Control and prevention of cervical cancer among women living with HIV

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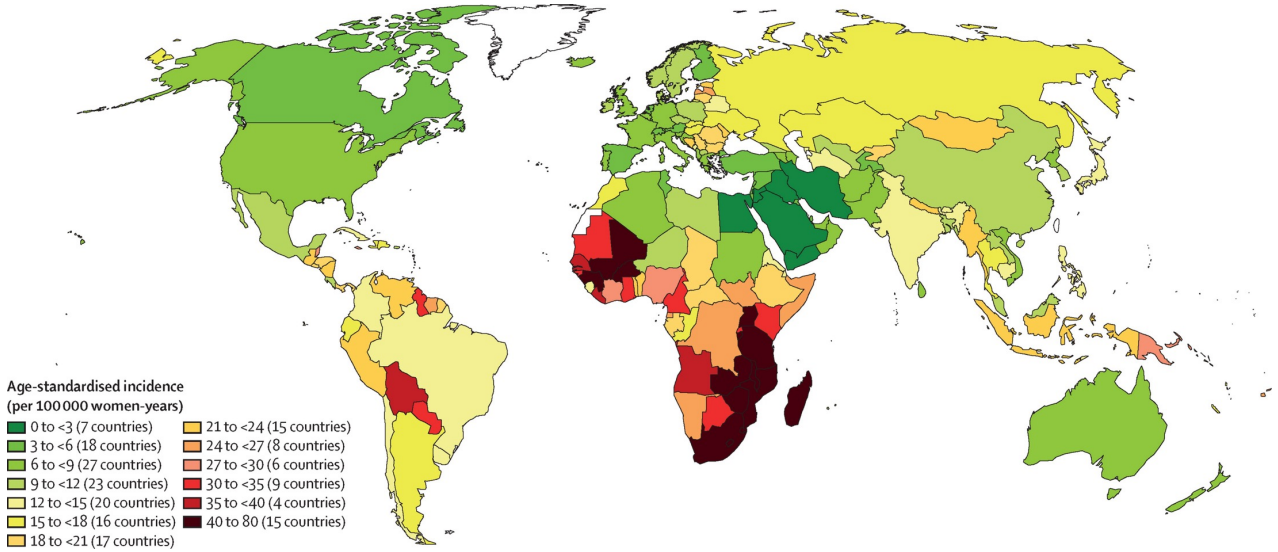
Invasive Cervical Cancer incidence



- **604,127 cases in 2020**
- >80% in low income/developing countries

Cervical cancer screening coverage (2019) in women **aged 30-49** years **:**

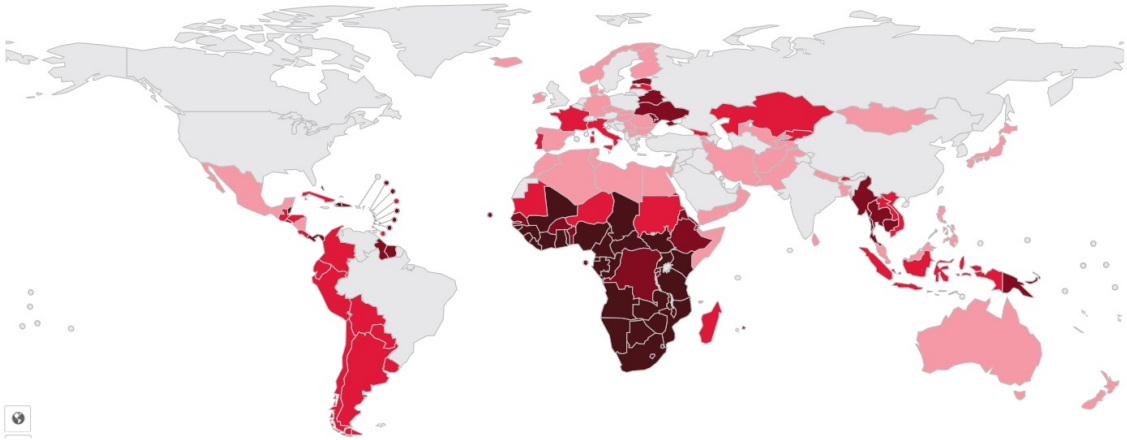
- **88%** in HIC vs. **13%** in MIC vs. **15%** in LIC [(1)]

