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Cervical Cancer: Viruses, Immunization and Screening

Symposium Molecular Diagnostics 2025
Zurich, 27.02.2025

Dr. Nobila Ouédraogo
Cancer Prevention Unit – German Cancer Research Center

Structure

1. Introduction
2. HPV - Molecular and Biological Insights
3. Immunization
4. Screening and Diagnostics
5. Future Directions

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1-Which statements about cervical cancer and its prevention are true?

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1. Introduction

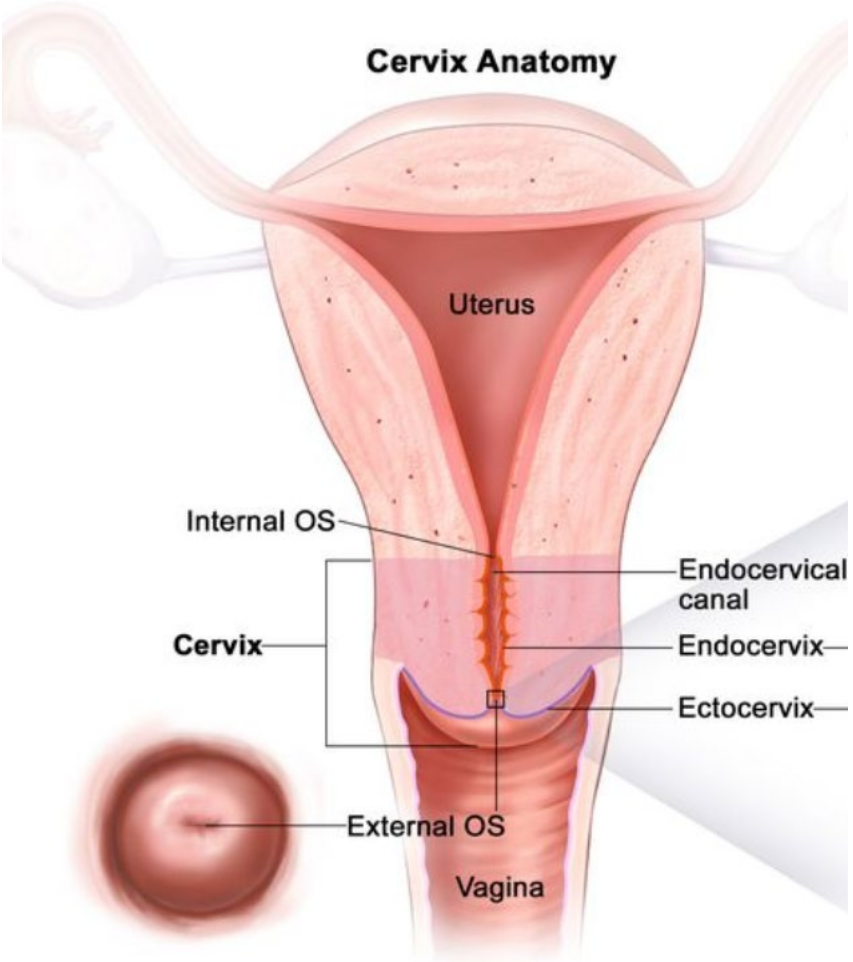
1.1. Cervical cancer

Cervical cancer = C53 –
Malignant neoplasm of cervix uteri [ICD-10]

Types of cervical cancer:

- Squamous cell carcinoma
- Adenocarcinoma
- Mixed (carcinoma or adenosquamous carcinoma)

Variable progression (10 – 20 years from infection to cervical Cancer).



1.2. HPV as causative agent of cervical cancer

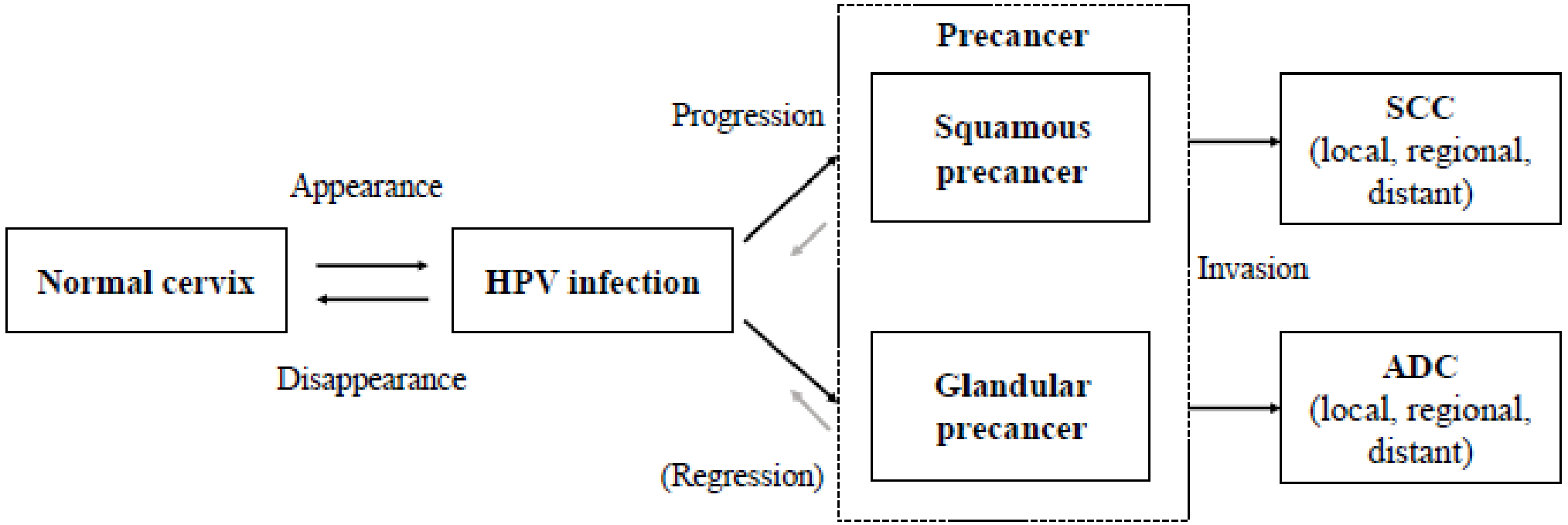
1842 – Suggestion of an infectious cause of cervical cancer by **D. A. Rigoni-Stern** (1810–1855).

1970s → Discovery of HPV by German virologist **Harald zur Hausen**

1983 – 1984 → Isolation of HPV-16 and 18 DNA from cervical cancer tissues

1996: Classification of HPV as a cause of cervical cancer (IARC).

