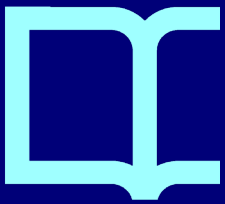

HPV Prevention and Control – the way forward (1490 words, 1500 limit)

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ABSTRACT (241 words, 250 limit)

The global confrontation with COVID-19 has not only diverted current healthcare resources to deal with the infection but has also resulted in increased resources in the areas of testing and screening, as well as educating most of the global public of the benefits of vaccination. When the COVID-19 pandemic eventually recedes, the opportunity must not be missed to ensure that these newly created resources are maintained and redeployed for use in testing and immunisation against other vaccine-preventable infectious diseases. A notable example is infection by human papillomavirus (HPV), the commonest sexually transmitted human virus and the leading cause of a variety of cancers in both men and women, such as cervical, head and neck, anal, vaginal, vulvar and penile cancers. The most important is cervical cancer, the objective of the global elimination goals targeting the vaccination of young female and male adolescents, screening all women and treatment of all infected women. As the campaigns to control SARS-CoV-2, the eradication of HPV-induced cancers also relies on effective prevention and control programs. The lessons learned and the technical, logistical and human resources which have been established to combat COVID-19 by vaccination and testing must be applied to the eradication of other infections which affect the global population. This commentary summarizes the opportunities that the COVID-19 pandemic has created for HPV prevention and control, lists the already available tools for HPV control, and emphasizes the potential public health threats amidst the ongoing COVID-19 pandemic.

The global COVID-19 pandemic has generated intense public interest worldwide in the effectiveness of screening, testing and vaccination to protect populations against an infectious disease, as well as in novel treatments for those most severely infected. Indeed, global measures have been deployed with unprecedented speed to combat the pandemic; since the authorization of the first COVID-19 vaccines in December 2020 around 8.7 billion doses of newly developed vaccines have been administered in less than 13 months (*WHO, 2021a*). There has also been a boom in self-testing, raising public awareness of this possibility, as well as a major expansion in PCR testing facilities all over the globe (*M. Poljak et al., 2021; UNICEF, 2021*). When COVID-19 recedes, these facilities and the awareness of them must be maintained and repurposed to combat other infectious threats. Although an increase in global equity is still required, we want to highlight a potential silver lining in the cloud of COVID-19, the opportunity to apply the experience of this pandemic to pursue aspirational goals to eradicate other infectious diseases. A notable example is human papillomavirus (HPV), the most common sexually transmitted viral infection globally, the causative agent of cervical cancer; with genotypes HPV 16 and 18 being responsible for up to 70% of cases globally (*S. de Sanjose et al., 2010*). Of the 570,000 new cases of cervical cancer reported annually most occur in low- and middle-income countries (LMICs), representing the second most frequent cancer in women (*M. Arbyn et al., 2020*). HPV is also an important causative factor in a number of other reported cancers in women and men such oropharyngeal (31%), anal (88%), vaginal (78%), vulvar (25%) and penile (50%) cancers; and so may be vaccine-preventable (*C. de Martel et al., 2017*).

The WHO cervical cancer elimination strategy has three complementary pillars to fight HPV, with aspirational targets to be met by 2030: i) vaccination of 90% of girls by 15 years of age, ii) high performance cervical screening of 70% of women at 35 and 45 years of age, and iii) treatment of 90% of detected cases of cervical disease (*WHO, 2020a*). The potential impact of this strategy should not be underestimated; comparative modelling of successfully meeting the goals of these three pillars has estimated that elimination could be achieved in all 78 LMIC with 62 million deaths averted over a century (*M. Brisson et al., 2020; K. Canfell et al., 2020*).