HPV vaccination coverage (2020):

- **88%** HIC vs. **40%** LMIC [(2)]

WLHIV **6x ↑ cervical cancer** [(3)]

HIV prevalence



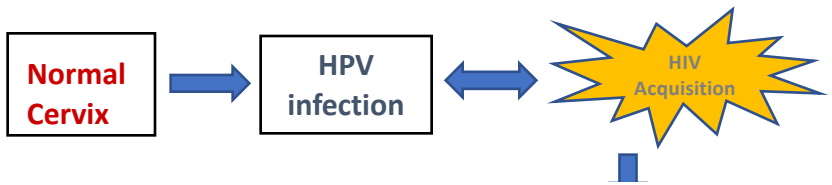
15.6 million WLHIV globally
12.5 million (80%) WLHIV in SSA

Arbyn 2020. Lancet Glob Health; UNAIDS 2018; 1Bruni et al, 2022 Prev Med 2021 Mar; 144; 3Stelzle, Lancet Glob Health 2021;

HPV, HIV and Cervical Cancer

HPV is a risk factor for **HIV acquisition** (**x2**) [(1)]

HIV ↑ **HPV incidence** (**x2**) and ↓ HPV clearance [(1)]

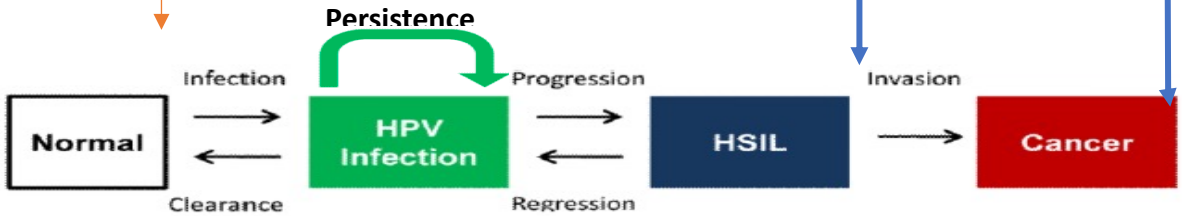


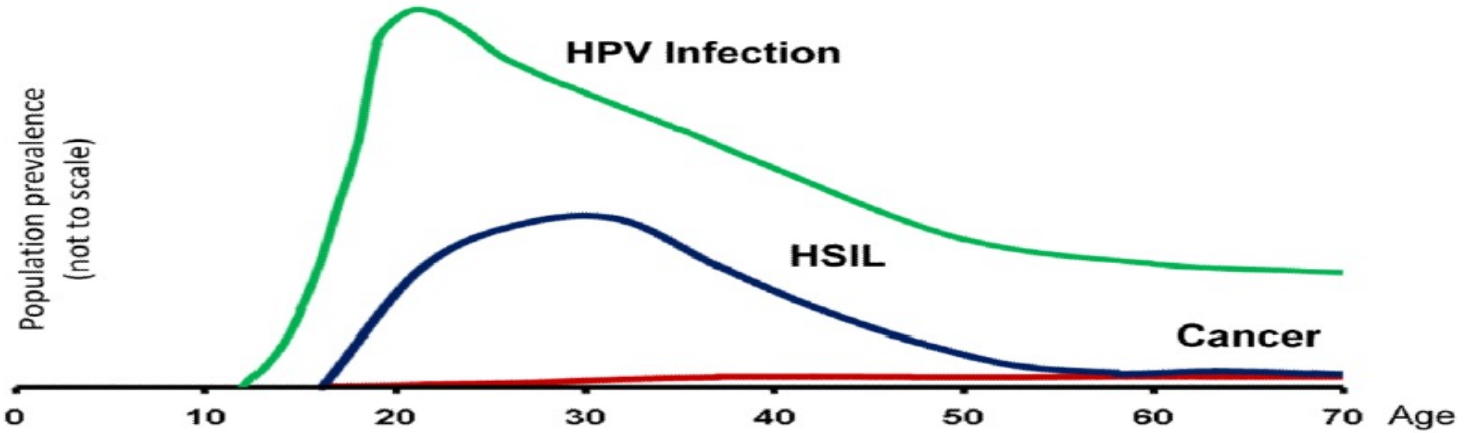
[1]Looker *JIAS* 2018, 21:e25110 ; [2]Clifford, *AIDS*, 2006; [3]Stelzle, Lancet Glob Health 2021; [4]Machalek, *Lancet Oncol* 2012; [5]Stier, *Am J Obs & Gynecol* 2015; [6]Low, *BMC Infect Dis* 2011; [7]Silverberg, *STD* 2002;