1.3. From HPV-Infection to Cervical Cancer



Campos et al. 2021

1.4. Risk factors of cervical cancer

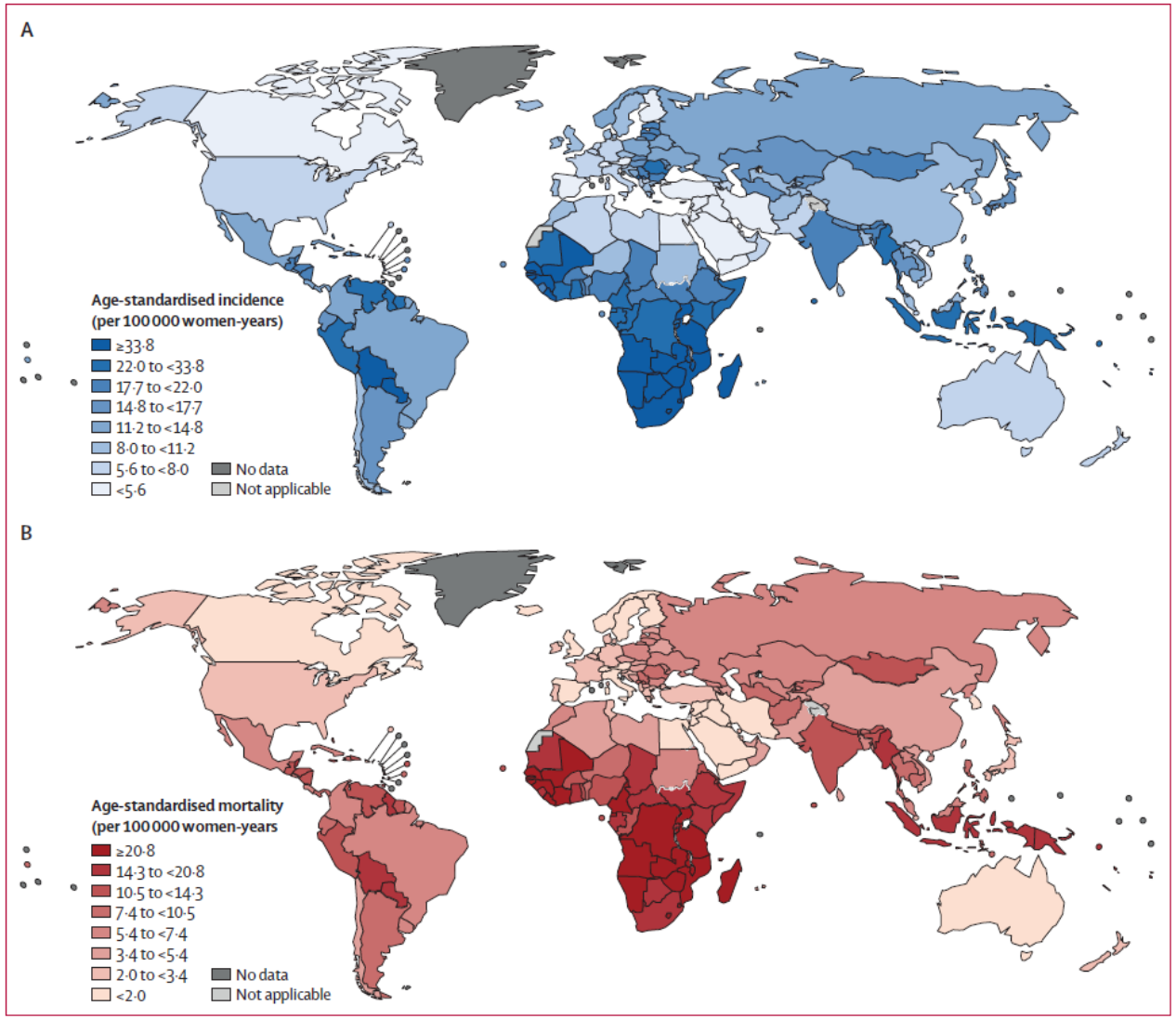
HPV-related risk factors: Persistent infection with high-risk HPV types (HPV-16 and HPV-18) + viral load.

Behavioral and lifestyle risk factors: e.g. Early sexual activity, multiple sexual partners, smoking, long-term use of oral contraceptives, high parity.

Biological risk factors: e.g. HIV infection, Immunosuppressive therapy.

Medical and socioeconomic risk factors: e.g. Co-infection with other sexually transmitted infections (STIs), poor socioeconomic status.

1.5. Global Burden of Cervical Cancer



Incidence: ~ **604.000**
news cases annually

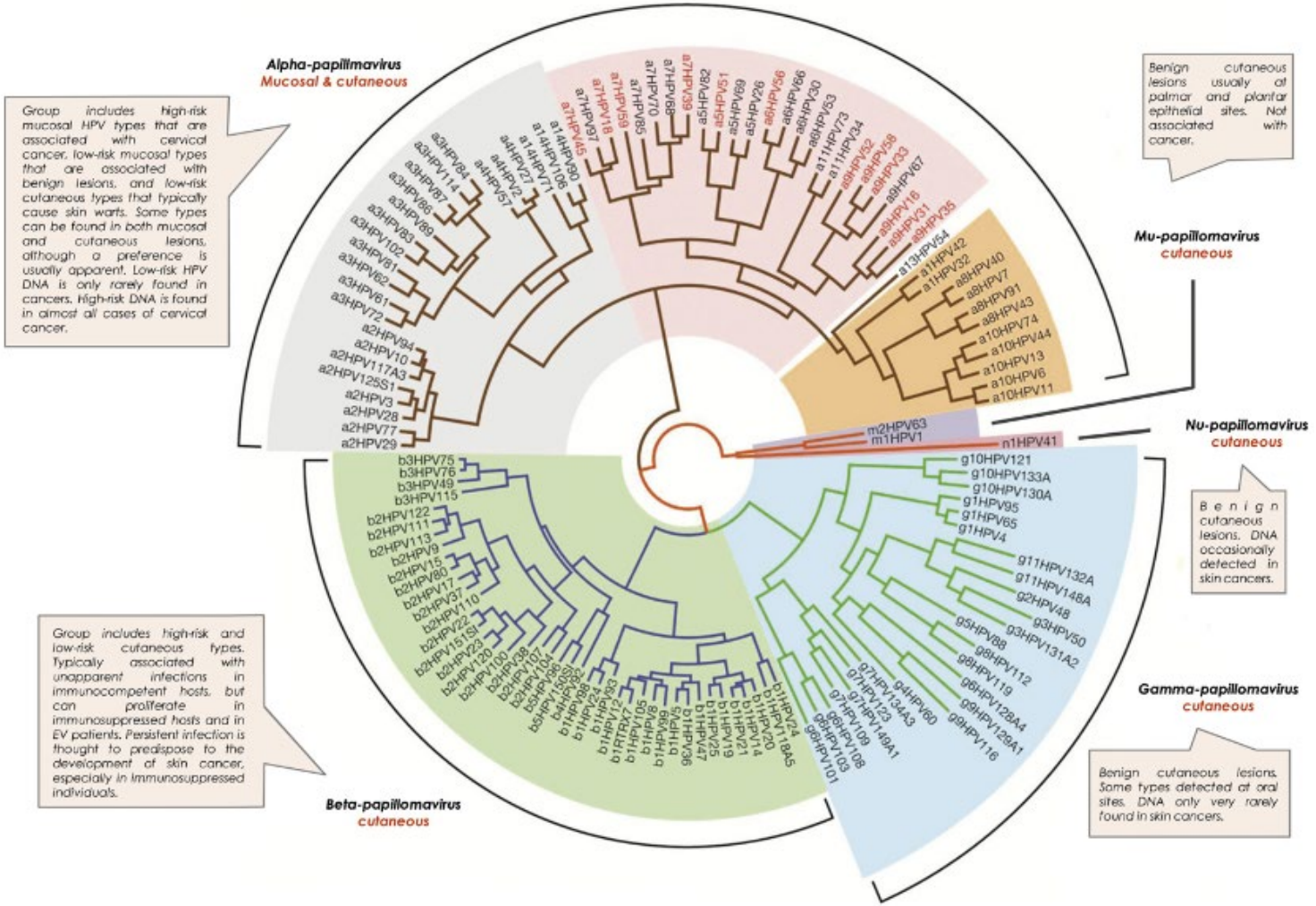
Mortality: ~ **342.000**
deaths annually

