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An update on one-dose HPV vaccine studies, immunobridging and humoral immune responses – A meeting report

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ABSTRACT

The 12th HPV Prevention and Control meeting was held on June 2–3, 2022, in Antwerp, Belgium. This technical meeting focused on several topics. This report summarises the discussions and lessons learned on two topics: an update on one-dose HPV vaccination studies and humoral immune responses upon HPV vaccination. Long-term follow-up studies from Costa Rica (eleven years) and India (ten years) report stable levels of antibodies after a single HPV vaccination. High vaccine effectiveness against incident persistent HPV 16/18 infection was seen in India (95.4%, 85.0–99.9) ten years postvaccination and in Kenya (97.5%, 81.7–99.7) eighteen months post-vaccination, an important observation in a setting with a higher HPV prevalence. The potential impact of HPV vaccination using a one-dose schedule in India was modelled and showed that implementation of one-dose schedule can contribute towards achieving WHO Cervical Cancer elimination goals. These data support the WHO SAGE recommendations for adopting a one-dose schedule for females aged 9–20 years. Immunobridging studies were discussed during the meeting. General agreement was reached that when thoughtfully applied, they can support and accelerate the expanded use of HPV vaccine with new vaccine schedules, age cohorts, or vaccine formulations. Internationally standardised measurements of HPV immune responses important for the progress of HPV vaccinology field. Humoral immune responses upon HPV vaccination plateau at 24 months regardless of number of doses, therefore, data should be analysed after at least 24 months of follow-up to bridge studies accurately.

Abbreviations: 2vHPV, Bivalent HPV vaccine; 4vHPV, Quadrivalent HPV vaccine; 9vHPV, Nonavalent HPV vaccine; CVT, Costa Rica vaccine trial; DoRIS, A DOse Reduction Immunobridging and Safety study; FCM, Finish Maternity Cohort; FVU, First-Void Urine; GMC, Geometric Mean Concentration; HIV, Human Immunodeficiency Virus; HPV, Human Papillomavirus; IARC, International Agency for Research on Cancer; KEN SHE, KENya Single dose HPV vaccine Efficacy study; MCV, Meningococcal Vaccine; Nabs, Neutralizing antibodies; PBNA, Pseudovirion-Based Neutralization Assay; SWOT, Strengths, Weaknesses, Opportunities, and Threats; VE, Vaccine Efficacy; VLP, Virus-like particle; WHO, World Health Organization.

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1. Introduction

The HPV Prevention and Control Board is an independent, international, and multidisciplinary group of experts, created in 2015 to provide evidence-based guidance and reflection on strategic, technical, and policy issues regarding the implementation and sustainability of HPV prevention and control programmes. The board aims to disseminate and amplify relevant information on HPV prevention and control to a broad array of stakeholders by organising two meetings every year; a technical meeting covering topics such as vaccine characteristics, vaccine safety, screening technologies and landscape, treatment strategies, the role of healthcare providers in vaccination programmes, and dealing with anti-vaccine messages (Vorsters et al., 2017; Vorsters et al., 2019; Waheed et al., 2021); and a country meeting, covering a strengths, weaknesses, opportunities, and threats (SWOT) analysis of a country or region HPV prevention and control programs (Vorsters et al., 2020).

The objectives of the meeting were focused on:

1) One-dose HPV vaccination studies:
   - Update on efficacy and effectiveness data on HPV vaccination one-dose schedule.
   - Evaluate immunobridging results from current one-dose HPV vaccination trials to historical one-dose efficacy data.
   - Discuss the global recommendation landscape of HPV vaccination one-dose schedule.
2) Humoral immune responses upon HPV immunization:
   - Availability and use of standardized measurements for reporting humoral immune responses.
   - Characterisation of humoral immune responses for evaluating HPV vaccines immunogenicity.
   - First-void urine as a sampling mechanism to evaluate humoral immune responses.

This report presents an overview of available data and discussions taking place during the June 2022 meeting. It is worth noting that not all available studies on the topics are included due to data availability. Furthermore, the allocated time of 0.5 days for this topic within the meeting restricted the time available for in-depth discussion of certain subtopics. Despite these limitations, the discussions held among authors and various experts from academia, regulatory authorities, and other stakeholders are unique and provide important discussion points essential for future research.

2. Updates on one-dose HPV vaccination studies

Over the past few years, there has been growing evidence that a single dose of HPV vaccine can provide protection against cervical cancer. Long-term follow-up data is available from the Costa Rica HPV Vaccine Trial (CVT, launched in 2004) conducted prior to licensure of 2vHPV (Cervarix®) in 18–25-year-old women using three doses; In the CVT trial the vaccine efficacy (VE) of the one dose group for prevalent HPV 16/18 infection was 82.1% (40.2–97.0) at 11.3 years after vaccination. HPV16 serum antibodies are stable after a follow-up of 11 years in participants that received one, two and three doses. Immunologic follow-up is set to continue for up to 20 years (Kreimer et al., 2020) **See** Table 1.