The table shows many of the tools and initiatives for vaccination and screening that have already or soon will be made available to meet many of the outstanding issues, to allow these ambitious WHO targets to be met. Further, the global experience of fighting COVID-19 has provided additional opportunities to exploit the newly created resources to combat HPV. Since the first HPV vaccine was licensed in 2006 there are now four safe, well tolerated, and highly immunogenic vaccines prequalified by the WHO and licensed around the world, with more

vaccines in advanced stages of clinical development. Equally important, unlike the supply issues for COVID-19 vaccines, commitments have been made to ensure that HPV vaccine production capacity will be adequate to meet global demand within 5 years. If these global supply issues are resolved, supported by new approaches currently being investigated such as a one dose schedule instead of the two or three currently recommended, it is anticipated that the ambitious target of 90% vaccine coverage can be met. COVID-19 has not only educated the world to the importance of vaccination but will leave a logistical legacy that must be exploited to ensure the equitable distribution of HPV vaccines. Importantly, lessons learned in establishing the new vaccination platforms designed to allow mass vaccination with digital tracking of the population's vaccination status can in part be applied to the field of HPV vaccination. The current strategy can be complemented by expansion of HPV vaccination to groups other than young girls. Efforts need to be made to incorporate HPV into national routine vaccination programs, as global coverage of the target age group of young girls under 16 years of age is unfortunately still only 15% (*L. Bruni et al., 2021*).

HPV vaccines are safe and highly effective, reducing high grade lesions and cervical cancer in up to 97% of young women vaccinated at 12–13 years of age (*M. Falcaro et al., 2021*). Substantial safety data on HPV vaccination accumulated from several million people are available and has been analysed by the Global Advisory Committee on Vaccine Safety (GACVS), allowing a comparison of the risks for a wide range of health outcomes in vaccinated and unvaccinated people. This shows that apart from a low risk of anaphylaxis (1.7 cases per million doses) and syncope (common anxiety or stress-related reaction to the injection) there are no frequent adverse reactions (*WHO, 2017*). However, despite this extensive safety database, attention has continued to focus on spurious case reports and unsubstantiated allegations. The GACVS has reported that one of the challenges associated with the continued generation of data is that artefacts will be observed, which could pose further challenges for communication when taken out of context and in haste, to be exploited by the anti-vaccine lobby in the absence of the overall body of evidence (*WHO, 2017*). This is an unfortunate lesson to be learned from the COVID-19 experience; that a significant proportion of the population will resist and indeed oppose vaccination, despite sound scientific arguments for the benefits of vaccines. Understanding the issues behind vaccine hesitancy will be a key part of overcoming this issue.

Another pillar is screening, the importance of which in the public perception has been highlighted by testing for COVID-19 which has made the value of PCR testing to identify asymptomatic infections after a high-risk contact much more widely understood. Randomised studies

consistently indicate that HPV-based primary screening offers stronger protection against future precancers and cancers than screening with cytology. Indeed, Pap cytology, as the method of choice for primary screening of women, is gradually being replaced with more sensitive, objective, and validated HPV molecular nucleic acid amplification testing [NAAT]. The latest WHO guidelines for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, contain a strong recommendation to use HPV DNA detection, including partial genotyping, as primary screening test rather than cytology or VIA (visual inspection with acetic acid) which increases the predictive power for future cancerous outcomes (*WHO, 2021b*). Three HPV NAAT tests are already WHO-prequalified and at least 11 assays have received international validation, with many more waiting for assessment (*M. Arbyn et al., 2021*). For the follow-up of HPV positive women triage methods allowing identification of women needing treatment or more intense follow-up are being developed using extended genotyping *(R. Adcock et al., 2018; M. Demarco et al., 2020),* methylation (*M. Clarke et al.,2018)*, cellular proliferation markers and assisted visual approaches using AI (*K. Desai et al., 2021)*.

New methods and approaches such as self-sampling may overcome societal and logistical barriers to screening. Foremost must be the application of the capacity for NAAT such as PCR-testing which has mushroomed for COVID-19 testing to improve HPV detection, while monitoring the effectiveness of vaccination programmes in reaching elimination targets. Current WHO recommendations for home-based self-sampling and remote counselling for safe delivery of services in the COVID-19 context could be applied to HPV testing to improve uptake (*WHO, 2020b*). Indeed, when using PCR-based HPV tests, a self-sample is a valid alternative to clinician-taken samples (*M. Arbyn et al., 2019*). The ROSE project, a successful example in Malaysia, integrates the latest advances in self-sampling, HPV screening and digital platforms to invite women for screening (*Y.L. Woo et al., 2021*).

