Selected Summaries

Population-based human papillomavirus testing: The new paradigm for cervical cancer screening

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Programmatic human papillomavirus testing in cervical cancer prevention in the Jujuy demonstration project in Argentina: A population-based, before-and-after retrospective cohort study. *Lancet Glob Health* 2019;**7:**e772–83.

SUMMARY

Arrossi *et al*. conducted a population-based retrospective study from the National Cervical Cancer Prevention Program in Jujuy province, Argentina. They collected data of cytology-based and human papillomavirus (HPV) screening in women aged >30 years. The primary outcome was detection rate of high-grade cervical intraepithelial neoplasia (CIN2+) by each test, and the Reach, Effectiveness, Adoption, Implementation and Maintenance framework was used for programmatic analysis.

Cytology-based screening was done in 29 631 females during 2010–11, of whom 4% tested positive. The histologically proven CIN2+ detection rate was 0.8% and the positive predictive value was 20.0%. HPV screening was done in 49 565 females during 2012–14 (clinician-collected, *n*=44 700; self-collected, *n*=4865). Of these, 13.7% of the clinician-collected and 13% of self-collected samples were HPV-positive. The detection rate for CIN2+ was 1.4%, and the chance of being diagnosed with CIN2+ was 2.3 (p<0.001) with a clinician-collected sample and 1.08 (p=0.68) with a self-collection sample compared to cytology. The positive predictive value was 10.8% and 5.5% for clinician- and self-collected tests, respectively. Reach was measured in terms of coverage, which was 52.7% and 53.2% with cytology- and HPV-based screening, respectively. For measuring adoption, three variables were used, namely, healthcare centres which provided screening method in each study period (100% *v*. 100%), females of the recommended age screened in each study period (79.3% *v*. 98.8%) and over-screening in each period (6.6% *v*. 0%) in cytology- and HPV-based screening, respectively. Implementation indices were also in favour of HPV screening in terms of fewer inadequate test samples (3.6% *v*. 0.2%) and a high similar rate for follow-up (80.3% *v*. 83.9%) in cytology- and HPV-based screening, respectively.

COMMENT

The worldwide incidence and mortality of carcinoma cervix is 13.1 and 6.9/100 000 population, respectively. More than 85% of cases are contributed by low- and middle-income countries (LMICs), where deaths from cervical cancer now exceed maternal mortality in most countries.[1] The enormity of this public health problem combined with the tragedy of losing relatively young females to a preventable disease led the WHO Director-General in 2018 to announce a call to action towards the elimination of cervical cancer by 2030.[2] Three essential interventions have been proposed in this call: 90% coverage of girls <15 years by HPV vaccination, 70% screening of women at 35 and 45 years with an HPV test and treatment of 90% of detected lesions.

HPV testing is expensive and not universally available. Nevertheless, the rationale for promoting worldwide HPV screening was the recognition that primary HPV screening has been found to be superior to cytology as a screening method in various studies including randomized trials. In a meta-analysis of results from North America and Europe, it was found that HPV testing had higher sensitivity than cytology for the detection of CIN2+ lesions (96.1% *v*. 53%), although with less specificity (90.7% *v*. 96.3%).[3] A majority of the well-known trials on efficacy and cost-effectiveness (ARTISTIC, Swedescreen, NTCC and POBASCAM) were conducted in high-income countries.

A study in Nicaragua, Central America, also confirmed that HPV testing is cost-effective compared with Pap testing, due to higher test sensitivity and the longer screening interval.[4] This large population-based study from a province in Argentina by Arrossi *et al*. is the first one to evaluate the feasibility of HPV screening in real-world programmatic considerations of middle-income settings, compared with cytology-based screening. HPV-based screening was initiated in 2011, prior to which there was a well-designed programme of cytological screening by the National Program on Cervical Cancer Prevention. Thus, it was possible to compare the results of the two systems. Although the time periods were sequential, the screening coverage was similar in both. HPV testing allowed better laboratory centralization, less over-screening, increased interval of screening and decrease in the number of inadequate samples, with twice the rate of detection of CIN2+.

In a cluster-randomized trial in rural India, Sankaranarayanan *et al*. showed that even a single round of HPV testing was associated with a considerable reduction in the number of advanced cervical cancers and deaths from cervical cancer compared to cytology and visual inspection with acetic acid (VIA) (hazard ratio 0.52; 95% CI 0.33–0.69).[5] The study also found that the likelihood of developing cervical cancer was significantly reduced following a negative HPV test, compared with normal cytology or negative VIA (hazard ratio 0.47, 95% CI 0.32–0.69; 0.77, 95% CI 0.51–1.10 and 1.04, 95% CI 0.72–1.49, respectively).[5] Mezei *et al*. in a systematic review concluded that HPV testing and VIA are more cost-effective screening methods than cytology in LMICs.[6] Although these laid the foundation for using HPV testing in LMICs, it still did not address the problems of lack of infrastructure and personnel, especially at last-mile facilities in difficult terrains. Self-sampling was proposed as an option for females who were not compliant with the screening protocols in developed countries and seemed