Furthermore, the India IARC trial, a multicentric cohort study to compare the efficacy of a two-dose versus three-dose 4vHPV (Gardasil-4®) schedule in 10–18-year-old females in India, provides 10-year follow-up data on one dose efficacy (Basu et al., 2021). After the suspension of recruitment and vaccination, the study became a longitudinal, prospective cohort study by default. Participants were allocated to four cohorts based on the number and timing of vaccine doses received. **See** Table 1 for further details. At 10 years post-vaccination, 96% and 97% of one-dose recipients had detectable HPV16 and HPV18 antibodies, respectively, with titres 15 and 10 times higher than natural immunity. All vaccinated cohorts had a similar incidence of HPV16/18 infections [one-dose cohort 3.1 (2.6–3.8) vs two-dose regimes 2.6 (2.0–3.3) vs 3-dose cohort 3.0 (2.3–3.8)] while the control arm had an increased incidence [unvaccinated 9.7 (8.2–11.3)]. Adjusted VE for incident persistent HPV 16/18 infections was 93.3% (77.5–99.7) for the three-dose cohort, 93.1% (77.3–99.8) for the two-dose cohort, and 95.4% (85.0–99.9) for the one-dose cohort.

Two important randomised controlled trials aiming to evaluate one dose HPV VE are currently ongoing in Tanzania and Kenya.

The KEN SHE Study investigates one-dose HPV vaccination between Gardasil-9® (9vHPV) Cervarix® (2vHPV) VE for incident persistent HPV infection among sexually active adolescent girls and young women in Kenya. At month 18 the incidence persistence of non–vaccine-type HPV infections was similar between study arms, ranging from 22.2 to 24.5 per 100 woman-years. However, the incidence persistence of HPV16/18 infections was significantly lower in 2vHPV and 9vHPV than in the control arm (0.17 in both study arms vs 6.83 per 100 woman-years), with a VE of 2vHPV of 97.5% (81.6–99.7) and 9vHPV of 97.5% (81.7–99.7) **See** Table 1 (Barnabas et al., 2022). Finally, the incidence of HPV16/18/31/33/45/52/58 infections (the vaccine types in the non-avalent vaccine) was significantly lower in the 9vHPV study arm than in the control arm (1.03 vs 9.42 per 100 woman-years, VE = 88.9% (68.5–96.1) **See** Table 1.

The Dose Reduction Immunobridging & Safety Study (DoRIS) offered one, two or three doses of the 2vHPV (Cervarix®) or 9vHPV (Gardasil-9®) vaccine in order to demonstrate non-inferiority of HPV16/18 seroconversion after one dose compared with two or three doses of the same vaccine. At month 36, one dose was non-inferior to two doses and three doses for HPV16 for both vaccines, but for HPV18 non-inferiority was only met for two doses versus three doses for both 2vHPV and 9vHPV. HPV16/18 antibody levels after one dose reached plateau from month 12 to month 36 for both vaccines. The HPV 16/18 avidity index was very similar between one dose, two doses, and three doses, for both vaccines and both HPV types, with avidity index ratios close to 1.

Given the challenge of recruiting and sampling younger age cohorts to evaluate the efficacy of HPV vaccines, immune responses were bridged to populations where efficacy has been shown. Similar to the original licensure of HPV vaccines, non-inferiority of immune responses were used to infer efficacy in younger girls through a comparison of anti-HPV ELISA titres (IARC, 2014). Historic efficacy data used for immunobridging include antibody levels from CVT (11yearsfollowup), India IARC (10yearsfollowup) and KEN SHE (18 months).

For all these trials, after one dose HPV vaccination schedule, antibody levels in DoRIS were shown to be non-inferior for HPV16 and 18, for both 2vHPV and 9vHPV in comparison to the similar vaccine in the older aged efficacy populations. **See** Table 1.

2.1. Prospects: Studies investigating the efficacy and impact of one-dose HPV vaccination in preventing cervical cancer

The ESCUDDO trial compares the efficacy of one versus two doses of 2vHPV (Cervarix®) and 9vHPV (Gardasil-9®) vaccines in Costa Rican girls aged 12–16, with results expected in 2025.The PRIMAVERA trial, an immunobridging trial comparing antibody levels in girls receiving one dose of 2vHPV from ESCUDDO to those receiving three doses of 4vHPV (Gardasil-4®) in historical cohorts, with results expected by 2023/2024.

The PRISMA study evaluates the efficacy of one dose of 2v- (Cervarix®) and 9vHPV (Gardasil-9®) vaccines against persistent HPV16/18 cervical infections in HPV16/18-DNA baseline negative women aged 18–30, with data expected by 2027. This will provide an opportunity to protect additional women from HPV-related disease, as a one-dose schedule in adult women may allow for a massive, one-time catch-up.

