Vaccine 40 (2022) 5843–5855

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

Understanding the public health value and defining preferred product characteristics for therapeutic human papillomavirus (HPV) vaccines: World Health Organization consultations, October 2021—March 2022

Holly J. Prudden [a], Sharon L. Achilles [b], Celina Schocken [b], Nathalie Broutet [a], Karen Canfell [c], Hiroki Akaba [a], Partha Basu [d], Neerja Bhatla [e], Z. Mike Chirenje [f], Sinead Delany-Moretlwe [g], Lynette Denny [h], Deepa G. Gamage [i], Rolando Herrero [j], Raymond Hutubessy [a], Luisa Lina Villa [k], Raul Murillo [l], John T. Schiller [m], Margaret Stanley [n], Marleen Temmerman [p], Fanghui Zhao [q], Gina Ogilvie [r], David C. Kaslow [s], Peter Dull [b], Sami L Gottlieb [a,*], Therapeutic HPV Vaccine PPC Expert Consultation Group*

[a] World Health Organization, Switzerland
[b] Bill & Melinda Gates Foundation, USA
[c] The Daffodil Centre, The University of Sydney, a joint venture with Cancer Council NSW, Australia
[d] International Agency for Research on Cancer, France
[e] All India Institute of Medical Sciences, New Delhi, India
[f] University of Zimbabwe, Zimbabwe
[g] Wits RHI, University of the Witwatersrand, South Africa
[h] University of Cape Town, SA MRC Gynaecology Cancer Research, South Africa
[i] Epidemiology Unit, Ministry of Health, Sri Lanka
[j] Agencia Costarricense de Investigaciones Biomédicas, Fundación INCIENSA, Costa Rica
[k] Universidade de São Paulo, Brazil
[l] Hospital Universitario San Ignacio, Colombia
[m] National Cancer Institute, USA
[n] University of Cambridge, UK
[p] Aga Khan University, Kenya
[q] National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China
[r] School of Population and Public Health, Faculty of Medicine, University of British Columbia, Canada
[s] PATH, USA

ARTICLE INFO

Article history:
Received 3 August 2022
Accepted 10 August 2022
Available online 22 August 2022

Keywords:
Cervical cancer
HPV
Therapeutic HPV vaccine
Preferred product characteristics

ABSTRACT

The World Health Organization (WHO) global strategy to eliminate cervical cancer (CxCa) could result in >62 million lives saved by 2120 if strategy targets are reached and maintained: 90% of adolescent girls receiving prophylactic human papillomavirus (HPV) vaccine, 70% of women receiving twice-lifetime cervical cancer screening, and 90% of cervical pre-cancer lesions and invasive CxCa treated. However, the cost and complexity of CxCa screening and treatment approaches has hampered scale-up, particularly in low- and middle-income countries (LMICs), and new approaches are needed. Therapeutic HPV vaccines (TxV), which could clear persistent high-risk HPV infection and/or cause regression of pre-cancerous lesions, are in early clinical development and might offer one such approach. During October 2021 to March 2022, WHO, in collaboration with the Bill and Melinda Gates Foundation, convened a series of global expert consultations to lay the groundwork for understanding the potential value of TxV in the context of current CxCa prevention efforts and for defining WHO preferred product characteristics (PPCs) for TxV. WHO PPCs describe preferences for vaccine attributes that would help optimize vaccine value and use in meeting the global public health need. This paper reports on the main discussion points and findings from the expert consultations. Experts identified several ways in which TxV might address challenges in current CxCa prevention programmes, but emphasized that the potential value of TxV will depend on their degree of efficacy and how quickly they can be developed and implemented relative to ongoing scale-up of existing interventions. Consultation participants also discussed potential use-cases for TxV, important PPC considerations (e.g., vaccine indications, target populations, and delivery strategies), and critical modelling needs for predicting TxV impact and cost-effectiveness.

* Corresponding author.

https://doi.org/10.1016/j.vaccine.2022.08.020
0264-410X/

1. Introduction

Cervical cancer (CxCa), the fourth leading cause of cancer deaths for women globally, is a vaccine-preventable global public health problem, caused almost exclusively by sexual transmission of oncogenic types of human papillomavirus (HPV) [1]. In 2020, an estimated 604,000 women were diagnosed with CxCa, and approximately 342,000 women died of CxCa [2]. Nearly 90% of CxCa-associated deaths occurred in women in low- and middle-income countries (LMICs), largely due to limited access to public health services including CxCa screening and treatment.

In response to this, the World Health Organization (WHO) published a Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Issue in 2020, which set a goal for reducing cases below a global threshold of 4 cases per 100,000 women [3]. The strategy includes 2030 programmatic targets which all countries should aim to achieve and maintain to reach this goal. These are:

- To fully vaccinate 90% of girls with prophylactic HPV vaccines by the age of 15.
- To ensure 70% of women receive CxCa screening twice in their lifetime with a high-performance test (e.g. HPV DNA testing).
- To provide treatment to 90% of women with cervical lesions (pre-cancer and CxCa).

This global strategy provides a roadmap for eliminating CxCa as a public health problem within a century, with the potential to save 62 million lives by 2120 if the three 2030 targets are successfully reached and sustained [4,5]. Scale-up of prophylactic HPV vaccine for adolescent girls will have a significant effect in preventing CxCa and its associated mortality, but substantial impact will likely not be seen for 30–40 years [4]. Reaching the WHO 2030 target for delivering prophylactic vaccination is predicted to avert >45 million deaths from CxCa. CxCa screening and treatment is crucial to address the prophylactic vaccine coverage gap, including for women who did not receive the prophylactic vaccine due to age or access restrictions and women and girls who received the prophylactic vaccine after having already acquired an oncogenic HPV infection. Reaching 2030 targets for screening and treatment, in addition to vaccination, is predicted to save an additional 17 million lives by 2021, with a total of 62 million lives saved from all three pillars of the WHO strategy [5]. The complexity of CxCa screening and treatment approaches, which may require several visits for women testing positive for high-risk (hr) HPV, and persistent inequities in access to both prophylactic vaccination and screening and treatment programs are both major hurdles to reaching the 2030 goals, particularly in LMICs [6].

Therapeutic HPV vaccines (TxV) that could clear persistent hrHPV infection and/or cause regression of CIN2/3 lesions offer the potential to address the gaps currently left by prophylactic vaccine and screening and treatment programs, which might in turn reduce CxCa mortality on the path to CxCa elimination. Several TxV candidates are currently in development. The potential value of TxV increases if they can be developed and rolled out quickly. Understanding the potential added value of such a product will be critical in guiding its development. It will also be important to consider how these vaccines would be used and delivered within the broader CxCa prevention and treatment context, as well as what vaccine attributes would optimise public health impact. The vaccine characteristics may also affect the relative benefits and numbers needed to vaccinate when considering different use cases. High quality modelling offers an approach to assess the relative values of uses cases, delivery approaches, and vaccine attributes.

As part of its mission to facilitate rapid vaccine development for global public health, WHO has three main workstreams to develop guidance on vaccine development (Box 1).

Box 1. WHO Guidance on Vaccine Development.

Workstreams:	Objectives:
Full value of vaccines assessments [5]	Quantify the health, economic, and societal burden the vaccine would address, and predict the impact and value the vaccine would have in addressing those outcomes.
Preferred product characteristics (PPC) documents [7]	Describe the attributes that would optimise the vaccine's benefit for global health, who would receive it, and how it would be used and delivered.
Research and development roadmaps and clinical development pathways	Assess what it will take to develop effective vaccines, evaluate them in clinical trials, and complete relevant regulatory processes, and address knowledge gaps.

WHO has embarked on efforts to understand the potential health, economic, and societal value of TxV, particularly for LMICs, while vaccine candidates are still in early stages of development [5]. This approach parallels efforts to identify, early on, the use case (s) (how and for whom the vaccine would be used) and vaccine attributes that would help optimise the global public health value. Preferred product characteristics (PPCs) outline WHO's preferences for product attributes that will help meet the global public health need for vaccines, with a focus on LMICs. PPCs are pathogen-specific and intended to guide product-specific target profiles for products that will eventually seek WHO policy recommendations and pre-qualification. PPCs include characteristics such as vaccine indications, target populations, immunization delivery strategies, safety and efficacy considerations, and dosing schedules [7].

To lay the groundwork for understanding the potential value of TxV and key considerations for defining optimal use cases and PPCs for TxV, WHO, in partnership with the Bill & Melinda Gates Foundation, held a series of global expert online consultations starting in October 2021. The initial consultation brought together around 65 experts in HPV and CxCa science, epidemiology, modelling, and public health control programs, along with experts in vaccine development and implementation. A list of all participants is included at the end of this document, in Annex 1.

The objectives of the initial consultation were to:

1. Define the public health need for TxV and discuss the vaccines' potential value in the context of existing CxCa prevention programs.
2. Outline important use cases and key considerations for TxV PPCs, in particular: preferred indication(s), target populations, and programmatic delivery approaches in LMICs.
3. Define modelling efforts, key modelling scenarios, and data needs to inform the full value of vaccines assessment and PPCs for HPV therapeutic vaccines.