Over **90%** of cases
and death in **LMICs**

Singh et al. 2020

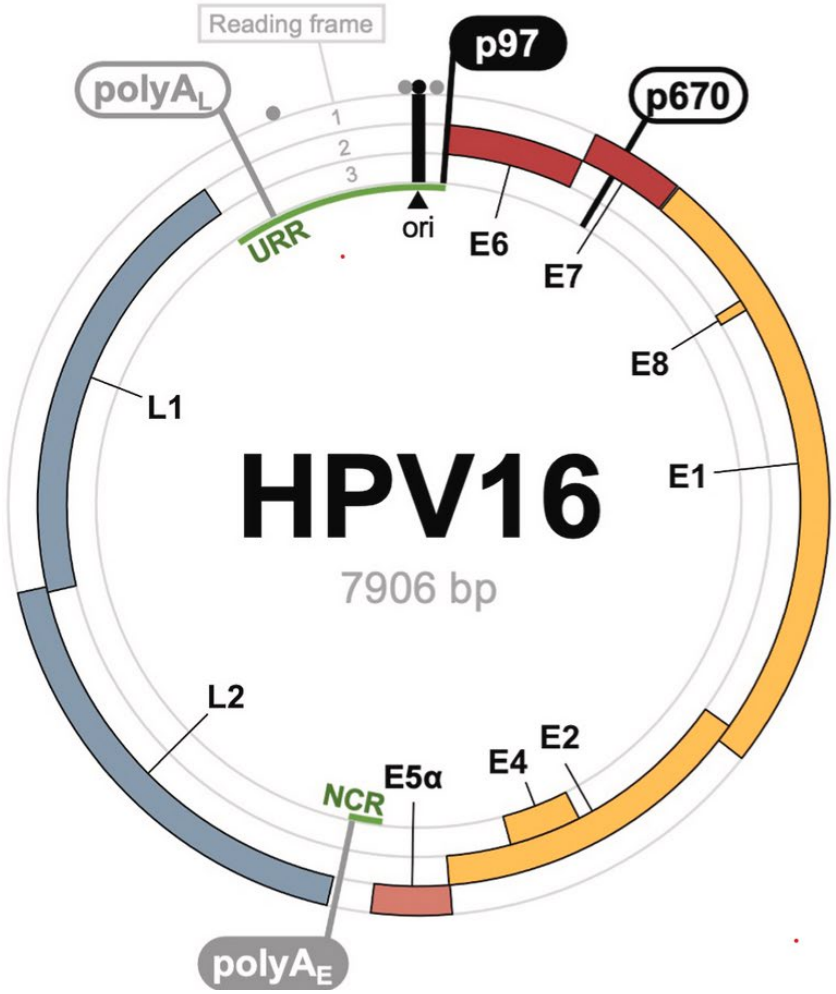
2. HPV - Molecular and Biological Insights

2.1. Evolutionary Relationship between HPV



Doorbar et al. 2012

2.2. Viral Structure - Genome Organization



Genomic features

- E1 binding site
- E2 binding sites
- promoter (p)
- polyadenylation site (polyA)
- Upstream Regulatory Region
- Non-Coding Region

ORF type

- oncoprotein
- accessory oncoprotein
- replication/release
- structural

Nelson & Mirabello 2023

2.3. Implications for Prevention and Treatment

Prophylactic Vaccines: Target the L1 protein to elicit neutralizing antibodies, preventing initial infection.

Screening: HPV DNA testing identifies high-risk infections.

Therapeutic Targets: Future treatments may target E6 and E7 oncoproteins or restore p53 and Rb function.

3. Immunization

3.1. HPV Prophylactic Vaccines

First-Generation Vaccines: Virus-Like Particles (VLPs) – L1 capsid protein, ~70% of cervical cancer cases.

Gardasil 4 (2006): HPV-16, HPV-18, HPV-6, and HPV-11;

Cervarix (2007): HPV-16 and HPV-18;

Cecolin (2019): HPV-16 and HPV-18.

Second-Generation Vaccines: Virus-Like Particles (VLPs) – L1 capsid protein, ~90% of cervical cancer cases.

Gardasil 9 (2015): HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, HPV-58 (high-risk types), and HPV-6, HPV-11

3.2. Vaccines Efficacy and Effectiveness

High Efficacy of ~95–100% against precancerous lesions

Effectiveness of ~90% in HPV infections and high-grade cervical lesions in countries with high vaccine coverage (e.g., Australia, Sweden, UK).

Effectiveness Determinants: vaccine uptake, adherence to vaccine schedule and population factors.