TOOLS TO PREVENT CERVICAL CANCER

Antiretroviral therapy

Primary prevention	Secondary prevention: Screening	Treatment precancer	Treatment cancer
HPV vaccine	HPV-DNA Visual inspection Cytology (“pap”)	Ablation/excision	Surgery, radio-, chemo-therapy





Schiffman, 2016 Nat Rev Dis Primers. 2016 Dec 1;2:16086

Control and prevention of HPV related disease among WLHIV

Association of antiretroviral therapy (ART) and HPV & ICC

For HR-HPV:

- Women on ART have ↓ 17% risk of HR-HPV prevalence

For SIL/CIN:

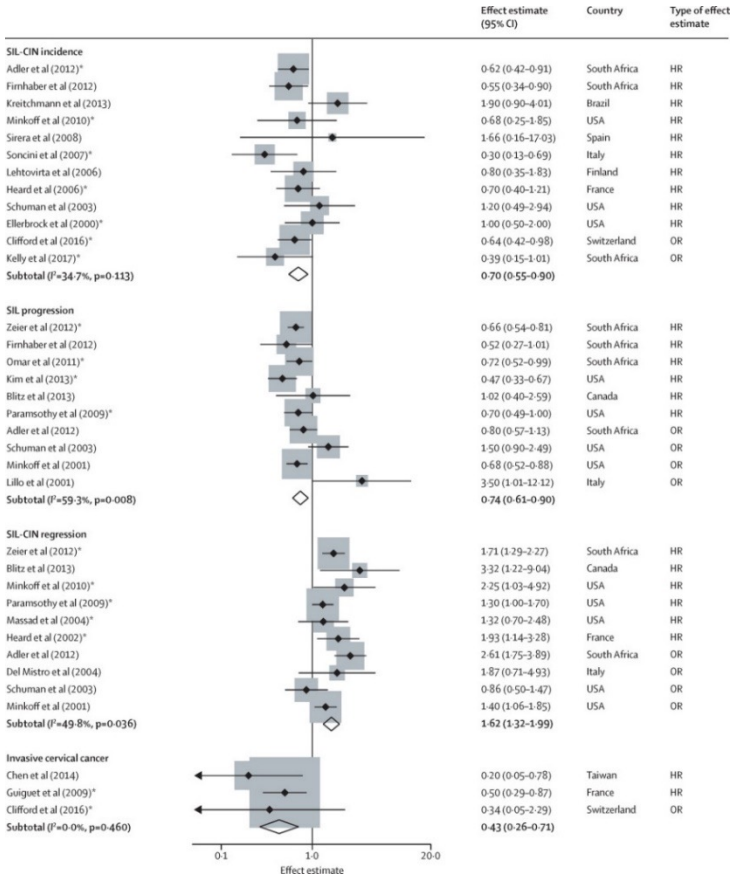
- Incidence: ↓ 41%
- Progression: ↓ 36%
- Regression: ↑ x2

For ICC:

- Incidence: ↓ 60%

- **RISK is LOWER if:**
  - **Initiated early (higher nadir CD4)**
  - **Prolonged ART duration, good adherence & effective treatment (sustained viral suppression and increasing CD4)**

52 studies worldwide
38,515 WLHIV



With universal ART (95-95-95), will risk of CIN2/3 and ICC among WLHIV = risk among HIV negative women?