Following the October 2021 consultation, several smaller virtual consultations took place with focused groups of experts in HPV vaccine development, CxCa clinical and technical aspects,

CxCa program implementation, and modelling. The purpose of these meetings was to discuss the key considerations related to understanding the potential value and PPCs for TxV in more depth, and to provide guidance to modellers commissioned to evaluate the predicted impact and cost-effectiveness of TxV. Experts provided guidance on important model parameters, and on the most reasonable assumptions related to TxV characteristics, background coverage for prophylactic vaccination, screening and treatment, and TxV implementation options.

This report describes the outcomes of the consultations, which will lay the groundwork for developing a PPC document for TxV and contribute to future value assessments.

2. Background on HPV and cervical cancer

2.1. Biology and natural history

The vast majority of CxCa are caused by infection with one of a subset of human papillomaviruses (HPVs) that preferentially infect the mucosal epithelia of the anogenital, oral and upper respiratory tract. Thirteen of these viruses are recognized as high risk (hr) since they encode genes whose protein products can transform normal healthy cells and cause cancer (oncogenic). Two hr types, HPV16 and HPV18 are associated, with 70% of all cervical cancers. In addition to CxCa, oncogenic HPVs, particularly HPV16, are associated with a proportion of anal, oro-pharyngeal, penile, vulval, and vaginal cancers. Overall, HPV causes >5% of all cancers.

The HPV genome (Fig. 1) can be divided into three domains: the upstream regulatory region (URR); the early (E) genes; and the late (L) genes. The URR is the noncoding region that contains regulatory elements that controls the expression of the eight viral genes that make up the remainder of the genome. The early gene region encodes E1, E2 and E4–E7, which express proteins essential for viral replication, viral DNA synthesis, and amplification. The late region encodes the viral capsid proteins L1 and L2. All current highly effective prophylactic HPV vaccines target L1.

Multiple modifiable risk-factors may contribute to the risk of acquiring HPV, including the age at sexual debut and the number of lifetime sexual partners [8]. There is increased biological vulnerability in younger females associated with the cervical transformation zone that is undergoing active metaplastic changes. This, coupled with an HPV-naïve immune system and frequent sexual partner changes that are common among 15–24 year olds, makes this age group particularly vulnerable and correlates with observed HPV prevalence [9].

The one-year clearance rate of incident HPV infections in women ranges from 40% to 70%, depending on the population studied and HPV type. Clearance rates as high as 70–100% have been observed in young women 2–5 years post- infection [9]. Whilst infections tend to clear at the same rate, regardless of age [10], low-risk HPV infections clear more quickly than hrHPV [11]. Amongst women who do not clear the infection, progression to cervical intraepithelial neoplasia (CIN)2/3 – pre-cancerous cervical lesions – is estimated to occur in 8–28%, depending on the HR type. Without intervention in these individuals, an additional 3–5% will progress to invasive CxCa [9]. Generally CxCa takes 15–20 years to develop in women with normal immune systems. For those with weakened immune systems, such as women with untreated HIV infection, CxCa may develop faster (5–10years) [12].

2.2. Epidemiology

Data from high-income settings show that between 50% and 79% of women have a lifetime risk of acquiring a genital HPV infection, with 40% of women infected within the first two years of sexual debut [13] and an additional 40% infected with a hrHPV type at some point in their lives [14]. Data from 2019 demonstrate that the estimated global prevalence of HPV, among women of all age groups with normal cervical cytology, is 9.9% [13].

The estimated age standardized global mortality rate per year in 2020 from CxCa is 13.3/100,000 women, but with marked inequity in the distribution. In many higher income countries, this figure is

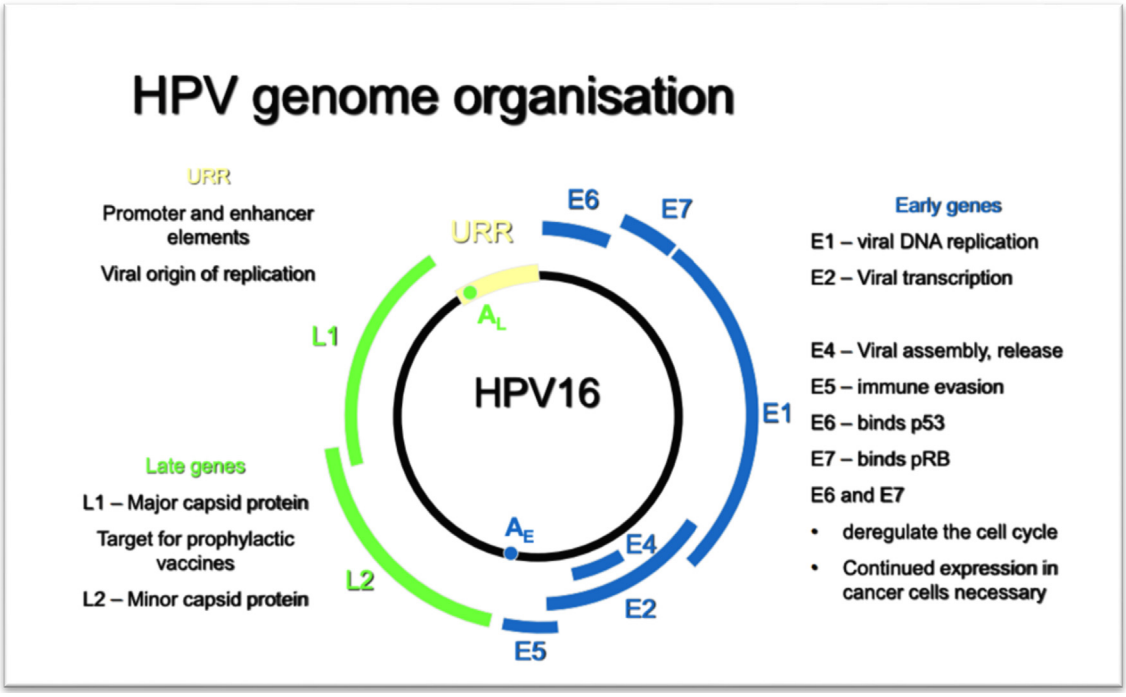

Fig. 1. The HPV Genome.

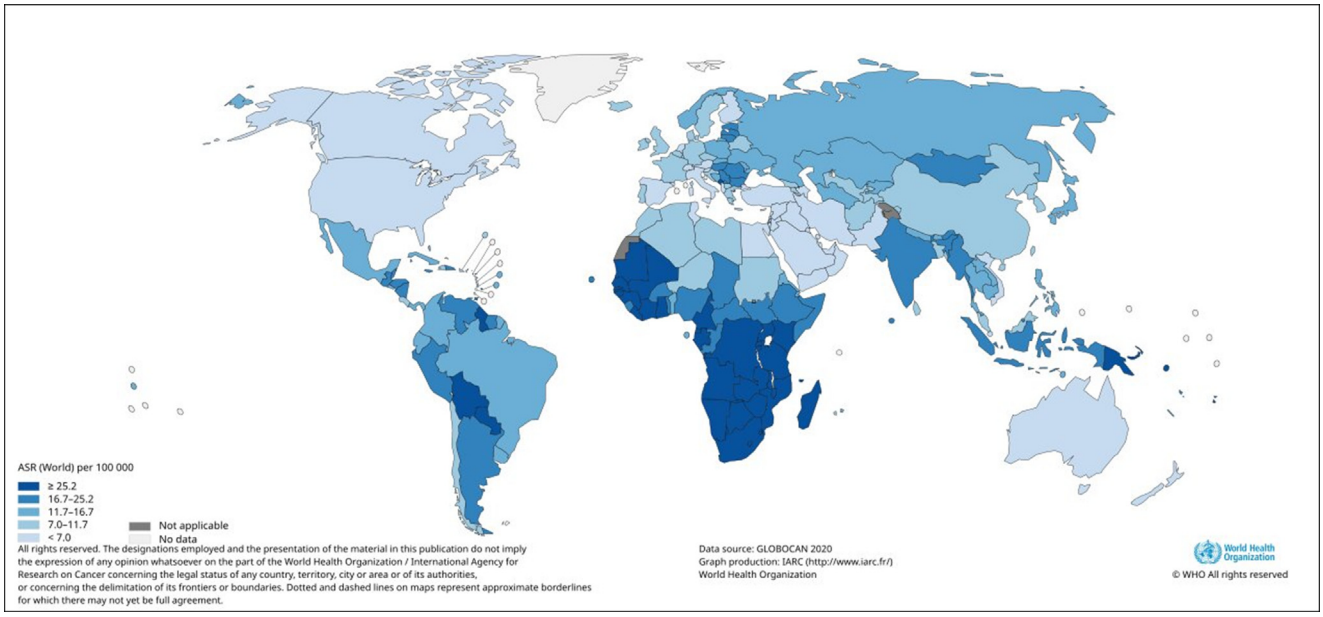

Fig. 2. Estimated age-standardized incidence rates of cervical cancer in 2020 (all ages), from GLOBOCAN 2020, IARC.

fewer than 7 cases per 100,000, with rates above 25 per 100 000 in many countries in sub-Saharan Africa [2] (Fig. 2). These higher rates are not only explained by lower rates of CxCa screening and treatment in this area, but also by the higher incidence of HIV, which increases by six-fold women's risk for CxCa [15,16]. Globally, 5.8% of new CxCa cases in 2018 were diagnosed in women living with HIV (WLHIV). In southern Africa, 63.8% of women with cervical cancer were living with HIV, as were 27.4% of women in eastern Africa, where HIV prevalence levels range from 2% to 27% in the general population within these regions [17], showing the significant burden of CxCa in WLHIV [15]. Consequently, the increased burden and more limited access to screening and treatment in both lower-middle income and upper-middle income countries results in 91% of all deaths from cervical cancer occurring in LMICs [18].

