Advancements on HPV-related cancer screening

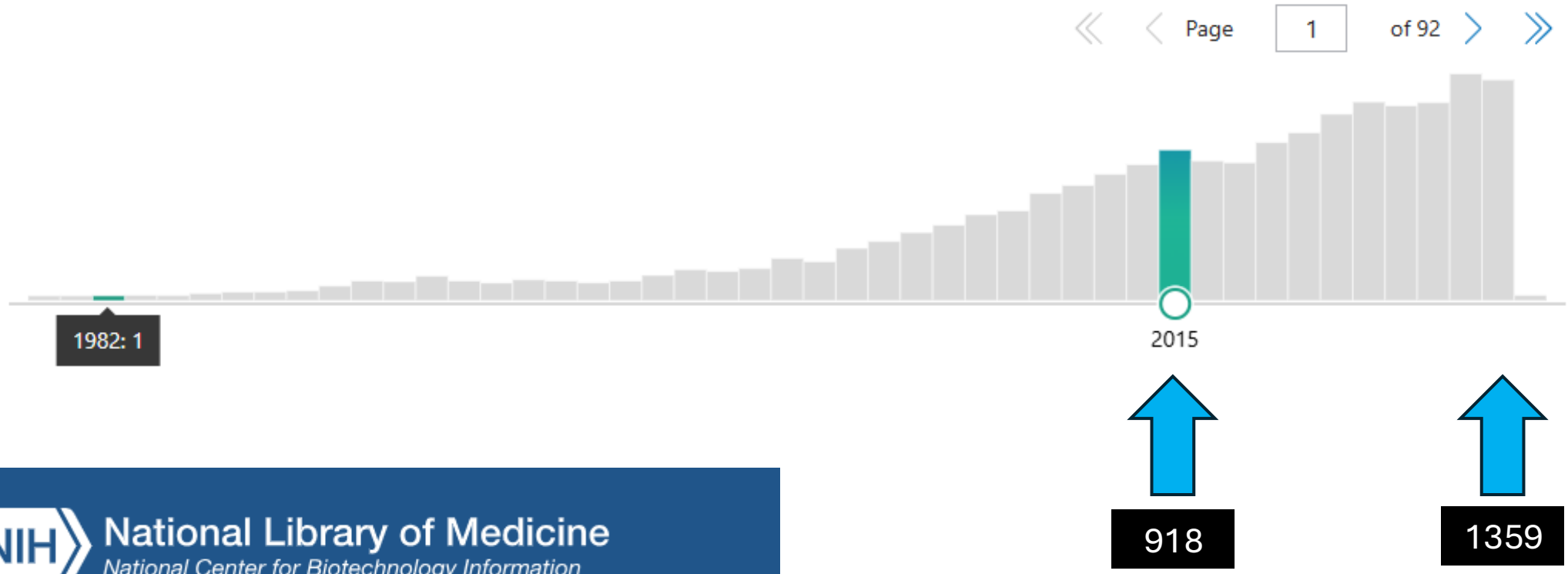
Dr Kate Cuschieri

Director - Scottish HPV Reference Laboratory

Royal Infirmary of Edinburgh

Presented at 10 year celebration of HPV Prevention and Control Board

“HPV”; “Cervical”; “Screening”



National Library of Medicine
National Center for Biotechnology Information

2015 Perspective, presented at Inaugural Prevention and Control Board in Antwerp

Do we have reliable baseline data about cervical cancer screening practices *in Europe* ?

Overview of challenges at the level of HPV-based cervical cancer screening

Mario Poljak

Institute of Microbiology and Immunology
Faculty of Medicine, University of Ljubljana, Slovenia

Do we have clear guideline recommending HPV-based primary screening in Europe ?