The HOPE study was set up to monitor the impact of a two-dose and one-dose HPV vaccination schedule on community-level HPV prevalence using repeat cross-sectional surveys, collected from independent

Table 1
Summary of studies studying efficacy and immunogenicity of cohorts that received one-dose regime of any HPV vaccine product.

Study acronym. Location. (Clinical Trial #) Status	Objectives	Vaccine Product Cohorts	Population Age Sample size	Timing of measure	Results	
KEN SHE KENya Single-dose HPV-vaccine Efficacy	Individual randomised, double blind, control, three group study.		Women 15–20 years old.	Month 18	•Incident persistent HPV 16/18 infections was significantly lower in vaccine group.	**VE** (95% CI)
Kenya. (NCT03675256). Active, not recruiting.	1. Test efficacy of immediate single-dose 9vHPV vs 2vHPV vs MCV control) vaccination to prevent incident persistent HPV 16/18 infection	9vHPV **vs** 2vHPV **Vs**	(N = 750) (N = 750)		- mITT at m18 (9vHPV) - mITT at m18 (2vHPV)	97.5(81.7–99.7) 97.5(81.6–99.7)
	2. Test efficacy of immediate single-dose 9vHPV to prevent incident persistent HPV 16/18 /31/33/45/52/58	MCV	(N = 750)		• Incidence of HPV 16/18/31/33/45/52/58 infections - mITT at m18 • These data provide strong evidence for single-dose HPV vaccine efficacy, showing that adolescent girls and young women were effectively protected from HPV infection over the first 18 months after vaccination.	 88.9 (68.5–96.1)
DoRIS A Dose Reduction Immunobridging and Safety Study.	Open label randomised study of two different HPV vaccines.	2vHPV	Girls 9–14 years old.	Month 24	• >99% HPV 16 seropositive and > 98% HPV 18 seropositive.	
Tanzania. (NCT02834637). Active, not recruiting.	1. Demonstrate non-inferiority of HPV 16/18 seroconversion after 1-dose vs 2-dose and 3-dose of same vaccine at M24.	1D 2D 3D	N = 155 N = 155 N = 155		•Non-inferiority for seroconversion was met (1D is not inferior than 2D/3D) for HPV 16 for both vaccines. • For HPV18, non-inferiority of 1D was not met.	
	2. Immunobridging: Demonstrate non-inferiority of HPV 16/18 ab GMT at M24 1D DoRIS vs historical efficacy cohort on 1D.	**vs** 9vHPV 1D 2D	 N = 155 N = 155		• HPV 16/18 Ab concentrations on 2D and 3D cohorts declined after peak in M7, while 1D cohort concentration remain constant from M7. • Avidity index similar between dose groups, for HPV16 and HPV18, for both vaccines products.	
		3D	N = 155		• 1D in DoRIS is non-inferior to 1D in historical cohorts at M24,for HPV-16 & HPV-18, for both vaccines. ○ 2vHPVDoRIS vs 2vHPV CVT (HPV 16) ○ 9vHPV DoRIS vs 4vHPV India (HPV 16) ○ 2vHPV DoRIS vs 2vHPV CVT(HPV 18) ○ 9vHPV DoRIS vs 4vHPV India (HPV 18)	**GMC ratio** (95% CI). 1.30 (1.00–1.68) 1.29 (0.91–1.82) 1.23 (0.95–1.60) 1.75 (1.22–2.50)
CVT Costa Rica Vaccine Trial. **Costa Rica.** (NCT00867464). Active, not recruiting.	Extended follow-up of young women from CVT Phase III. Evaluate impact of HPV 16/18 immunisation. Evaluation of immune responses and HPV-related disease.	2vHPV	Woman who participated in the Phase III CVT. (18-25y/o) Some women missed visits, only received 1-dose. (N= 112).	11 years	• Vaccine effectiveness for persistent HPV16/18 infection with 1D is above 80%. • HPV16 or 18 antibody levels did not qualitatively decline between years four and 11 regardless of the number of doses given.	**VE** (95% CI) 82.1 (40.2–97)
Trial of two vs three Doses of Human Papillomavirus (HPV) Vaccine in India. **India.** (NCT00923702) Active, not recruiting.	Multi-centre cluster randomised trial of two vs three doses of 4vHPV in India. Suspension of the vaccination led to per protocol and partial vaccination of unmarried 10–18 y/o girls.	4vHPV 3D 2D (0-6m) 2D (0-2m) 1D	Woman 10–18 y/o N=4,348 N=4,980 N=3,452 N=4,949.	10 years.	• HPV 16/18: 96%/97% of one-dose recipients had detectable Ab at 10 years; Ab titre was 15X/10higher than natural immunity. • Adjusted VE against HPV16/18 persistent infection. ○ 3D ○ 2D ○ 1D • Incident infection from HPV 31, 33, 45 ○ 3D ○ 2D ○ 1D ○ Non vaccinated	**VE** (95% CI) 93.3 (77.5–99.7) 93.1 (77.3–99.8) 95.6 (85.0–99.9) **Incidence** (95% CI) 4.8 (4.0–5.6) 4.1 (3.3–5.0) 4.1 (3.4–5.1) 10.5 (9.0–12.12)