2.3. Cervical cancer intervention programmes

Programmes to prevent CxCa morbidity and mortality are currently three-fold: primary prevention, which includes administration of prophylactic HPV vaccines; secondary prevention, which involves a "screening with or without triage of screen-positives" approach to identify women who have HPV-related CIN2/3 for treatment to prevent progression to CxCa; and treatment of invasive cancer with access to palliative care.

2.3.1. Prophylactic HPV vaccines

Prophylactic HPV vaccines are comprised of HPV L1 proteins self-assembled into virus-like particles with the ability to induce high levels of neutralising antibodies that protect against HPV infection [19]. Clinical trials have shown prophylactic HPV vaccines to be safe and highly efficacious in preventing initial infection with the HPV types included in the vaccine, among type-naïve participants [20],[21],[22],[23]. The first HPV vaccine licensed in 2006 was an aluminium salt-adjuvanted quadrivalent vaccine (HPV4) that protects against HPV 6, 11, 16 and 18. A Toll-like receptor (TLR) 4 agonist-alum adjuvanted bivalent vaccine (HPV2) targeting only the most common hrHPV types 16 and 18 was licensed in 2007. In 2014, a nine-valent vaccine (HPV9) was licensed, offering protection against HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58. The five additional types targeted by HPV9 are estimated to be responsible for an additional 20% of CxCa in addition to protection from HPV 16 and 18 that are responsible for approximately 70% of CxCa cases [11]. In 2021, an additional alum-adjuvanted bivalent vaccine protecting against HPV 16 and 18 was also licensed and will help further improve global supply and demand for HPV vaccines [24]. Although there may be some evidence of more limited cross protection against other HPV types [25], the vaccines are not efficacious against some other HPV types, the vaccines do not have a therapeutic effect on existing infection or lesions.

Because HPV infections are commonly acquired soon after sexual debut, WHO recommends use of prophylactic HPV vaccines in early adolescence, with the primary target being girls before the initiation of sexual activity (9–14year–olds) for the prevention of CxCa [26]. Vaccination of both sexes is typically less cost-effective than vaccination of girls only [27]; however, some countries, especially HICs, include boys as a target cohort [28]. School-based programmes are mainly used as the vaccine delivery strategy among LMICs, resulting in relatively higher coverage than the facility-based programmes [28].

Prophylactic HPV vaccines have been shown to have a positive impact on a population level. Countries that have achieved high coverage of adolescent girls with prophylactic HPV vaccination have observed dramatic declines in HPV prevalence and the incidence of cervical pre-cancers [29]. A recent study from England, where adolescent HPV vaccination programmes are longstanding, demonstrated a substantial reduction in CxCa and CIN3, especially in women who were offered the vaccine at age 12–13 years of age [20]. An earlier study from Australia had similar findings [30]. In Sweden, vaccination has decreased the incidence of CxCa in young women by 85% [21].

2.3.2. CxCa screening and treatment

There are three principal approaches to CxCa screening: cytology, visual inspection with acetic acid (VIA), and HPV DNA or mRNA testing. The Papanicolaou test, based on conventional cytology has largely been replaced by Liquid Based Cytology (LBC), a more advanced variation of conventional cytology [31]. Cytology results are positive when cellular abnormalities are seen suggestive of dysplasia, which then must be confirmed by colposcopy,

and appropriate treatment is determined by colposcopic-directed biopsy of suspected lesions for histological diagnosis. This approach has yielded excellent results in reducing CxCa mortality in HIC [32] and has been less successful in LMIC settings due to the lack of cytologists and expert colposcopists in many LMICS, as well as the lack of lab infrastructure to perform the tests [33]. Visual inspection with acetic acid (VIA), with sensitivity and specificity values ranging from approximately 22–91% and 47–99% for detecting CIN2, is an alternative method of diagnosis, and like colposcopy, accuracy is strongly dependent on the quality of training of the practitioner conducting the test [34]. The newest screening method with high-risk HPV DNA or HPV mRNA detection are the most sensitive and cost-effective diagnostic. In a comparison of HPV to cytology for detecting pre-cancerous lesions, the relative sensitivity is 1.35 (1.23–1.48, 95 %CI), showing hrHPV DNA testing to have a higher sensitivity, but slightly lower specificity at 0.94 (0.93–0.95, 95 %CI) [31].

WHO recommends the HPV DNA test as the primary screening test starting at age 30 for women in the general population and repeated every 5–10 years, rather than cytology or VIA because of the superior test performance [34]. For the general population of women, WHO also recommend the use of HPV mRNA starting at age 30 with a screening interval of every five years. For women living with HIV (WLHIV), HPV DNA is also the recommended primary screening test to start at age 25, with 3–5 years between screening intervals [34]. For women with a positive HPV test, WHO recommends either "screen and treat" or "screen, triage and treat".

In the "screen and treat" approach, the decision to treat is based on a positive primary screening test only, preferably HPV DNA or mRNA test. Before treatment, all women who have screened positive should undergo a visual examination of the cervix with acetic acid to exclude cervical cancer and to determine appropriateness for ablative treatment.

In the "screen, triage and treat" approach, the decision to treat is based on a positive primary screening test followed by a positive second ("triage") test. The WHO recommended primary test is HPV DNA detection followed by partial genotyping, colposcopy, VIA or cytology as a triage test [28]. If treatment is indicated and the lesion is appropriate (small and entirely visible on the ectocervix), it can be treated with ablation, which destroys abnormal tissue by freezing (cryotherapy) or application of heat (thermal ablation). If the lesion is not appropriate for ablation, it can be surgically excised by removing the entire abnormal transformation zone, using large loop excision of the transformation zone (LLETZ), loop electrosurgical excision procedure (LEEP), or cold knife conization (CKC). Women with suspected cancers must be referred for further evaluation and management [28].

2.3.3. CxCa management and treatment

Case management is based on staging of the disease. Early stage CxCa is treatable by surgery or radiotherapy, with long-term survival and cure in around 80% of individuals where timely diagnosis and high-quality treatment are available [35]. WHO recommends surgery and radiotherapy, with or without chemotherapy, for early stages of CxCa [34]. WHO also recommends integrating palliative care into the treatment plan throughout the course of the disease. Effective early stage treatment is paramount, as standard of care radio- and chemotherapies of late stage, metastatic CxCa tend to have low cure and survival rates [36].

Cancer diagnostic and treatment services show wide disparities. Coverage levels of CxCa management services in the public sector are generally above 90% in HICs; however, coverage of such services is generally under 30% in low-income countries and ranges from around 40% to 70% for access to cancer centres, surgery, radiotherapy, chemotherapy and pathology services in lower-middle income countries. Cost, complexity, and lack of health system infrastructure and human resources remain barriers to effective widespread implementation.

3. Therapeutic HPV vaccine development

No licensed TxV currently exist. To date, a wide variety of approaches have been used to develop TxV, including peptide, protein, DNA, RNA, and viral-vectored vaccine candidates. These have been predominantly based on the E6/E7 antigens. A review by BMGF in 2019 of TxV candidates in clinical trials at that time is shown in Table 1. Most TxV candidates in clinical development target advanced CxCa and pre-cancerous cells (e.g., CIN2/3).

3.1. Scientific challenges in developing therapeutic HPV vaccines

The development of a therapeutic HPV vaccine is challenging, in part because the mechanism of the virus in evading the innate immune response requires that a vaccine must be highly immunogenic and elicit a strong antigen-specific cytotoxic response. To date, TxV development has focused on targeting invasive CxCa and CIN2/3 lesions. However, where advanced lesions have often undergone immune selection, a T-regulatory dominance and greater immune repressive local environment provide scientific and immunological challenges to achieving an efficacious vaccine. Experts suggested that TxV targeting HPV infection or low-grade lesions may be more effective compared to CIN3 or cancer because they are less likely to have undergone immune selection.

For either a vaccine targeting hrHPV infection or a vaccine targeting advanced CIN2/3 lesions or cervical cancer, experts agreed that an effective single dose vaccine was unlikely. However, they noted the possibility that a single-encounter visit could be done if an additional dose (or doses) were self-administered, such as an intra-vaginal administration booster dose [37].

4. Public health need for therapeutic HPV vaccines in LMICs

Meeting participants discussed the public health need for TxV within the context of existing CxCa programmes, with the overarching aim of reducing global CxCa deaths over the next three to four decades. This involved considering current and predicted future gaps in scaling up existing interventions and the potential role TxV might have in filling those gaps. To stimulate discussion, following presentation of global data on intervention coverage, a panel including experts from China, Colombia, South Africa, Zimbabwe, and the International Agency for Research on Cancer (IARC) highlighted challenges and opportunities for scaling up existing CxCa prevention and management interventions and how gaps might be addressed by TxV.