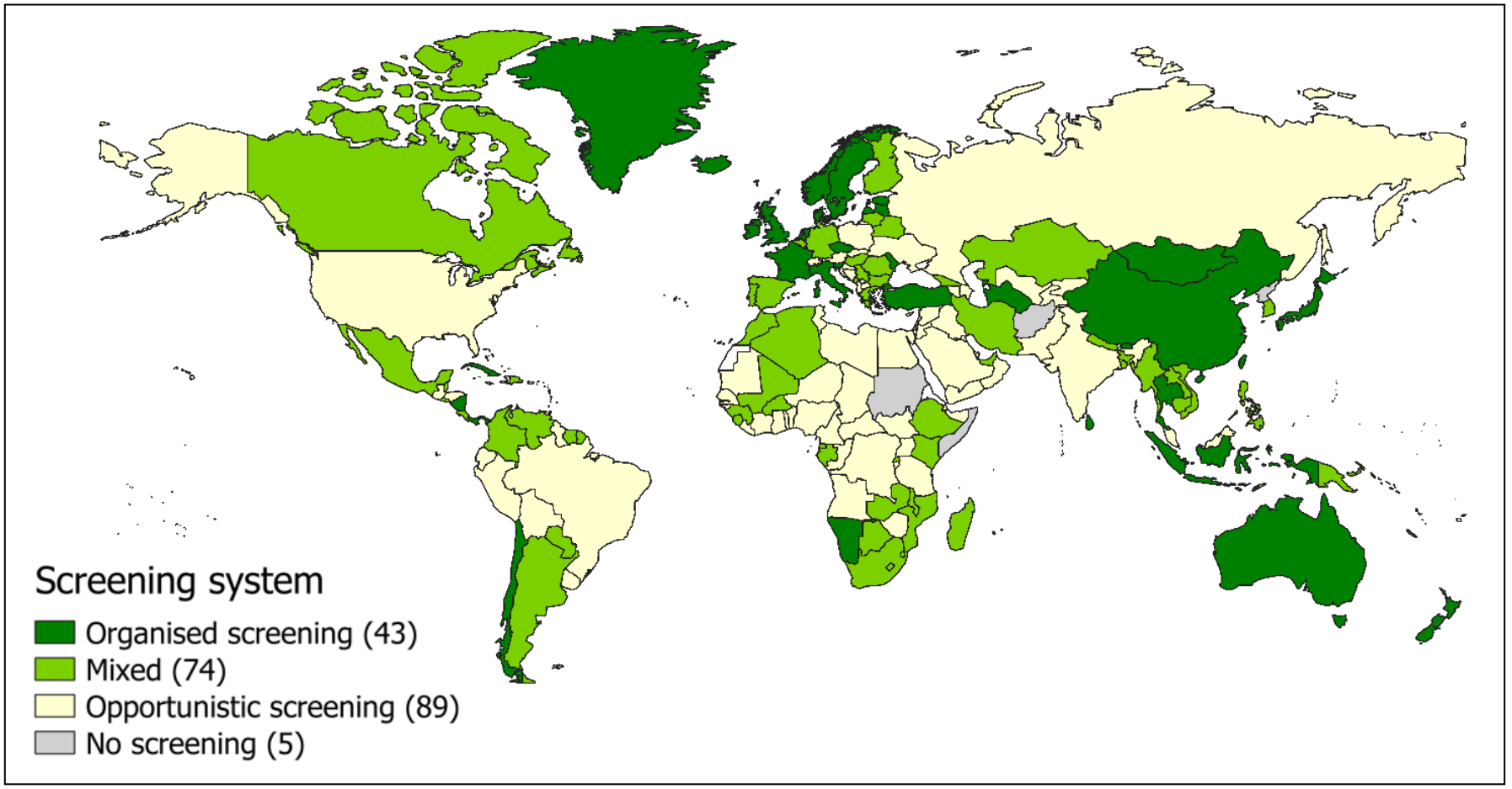
HPV !!!

HPV test ?

Year 2015: 193 commercial HPV assays (and 127 variants) on the market
11 considered clinically validated for screening

Antwerp, Belgium - December 2015 - HPV Prevention and Control Board & Poljak et al J Clin Virol 2024