(*continued on next page*)

Table 1 (*continued*)

Study acronym. Location. (Clinical Trial #) Status	Objectives	Vaccine Product Cohorts	Population Age Sample size	Timing of measure	Results
HOPE HPV One and two-dose Population Effectiveness. **South Africa.**	Aims to monitor the effectiveness of a 2D and 1D HPV vaccination schedules on community-level HPV prevalence among South African adolescent girls.	2vHPV (2D) **vs** 2vHPV (1D)	Girls (> 9 y/o) (N=6673) 28% unvaccinated 72% vaccinated.	Impact survey 1 carried out.	One-dose analysis in progress. • Manuscript in preparation
PRIMAVERA Puente de Respuesta Inmunológica Para Mejorar el Acceso a Vacunas y ERrAdicar el Cancer. **Costa Rica.** (NCT03728881) Active, not recruiting.	Demonstrate non-inferiority of the ab response in girls who receive 1D 2vHPV vs young women who receive 3D of 4vHPV.	2vHPV (1D) **vs** 4vHPV (3D)	Girls (9–14 y/o) (N= 620) Woman (18-25y/o). (N=620).	Serology at month 12, 24 and 36	Expected results by 2023–2024.
ESCUDDO Estudio de Comparacion de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano (VPH). **Costa Rica.** (NCT03180034) Enrolling by invitation.	Evaluation of 1D or 2D of vaccine against HPV with randomised parallel assignment of vaccine product 2vHPV vs 9vHPV and dose regime 1D vs 2D.	2vHPV (1D) Vs 2vHPV (2D) vs 9vHPV (1D) vs 9vHPV (2D)	Girls (12–16 y/o) (N= 20,300)	Serology, cytology and urine at months 12, 18, 24, 30, 36, 42, 48, 54, 60.	Results expected by 2024/2025
PRISMA PRevencion del cancer de cervix con una sola dosIS de vacuna contra VPH en Mujeres Adultas jovenes. **Costa Rica** (NCT05237947) Enrolling by invitation	Randomised, blinded, controlled trial. Evaluate one dose of the HPV vaccines compared to no vaccination in the protection against incident HPV16/18 cervical HPV infections that persist six months or more in women 18 to 30 y/o who are HPV16/18 DNA–negative prior to and at the time of vaccination	9vHPV (1D) vs 4vHPV (1D) vs 2vHPV (1D)	Woman (18-30y/o) (N=5,000+)	Serology, cytology and urine at months 12, 18, 24, 30, 36, 42, 48, 54, 60.	• Study launched • Goal is to have data ready for 2027, when HPV vaccine supply exceeds demand • The study is an opportunity to save additional women- 1 dose in women may allow for a massive, one-time catch-up

mITT: Modified intention-to-treat, y/o: years old, ab: antibodies, VE: Vaccine efficacy, GMC: Geometric Means Concentration, MCV: Meningococcus vaccine, CI: Confidence Interval, M: Months, 1D: 1-dose, 2D: 2-dose. 3D: 3-dose, CVT: Costa Rica Vaccine Trial. 9vHPV: nonavalent HPV vaccine (GARDASIL 9, Merck Sharp & Dohme Corp), 4vHPV: quadrivalent HPV vaccine (Gardasil 4; Merck & Co., Inc), 2vHPV: bivalent HPV vaccine (Cervarix; GlaxoSmithKline), MCV: meningococcal vaccine (MENVEO; GlaxoSmithKline).

cohorts of South African adolescent girls, from before ("pre-vaccine cohort") and after ("vaccine eligible cohort") implementation of the programme. Additionally, the investigators wanted to measure the population impact of a one-dose vaccine schedule, delivered as a catch-up, to Grade 10 pupils in one district, in protecting against infection with HPV16 and/or 18 (Machalek et al., 2022).

Of 6,673 potential recipients, 4,807 (72%) received a single HPV vaccine dose. The median age of the vaccine recipients was 16 (interquartile range 15–17) years. The primary reason for non-vaccination was lack of signed parental consent or absenteeism (98%). Analysis of the data is currently in progress. **See** Table 1 for further details of these trials.

2.2. Evidence-based impact projections of single-dose HPV vaccination in India

EpiMetHeos model was used to predict the impact of HPV vaccination under the one-dose schedule in India, looking at its effectiveness on HPV infection and cervical cancer, the potential of elimination according to different indicators, the relative efficacy of one-dose compared to the two-dose schedule, the impact of catch-up, and the variability of impact across India (Man et al., 2022).