Kelly et al, *Lancet HIV* 2018; 5: e45–58

Diagnostic accuracy of screening for CIN2+ detection - WLHIV

Screening	N studies	% positive	Sensitivity (95%CI)	Specificity (95%CI)
Visual Inspection (VIA)	14	6 – 56%	**44-87%**	**47-97%**
Cervical cytology (≥ASCUS)	19	41%	**58-100%**	**9-94%**
HPV-DNA (14 HR types)	28	45%	**92% (88-94)**	**62% (58-66)**

- HPV based tests had **lower specificity** in **WLHIV vs. HIV negative women** (55% vs. 83%; Relative Specificity=0.67, 95%CI: 0.62-0.72).

- **Specificity** of HPV DNA test **higher** in:
  - older vs. younger women
  - Women with higher CD4+
  - Long duration ART

  => corresponding with ↓ HR-HPV

Kelly et al, EClinicalMedicine, 2022 Sep 27;53:101645

Summary Recommendations
WHO suggests using the following strategy for cervical cancer prevention

For the general population of women

Screen and Treat OR Screen, Triage and Treat

- HPV DNA as primary screening test
- Starting at age 30
- Every 5 to 10 years screening interval

For women living with HIV

Screen, Triage and Treat

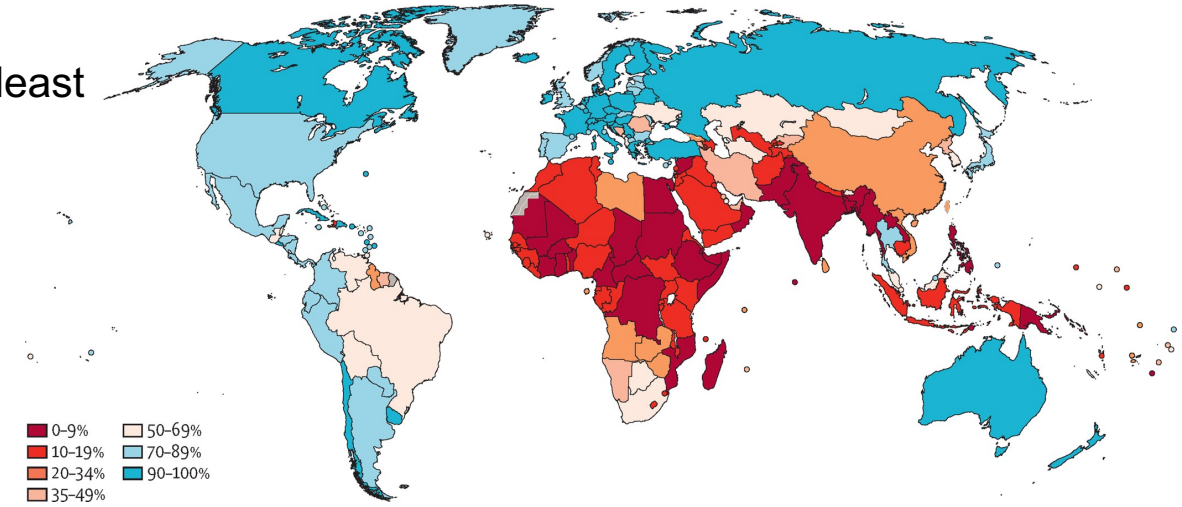
- HPV DNA as primary screening test
- Starting at age 25
- Every 3 to 5 years screening interval

* Where HPV DNA testing is not yet operational, use a regular screening interval of every 3 years when using VIA or cytology as the primary screening test among WLHIV

When providing HPV DNA testing, WHO suggests using either provider or self-collected samples

Screening access/coverage

- Estimated cervical cancer screening coverage in 2019, women **aged 30-49** years in **127 countries** worldwide
- **38%** of women aged 30-49 years have been screened at least once in their lifetime;
- **88%** in high-income settings
- **15%** in low-income countries



HPV DNA test or cytology most common in high-income settings, **VIA** most used in Sub-Saharan Africa