Screening systems globally (2024-25)*

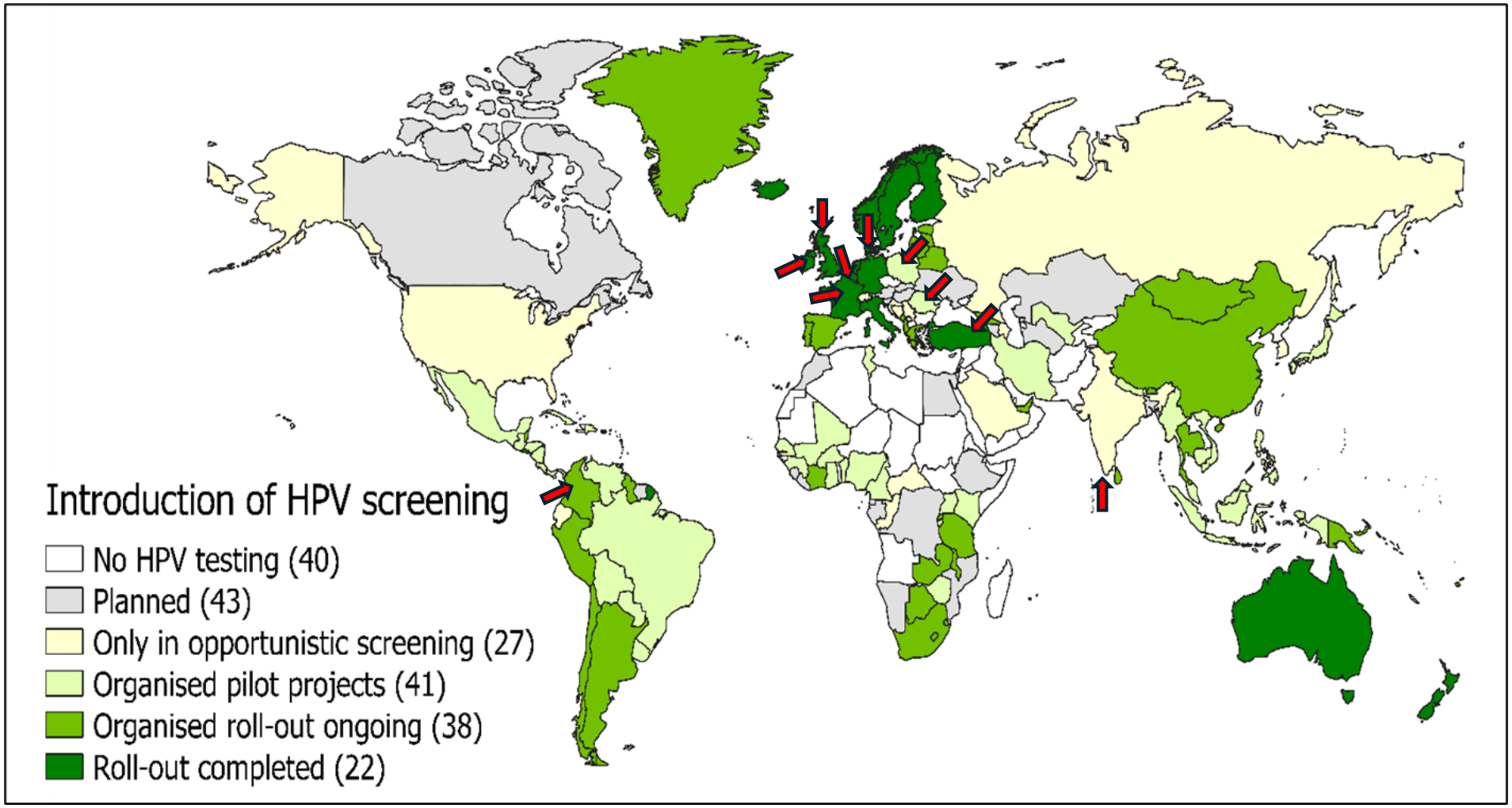


Arbyn et al Presented at IPVS 2025

Do we have reliable baseline data about cervical cancer screening practices *in Europe* ?

HPV based screening (March, 2025)

HPV Prevention and Control Board



Updates on **<u>Implementation (and barriers therein)</u>, key feature of the HPV Prevention and control board**

Arbyn et al Presented at IPVS 2025

European guidelines on cervical cancer screening and diagnosis

Select a topic

Primary prevention

1. Screening ages and tests

Select presentation view

For healthcare professionals | Summary information in plain language

Screening ages and tests

Select sub-topic

Screening populations aged 30 to 50 years

Screening populations aged 30 to 50 years

Issued on: February 2025

Healthcare question

Should cervical cytology or co-testing vs. HPV detection test be used as the primary screening test for cervical screening in asymptomatic populations with a cervix aged 30–50 years?

Recommendation

The EC-CvC Working Group (WG) recommends using HPV detection test for primary screening in asymptomatic populations with cervix aged 30–50 years in the context of an organised population-based screening programme (strong recommendation, high certainty of the evidence).

The EC-CvC Working Group (WG) recommends not using cervical cytology for primary screening in asymptomatic populations with cervix aged 30–50 years in the context of an organised population-based screening programme (strong recommendation, high certainty of

Do we have clear guideline recommending HPV-based primary screening in Europe ?