to be a possible solution for LMICs. Bhatla *et al*. reported the sensitivity and specificity of HPV-DNA for detection of CIN2+ disease to be 82.5% and 93.6%, respectively, for self-collected samples, compared to 87.5% and 93.2% for physician-collected samples in an Indian population, and found the method to be acceptable.[7] In a meta-analysis, Arbyn *et al*. found that the sensitivity and specificity of HPV testing of self- and clinician-collected samples were comparable using polymerase chain reaction-based assays.[8] In the present study, there was increased acceptance for self-collection sample, which increased the participation. Although the clinician-collected sample performed better than the self-sample, the latter was comparable to cytology in its performance. Thus, it is a suitable method for reaching large unreached populations. However, the coverage could not be increased beyond 57%, which is lower than the recommended target of 70%, and needs further strategies to improve awareness and participation. Follow-up in the self-sampling group was less compared to that in the clinician-collected samples (69% *v*. 98%). This could be due to the need for a repeat visit, which is a drawback mentioned in other studies too. Development of an affordable, point-of-care test may help to minimize this problem in the future. Presently, the WHO is exploring the possibility of using other platforms such as GeneXpert to improve the coverage and availability in low-resource settings.[9]

HPV testing is highly sensitive, and many HPV-positive females will not have major cervical disease. Over-referral to colposcopy can be reduced with appropriate triage tools. In the present study, the HPV-positive females underwent cytology triage before referral to colposcopy. However, depending on the resource situation, it is also possible to use other triage tools such as HPV genotyping, where available, or VIA in low-resource settings.[10] Further management by ablative or excisional techniques is based on the type and location of lesion detected.

In the post-vaccination era, it is anticipated that low prevalence of the disease will result in low sensitivity and high false-negative results of cytology-based tests, which will further increase the value of HPV testing. The major advantages for HPV testing are increased sensitivity and less frequent testing than cytology, with an option of self-sampling, which helps in increased coverage and acceptance. The greater assurance provided by a negative test supports the WHO recommendation for only two tests in a lifetime at 35 and 45 years of age when HPV testing or a similar high-precision test is used. The results from the Jujuy study are useful to inform HPV-based screening programmes about real-world experiences and expectations.

Conflicts of interest. None declared

REFERENCES

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68:**394–424.

2 World Health Organization. Available at *www.who.int/reproductivehealth/call-to-action-elimination-cervical-cancer/en/* (accessed on 28 May 2019).

3 Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand MH, *et al*. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine* 2008;**26** (Suppl 10)**:**K29–41.

4 Campos NG, Myundura M, Jeronimo J, Holme F, Vodicka E, Kim JJ. Cost-effectiveness of HPV-based cervical cancer screening in the public health system in Nicaragua. *BMJ Open* 2017;**7:**e015048.

5 Sankaranarayanan R, Nene BM, Dinshaw KA, Mahe C, Jayant K, Shastri SS, *et al*. A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *Int J Cancer* 2005;**116:**617–23.

6 Mezei AK, Armstrong HL, Pedersen HN, Campos NG, Mitchell SM, Sekikubo M, *et al*. Cost-effectiveness of cervical cancer screening methods in low- and middle-income countries: A systematic review. *Int J Cancer* 2017;**141:**437–46.

7 Bhatla N, Dar L, Patro AR, Kumar P, Kriplani A, Gulati A, *et al*. Can human papillomavirus DNA testing of self-collected vaginal samples compare with physician-collected cervical samples and cytology for cervical cancer screening in developing countries? *Cancer Epidemiol* 2009;**33:**446–50.

8 Arbyn M, Smith SB, Temin S, Sultana F, Castle P; Collaboration on Self-Sampling and HPV Testing. *et al*. Detecting cervical precancer and reaching under screened women by using HPV testing on self-samples: Updated meta-analyses. *BMJ* 2018; **363:**k4823.

9 WHO Prequalification of in vitro diagnostics; 2017: version 2. Available at *www.who.int/diagnostics_laboratory/evaluations/pq-list/hiv-vrl/170720_final_pq_report_pqdx_0192_0193_0194_0195_070-00.pdf?ua=1* (accessed on 14 May 2020).

10 Bhatla N, Singhal S, Saraiya U, Srivastava S, Balerao S, Shamsunder S, *et al*. Screening and management of preinvasive lesions of the cervix: Good clinical practice recommendations from the Federation of Obstetrics and Gynaecologic Societies of India (FOGSI). *J Obstet Gynaecol Res* 2020;**46:**201–14.

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