Uncertain for WLHIV, but reported that WLHIV 2x ↑ ever having had screening event

Bruni, 2022 Lancet Glob Health. 2022 Aug;10(8):e1115-e1127; Yang et al, PLoS Med. 2023 Jan 12;20(1):e1004143

Integration of cervical cancer screening in HIV services

WHO think tank meeting, May 2023, document successes, challenges and lessons learned for cervical cancer screening and treatment for **WLHIV**

1. Harnessing existing infrastructure

- Existing human resources, established referral networks, integration lab testing multi-disease platforms (HPV, CD4+, HIV VL monitoring, TB) and reporting platforms (LMIS)
- Alignment of screening and treatment visits with the ART-visit schedule

2. Innovations in ART delivery

- **Differentiated service delivery** (DSD), community-based models of care provide opportunity to offer **HPV self-collection** to women in their homes.
- Role of **patient navigators** in linking screen positive women to triage and treatment

3. Established civil society experience

- **Community-based and civil society organizations** and patient navigators for demand generation, rolling-out self-sampling, linkage to care and health education
- Financing and out of pocket payments (esp for triage and treatment)

4. Monitoring and evaluation

- Comprehensive tracking and data systems for HIV => integrate data on cervical cancer screening and treatment
- Interoperability of HIV and cancer monitoring systems important

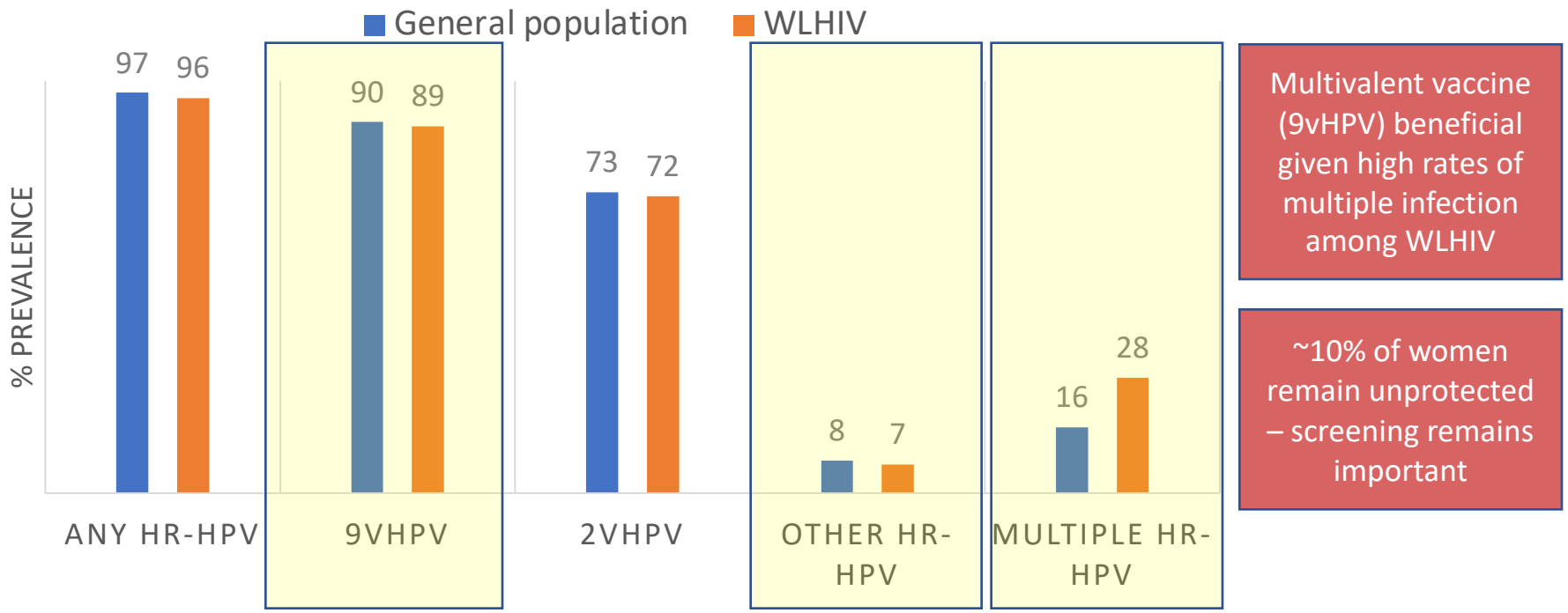
Cervical precancer recurrence post-treatment