4.1. Implementation and scale-up of existing cervical cancer programmes

4.1.1. Prophylactic HPV vaccines

As of April 2022, a total of 120 countries had introduced HPV prophylactic vaccines into their national immunization programmes [38]. However, only an estimated 13% of young girls are fully vaccinated globally [39], and HPV vaccines had not reached those settings most in need: 60% of CxCa cases occur in countries that have not yet introduced the prophylactic HPV vaccine [15].

Additionally, in some LMICs where HPV vaccines are available, uptake varies widely. For example, in the Americas region, where most countries have introduced HPV vaccines, coverage of 15 year-old girls with two doses ranges from 4% in Suriname to 72% in Brazil [37].

Table 1
TxV HPV trials (as of 2019), information sourced from https://clinicaltrials.gov/.

Vaccine[1]	Sponsor	Phase	Disease Stage[4]	Trial population[2]	Route of administration	Dosing Schedule[5]
ADXS11-001	Advaxis, Inc	3: active, not recruiting	CCx	>18, women only	IV (infusion)	3 doses every 3 wks + 5 doses every 8 wks
VGX-3100	Inovio Pharmaceuticals	3: active, not recruiting	HSIL, CIN2, CIN3	>18, women only	IM (electroporation)	3 times at day 0, wk 4, 12
ISA 101	ISA Pharmaceuticals	2: completed	CCx	>18, women only	IM (injection)	3 doses every 3 wks
TA-HPV	EORTC[3]	2: completed	CCx	>18, women only	IM (injection)	2 doses every 4 wks + surgery
TS	Hoffmann-La Roche	2: completed	CIN2, CIN3	>18, women only	SQ (injection)	3 doses at day 0,8,15
TVGV-1	TheVax Genetics Vaccine	2: active, not recruiting	HSIL	18-55 women only	IM (injection)	Unknown
BLS-ILB-E710c	BioLeaders Corporation	2: recruiting	CIN2, CIN3	20-49 women only	Oral	4/day for 5 consecutive days at wk 1,2,4,8
DPX-E7	Dana Farber	2: recruiting	CCx	>18, women and men	IM (injection)	2 priming every 3 wks + booster every 8 wks
PepCan	U of Arkansas	2: recruiting	HSIL	18-50, women	ID (injection)	4 doses every 3 wks
GX-188E	GeneXine Inc.	2: unknown	CIN2, CIN3	18-60 women only	IM (electroporation)	3 times at day 0, wk 4, wk 12.

Route of administration:
Oral, IM (intramuscular), SC (subcutaneous)
ID (intradermal)
IV (intravenous)

Dosing Schedule:
Unknown
Fixed number of doses
Number of doses dependent on patient

1. Included vaccines in Phase 2+, focused on cervical cancer treatment; Excluded vaccines that are cell-based or used in combination with other biologics. **2**. Based on population being tested in the clinical trial. **3**. European Organisation for Research and Treatment of Cancer. **4**. CCx= Cervical Cancer, HSIL= High-grade squamous intraepithelial lesion, CIN= Cervical intraepithelial neoplasia. **5**. Treatment is for duration of trial and varies for each vaccine based on endpoint for subject enrolled.

Among 47 countries in the WHO African Region, which has the highest rates of CxCa in the world, 23 countries have introduced HPV vaccine into their national immunization programme as of April 2022 [25]. Vaccine coverage varies across countries from 0% to 77% of eligible girls (9–14–year–olds), through mostly school-based delivery [28],[40]. In South Africa, where prophylactic HPV vaccines were introduced in 2014 for 9-year-old girls, 95% of schools are reached by the programme, with a coverage of 75% of eligible girls with the first dose [41].

Challenges associated with meeting vaccination targets have included insufficient global supply of vaccines, costs of the programme, low acceptance of the vaccine, and additional resources required to engage stakeholders. For example, in China, where there is no national programme, families are required to pay for the vaccine for their daughters, and marketing is poor, resulting in low population demand [42]. Some meeting participants also noted challenges in areas such as cold-chain management and integration into existing vaccination programmes.

Nonetheless, it has been demonstrated that it is feasible to achieve high coverage of prophylactic HPV vaccines, even in resource-poor settings [43]. Furthermore, a Strategic Advisory Group of Experts on Immunization (SAGE) meeting held in April 2022 advised that countries may now choose a one- or two-dose schedule for 9–14-year-old girls, the primary target cohorts, and for women aged 15–20-years-old [44], which would simplify immunization implementation, increase supply, and reduce production bottlenecks and overall costs [45].

4.1.2. Cervical cancer screening and treatment

Access to CxCa screening is very limited in many LMICs. Only 76 countries have achieved an 'ever' lifetime screening coverage rate of over 70%, with 126 countries below this level, and many countries still with levels of only 0–9% [6], primarily in LMICs (Fig. 3). This demonstrates the significant challenge of reaching the WHO elimination targets for 2030. To date, very few countries have fully transitioned to using HPV DNA testing, with many LMICs still using VIA, which has limitations and gives variable results.

The complexity and costs of screening and treatment programmes have been the primary barriers in many LMICs. For example, in South Africa, screening is only practiced within research settings or the private sector, with the programme

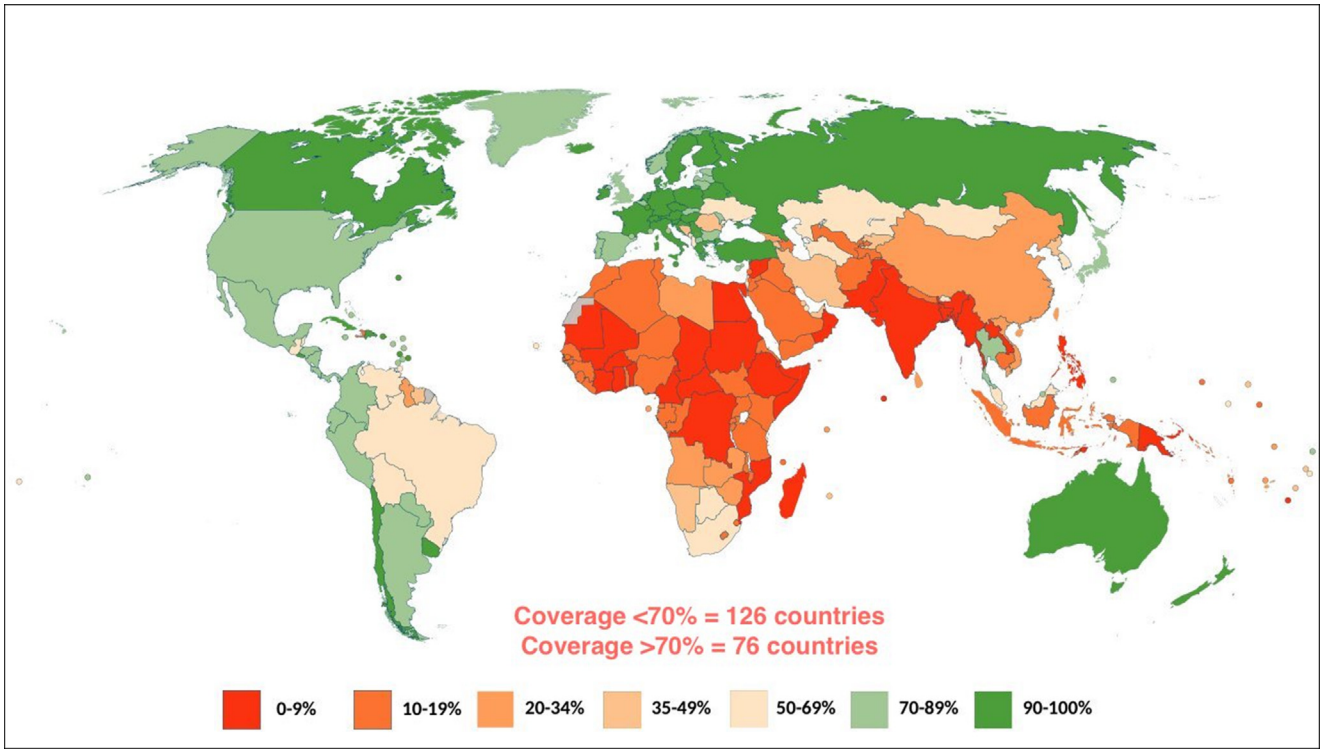

Fig. 3. Global map showing the distribution of country's lifetime screening coverage (2019), women aged 30–49 years by country. Adapted from Lancet Global Health, 2022, Bruni et al. (https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(22)00241-8/fulltext).

deemed to be too expensive to expand to the public sector. Cytology is currently the main screening test used; HPV DNA testing is recommended at the national level, although continued lack of lab capacity for this testing has continued to limit use. Many settings report challenges in switching to primary HPV DNA testing, including inadequate laboratory facilities and staffing, the high expense of the diagnostic tests, and weak communication systems to contact women who test positive.

Many meeting participants highlighted that even when screening occurs, the biggest gap within the cascade of care is often from screening to treatment, with substantial loss to follow-up after a positive screening test or limited capacity of the system to deliver quality treatment. Many challenges contribute to loss to follow up for women requiring treatment, including costs, lack of experienced staff or equipment at the site of screening, and difficulties with travel to referral centres. For example, given lack of national programmes in many countries in the Southern African region, many women with positive screening tests must pay for their treatment, resulting in large loss to follow-up. A study by IARC in Africa demonstrated that one-third of women referred for colposcopy never reached the colposcopy centre [46]. Even when women reach referral centres, a lack of trained clinicians and difficulties with quality control are problematic in several settings, and *peri*-operative and pregnancy complications following LLETZ and other excision remain a concern [47]. In countries with high HIV prevalence, major barriers to CxCa prevention include high recurrence rates of dysplasia following treatment in WLHIV [48]. There are also difficulties in treating larger lesions or lesions that occur predominantly inside the endocervical canal. These lesions tend to have higher failure rates and are more common in the unscreened population in LMICs [49].