For the third pillar, treatment options for detected cervical cancers and their precursors remain highly complex, requiring equipment and expertise that are currently found only in established clinical settings. Major investment in infrastructure and trained healthcare personnel for treatment of invasive cancer remains a long-term goal. However, treatment of precursors of cancers (CIN3) in other settings may be possible with the development of new portable ablative technologies allowing screening and treatment at the same visit.

As the current COVID-19 pandemic has increased public awareness of the value of vaccination and testing for infectious disease, the HPV Prevention and Control Board and the International Papillomavirus Society want to take the opportunity to re-emphasise the importance of HPV

prevention and control to a more aware public. With the tools and knowledge currently available, elimination of cervical cancer must be kept high on the list of medical priorities. Enhanced access to affordable prophylactic HPV vaccines globally will prevent and control HPV infection and transmission, while access to appropriate screening and management of those positive at screening will significantly reduce the burden of HPV-caused disease; together these are potent weapons against HPV infection and resulting disease. As stated during the last World Health Assembly, cervical cancer stands as one of the world's greatest public health failures, but through strong action and aligned intervention, elimination is within reach for all countries (*WHO, 2020c*).

Abbreviations:

AI, Artificial Intelligence; AIDs, Acquired immunodeficiency syndrome; COVID-19, COronaVirus DIsease of 2019; GACVS, Global Advisory Committee on Vaccine Safety; GAVI: The Global Alliance for Vaccines and Immunizations; HPV, human papillomavirus; HIC, High income countries; HIV, Human immunodeficiency virus; LMIC, low- and middle-income countries; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; UNICEF, United Nations Children's Fund; VIA, visual inspection with acetic acid; WLWHIV, women living with HIV; WHO, World Health Organization.

Elimination of cervical cancer: Assessing and evaluating opportunities for the three WHO pillars.		
	1. HPV Vaccination	**2. HPV Screening**
Mass intervention technology availability and production capacity	• 4 WHO-prequalified vaccines licensed by all major agencies and endorsed by over 100 countries • Good safety data available • More than 2 vaccines in clinical development • Commitment made for production capacity to meet global needs within 5 years • Consolidated programs exist in many HIC and LMIC • Build on experience with paediatric vaccines coordinated by UNICEF, GAVI, WHO, etc	• Pap smear still widely used • Primary screening alternatives being implemented/evaluated • 11 HPV assays validated against international criteria, some already providing partly genotype information • 3 HPV tests are WHO prequalified • Over 200 tests in the market with limited validation • 1 assay validated according to international criteria with point-of-care applicability
Opportunities for future growth to increase impact: current hypotheses being researched	• One dose schedule • Expansion of age groups • Expansion to males • Expansion to high-risk groups, e.g., people living with HIV/AIDs • Prevention of transmission, by vaccinating HPV-infected women • Integration with other vaccination programs • Reimbursement policies for other than priority target groups	• Self-sampling systems • Development of economically viable, user-friendly, validated screening assays applicable to field conditions • Clarifying triage alternatives, including use of partial genotyping and also taking into account WLWHIV • Improving logistics and societal acceptance of screening • Research to improve participation and tackle inequity • Integration of screening with other health programs • Screening protocol definition for vaccinated women • Setting up a GAVI equivalent platform for cervical cancer screening
Opportunities generated by the COVID-19 pandemic	• Increased awareness of the benefits of vaccination to overcome infectious disease • New vaccination platforms and information systems have been set-up	• Extensive PCR testing capacity has been deployed all over the world • Potential to use this infrastructure and staffing expertise for HPV testing and follow-up after treatment
	3. Treatment	
	Treatment after positive screening (i.e., CIN 2+)	**Treatment of invasive cancer**

Status and opportunities for future	• Well organised in some countries • Instruments that are portable and accessible are being evaluated for resource-limited settings • Progress on artificial intelligence (AI) imaging and triage markers on self-samples will further help to identify women in LMIC that can be treated by minimal ambulant interventions	• Remains challenging and needs highly qualified personnel and major hospital facilities for surgery, radiotherapy, chemotherapy, etc

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