Recent work from European Commission Initiative on Cervical Cancer: EC-CvC

Objective: **Develop evidence based recommendations for cancer screening and diagnosis**, and a *"voluntary European quality assurance scheme for cervical cancer care services"**

**in preparation*

https://cancer-screening-and-care.jrc.ec.europa.eu/en/ec-cvc/european-cervical-cancer-guidelines?topic=328&usertype=327

Public Health 239 (2025) 185–192

Contents lists available at ScienceDirect

Public Health

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

Original Research

Prioritizing performance and outcome indicators for quality assessment of cancer screening programs in the EU

Brian Sheridan [a,*], Abyan Irzaldy [a], Eveline A.M. Heijnsdijk [a], Nadya Dimitrova [c], Carlo Senore [b], Partha Basu [c], Harry J. de Koning [a]

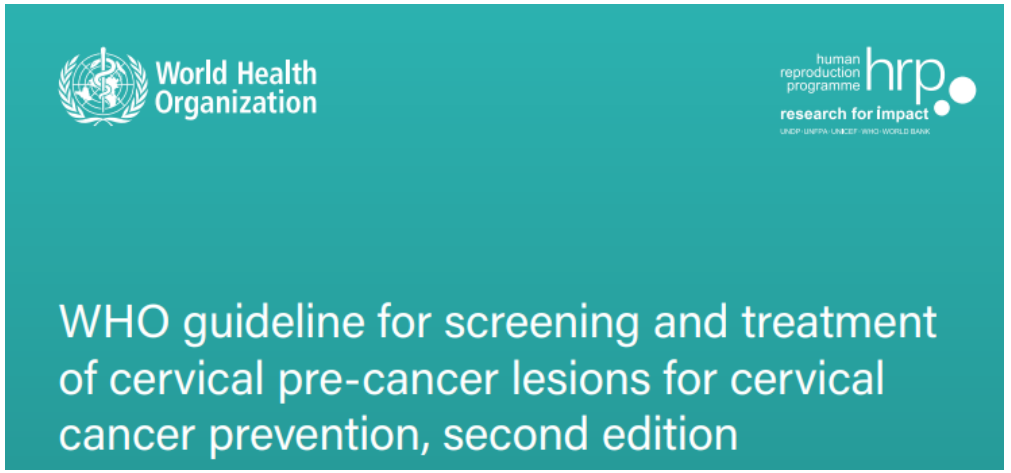
[a] Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[b] CPO Piemonte, AOU Città della Salute e della Scienza, Turin, Italy
[c] Early Detection, Prevention, and Infections Branch, International Agency for Research on Cancer, Lyon, France

Additional European initiative – creation of priority set of performance and outcome indicators to be used in breast colorectal and **cervical** cancer – 23 indicators chosen. Project conducted as part of the CanScreen-ECIS project (EU4H) of the European Commission.