3.3. HPV Vaccination Programm Status

World Health Organization

Global Map area

Country profile area

Coverage Analysis Global/Regional

Effectiveness studies

194

Total countries reported

HPV national schedule	No. of countries
A. Yes	146
B. Yes (Partial)	2
C. No	46

Last update:

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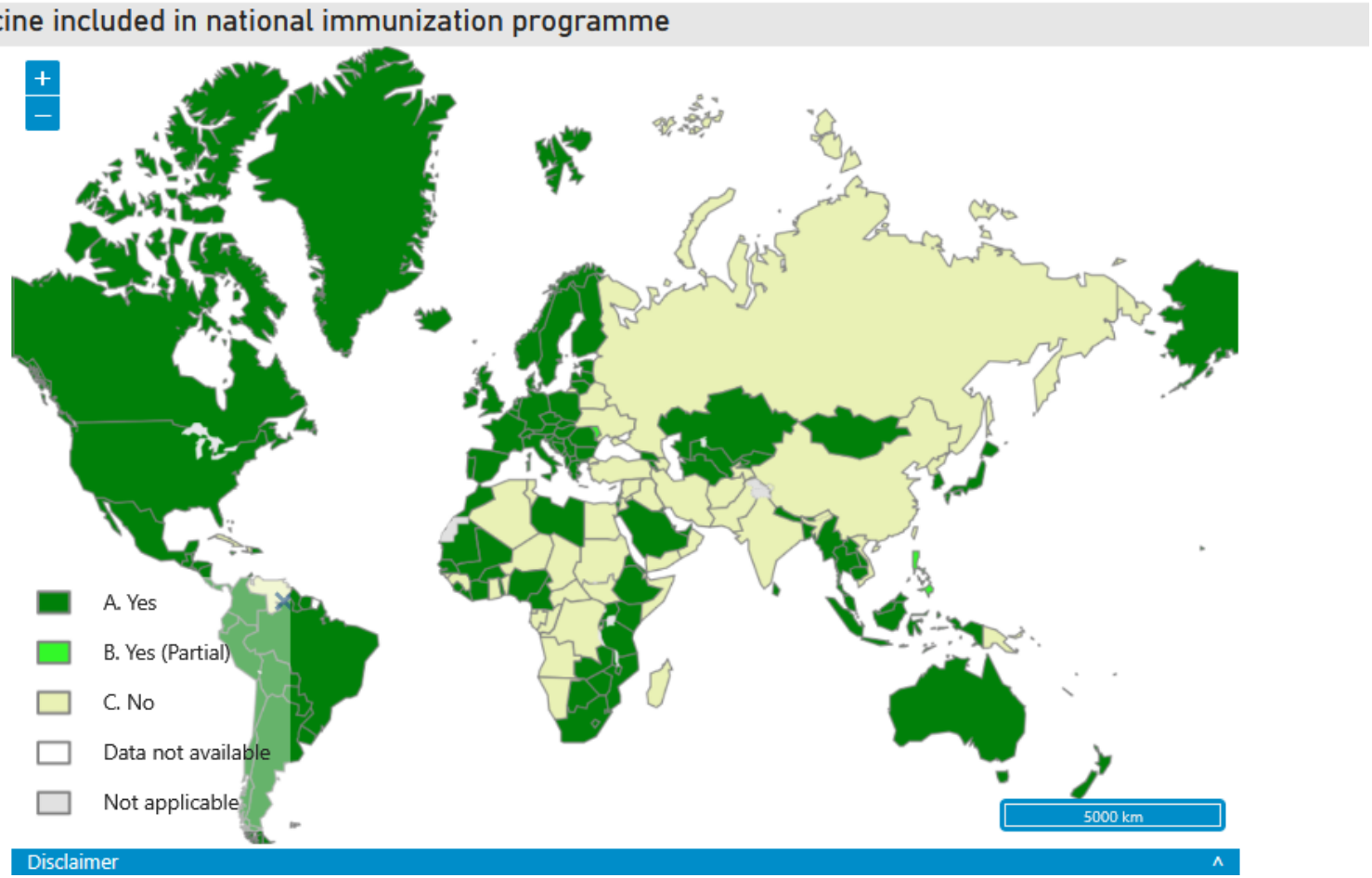
Introduction Status | Introduction Year | Delivery strategy | Targeted Sex | HPV1 coverage | HPVc coverage | Schedule (interval between doses)



WHO 2025

dkfz.

3.4. HPV Vaccination Target Groups

World Health Organization

Global Map area

Country profile area

Coverage Analysis Global/Regional

Effectiveness studies

148

Total countries reported

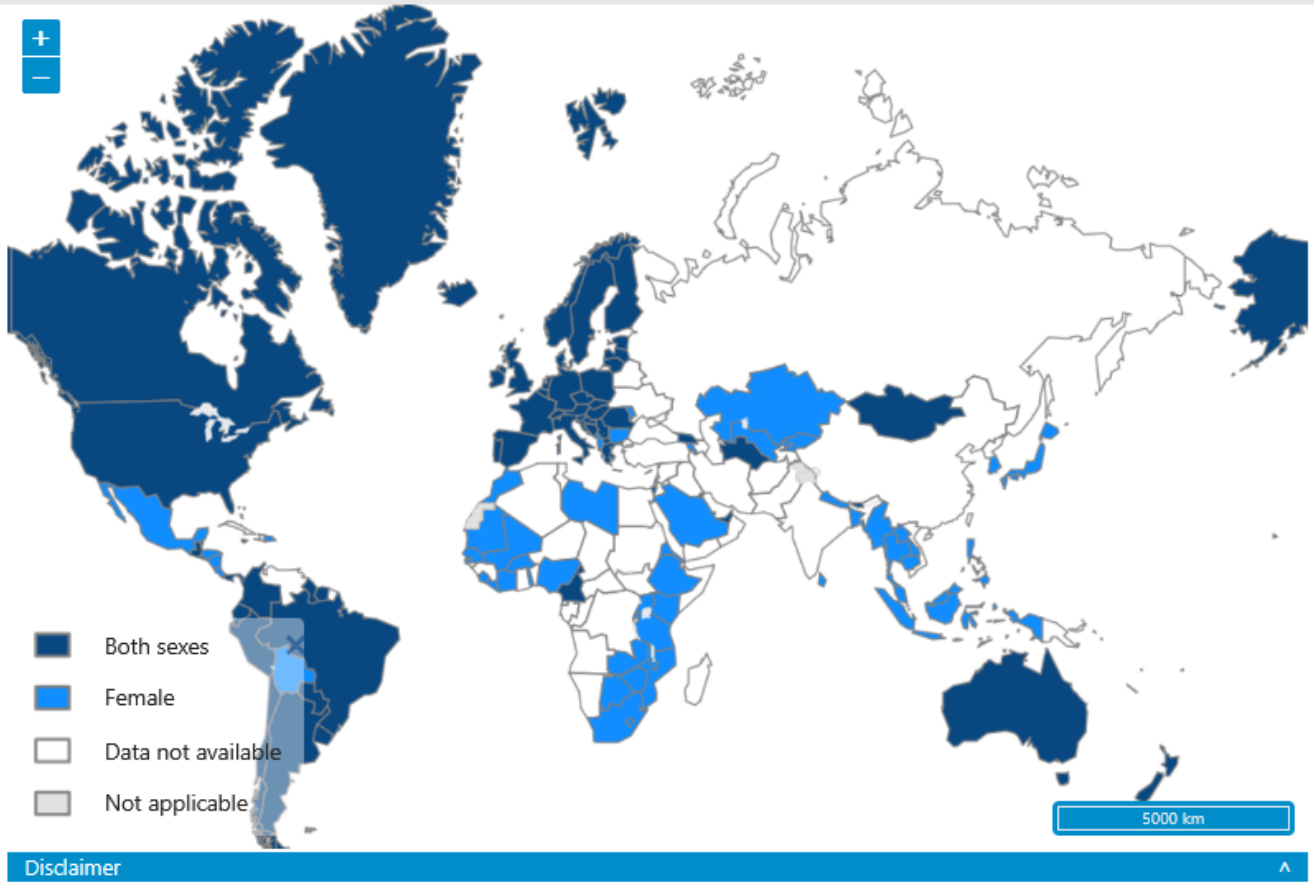
HPV Sex	No. of countries
Female	72
Both sexes	76