In the future, HPV rapid point-of-care-tests could help to reduce issues with loss to follow-up, if treatment can be performed at the same time in a single visit. Whilst these tests are not yet available, modelling has shown they have the potential to be both effective and cost-effective, particularly in high-burden settings [50,51], but many facilities still lack the means to provide adequate follow-up treatment.

4.2. Potential role and use cases for therapeutic HPV vaccines

Meeting participants agreed that efficacious TxV could be a valuable addition to CxCa prevention and treatment efforts, given the large numbers of women at risk for CxCa who did not and will not have received a prophylactic vaccine in adolescence and/or prior to infection with hrHPV, and the substantial challenges related to implementing and achieving high coverage of screening and treatment. However, the extent to which TxV might fill existing gaps will depend on their characteristics and how they would be used. Two high-level use cases were envisioned and discussed by the group. Whilst these are presented as separate entities, each approach could be adopted concurrently in several formats:

- Use case 1 – population-based approach: therapeutic HPV vaccine would be delivered broadly to an entire population, unlinked from testing or evaluation; for example, offered to all adult women at a given age.
- Use case 2 – screening-based approach: therapeutic HPV vaccine would be targeted to a specific subset of people based on a positive test; for example, given to all women with a positive HPV DNA or mRNA test.

Both use cases would present an opportunity to clear hrHPV infection, and potentially regress CIN2/3 lesions, for women who have or have not previously received prophylactic vaccination. Both could also address gaps in realization of comprehensive screening and treatment programs. Use case 1, the broad population-based approach, would not require any existing screening infrastructure or coverage, although it would require an infras-

tructure for mass vaccination. Use case 2, the screening-based approach, would at least require the capacity to conduct testing and/or screening for determining eligibility for vaccination. However, this approach may address some of the existing gaps related to loss to follow-up, for example vaccination could be given immediately at the time of HPV diagnosis, before referral for management and/or treatment. In addition, this approach could address some of the gaps related to inadequate treatment infrastructure, by providing a more simplified, non-invasive means of treatment administered with minimal training. The vaccine might also be given at the same time as standard treatment, if it were shown to improve treatment outcomes and reduce recurrence rates. Therapeutic HPV vaccines that could treat invasive cancer would address large gaps in services; however, the feasibility of developing such a vaccine was considered very low by experts. Continued efforts to strengthen existing CxCa prevention and treatment programmes are needed as work toward development of therapeutic vaccines progresses.

5. Understanding the potential value of therapeutic HPV vaccines

Multiple factors will need to be simultaneously considered to understand the potential value of TxV, within the context of broader CxCa prevention programmes. The added value of a therapeutic vaccine, and its optimal characteristics, will be strongly influenced by each individual country setting in which it will be used. Mathematical modelling will be critical in predicting the impact and cost-effectiveness of TxV in different settings and contexts. Based on discussions at the expert consultation meeting, a modelling exercise is being undertaken, considering different vaccine characteristics, use cases, and background implementation of other interventions. The modelling platform has previously been used to evaluate the CxCa elimination strategy in 78 LMICs [4,21].

Meeting participants discussed important parameters that contribute to understanding the potential value of therapeutic vaccines, which is being incorporated into the modelling. One of the important parameters is the timeline to develop a therapeutic vaccine, relative to efforts to increase infrastructure and access to existing screening and treatment interventions and to the aging of cohorts vaccinated with prophylactic HPV vaccines in adolescence. Experts felt that a base-case scenario was vaccine development by 2030; however, the modelling will be useful to understand the added value of TxV in a highly optimistic scenario of development by 2027, and also by vaccines over longer development periods. The main benefits of TxV would accrue to women who did not receive prophylactic vaccination in adolescence and where screening and treatment coverage is low. As cohorts vaccinated with PxV in adolescence age, the value of a TxV will diminish. Scale-up of screening and treatment and even expansion of catch-up vaccination to older ages, especially if one dose is proven effective [52], has the potential to have a similar and more proximate impact if they can occur quickly. The most optimistic scenario for scale-up of current prevention programmes assume that the 2030 targets set out by WHO are met, yet this would require significant mobilisation and heightened efforts that may not be feasible in many geographies. More conservative timelines for reaching these targets could make development and use of a TxV more favourable. Development of alternative interventions, such as rapid point-of-care-tests for HPV DNA or pharmacologic treatments for HPV, in the interim could also shift value considerations [51].

Another important factor in determining impact is the predicted efficacy of the vaccine for clearing hrHPV infection and/or for regressing pre-cancerous lesions, which are not mutually exclusive. This parameter will interplay with the use cases for the vaccine outlined above and the setting in which the TxV is being implemented. For example, in settings with a well-established and effective screening programme with good coverage, a greater priority may be for a vaccine that improves treatment rates and targets pre-cancers within the context of a screening programme. However, current ablative and excisional treatments already have a high success rate, therefore an HPV Tx targeting pre-cancerous lesions would need to show significant efficacy and safety advantages in this scenario. In settings where screening coverage is low and factors which prohibit the scale-up of such programmes are unlikely to be addressed in the near future, a vaccine targeting HPV infections, provided more broadly, may offer greater value. However, to compare the use cases for vaccines with different characteristics, modelling will help to understand the relative impact as well as the cost-effectiveness. The numbers needed to vaccinate will be higher to prevent one case of CxCa under use case 1 (population-based approach), because approximately 80% of individuals receiving the vaccine will not be positive for HPV infection, and because around 90% of those with HPV infection and/or low-grade dysplasia will clear infection and dysplasia naturally and will not go on to develop CxCa even without vaccination [53]. This must be weighed against the capacity to reach women infected with hrHPV if vaccination is linked to screening programmes such as in use case 2.

The targeting of different HPV types will also be important. A minimum expectation will likely be a vaccine targeting HPV 16 and 18, which cause 70% of all cervical cancers [54]. A vaccine that primarily clears HPV infection may provide additional cross protection against other types, and therefore a higher valency vaccine may not be a necessity – although potentially useful to have, particularly for WLHIV.

Finally, a variety of end-user values and preferences, including from women who could ultimately use such a product, will be important, related to acceptability and vaccine confidence. Understanding these preferences and developing demand creation and communications strategies in advance will be important to the ultimate success of a potential new product.

5.1. Modelling considerations for assessing the value of an HPV Tx

The role of mathematical modelling will be important to further our understanding of the relative value of both use cases, whilst considering other factors which impact the potential value of a TxV.

The modelled evaluation will use the established and well-validated *Policy1-Cervix* platform [4,18], and will explore the potential impact of a TxV across 78 LMICs and assess the benefits, harms and cost-effectiveness of each scenario. It will also consider the impact of HIV infection, and the likely chance that the TxV will be less effective in WLHIV. The modelling will be conducted in three stages and at each stage a consultation process will take place with an expert advisory committee to review results and provide further recommendations.

During the initial October 2021 stakeholder consultation, the group of experts reviewed the parameters for consideration, the vaccine assumptions, and the outputs within the context of both use-cases. The initial stakeholder consultation provided an opportunity for initial feedback and reflections on defining the value of a therapeutic vaccine for CxCa. Following on from the meeting a series of more focused expert consultations took place in February and March 2022 to inform and guide the modelling exercise. These consultations involved independent groups of vaccine developers, cervical cancer experts and cervical cancer implementation experts. Given the complexity of the modelling exercise and the significant number of scenarios that could be explored (thousands of scenarios are considered possible, with a model run time of

approximately 3 h per scenario), it will be important to focus on those scenarios which are most feasible and credible for consideration.

The first stage of the modelling to be carried out in the first half of 2022 will use a range of scenarios reflecting TxV deployment under the two major use cases, varying the characteristics of the TxV and background PxV and screening. The consultations held in February and March 2022 focused on defining the 'reasonably expected' TxV characteristics to be assumed as base case (default) input parameters in the modelling, and to define the feasible range (i.e. 'best' and 'worst') of parameter assumptions for TxV characteristics. Key considerations also included defining scenarios for different background scale-up assumptions for prophylactic vaccine coverage, screening and treatment coverage, considering variations on whether prophylactic vaccine is co-administered and if so, for which age groups. TxV efficacy assumptions were assessed, in addition to and how a TxV could be used within clinical management algorithms.

Table 2 below, provides a summary of the outcomes and agreements reached from the series of expert consultations. These will be carried forward and applied to the initial stages of the modelling and further refined and consolidated in the later stages.

The modelling component of this work, including the model structure and the key assumptions related to the exercise were reviewed by an expert panel from the WHO Immunization and Vaccines Implementation Research Advisory Committee (IVIR-AC), in March 2022. IVIR-AC's role is to put modelling evidence into both a methodologic context and best practices for the SAGE and the Immunization, Vaccines and Biologicals (IVB) Department at WHO. The approach was largely supported and endorsed by the committee with several recommendations and considerations provided [55].