Four scenarios were used, based on India IARC trial 10 year efficacy data where vaccine efficacy of incidence persistent infection for HPV16/18 is 95% and HPV31/33/45 is 9%. Scenario A assumed lifelong vaccine protection for both, single-dose and two-dose HPV vaccination. Scenario B assumed similar initial HPV16/18 VE (95%/95%) but waning of protection for single-dose vaccination. Scenario C, similar to assumption B, but lower initial HPV 16/18 VE (90%/85%) and faster waning of protection for single-dose vaccination. Lastly, scenario D with lower initial HPV 16/18 VE (85%/55%) and faster waning of protection for single-dose vaccination. These assumptions were derived from the lower bound of efficacy estimated by the IARC India HPV vaccine trial and by projecting the time until HPV16 and HPV18 antibody levels observed in the trial decreased below predefined thresholds.

The base-case scenario reached the WHO elimination threshold in the long term, with a 71% reduction in cervical cancer risk in the first five vaccinated cohorts. With the three alternative scenarios, elimination was still attained in most scenarios. Furthermore, under any scenario, the two-dose schedule needed more doses than the one-dose schedule to prevent one case of cancer, 26% more under the less favourable set of assumptions. Hence, in most scenarios the one-dose schedule is cost-saving (when undiscounted) and cost-effective (when discounted), whereas introducing a second dose is not cost-effective (Man et al., 2022). These projections indicate that single-dose vaccination can substantially decrease cervical cancer burden across India and that some Indian states with the highest burden would benefit from additional control measures.

2.3. Update on SAGE advice on HPV schedule optimisation and the permissive single-dose recommendation in younger women

High interest in HPV vaccination by countries across all income groups has resulted in increased demand in the past several years. However, a combination of factors, primarily linked to continued supply constraints, has slowed the pace of introductions, particularly in low-resource settings (WHO Health Organization, 2022). It was in this setting that the WHO Strategic Advisory Group of Experts on Immunization (SAGE) took up a review of the new evidence around HPV reduced dose schedule in 2022.

SAGE advised that the target population for vaccination should remain 9–14-year-old girls. For this target population, one dose or two doses can be used. Similarly, for 15–20-year-olds, one dose or two doses can be used, whereas, from the age of 21, a two-dose schedule can be used. Finally, regardless of age, at least two doses should be used in immunocompromised patients, while ideally, three doses are recommended. SAGE recommended that countries, where feasible and affordable, prioritise a catch-up of older cohorts and missed girls through multi-age cohort vaccination. Introducing the vaccination of boys and older females should be carefully managed until the global supply situation is fully resolved. Where gender-neutral vaccination is introduced, males can receive the same schedule as females (World Health Organization, 2022).

Data gaps that still exist are: first, the immunogenicity, protective efficacy, and duration of protection, with reduced-dose schedules in immunocompromised individuals, especially the level of protection provided when HIV seroconversion happens after one dose of HPV vaccine; second, long-term immunogenicity, efficacy, and duration of protection of one-dose HPV vaccine schedule in girls and boys 9–14 years old; third, the use of one-dose schedules in older adults and children below 9 years of age; and finally, implementation research to identify strategies to improve HPV vaccine coverage, including among populations at high risk of early HPV infection and immunocompromised individuals (World Health Organization, 2022).

2.4. Panel discussion on one-dose HPV vaccine trials and introduction of a one dose schedule

During the panel discussion, experts involved in the previously presented clinical trials had the opportunity to discuss among them, raising relevant points and concerns from the evidence showed.

2.4.1. Background HPV prevalence and selection bias

Several attendees raised the concern of one-dose HPV vaccine performance being subject to the difference in background HPV prevalence in the settings where these trials were carried out. The data from the KEN SHE study seem to argue against this suggestion where single-dose HPV vaccination provides high efficacy against incident persistent HPV 16/18 infection even in the setting of a high incidence of HPV infection. Although the efficacy follow-up in KEN SHE is relatively short (18 months) and the antibody levels in participants receiving two or three-dose schedules is considerably higher across studies, there are suggestions that immune responses will be stable over time as presented from the African setting study (DoRIS) in Tanzania. Moreover, in all presented trials measuring one dose schedule, immunogenicity reports minimal HPV 16/18 antibody decay after plateau. Similar observations were presented in Costa Rica and India, where 10 years of follow-up has been done. DoRIS data presented during the meeting showed stable immune response at 3 years after a single dose of HPV vaccine. This may suggest that regardless of the number of doses administered, there is a stable long-lived plasma cells niche produced which continue to generate antibodies. Results from the HOPE study are expected to provide insight on the impact and effectiveness of one-dose HPV vaccination schedule at a wider level.

2.4.2. Genotype replacement

Levels of protection elicited by one-dose HPV vaccination were raised as a point of concern, specifically with uncertainties of reduced dose schedules to allow type-replacement of oncogenic genotypes. However, for type replacement to take place there needs to be competition, which is not seen at a lesion level. Although multiple infections can be found, lesions are known to be driven by only one genotype. Furthermore, characterisation of humoral responses following HPV vaccination have not shown results suggesting type replacement, in the contrary, the responses have suggested to be more cross-protective than expected. According to transmission modelling, however, it is still too early to preclude type replacement and monitoring of non-vaccine types remains pivotal (Man et al., 2021).