Last update:

2/4/2025 11:11:12 A...

Introduction Status | Introduction Year | Delivery strategy | Targeted Sex | HPV1 coverage | HPVc coverage | Schedule (interval between doses)

HPV vaccine included in national immunization programme, by targeted sex



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3.5. HPV Vaccination Schedule

World Health Organization

Global Map area

Country profile area

Coverage Analysis Global/Regional

Effectiveness studies

Introduction Status | Introduction Year | Delivery strategy | Targeted Sex | HPV1 coverage | HPVc coverage | Schedule (interval between doses)

HPV vaccination programme schedule (9-14 years old)

Interval_doses	No. of countries
1 dose	67
2 doses (12 months)	4
2 doses (6 months)	73
Not yet introduced	46
Unknown schedule	4

Last update:

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3.6. HPV Vaccine Delivery Strategies

World Health Organization

Global Map area

Country profile area

Coverage Analysis Global/Regional

Effectiveness studies

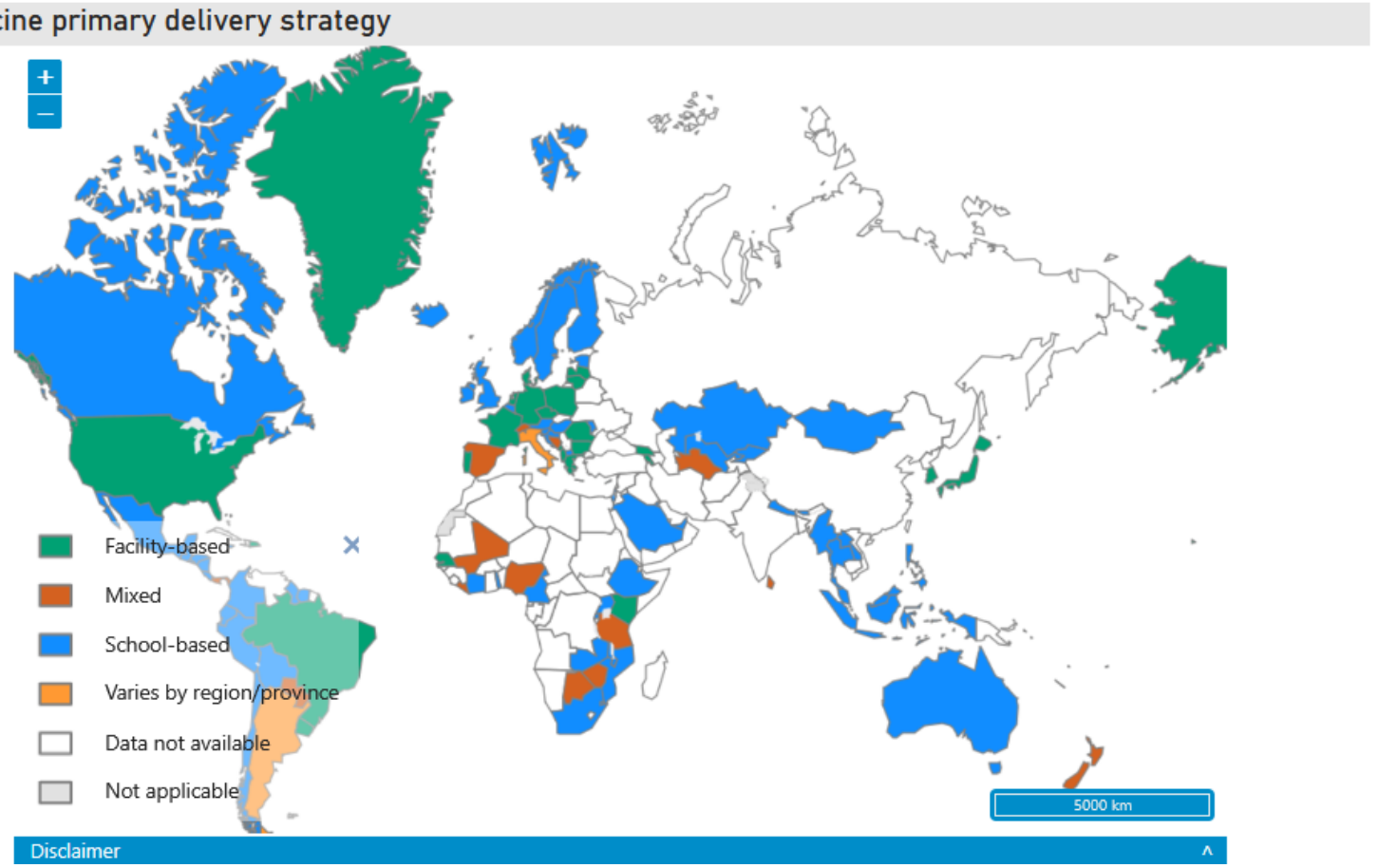
129

Total countries reported

Delivery strategy	No. of countries
Facility-based	29
Mixed	18
School-based	80
Varies by region/ province	2