- **3x** ↑ CIN2+ *recurrence* post-treatment in WLHIV (**22%**) vs. HIV negative women (**9%**)[1]
- **1.7x** ↑ CIN2+ *recurrence* **cryotherapy** (22%) vs. **LEEP** (13%) up to 2 years[1,2]
- ART **2x** ↓ CIN2+ *recurrence* if suppressed viral load and with early initiation[3]

- Frequent follow-up of women following treatment for cervical precancer
- Diagnostic accuracy of test strategies for detection of CIN2/3 up to 6 months post treatment in WLHIV *=> limited data*

1DeBeaudrap et al, 2019 Clin Inf Dis;69(9):1555–65; 2Greene et al, 2020; JAMA 22;322(16):1570-1579; 3*Mungo, 2022, JCO Global Oncology;* 4Atemnkeng et al, 2020; Clin Infect Dis. Mar 11;ciaa238; 4 Joshi,2023 Int. J. Cancer. ;152:249–258. Omenge Orang'o et al, 2017; AIDS, 31:233–240; DeVuyst et al, 2014, PLoS ONE 9(10): e111037

HPV vaccination among women living with HIV



HPV prevalence among women with invasive cervical cancer

9vHPV=HPV16/18/31/33/45/52/58; 2vHPV=HPV16/18

Clifford, *AIDS* 2016

HPV vaccination among PLHIV

- First studies in adult women living with HIV => Vaccine is immunogenic and safe
- Post-vaccination seroconversion rate is high & similar to women without HIV : 92-100% for 3 licenced vaccines[1,2, 3]
- Antibody titres post-vaccination similar among WLHIV and HIV-women at 12-months post-vaccination[1,2]
  - higher among PLHIV taking ART, who had higher CD4 cell counts or who had undetectable plasma HIV viral loads.
- Declines over time but above seropositivity cut-off, levels required for clinical protection currently unknown
- No efficacy data against infection or disease endpoints yet
- No published data on immunogenicity or effectiveness of 1- or 2-dose schedules among PLHIV

Staadegaard L et al. l EClinicalMedicine. 2022;52:101585.; Kahn, *Clin Infect Dis* 2013; Denny, *Vaccine* 2013; Zizza *Sci Rep* 2021; Mavundza, *Hum Vaccin Immunother* 2020; McClymont *Clin Infect Dis* 2019.

New WHO recommendations on HPV vaccine schedules can optimize vaccine coverage

Primary target : girls 9 to 14 years of age

2-dose schedule for all ages starting from 9 years old

Option: 1-dose schedule for 9 to 20-year-olds

Two doses with a 6-month interval for women **older than 21 years**

Prioritize the vaccination of Immunocompromised/HIV+ populations – also at ages beyond primary target - with at least 2 doses, ideally 3

2022, 97, 645–672 No 50

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

16 DECEMBER 2022, 97th YEAR / 16 DÉCEMBRE 2022, 97e ANNÉE
No 50, 2022, 97, 645–672
http://www.who.int/wer

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Human papillomavirus vaccines: WHO position paper (2022 update)

Introduction

In accordance with its mandate to provide normative guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers[1] on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale vaccination programmes.

