approach is that in practice, uptake rates have been highly variable (between 6.4% and 34%)[29] and there is significant waste and cost associated with unused kits[35]. In a research setting, large trials have used door-to-door recruitment, where community health workers offer sampling to eligible women at their homes, yielding participation rates higher than 90%[29]; however, this is resource intensive and not feasible in many settings. In an opt-in approach, under-screened women are invited to request a kit to their homes, either by phone or through a digital system such as a website[26]. This approach assumes that there are fewer wasted kits, but it could result in lower gains in population coverage, and in some studies, opt-in HPV screening did not demonstrate a significant improvement over invitation letters to cytology[29]. Alternative self-collection strategies may need to be evaluated to identify optimal approaches in different population settings.

HEALTH CARE SYSTEM CONSIDERATIONS

Cytology-based cervical cancer screening via a clinician is an important entry point to health care for many women and offers the opportunity for clinicians to provide more comprehensive reproductive health services and counselling such as testing for sexually transmitted infections and family planning[36]. In settings with established screening programs, HPV self-collection is recommended to complement, not replace, existing programs, as an approach to reach under-served women. Research has shown good attendance to follow-up with a health care provider among women who screen HPV-positive with self-collection[37], suggesting self-collection could potentially act as a re-entry point for women into the screening program or health care system. However, for marginalized women or women who lack access, the follow-up necessary for an HPV-positive result, which usually takes place in a clinic setting, could be a barrier, and these women are at higher risk for developing cervical cancer[35].

Using HPV self-collection to reach marginalized and never-screened women presents both opportunities and challenges, including offering it in an outreach setting[23]. Health care services for street-involved women are often provided by nurses and nurse practitioners who may not be trained, or have the infrastructure, time, or capacity to offer Pap screening. Human papillomavirus self-collection is ideal in these settings; however, consideration should be given to how screening records will be maintained. Ideally, all cervical cancer screening records, including HPV screening, would be kept in a centralized registry. Access to electronic health records may not always be available during outreach care, presenting challenges to appropriately track and follow up women and maintain their screening history.

To prevent over-screening and truly reach those who do not attend, it will be important for programs to consider having systems in place to verify whether women are already up to date and engaged in screening. Particularly as women vaccinated against high-risk HPV types mature and coverage increases, close evaluation and cost-effectiveness should be considered[38]. The high sensitivity of high-risk HPV tests will inevitably detect transient infections that would otherwise resolve without the need for treatment, especially among young women aged 25 to 34[39]. This could lead to excessive referral to colposcopy, biopsy, and treatment[40], which is not only a burden and cost to the health care system but can be harmful to women[38,41-43]. For these reasons, the recommended age to start screening (between 25 and 30 years) is older with HPV screening than with cytology. The screening interval between HPV tests is also longer (4 to 5 years)[5,6] because a negative HPV test provides greater reassurance than negative cytology. Studies have noted that women's concerns about an extended screening interval for HPV could affect the acceptability of HPV screening[44,45]. This stems from the misconception that the longer interval could result in missed detection of pre-cancerous lesions, and it could lead to over-screening if women present for screening more frequently[46]. Regional guidelines on screening interval, age of screening commencement, and appropriate triage pathways, coupled with comprehensive education and dissemination throughout the health care system play an important role in mitigating over-screening. However, in order for HPV-based screening to be optimized,

practitioners will need to be adequately educated on how to manage HPV-positive results and equipped with messaging to handle concerns and questions women may have about HPV, given recommendations from physicians and other clinicians are known to influence patient behaviours[47]. Physician education should include strategies to address adverse emotional responses women may have when informed they have an HPV infection[48].

In the era of primary HPV screening for cervical cancer, self-collection is a powerful tool that can be used to increase screening coverage among under-served and under-screened women. Human papillomavirus self-collection should be implemented with careful consideration to the local context, in coordination with various sectors of the health care system, and coupled with careful evaluation.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES

1. Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. [Comment]. *CMAJ* 2001;164:1017–25.
2. Murphy J, Kennedy EB, Dunn S, *et al.* HPV testing in primary cervical screening: a systematic review and meta-analysis. *J Obstet Gynaecol Can* 2012;34:443–52.
3. Walboomers JM, Jacobs MV, Manos MM, *et al.* Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12–9.
4. Murphy J, Kennedy EB, Dunn S, *et al.* HPV testing in primary cervical screening: a systematic review and meta-analysis. *J Obstet Gynaecol Can* 2012;34:443–52.
5. Ronco G, Dillner J, Elfström KM, *et al.* Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet* 2014;383:524–32.
6. Arbyn M, Ronco G, Anttila A, *et al.* Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. *Vaccine* 2012;30(Suppl 5):F88–99.
7. Murphy J, Kennedy EB, Dunn S, *et al.* Cervical screening: a guideline for clinical practice in Ontario. *J Obstet Gynaecol Can* 2012;34:453–8.
8. Moyer VA, US Preventive Services Task Force. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012;156:880–91, W312.
9. Australian Government Medical Services Advisory Committee. Renewal of the National Cervical Screening Program. *MSAC 61st Meeting*. Canberra: Australian Government Department of Health; 2014.
10. Snijders PJ, Verhoef VM, Arbyn M, *et al.* High-risk HPV testing on self-sampled versus clinician-collected specimens: a review on the clinical accuracy and impact on population attendance in cervical cancer screening. *Int J Cancer* 2013;132:2223–36.
11. Ogilvie GS, Patrick DM, Schulzer M, *et al.* Diagnostic accuracy of self collected vaginal specimens for human papillomavirus compared to clinician collected human papillomavirus specimens: a meta-analysis. *Sex Transm Infect* 2005;81:207–12.
12. Arbyn M, Verdoodt F, Snijders PJF, *et al.* Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncology* 2014;15:172–83.
13. Sultana F, Mullins R, English DR, *et al.* Women's experience with home-based self-sampling for human papillomavirus testing. *BMC Cancer* 2015;15:849.
14. Cadman L, Waller J, Ashdown-Barr L, Szarewski A. Barriers to cervical screening in women who have experienced sexual abuse: an exploratory study. *J Fam Plann Reprod Health Care* 2012;38:214–20.
15. Marlow LA, Waller J, Wardle J. Barriers to cervical cancer screening among ethnic minority women: a qualitative study. *J Fam Plann Reprod Health Care* 2015;41:248–54.
16. Waller J, Jackowska M, Marlow L, Wardle J. Exploring age differences in reasons for nonattendance for cervical screening: a qualitative study. *BJOG* 2012;119:26–32.
17. Racey CS, Gesink DC. Barriers and facilitators to cervical cancer screening among women in rural Ontario, Canada: the role of self-collected HPV testing. *J Rural Health* 2016;32:136–45.
18. Hendry M, Pasterfield D, Lewis R, *et al.* Are women ready for the new cervical screening protocol in England? A systematic review and qualitative synthesis of views about human papillomavirus testing. *Br J Cancer* 2012;107:243–54.
19. Bos AB, Rebolj M, Habbema JD, van Ballegooijen M. Nonattendance is still the main limitation for the effectiveness of screening for cervical cancer in the Netherlands. *Int J Cancer* 2006;119:2372–5.
20. Sancho-Garnier H, Tamalet C, Halfon P, *et al.* HPV self-sampling or the Pap-smear: a randomized study among cervical screening nonattenders from lower socioeconomic groups in France. *Int J Cancer* 2013;133:2681–7.
21. Gesink D, Mihic A, Antal J, *et al.* Who are the under- and never-screened for cancer in Ontario: a qualitative investigation. *BMC Public Health* 2014;14:495.
22. Canadian Partnership Against Cancer. First Nations Cancer Control in Canada Baseline Report. Toronto, ON; 2013.
23. Ogilvie G, Krajden M, Maginley J, *et al.* Feasibility of self-collection of specimens for human papillomavirus testing in hard-to-reach women. *CMAJ* 2007;177:480–3.
24. Racey CS, Gesink DC, Burchell AN, Trivers S, Wong T, Rebbapragada A. Randomized intervention of self-collected sampling for human papillomavirus testing in under-screened rural women: uptake of screening and acceptability. *J Women Health (2002)* 2016;25:489–97.
25. Zehbe I, Moeller H, Severini A, *et al.* Feasibility of self-sampling and human papillomavirus testing for cervical cancer screening in First Nations women from Northwest Ontario, Canada: a pilot study. *BMJ Open* 2011;1:e000030.
26. Lam JU, Rebolj M, Moller Ejegod D, *et al.* Human papillomavirus self-sampling for screening nonattenders: opt-in pilot implementation with electronic communication platforms. *Int J Cancer* 2017;140:2212–9.
27. Racey CS, Withrow DR, Gesink D. Self-collected HPV testing improves participation in cervical cancer screening: a systematic review and meta-analysis. *Can J Public Health* 2013;104:e159–66.
28. Sultana F, English DR, Simpson JA, *et al.* Home-based HPV self-sampling improves participation by never-screened and under-screened women: results from a large randomized trial (iPap) in Australia. *Int J Cancer* 2016;139:281–90.
29. Verdoodt F, Jentschke M, Hillemanns P, Racey CS, Snijders PJ, Arbyn M. Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials. *Eur J Cancer* 2015;51:2375–85.