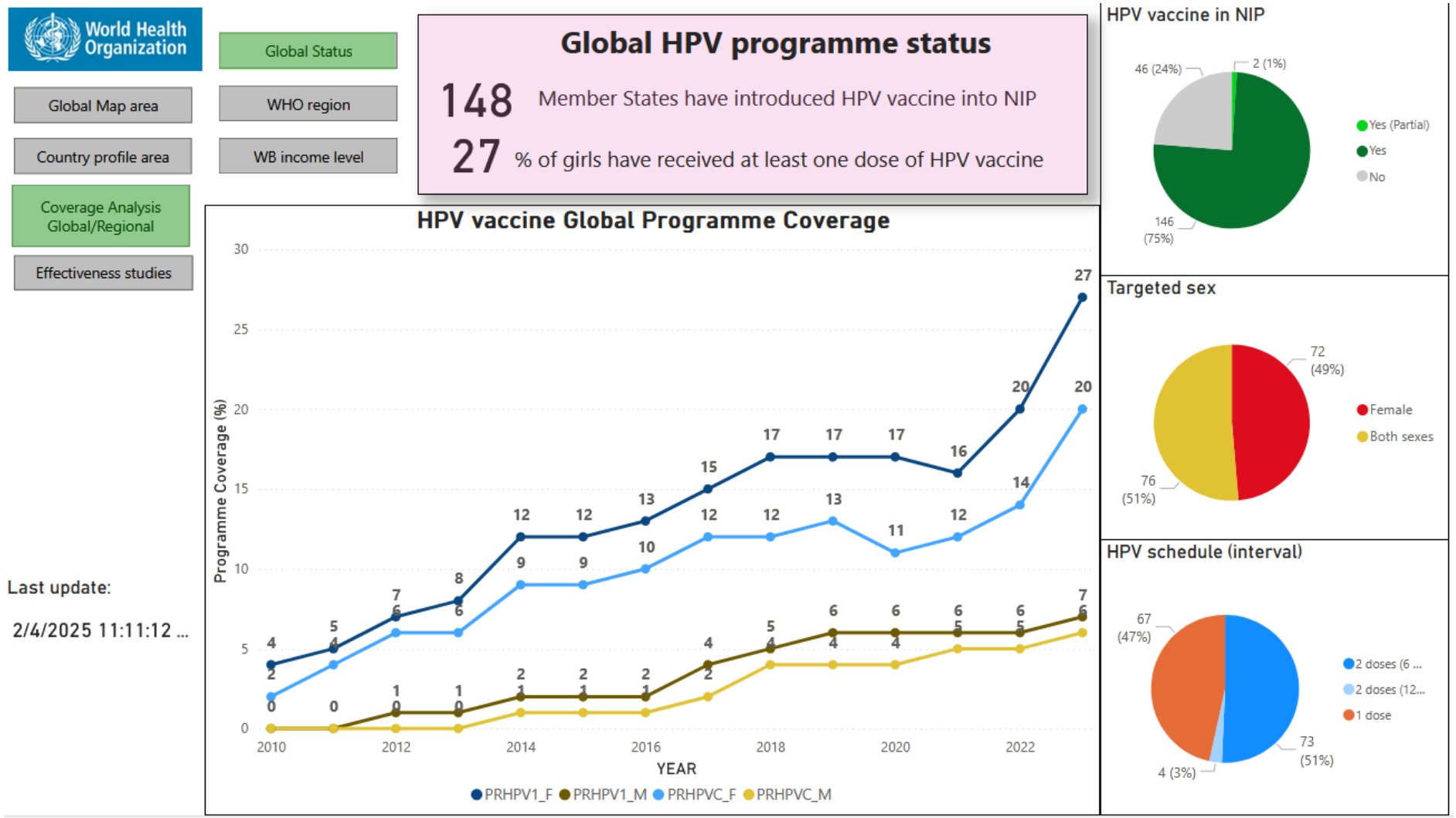
Last update:

Introduction Status | Introduction Year | Delivery strategy | Targeted Sex | HPV1 coverage | HPVc coverage | Schedule (interval between doses)



WHO 2025

3.7. HPV Vaccination Coverage



WHO 2025

4. Screening and Diagnostics

4.1. Common Screening Methods

Pap Smear (Cytology): Detects existing abnormal cells using a microscope

Visual Inspection with Acetic Acid (VIA): Swab of the cervix with diluted acetic acid + visually inspect for white-colored lesions by health providers.

HPV Testing: HPV DNA testing (PCR, hybrid capture), RNA testing (E6/E7 mRNA)

4.2. Common HPV Tests

Biomolecule	Test Name	Target	Number of HPV types
DNA	Hybrid Capture® 2 (hc2)	Full HPV genome	13
DNA	Cervista HPV HR	E6/E7	14
DNA	RealTime High Risk HPV assay	L1	14
DNA	BD Onclarity HPV	E6/E7	14
DNA	Cervista HPV 16/18	E6/E7	2
DNA	Anyplex II HPV28	L1	28
DNA	INNO-LiPA® HPV Genotyping Extra II	L1	32
DNA	PapilloCheck	E1	24
RNA	Aptima HPV Assay	E6/E7 mRNA	14
Protein	OncoE6 HPV Test	HPV 16/18 E6 oncoprotein	2

Bartosik et al. 2024

4.3. Cervical Cancer Screening Strategies

Screening Strategy	Screening Interval	Cost-Effectiveness
Primary HPV Screening	Every 5 years	Most cost-effective
HPV Screening with Triage	Every 5 years	Cost-effective
Visual Inspection with Acetic Acid (VIA)	Every 3 years	Less cost-effective
Cytology-Based Screening	Every 3 years	Less cost-effective