Clinical trials are a good setting to investigate possible vaccine failures by looking at breakthrough cases. In CVT trials, there are currently eight possible vaccine failures among the ~ 3000 women in the vaccinated arm, who had on average 11 years of follow-up. Investigations to

confirm these cases as vaccine failure include persistence of HPV infection that has not been detected in previous follow up, antibody levels and avidity and viral variance studies.

2.4.3. Implementation of HPV one-dose schedule in settings with high HIV prevalence

Questions regarding the impact of HPV vaccine–induced protection among people who will acquire HIV after being vaccinated with one dose HPV vaccination were raised. This is especially concerning in Sub-Saharan Africa, where six out of seven new HIV infection in adolescents aged 15–19 years occurs in girls (Schiller and Müller, 2015; UNAIDS data, 2022).

In persons living with HIV, HPV vaccination induce high rates of antibody seroconversion (Toft et al., 2014; Faust et al., 2016) and vaccine-induced antibody responses are sustained for at least four years (Levin et al., 2017), but cross-reactive antibody responses were diminished as compared to that reported in HIV-negative populations. Despite the reasonable evidence supporting the immunogenicity of HPV vaccines in HIV-positive individuals, the corresponding efficacy data is inconsistent (Lacey, 2019). Further research is needed to understand the functional and anatomical immunologic remodelling that occurs in HIV infection in regard to HPV-vaccine-induced protection. A major question for further research is looking at the impact of an HIV infection after HPV vaccination. This can only be investigated in areas with high HIV incidence. The question remains whether this will reduce the protection gained through vaccination. Results from the HOPE study, measuring the community-wide impact of one-dose HPV vaccination, are likely to provide further insight given the high prevalence of HIV in South Africa.

Lessons learned & the way forward one-dose HPV vaccination studies

IARC India trial and Costa Rica trial (CVT) present long-term follow-up data on a substantial number of subjects that received one dose. These ten-year follow-up results show sustained HPV16/18 antibody levels and > 80% VE for incident persistent HPV infecton.

DoRIS and KEN SHE trials provide further insight into vaccine-induced antibodies up to 36 months after vaccination with a one-dose regime. These studies are especially important because they are carried out in countries with the highest HPV incidence/attack rate in the world.

HPV type replacement is currently not an issue as no evidence of genotypes competition has been demonstrated. However, surveillance of non-vaccine types remain warranted.

Modelling studies in India, suggesting different scenarios for one-dose including stable or waning of protection, based on detection and seropositivity thresholds, shows one dose strategy to be cost saving and cost effective in most scenarios.

To ensure accurate immunobridging responses comparison, samples from prospective trial and historical trials must be from the same sampling timepoint and tested in the same laboratory with the same serologic validated assay.

Increase need for evidence base data and policies on immunogenicity, protective efficacy, and duration of protection of HPV immunisation in immunocompromised individuals.

One-dose HPV vaccination on cohorts with high-risk HIV acquisition should be further studied. However, it should not be a reason to delay adoption of the one-dose schedule in the general population.

3. Humoral immune responses upon HPV vaccination

3.1. Immunogenicity of HPV prophylactic vaccines: serology assays and their use in HPV vaccine evaluation and development: Importance of international units for reporting immune response

HPV serology is used to evaluate vaccine-induced antibody duration and antibody levels. HPV serology can be used to determine the quality of vaccine-induced antibodies and to report in a standardised manner humoral immune responses regardless of serologic assay, laboratory or vaccine used. In all these cases, the availability, relevance, and proficiency of internationally standardised tests are important to report HPV immunogenicity and validate improvements in serologic HPV assays. International standards are required to define an International Unit. International monospecific standard sera have been established for HPV16 and HPV18 (Faust et al., 2016; Ferguson et al., 2011), while work on sera for HPV6, 11, 31, 33, 45, 52 and 58 is ongoing. Secondly, reproducible methods for analysing readouts should be used. The parallel line method is the method of choice, as it increases reproducibility (Grabowska et al., 2002).

In a head-to-head comparison (vaccine induced antibodies against pseudovirions from 17 different HPV types [HPV6/11/16/18/31/33/35/39/45/51/52/ 56/58/59/66/68/73]), using the standardised sera and the parallel line method, the 2vHPV Cervarix® vaccine induced higher antibody titres to HPV16 and HPV18 than the 9vHPV. Also, the analysis suggested that the 2vHPV(Cervarix®) and 9vHPV vaccines may afford some cross-protective efficacy against HPV35. International Units are useful to quantitate the level of protection afforded, and new vaccine formulations that include HPV35 may need to be considered (Arroyo Mühr et al., 2022).