6. Key considerations for developing preferred product characteristics

Meeting participants discussed key considerations for TxV preferred product characteristics (PPCs) as a starting point for developing a formal WHO PPC document through a multistep consultative process [7]. The discussions revolved around three key PPCs: vaccine indications, target populations, and delivery strategies. PPCs focus primarily on preferences for LMICs to encourage development of TxV for global use.

6.1. Vaccine indications

Vaccine indications provide the basis for licensure and reflect the main outcomes to be evaluated in vaccine clinical trials. The choice of the target indication should reflect what the public health goals of the product are (i.e., reducing CxCa deaths) and link to the putative mechanism of action. The two main indications that were discussed by the group were:

(1) an indication to clear HPV infection; and
(2) an indication to regress pre-cancerous lesions.

Meeting participants felt that both indications were likely to contribute to meeting public health goals, but the indication would influence how the vaccine would be used. Whilst the first indica-

Table 2
HPV TxV vaccine characteristics, coverage of current programmes, and delivery of HPV Tx for the base-case modelling scenario.

Model input (vaccine characteristic, programme considerations, target population, delivery)	Recommendation for the base-case* and the range for the 'best' and 'worst' scenarios
Vaccine indications	TxV targets HPV 16/18 infection and lesions
Direct efficacy against 16/18 infection+/-CIN1	90% net clearance of HPV +/- CIN1 (for pre-cancerous lesions that do not spontaneously clear)
Direct efficacy against 16/18-related CIN2/3	50% regression + clearance of CIN2/3
Direct efficacy against cancers	No action on cancers
Cross-efficacy against HPV 31, 33, 45	50% (of vaccine efficacy in the base-case) cross-protection against 16/18-related types
Efficacy in WLHIV	As in general population (base case); Lower efficacy explored in sensitivity analysis
Timing of introduction	Population-level scale-up of TxV in LMIC to start from 2027 (best case); 2030 (base case); 2040 (worst case)
Mechanism of delivery	Vaccine delivered IM or IM prime/intravaginal boost
PxV background coverage (by 2030)	Range (0–90%) 90% by 2030 (best case) no change from current rates (worst case)
Screen-and-treat background coverage (by 2030)	Range (0–70%) 70% by 2030 (best case) no change from current rates (worst case)
Cancer treatment access (by 2030)	Range (33–90%) 90% by 2030 (best case) 33% no change from current rates (worst case)
Concomitant PxV after TxV	Not modelled in base case (considered in sensitivity analysis)
Age of administration considered	Age 20–60 years (use-case 1) Age 30–60 years (use-case 2)
Delivery of TxV after primary HPV test positive	For Use case 2, assume TxV administered in women who receive an HPV test and Screen 16/18 positive (genotyping only) Screen any HR-HPV positive (any primary HPV)
Follow-up after delivery of TxV for HPV positive women	For Use case 2, after TxV in HPV-positive women we assume All women are lost to follow-up (worst case); No women are lost to follow-up for missed disease (best case) Relative benefits and cost-effectiveness assessed
Vaccination coverage (2020–2030)	Coverage informed by WHO/ICO and trajectories informed by metrics like DTP −10% (used by Gavi)
Screen-and-treat background coverage (2020–2030)	Coverage informed by regional-level studies Published data along with studies on screening coverage in AFRO region stratified by HIV-status will be obtained Data should be interpreted cautiously, due to differences in screening tests used, lack of formal QA and monitoring, etc.
Cancer treatment access (2020–2030)	Radiotherapy used as surrogate marker for access
Target groups	Focus should be on optimising outcomes in groups at highest-risk in the first instance, (i.e women in LMIC at risk of cervical cancer); Impacts of TxV on males and other cancers considered at a later stage

*These assumptions will be used for the base case; in Stage 2, a range of vaccine parameters will be explored.

tion (clearing infection) has the greatest potential to be implemented at a population-level (use case 1), the implementation of the second indication (regressing pre-cancerous lesions) is more likely to take place within the context of existing screening and treatment programmes, although both use cases could be applied to both indications. Additionally, both indications are not mutually exclusive and a TxV may ultimately target both hrHPV infection as well as pre-cancerous lesions. In all cases, there will be implications and considerations for both the cost and scale-up of either programme. Whilst developmental challenges exist for both indications, a vaccine with an indication to clear hrHPV infection may also lead to regression of lesions. An indication of regression of pre-cancerous lesions may need to prove additional or greater benefit than the current standard of care recommending ablative treatment.

6.2. Target populations

A number of factors need to be considered in determining the most appropriate target populations, including determination of the population that would receive the greatest direct benefit of vaccination, the epidemiology and natural history of the infection, the ability to reach the population through programmes, cost and cost-effectiveness, and equity. Meeting participants felt that the primary focus should be on women, who stand to receive the most direct benefits from the vaccine. However, they suggested that there may also be a potential role for providing the vaccine to men, and in particular men who have sex with men (MSM), which should be explored in modelling, as men may contribute to herd immunity and gain individual benefits related to other HPV-related cancers, particularly anogenital lesions for MSM. Cost-effectiveness will likely be a key determinant of the value of gender-neutral vaccination.

Age is an important consideration for choice of target population, and target age may vary according to the vaccine indication and use case. For broad population-based delivery of vaccines to clear HPV infection (use case 1), targeting younger ages of adult women (e.g., 20–25 years) would occur before many women have pre-cancer lesions, but would clear many infections that would likely have cleared naturally, and would run the greatest risk of new infections being acquired after vaccination given the age-associated incidence of infection. However, this is dependent on whether the TxV is capable of inducing sufficient memory to infections or lesions acquired at a later date, and for how long, following initial vaccination. It is not yet known whether a TxV will have this property. Targeting older ages (e.g., 30–35 years) would capture more infections acquired during the peak years of incidence and would clear more persistent HPV infections but may also occur in the setting of more pre-cancer lesions that have already developed and thus may be more challenging to regress. A vaccine primarily targeting pre-cancerous lesions is more likely to be targeted at older age groups (30–35 years and older, or 25 year-olds in WLHIV), in conjunction with screening recommendations. Such a vaccine could replace or be used alongside existing treatments to increase uptake, thus mitigating the effects of loss-to-follow-up with the population having received an effective treatment.

Special consideration will need to be given to WLHIV as a target population, as CxCa risk is six times higher amongst WLHIV (Stelzle et al., 2021). However, the vaccine may not achieve as high an efficacy in WLHIV.

6.3. Delivery strategies

Preferred delivery strategies will need to consider the ability to reach the target population to have an impact; the feasibility of implementation–e.g., considering whether there is an existing immunization platform for the proposed target populations; staff and training requirements, and challenges with implementation; and costs and cost-effectiveness. To better understand these considerations related to how TxV could be implemented and the feasibility of implementation, a panel session with experts from Brazil, India, Peru, South Africa, and Sri Lanka started the discussion.

The availability of an existing delivery platform will be an important consideration. For broad-based vaccination (use case 1) to clear infection, historically there has not been an immunization platform for adults of reproductive age, particularly for a single sex. However, the COVID-19 pandemic has provided adult vaccination platforms that may be a new opportunity for delivery of other vaccines. Whether they will be as successful outside of a pandemic is unclear, but the infrastructure and staff training required for delivering vaccines has been established in many settings. Campaigns were also proposed by meeting participants as an effective means to deliver such a programme which can be done at a relatively low cost. The optimal approach would also depend on the vaccine indication: a vaccine with an indication to regress pre-cancerous lesions would clearly be best suited for a more targeted, screening-based vaccination approach (use case 2). Even for a persistent infection indication, contact with the health system might make vaccine delivery more straightforward; if the clinical setting involved with CxCa screening includes health workers who are able to deliver injectables. Several experts felt that, in many settings, implementation of HPV DNA testing and a possible future TxV would be best suited to a primary care setting, particularly using self-collection vaginal swabs for screening, and would be even more effective if rapid HPV POCTs become available [51]. In a primary care setting, delivery of vaccine at the point of a positive HPV diagnosis may be simpler, followed by referral to receive a pelvic examination. Other potential delivery platforms could be linked to existing programmes, such as post-partum care, family planning, HIV or STI clinics, or following the first vaccination of a newborn infant. Of note, HIV care services offer a unique opportunity to target those at highest risk for CxCa in a well-established and well-attended care system.

Many experts favored targeted screening-based delivery given the large numbers of women that would need to be vaccinated using a population-based approach, with only a fraction having hrHPV infection, many of which would clear on their own. On the other hand, in settings where scale-up of CxCa screening programmes has been extremely difficult, as is the case for many LMICs, it might also be difficult to scale-up a new therapeutic vaccine, and a population-based approach may be preferred. Where scale-up of prophylactic HPV vaccines is also problematic, even in the context of school-based programmes, delivery of the vaccine in any setting may be challenging. The screening-based approach may be most relevant in those settings where the largest barriers are related to loss to follow-up or inadequacy of treatment infrastructure. The vaccine in this context could significantly reduce the drop-out from screening to treatment, and there would be less urgency to follow-up if the vaccine were able to treat and clear the infection.