Simms et al. 2023

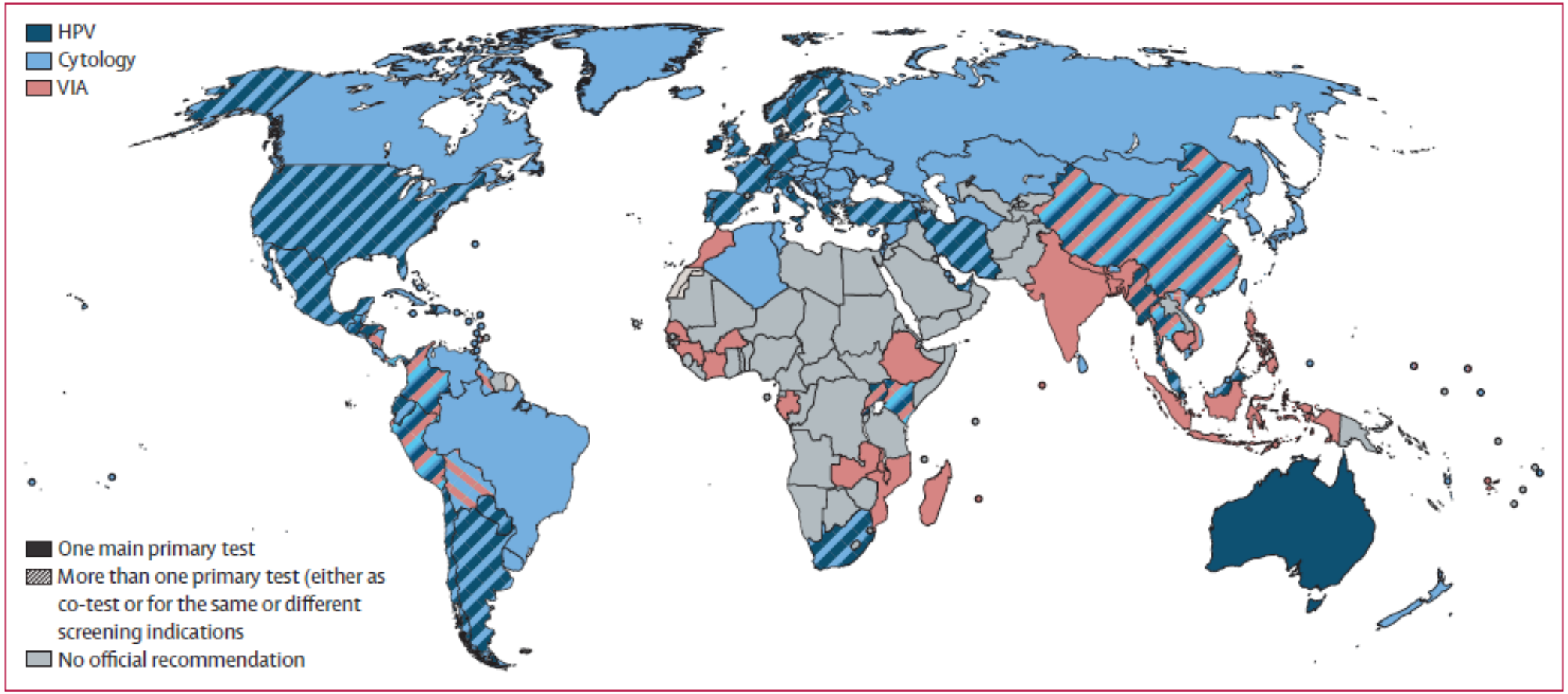
4.4. Recommendations and Good Practices

General population of women: HPV DNA detection - in **screen-and-treat approach** or in **screen, triage and treat approach** starting at age of 30 years with 5 to 10 years screening interval.

Women living with HIV: HPV DNA detection - **screen, triage and treat approach -** starting at age of 25 years with 3 to 5 years screening interval.

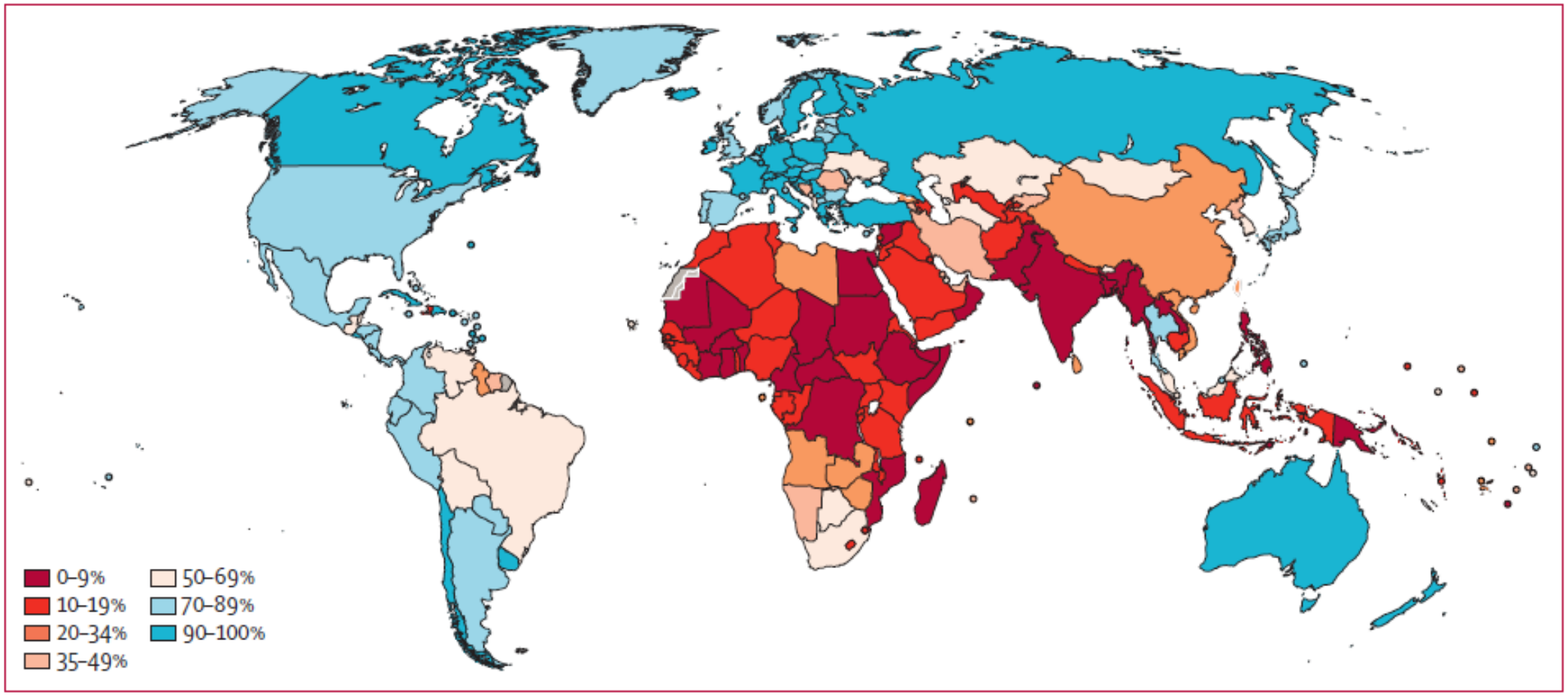
Good practice: Once a decision to treat a woman is made - it is good practice to treat as soon as possible **within six months** to reduce the risk of loss to follow-up.