3.2. Neutralising and cross-neutralising antibody levels to HPV following vaccination

HPV vaccines induce a type-specific neutralising antibodies (NAb) response directed to the L1 loop regions exposed on the HPV capsid surface. Anti-L1 antibodies can reach the cervix via transudation from the systemic circulation and are postulated to be the primary mechanism of protection against HPV infection. In human studies, antibody-induced neutralisation responses measured in vitro correlate well with the observed endpoints, including protection against HPV-caused pre-malignant lesions or prevention of persistent infection (defined as infections lasting > 6 months) (Schiller et al., 2012). NAbs are, therefore, convenient correlates of protection but the minimal protective levels are currently unknown.

A head-to-head comparison study with serum samples collected from participants of the PATRICIA (2vHPV Cervarix®) clinical trial in Finland and the India clinical trial (4vHPV), who had received three doses of the vaccines when aged 16–17 years old, showed that 2vHPV recipients had significantly higher HPV16/18 peak antibody levels than 4vHPV recipients, as determined by a semi-automated high-throughput Pseudovirion-Based Neutralisation Assay (PBNA). Furthermore, cross-neutralising HPV31/33/45/52/58 Abs were induced by the 2vHPV Cervarix® significantly more frequently and at higher concentrations than by the 4vHPV (Mariz et al., 2020). Similarly, analysis of serum samples from 4vHPV recipients and 2vHPV Cervarix® recipients that were enrolled in the FUTURE and PATRICIA clinical trials and then followed up by the population-based Finnish Maternity Cohort showed that NAb to HPV 16/18 were generally found up to 12 years after vaccination, as well as HPV6 antibodies in 2vHPV Cervarix® recipients (Mariz et al., 2021). However, 15% of the 4vHPV recipients had no detectable HPV18 NAb 2–12 years after vaccination, whereas all corresponding 2vHPV recipients had HPV18 NAbs. Cross-neutralising Abs to HPV31, 33, 45, 52, and 58 were more prevalent in the 2vHPV Cervarix® recipients, but similar GMCs to vaccine types were found up to 12 years after vaccination in both vaccine cohorts.

When comparing the immunogenicity and reactogenicity of the 2vHPV Cervarix® and 4vHPV vaccines in HIV-positive adults recipients of a three-dose vaccination schedule, anti-HPV18 NAb titres were higher in the bivalent group compared with the quadrivalent group at seven and twelve months (Toft et al., 2014). Interestingly, only a moderate NAb seroconversion (50%) limited to non-vaccine HPV31 in 2vHPV Cervarix® recipients was observed in this HIV-positive cohort (Faust et al., 2016). Finally, children with well-controlled HIV infection who receive three doses of the 4vHPV vaccine maintain NAbs for at least four years (Levin et al., 2017). Although the 2vHPV Cervarix® provides slightly broader long-term protection than the 4vHPV in participants of the PATRICIA and FUTURE trials, the cross-reactivity induced in HIV-positive adults seems, however, diminished in relation to HIV-negative cohorts, whereas data on long-term immunity following HPV

vaccination in HIV cohorts is scarce.

Although NAb titres after vaccination are correlated with protection against persistent infection for vaccine HPV types, the correlation is weaker for non-vaccine types in 4vHPV recipients (Mariz et al., 2021). It is still to be confirmed whether cross-NAb responses are the main effectors of protection against non-vaccine HPV types. Other Ab-mediated cellular cytotoxicity responses, which are not measured by in vitro neutralisation assays, may contribute to prevent infection and virus clearance (Wang et al., 2018). Vaccination with HPV Virus-Like-Particles VLP also triggers cell-mediated responses (Pinto et al., 2003; Stanley, 2006) to T helper epitopes conserved across distinct genotypes (Pinto et al., 2003), which may play some role in both cross-protection and immunological memory.

In contrast, for considerably more 4vHPV recipients, NAb titres remained below test sensitivity, remarkably for HPV18. This triggered a discussion about the impact of the valency (the number of genotypes included in the vaccine) of a given vaccine on the immune response against that vaccine. The immunogenicity data suggest that HPV16 VLP are immunodominant because at similar (2vHPV Cervarix®) or lower concentrations (4vHPV), these particles induce higher NAb titres than HPV18 VLP. Considering that adjuvants are key factors determining the balance of antigenic immunodominance (Chen et al., 2021; Maeda et al., 2017), the distinct adjuvant systems employed by these vaccines, in addition to the valency and antigen concentration, are likely to differently impact the resulting Ab levels. Nevertheless, while NAb titres induced by each of these vaccines to HPV16 and HPV18 are different, their effectiveness levels against corresponding infection seem to be comparable.