30. Madzima TR, Vahabi M, Lofters A. Emerging role of HPV self-sampling in cervical cancer screening for hard-to-reach women: focused literature review. *Can Fam Physician* 2017;63:597–601.
31. Williams D, Davies M, Fiander A, Farewell D, Hillier S, Brain K. Women's perspectives on human papillomavirus self-sampling in the context of the UK cervical screening programme. *Health Expect* 2017;20:1031–40.
32. Wikstrom I, Lindell M, Sanner K, Wilander E. Self-sampling and HPV testing or ordinary Pap-smear in women not regularly attending screening: a randomised study. *Br J Cancer* 2011;105:337–9.
33. Enerly E, Bonde J, Schee K, Pedersen H, Lönnberg S, Nygård M. Self-sampling for human papillomavirus testing among non-attenders increases attendance to the Norwegian cervical cancer screening programme. *PLOS One* 2016;11:e0151978.
34. Rozemeijer K, de Kok IM, Naber SK, *et al.* Offering self-sampling to non-attendees of organized primary HPV screening: when do harms outweigh the benefits? *Cancer Epidemiol Biomarkers Prev* 2015;24:773–82.
35. Arbyn M, Castle PE. Offering self-sampling kits for HPV testing to reach women who do not attend in the regular cervical cancer screening program. *Cancer Epidemiol Biomarkers Prev* 2015;24:769–72.
36. van Niekerk D, Grennan T, Ogilvie G. STI testing and cervical cancer screening: need for continued STI screening among young people in the era of new cervical cancer screening guidelines. *BC Medical J* 2016;58:468.
37. Virtanen A, Nieminen P, Luostarinen T, Anttila A. Self-sample HPV tests as an intervention for nonattendees of cervical cancer screening in Finland: a randomized trial. *Cancer Epidemiol Biomarkers Prev* 2011;20:1960–9.
38. Naber SK, Matthijsse SM, Rozemeijer K, Penning C, de Kok IM, van Ballegooijen M. Cervical cancer screening in partly HPV vaccinated cohorts—a cost-effectiveness analysis. *PLOS One* 2016;11:e0145548.
39. Castle PE. Gynaecological cancer: new standard of care—HPV testing for cervical cancer screening. *Nat Rev Clin Oncol* 2015;12:194–6.
40. Coldman AJ, Phillips N, van Niekerk D, *et al.* Projected impact of HPV and LBC primary testing on rates of referral for colposcopy in a Canadian cervical cancer screening program. *J Obstet Gynaecol Can* 2015;37:412–20.
41. Kyrgiou M, Mitra A, Arbyn M, *et al.* Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis. *BMJ* 2014;349:g6192.
42. Kola S, Walsh JC. Patients' psychological reactions to colposcopy and LLETZ treatment for cervical intraepithelial neoplasia. *Eur J Obstet Gynecol Reprod Biol* 2009;146:96–9.
43. Habbema D, Weinmann S, Arbyn M, *et al.* Harms of cervical cancer screening in the United States and the Netherlands. *Int J Cancer* 2017;140:1215–22.
44. Ogilvie GS, Smith LW, van Niekerk D, *et al.* Correlates of women's intentions to be screened for human papillomavirus for cervical cancer screening with an extended interval. *BMC Public Health* 2016;16:213.
45. Smith L, van Niekerk D, Coldman A, Krajden M, Franco EL, Ogilvie G. Recommendations for implementing human papillomavirus-based cervical cancer screening: lessons learned from the HPV FOCAL Trial. *J Obstet Gynaecol Can* 2016;38:723–6.
46. Hawkins N, Benard V, Greek A, Roland K, Manninen D, Saraiya M. Patient knowledge and beliefs as barriers to extending cervical cancer screening intervals in federally qualified health centers. *Preventive Medicine* 2013;57:641–5.
47. Ogilvie GS, Smith LW, van Niekerk DJ, *et al.* Women's intentions to receive cervical cancer screening with primary human papillomavirus testing. *Int J Cancer* 2013;133:2934–43.
48. O'Connor M, Costello L, Murphy J, *et al.* 'I don't care whether it's HPV or ABC, I just want to know if I have cancer.' Factors influencing women's emotional responses to undergoing human papillomavirus testing in routine management in cervical screening: a qualitative study. *BJOG* 2014;121:1421–30.