4.5. Implementation of cervical cancer Screening



Bruni et al. 2022

4.6. Implementation of cervical cancer Screening



Bruni et al. 2022

4.7. Advances in Molecular Diagnostics

Biomarkers for progression risk, e.g. p16INK4a, Ki-67, p16/Ki-67

HPV genotyping for risk stratification: Primary Screening, Triage of HPV-Positive Women, Post-Treatment Surveillance, Vaccine Impact Studies

Self-sampling methods and their clinical utility: Brush-based devices (e.g., Evalyn Brush), swabs, lavages.

4.8. Integrating Screening with Immunization

Rationale for integration: Even with **vaccination, screening remains necessary**

Age appropriated strategies:

Young adolescents (9–14 years old): Focus on HPV vaccination.

Young adults (20–30 years old): HPV vaccination +/- Screening.

Women ≥30 years: HPV-based screening with intervals of 5–10 years.

Screening Modifications for Vaccinated Women: less frequent screening or raising the starting age of screening

5. Future Directions

5.1. Cervical Cancer Elimination Goal

Rational: High global burden, Preventability and treatability

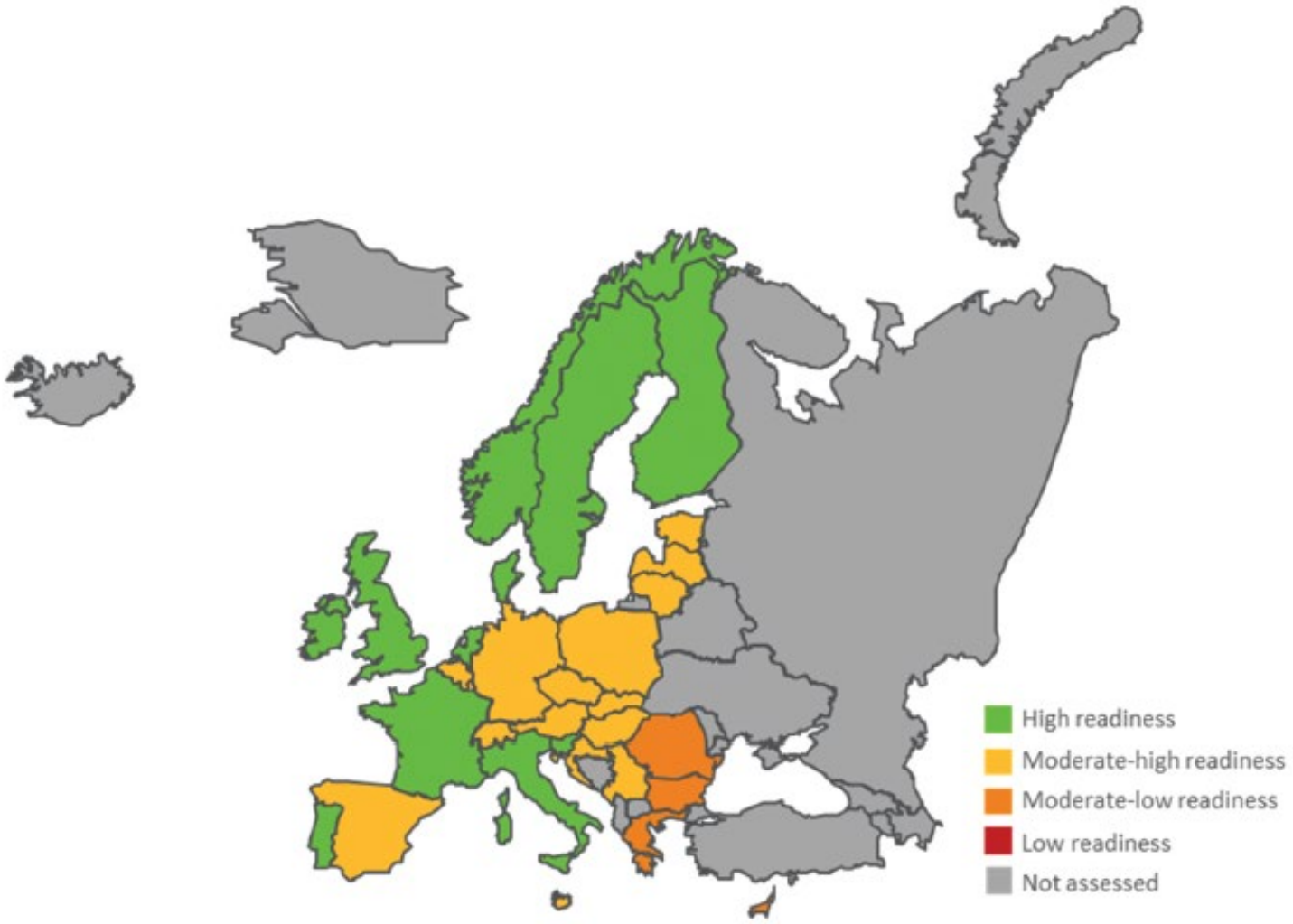
WHO’s 90 – 70 – 90 targets on cervical cancer elimination

Success stories worldwide

Australia, Nordic countries (Sweden, Norway, Denmark, Iceland), Rwanda

6.2. Readiness Assessment in Europe

93% Sweden
89% Ireland
87% UK
86% Finland
86% Norway
84% Denmark
84% Slovenia
83% Portugal
79% France
79% Italy
77% Netherlands
76% Estonia
71% Spain
70% Latvia
69% Germany
66% Czechia
64% Switzerland
61% Hungary
60% Luxembourg
60% Malta
59% Lithuania
59% Austria
59% Belgium
57% Slovakia
56% Poland
54% Serbia
51% Croatia
50% Romania
46% Greece
46% Cyprus
44% Bulgaria



Karamousouli et al. 2025

5.3.Next-Generation Prevention Tools

Third-Generation of HPV Vaccines, e.g.:

- Pan-HPV vaccines
- Therapeutic HPV vaccines
- Thermostable HPV vaccines

Artificial Intelligence (AI) in cytology and HPV test interpretation, e.g.:

- Automated Screening (e.g. AI assisted Pap smear)
- AI in HPV Test Interpretation (e.g. AI powered HPV DNA Testing)
- AI for Risk Stratification

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3-How would you rate this course overall (1 - Poor / 2 - Fair / 3 - Good / 4 - Very Good / 5 - Excellent

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for your attention!

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