The vaccine position papers are drafted by the WHO SAGE Secretariat; they summarize essential background information on diseases and vaccines and conclude with the current WHO position on the use of the vaccines worldwide. Before finalization, the position papers are reviewed by a large group of external subject-matter experts and end-users. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) and the evidence-to-recommendation tables are published alongside the position paper. The methods followed by SAGE[2] and the processes[3] for preparation of vaccine position papers are described on the WHO website. The position papers are intended for use by national public health officials and managers of immunization programmes. They may also be of interest to vaccine advisory groups, international funding agencies, health professionals,

Vaccins contre les papillomavirus humains: note de synthèse de l'OMS (mise à jour de 2022)

Introduction

Conformément à son mandat, qui prévoit qu'elle fournisse aux États Membres des orientations à caractère normatif en matière de politique sanitaire, l'OMS publie une série de notes de synthèse[1] régulièrement mises à jour sur les vaccins et les associations vaccinales contre les maladies ayant une incidence sur la santé publique internationale. Ces notes portent principalement sur l'utilisation des vaccins dans le cadre de programmes de vaccination à grande échelle.

Les notes de synthèse sur les vaccins sont rédigées par le secrétariat du SAGE de l'OMS; elles résument les informations essentielles sur les maladies et les vaccins associés et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation de ces vaccins à l'échelle mondiale. Avant leur mise en forme définitive, elles sont examinées par un large groupe d'experts externes et d'utilisateurs finals. Les résultats de l'évaluation GRADE (Grading of Recommendations Assessment, Development and Evaluation) et les tableaux des données à l'appui des recommandations sont publiés en même temps que la note de synthèse. Les méthodes employées par le SAGE[2] et la procédure suivie[3] pour élaborer les notes de synthèse sur les vaccins sont décrites sur le site Web de l'OMS. Les notes de synthèse sont destinées aux responsables nationaux de la santé publique et aux administrateurs des programmes de vaccination, mais elles peuvent également présenter un intérêt pour les

[1] WHO vaccine position papers. Geneva: World Health Organization (www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers, accessed August 2022).

[2] Guidance for the development of evidence-based vaccine-related recommendations. Geneva: World Health Organization; 2017 (www.who.int/publications/m/item/guidance-for-the-development-of-evidence-based-vaccine-related-recommendations, accessed August 2022).

[3] WHO position paper process. Geneva: World Health Organization; 2020 (www.who.int/publications/m/item/who-position-paper-process, accessed August 2022).

[1] WHO vaccine position papers. Genève: Organisation mondiale de la santé (www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers, consulté en août 2022).

[2] Guidance for the development of evidence-based vaccine-related recommendations. Genève: Organisation mondiale de la santé; 2017 (www.who.int/publications/m/item/guidance-for-the-development-of-evidence-based-vaccine-related-recommendations, consulté en août 2022).

[3] WHO position paper process. Genève: Organisation mondiale de la santé; 2020 (www.who.int/publications/m/item/who-position-paper-process, consulté en août 2022).

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Source: https://www.who.int/publications/i/item/who-wer9750-645-672

HOPE (HPV One and two dose Population Effectiveness) Study

- Repeated cross sectional surveys among young women aged 17–18 years in South Africa: 2019, 2021, 2023to evaluate Community-level impacts of both the one-dose and two-dose schedules compared with no vaccination
- National South African HPV vaccination programme, which has targeted grade 4 girls aged at least 9 years in public schools with two doses of vaccine since 2014

- Aims to detect of changes over time in human papillomavirus (HPV) prevalence before and after HPV vaccination programme
- Does HIV infection status affects the protective effectiveness of HPV vaccines

- HPV16/18 prevalence pre vs. post-vaccine: 33% vs. 21%, adjusted prevalence ratio=0.63, 95%CI: 0.41-0.95

- Duration of antibody response to understand need for booster ?

Delany-Moretlwe, IPVC April 2023

Summary

- WLHIV at higher risk of HR-HPV infection, cervical precancer and cancer compared to women without HIV
- => Beneficial impact of ART
- HIV prevention, testing, early initiation ART reduces risk of HR-HPV persistence, cervical precancer and cancer
- Regular screening important
  - novel technology to give even better diagnostic tools
  - opportunities for single visit (coincide with HIV visit), strong linkage to care
- PLHIV elicit robust immune response following HPV vaccination; more data needed on efficacy
- PLHIV have high prevalence of vaccine types but probability of being infected by ALL types low
- Combined with screening!
- More evidence on immune response and efficacy of reduced dose schedules in immunocompromised individuals and HIV-infected persons