For any platform, delivery considerations will be driven by cost and complexity of the approach, the vaccine attributes, the skill set required to deliver the vaccine, and local contextual factors. For example, a multi-dose vaccine would add complexity and such a programme may only be most realistic within ongoing care settings such as those for WLHIV. Storage and transportation will also be important. Both the upfront cost of the vaccine as well as the cost of implementation will be key considerations for any programme [56].

7. Conclusion and next steps

Global efforts are needed to address the major toll exacted by CxCa on millions of women around the world, particularly in LMICs. The development of therapeutic HPV vaccines has the potential to address several gaps in reaching global targets to prevent CxCa and reduce CxCa-related deaths over the next several decades. Understanding the potential added value of such a product in the context of existing CxCa prevention efforts, and the vaccine attributes and use case that would optimize the added value, will be critical in guiding TxV development.

A series of expert consultations has delineated several key considerations for understanding the potential public health value and defining PPCs for therapeutic HPV vaccines. They have also provided guidance on the likely scenarios and assumptions to be used in ongoing modelling work to predict the value and cost-effectiveness of TxV and inform vaccine characteristics that would optimize impact and value.

The next steps in the process include further advisory meetings to guide the later stages of the modelling exercise and presentation of modelling results at a second stakeholder consultation to be convened in Fall 2022. An end-user survey is also being conducted to understand the perspectives of people that will ultimately implement, deliver, use, or benefit from such vaccines (i.e., programme and service managers, health providers, and patients) on the potential value of a HPV Tx, its future use, and optimal characteristics. These activities will further inform and refine the development of a final WHO PPC document on TxV, which will be iterative and consultative, including online public consultation.

Funding

This work is supported by a grant from the Bill & Melinda Gates Foundation, Seattle, WA (grant number INV-021904) to the WHO Department of Research for Health and the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP). The authors alone are responsible for the views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: From the full list of authors, the following have declared potential conflicts of interest; Celina Schocken is currently conducting consultation work on HPV diagnostics for Roche Diagnostics; Margaret Stanley has provided consultancy services for Merck Pharmaceuticals. Karen Canfell, who is leading the modelling effort for this work is Co-principal investigator (Co-PI) on a cervical cancer trial, funded by VCS (a non-profit foundation) which is also supported by Roche Diagnostics. She also acts as Co-PI for a study on the elimination of CxCa, which is supported by Minderoo Foundation Frazer Family Foundation, which is supplied with equipment and donations from Cepheid Inc. Gina Ogilvie, as part of a regulatory, legislative or judicial process has provided expert opinion or testimony related to the subject of the meetings and work for a commercial entity (not specified), and in addition has held office or other position in which she has represented interests or defended a position relating to the subject matter (unspecified). Luisa Lina Villa provides consultancy services and has spoken on behalf of Merck Pharmaceuticals on the topic of prophylactic HPV vaccines.

All participants in the Therapeutic HPV Vaccine PPC Expert Consultations completed WHO Declaration of Interests statements, and their participation in these meetings and commenting on aspects of the PPC development were in accordance with the Organization's guidelines for Declaration of Interests for WHO experts. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Acknowledgements

Therapeutic HPV Vaccine PPC Expert Consultation Group:

Laith Abu-Raddad, Weill-Cornell, Qatar; Sharon Achilles, Bill & Melinda Gates Foundation (BMGF), USA; Hiroki Akaba, Immunizations, Vaccine and Biologicals (IVB), World Health Organization (WHO), Switzerland; Maribel Almonte Pacheco, International Agency for Research on Cancer (IARC), France; Phionah Atuhebwe, WHO Regional Office for Africa, Republic of Congo; Nyambat Batmunkh, WHO Regional Office of the Western Pacific, Philippines; Armando Baena, IARC, France; Iacopo Baussano, IARC, France; Partha Basu, IARC, France; Stephen Becker, BMGF, USA; Neerja Bhatla, All India Institute of Medical Sciences, India; Paul Bloem, IVB, WHO, Switzerland; Marc Brisson, Université Laval, Canada; Nathalie Broutet, Sexual and Reproductive Health and Research (SRH), WHO, Switzerland; Emily Burger, Harvard University, USA; Karen Canfell, The Daffodil Centre, The University of Sydney, a joint venture with Cancer Council NSW, Australia; Sarah Charnaud, Research for Health (RFH), WHO; Z. Mike Chirenje, University of Zimbabwe, Zimbabwe; Raveena Chowdhury, MSI, UK; Jamie Cohen, Institute for Disease Modeling (IDM), BMGF, USA; Michael Chung, University of Washington, USA; Shona Dalal, Global HIV, Hepatitis and STI Programmes (HHS), WHO; Silvia de Sanjose, National Cancer Institute, Spain; Sinead Delany-Moretlwe, Wits RHI, South Africa; Lynette Denny, University of Cape Town, South Africa; Mamadou Diop, Joliot Curie Cancer Institute, Senegal; Peter Dull, BMGF, USA; Linda Eckert, University of Washington, USA; Eleanor Edson, BMGF, USA; Kamal Fahmy, WHO Regional Office for the Eastern Mediterranean, Egypt; Deepa Gamage, Ministry of Health, Sri Lanka; Patricia Garcia, Cayetano Heredia University, Peru; Birgitte Giersing, IVB, WHO, Switzerland; Sami Gottlieb, SRH, WHO, Switzerland; Patti Gravitt, National Cancer Institute (NCI), USA; Rolando Herrero, Agencia Costarricense de Investigaciones Biomédicas, Fundación INCIENSA, Costa Rica; Raymond Hutubessy, IVB, WHO, Switzerland; Holger Kanzler, BMGF, USA; Sharon Kapambwe, WHO Zimbabwe Country Office; David C. Kaslow, PATH, USA; Jane Kim, Harvard University, USA; Luisa Lina Villa, Universidade de São Paulo, Brazil; Silvana Luciano, Regional Office of the Americas, WHO, USA; Maeve B. Mello, HHS, WHO, Switzerland; Kelle Moley, BMGF, USA; Liudmila Mosina, WHO Regional Office for Europe, Denmark; Raul Murillo, Hospital Universitario San Ignacio, Colombia; Emmanuel Njambe, WHO Regional Office for South-East Asia, India; Gina Ogilvie, BC Women's Hospital and Health Centre, Canada; Holly Prudden, SRH, WHO, UK; Helen Rees, Wits RHI, South Africa; Anna Laura Ross, RFH, WHO, Switzerland; Peter Sasieni, King's College London, UK; John Schiller, NCI, USA; Celina Schocken, BMGF, USA; Kate Simms, University of Sydney, Australia; Jenny Spencer, University of Texas, Austin, USA; Margaret Stanley, University of Cambridge, UK; Marleen Temmerman, Aga Khan University Hospital, Kenya; Cari van Schalkwyk, DST-NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), South Africa; Fanghui Zhao, China Cancer Institute, China.

References

[1] Okunade KS. Human papillomavirus and cervical cancer. J Obstetr Gynaecol: J Inst Obstetr Gynaecol 2020;40(5):602–8.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality

worldwide for 36 cancers in 185 countries. CA: A Cancer J Clin [Internet] 2021;71(3):209–49. Available from: 10.3322/caac.21660.
[3] The World Health Organisation. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva; 2020.
[4] Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet [Internet] 2020;395(10224):575–90. Available from: 10.1016/S0140-6736(20)30068-4.
[5] Hutubessy R, Lauer JA, Giersing B, Sim SY, Jit M, Kaslow D, et al. The Full Value of Vaccine Assessments (FVVA): a framework to assess and communicate the value of vaccines for investment and introduction decision making. social science research. Network 2021.
[6] Bruni L, Serrano B, Roura E, Alemany L, Cowan M, Herrero R, Poljak M, Murillo R, Broutet N, Riley LM, de Sanjose S. Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis. Lancet Glob Health. 2022;10(8):1115–27.
[7] The World Health Organisation. WHO Preferred Product Characteristics (PPCs) [Internet]; 2022 [cited 2022 Jan 28]. <https://www.who.int/teams/immunization-vaccines-and-biologicals/product-and-delivery-research/ppcs>.
[8] Jaisamrarn U, Castellsagué X, Garland SM, Naud P, Palmroth J, del Rosario-Raymundo MR, et al. Natural history of progression of HPV infection to cervical lesion or clearance: analysis of the control arm of the large, randomised PATRICIA study. PLoS One [Internet] 2013;8(11):e79260.
[9] Erickson BK, Alvarez RD, Huh WK. Human papillomavirus: what every provider should know. Am J Obstet Gynecol [Internet] 2013;208(3):169–75. , https://pubmed.ncbi.nlm.nih.gov/23021131.
[10] Adebamowo SN, Befano B, Cheung LC, Rodriguez AC, Demarco M, Rydzak G, et al. Different human papillomavirus types share early natural history transitions in immunocompetent women. Int J Cancer 2022.
[11] Richardson H, Kelsall G, Tellier P, Voyer H, Abrahamowicz M, Ferenczy A, et al. The natural history of type-specific human papillomavirus infections in female university students. Cancer Epidemiol Biomark Prevent: Publ Am Assoc Cancer Res, Cosponsor Am Soc Prevent Oncol 2003;12(6):485–90.
[12] The World Health Organisation. Cervical Cancer.
[13] UK Health Security. Human papillomavirus (HPV): the green book, chapter 18a; 2019.
[14] National Cancer Institute. Study Identifies Crucial Characteristic of High-Risk HPV. 2017.
[15] Stelzle D, Tanaka LF, Lee KK, Ibrahim Khalil A, Baussano I, Shah AS, et al. Estimates of the global burden of cervical cancer associated with HIV. Lancet Global Health [Internet] 2021;9(2):e161–9.
[16] Lemp JM, de Neve JW, Bussmann H, Chen S, Manne-Goehler J, Theilmann M, et al. Lifetime prevalence of cervical cancer screening in 55 low- and middle-income countries. JAMA [Internet]. 2020;324(15):1532–42. https://doi.org/10.1001/jama.2020.16244.
[17] The World Bank. Prevalence of HIV, total (% of population ages 15-49) – Sub-Saharan Africa; 2020.
[18] Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet [Internet]. 2020;395(10224):591–603. https://doi.org/10.1016/S0140-6736(20)30157-4.
[19] Schiller J, Lowy D. Explanations for the high potency of HPV prophylactic vaccines. Vaccine [Internet]. 2018/01/08. 2018;36(32 Pt A):4768–73. <https://pubmed.ncbi.nlm.nih.gov/29325819>.
[20] Falcaro M, Castañon A, Ndlela B, Checchi M, Soldan K, Lopez-Bernal J, et al. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. Lancet [Internet] 2021;398(10316):2084–92. doi:10.1016/S0140-6736(21)02178-4.
[21] Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. HPV Vaccination and the risk of invasive cervical cancer. New England J Med [Int] 2020;383(14):1340–8. doi: 10.1056/NEJMoa1917338.
[22] Lu B, Kumar A, Castellsagué X, Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis. BMC Infect Dis 2011 Jan;11:13.
[23] Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011;29(46):8279–84.
[24] Zou Z, Fairley CK, Ong JJ, Hocking J, Canfell K, Ma X, et al. Domestic HPV vaccine price and economic returns for cervical cancer prevention in China: a cost-effectiveness analysis. Lancet Glob Health [Internet] 2020;8(10):e1335–44. , https://www.sciencedirect.com/science/article/pii/S2214109X20302771.
[25] Malagón T, Drolet M, Boily MC, Franco EL, Jit M, Brisson J, et al. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. Lancet Infect Diseases [Internet] 2012;12(10):781–9. doi:10.1016/S1473-3099(12)70187-1.
[26] WHO position on HPV vaccines. Vaccine 2009;27(52):7236–7.
[27] Human papillomavirus vaccines. WHO position paper, May 2017-recommendations. Vaccine 2017;35(43):5753–5.
[28] The World Health Organisation. WHO HPV Vaccine Dashboard.
[29] Drolet M, Bénard É, Pérez N, Brisson M, Ali H, Boily MC, et al. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet [Internet]. 2019;394(10197):497–509. doi:10.1016/S0140-6736(19)30298-3.
[30] Machalek DA, Garland SM, Brotherton JML, Bateson D, McNamee K, Stewart M, et al. Very low prevalence of vaccine human papillomavirus types among 18- to 35-year old australian women 9 years following implementation of vaccination. J Infect Dis 2018;217(10):1590–600.
[31] Vilos GA. The history of the Papanicolaou smear and the odyssey of George and Andromache Papanicolaou. Obstet Gynecol 1998;91(3):479–83.
[32] Habbema D, de Kok IMCM, Brown ML. Cervical cancer screening in the United States and the Netherlands: a tale of two countries. Milbank Q 2012;90(1):5–37.
[33] Denny L, Kuhn L, Hu CC, Tsai WY, Wright TC. Human Papillomavirus–based cervical cancer prevention: long-term results of a randomized screening trial. JNCI: J Natl Cancer Inst [Internet] 2010;102(20):1557–67. doi:10.1093/jnci/djq342.
[34] The World Health Organisation. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition. Geneva; 2021.
[35] Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. Lancet 2019;393(10167):169–82.
[36] Yao G, Qiu J, Zhu F, Wang X. Survival of patients with cervical cancer treated with definitive radiotherapy or concurrent chemoradiotherapy according to histological subtype: a systematic review and meta-analysis [Internet]. Vol. 9, Frontiers in Medicine; 2022. <https://www.frontiersin.org/article/10.3389/fmed.2022.843262>.
[37] Çuburu N, Kim R, Guittard GC, Thompson CD, Day PM, Hamm DE, et al. A prime-pull-amplify vaccination strategy to maximize induction of circulating and genital-resident intraepithelial CD8(+) memory T cells. J Immunol 2019;202(4):1250–64.
[38] Bruni L, Saura-Lázaro A, Montoliu A, Brotons M, Alemany L, Diallo MS, et al. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010–2019. Preventive Medicine [Internet] 2021;144:106399. , https://www.sciencedirect.com/science/article/pii/S0091743520304308.
[39] The World Health Organisation. WHO Immunization coverage [Internet]; 2021 [cited 2022 May 19]. <https://www.who.int/news-room/fact-sheets/detail/immunization-coverage>.
[40] Bruni L, G A, B S, M M, JJ C, D G, et al. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Africa. Summary Report 22 October 2021.
[41] Amponsah-Dacosta E, Blose N, Nkwinika VV, Chepkurui V. Human papillomavirus vaccination in south africa: programmatic challenges and opportunities for integration with other adolescent health services? [Internet]. Vol. 10, Frontiers in Public Health; 2022. <https://www.frontiersin.org/article/10.3389/fpubh.2022.799984>.
[42] Wong LP, Han L, Li H, Zhao J, Zhao Q, Zimet GD. Current issues facing the introduction of human papillomavirus vaccine in China and future prospects. Human Vacc Immunother [Internet]. 2019;15(7–8):1533–40. doi:10.1080/21645515.2019.1611157.
[43] UNICEF. The World Health Organisation. Progress and Challenges with Sustaining and Advancing Immunization Coverage During the COVID-19 Pandemic; 2021.
[44] The World Health Organisation. One-dose Human Papillomavirus (HPV) vaccine offers solid protection against cervical cancer [Internet]. <https://www.who.int/news/item/11-04-2022-one-dose-human-papillomavirus-(hpv)-vaccine-offers-solid-protection-against-cervical-cancer#:~:text=SAGE recommends updating dose schedules,for women older than 21>.
[45] Barnabas R v, Brown ER, Onono M, Bukusi EA, Njoroge B, Winer RL, et al. Single-dose HPV vaccination efficacy among adolescent girls and young women in Kenya (the KEN SHE Study): study protocol for a randomized controlled trial. Trials [Internet]. 2021;22(1):661. doi: 10.1186/s13063-021-05608-8.
[46] Selmouni F, Sauvaget C, Dangbemey DP, Kpebo DDO, Dieng NM, Lucas E, et al. Lessons learnt from pilot cervical cancer screening and treatment programmes integrated to routine primary health care services in Benin, Cote d'Ivoire and Senegal. J Glob Oncol 2022.
[47] Maza M, Schocken CM, Bergman KL, Randall TC, Cremer ML. Cervical precancer treatment in low- and middle-income countries: a technology overview. J Glob Oncol [Internet] 2016;3(4):400–8. Available from: 10.1200/JGO.2016.003731.
[48] Castle PE, Einstein MH, Sahasrabuddhe VV. Cervical cancer prevention and control in women living with human immunodeficiency virus. CA: A Cancer J Clin [Internet]. 2021;71(6):505–26. doi:10.3322/caac.21696.
[49] Burmeister CA, Khan SF, Schäfer G, Mbatani N, Adams T, Moodley J, et al. Cervical cancer therapies: current challenges and future perspectives. Tumour Virus Res [Internet] 2022;13:200238. , https://www.sciencedirect.com/science/article/pii/S2666679022000040.
[50] Campos NG, Tsu V, Jeronimo J, Mvundura M, Kim JJ. Estimating the value of point-of-care HPV testing in three low- and middle-income countries: a modeling study. BMC Cancer [Internet] 2017;17(1):791. , https://pubmed.ncbi.nlm.nih.gov/29178896.
[51] Nguyen DTN, Simms KT, Keane A, Mola G, Bolnga JW, Kuk J, et al. Towards the elimination of cervical cancer in low-income and lower-middle-income countries: modelled evaluation of the effectiveness and cost-effectiveness of point-of-care HPV self-collected screening and treatment in Papua New Guinea. BMJ Global Health [Internet]. 202;7(3):e007380. <http://gh.

bmj.com/content/7/3/e007380.abstract>.
[52] Kreimer AR, Herrero R, Sampson JN, Porras C, Lowy DR, Schiller JT, et al. Evidence for single-dose protection by the bivalent HPV vaccine-Review of the Costa Rica HPV vaccine trial and future research studies. Vaccine [Internet]. 2018/02/01. 2018 Aug 6;36(32 Pt A):4774–82. <https://pubmed.ncbi.nlm.nih.gov/29366703>.
[53] Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet 2007;370(9590):890–907.
[54] de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer 2017;141(4):664–70.
[55] The World Health Organisation, IVIR-AC. Meeting of the Advisory Committee on Immunization and Vaccinesrelated Implementation Research (IVIR-AC) [Internet]. Geneva; 2022. <https://terrance.who.int/mediacentre/data/sage/220225-IVIR-AC-Pink-Book-March-2022.pdf>.
[56] The World Health Organisation. WHO Cervical Cancer Prevention and Control Costing (C4P) Tool.