3.3. Current status of using urine samples to monitor HPV vaccination status

First-void urine (FVU), or the initial stream of urine, captures impurities lining the urethra opening. These impurities include transudated Abs and biomarker-containing mucus and debris from exfoliated cells originating from the female genital tract. As it is a non-invasive sample, which can be obtained at home, it is an interesting option to reach non-attendees of the cervical cancer screening programme (Pattyn et al., 2019). Several studies have demonstrated that first-void urine is a suitable sample to detect HPV DNA and vaccine-induced HPV Abs originating from female genital tract secretions are detectable in FVU as well (Arbyn et al., 2018; Pathak et al., 2014). This presents an opportunity for non-invasive sampling to monitor HPV Ab status in women participating in large epidemiological studies and HPV vaccine trials (Pattyn et al., 2019, 2020; Van Keer et al., 2019). The simultaneous assessment of both HPV infection and immunogenicity on a non-invasive, readily obtained sample is particularly attractive.

Paired FVU and serum samples from female volunteers who participated in a 9vHPV trial (HPV V503-004 study) were collected before vaccination (month 0), one month after the third dose (month 7), and approximately three years after the third dose (month 43) (manuscript under preparation). HPV-specific antibody concentrations in FVU were detected in 0–16% at month 0, 95%–100% at month 7, and 84%–100% at month 43. In addition, results show significant spearman correlations between HPV-antibody titres of paired FVU and serum samples (Month 0 $r_s = 0.52$, Month 7 $r_s = 0.69$, Month 43 $r_s = 0.80$). In conclusion, HIV Abs can also be detected in urine, which might make FVU a valid sample in LMICs with a high HIV burden. However, due to biological differences in the genital tract, FVU is probably not an appropriate sample for HPV DNA or antibody detection in men.

3.4. Panel discussion on humoral immune responses

3.4.1. Optimisation of current antibody neutralization assays

An important remark was made in regard to the fact of not detecting neutralising antibodies 12 years post-vaccination in recipients of 2vHPV Cervarix® and 4vHPV does not necessarily mean that individuals are unprotected, as other factors should be considered, including suboptimal sensitivities of current NAbs serological assays. Important advances to address these research gaps are underway, including objective comparison between available testing platforms by the use of international units.

3.4.2. Cross-protective vaccine-induced neutralising antibodies

A head-to-head comparison between 2vHPV Cervarix® and 9vHPV provided important insight into the 9vHPV vaccine elicited higher cross-protective antibodies against HPV 35 (Arroyo Mühr et al., 2022). This is specifically important in Africa, where about 10% of cervical cancers have been shown to be caused by this genotype. Further research is needed to validate and understand the protective value of these antibodies against persistent infection. This could present an opportunity for implementation of these vaccines in countries and populations that are mostly affected by cervical cancer caused by oncogenic genotype HPV35.

3.4.3. Feasibility of using first-void urine to assess vaccine status and measure impact

Suboptimal vaccine registries in HICs and LMICs could benefit from the use of FVU sampling as a non-invasive sampling strategy to collect impact data. However, there were doubts in regard to the sensitivity of the sample to detect vaccine-induced antibodies in recipients of one-dose schedule. Data presented during the meeting shows that although stable, one dose HPV vaccination responses yields lower antibody titers in serum. While further validation and optimization of this strategy is needed, promising results, including the detection of antibody after natural infection in urine and a very good correlation between serum and FVU antibodies titers has been reported, making this sampling strategy a very promising asset for HPV vaccine effectiveness assessment worldwide.

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The availability of international standards is relevant, as it will facilitate HPV immunogenicity reporting and accurate data interpretation across labs and testing batches.
VLPs are highly immunogenic, resulting in high-affinity Abs. Due to intramuscular administration with adjuvant, the resulting Abs are of better quality than Abs resulting from natural infection.
Humoral immune responses following HPV vaccination reach a plateau at 24 months, irrespective of the number of doses administered. As such, it is essential to analyze data from studies with a minimum follow-up period of 24 months in order to accurately compare results across studies.
First-void urine sampling is a non-invasive, home-based sampling method that allows the detection of HPV-specific antibodies.
International Standards for 9 HPV vaccine genotypes need to be anchored, and for instance, peer reviewers should ask for international units when reviewing manuscripts.

4. Ethics approval

Not applicable.

5. Consent to participate

Not applicable.

6. Consent for publication

HPV Prevention and Control Board meetings are invitation-only meetings. All participants accepted the invitation and attended the meeting out of their free will. The HPV Prevention and Control Board asked the participants to fill out a ‘consent form’, agreeing that the

videos and photos of the meetings can be published online. The speakers are also asked to fill out a consent form to agree/disagree that their presentation can be published on the website, included in the meeting report or used for publication.

7. Availability of data and material

All the presentations of the meeting report are published on the website (https://www.hpvboard.org) after speakers' approval.

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10. Author's contribution

AV, MS, IB, FRB, DNW: defining the meeting objectives, speakers, and the program. CE, FCM, NM, DWJ: presenting, chairing sessions, leading discussions, providing and validating the meeting conclusions. MB, FRB, DNW, LT, AV: drafting the manuscript. All authors have contributed in editing the manuscript

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Given the nature of a meeting report, all data included has been already published unless otherwise stated by the author.

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