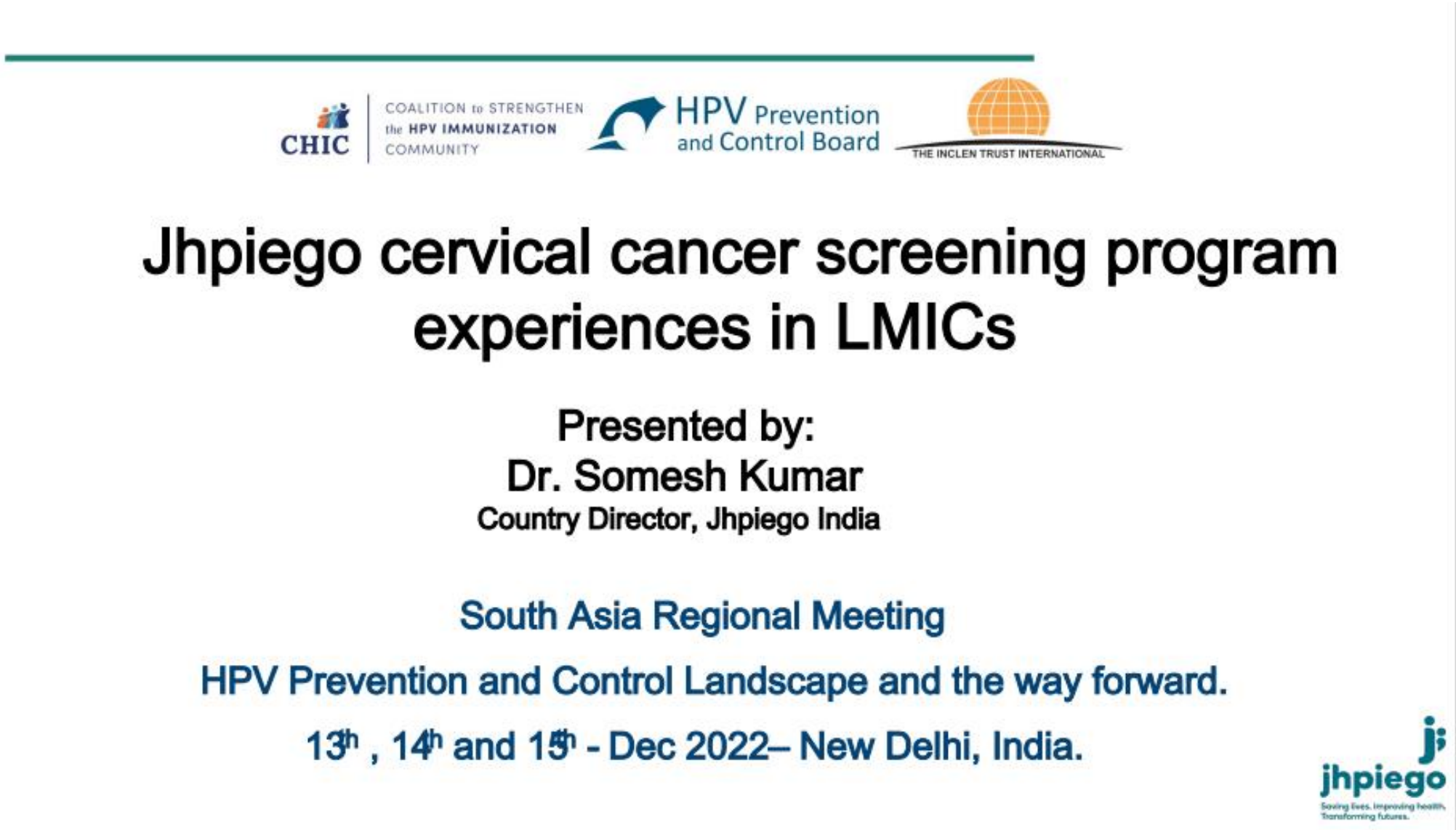
Do we have clear guideline recommending HPV-based primary screening in Europe ?

Recommendations for the general population of women[a]	*Strength of recommendation and level of evidence*	Recommendations for women living with HIV[a]	*Strength of recommendation and level of evidence*
1. WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV. *Remarks: Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of the inherent challenges with quality assurance.*	Strong recommendation, moderate-certainty evidence	21. WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV. *Remarks: Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of the inherent challenges with quality assurance.*	Strong recommendation, moderate certainty of evidence

https://www.who.int/publications/i/item/9789240030824
2021



Context specific experience essential – pursuit of the perfect must not be enemy of the good



https://www.hpvboard.org/new-delhi-india-2022/

Learnings from introduction of HPV tests

- Understand which HPV test is best suited for the country
- Facilitate arrangements with manufacturers and distributers for uninterrupted supply
- Invest in optimizing/supplement existing lab systems
- Set up sample transport systems
- Set up PATIENT NAVIGATION SYSTEMS (not same day screen and treat)
- Integrate services in existing womens health SD points
- Encourage self collection
- Invest in measurement

Kumar: https://www.hpvboard.org/new-delhi-india-2022/

Overview of challenges at the level of HPV-based cervical cancer screening

Mario Poljak

Institute of Microbiology and Immunology
Faculty of Medicine, University of Ljubljana, Slovenia

Do we have reliable baseline data about cervical cancer screening practices *in Europe* ?

Yes

Do we have clear guideline recommending HPV-based primary screening in Europe ?

Yes..but

HPV !!!

HPV test ?

Queries remain..

Year 2015: 193 commercial HPV assays (and 127 variants) on the market
11 considered clinically validated for screening

Year 2023: 264 commercial HPV assays (and 511 variants) on the market

Antwerp, Belgium - December 2015 - HPV Prevention and Control Board; Poljak et al J Clin Virol 2024, Arbyn HPV World 2024

ASSAY	MANUFACTURER	GENOTYPING CAPACITY	NUMBER OF TYPES	GENOTYPING DETAIL‡	HUMAN GENE¥	STORAGE MEDIA
A. Standard comparator hrHPV DNA tests (validated in population-based randomised trials), used as comparator in validation studies:						
A1. Hybrid Capture 2 HPV DNA Test	Qiagen, Gaithersburg, MD, USA	None	13	16/18/31/33/35/39/45/51/52/56/58/59/68	No	PC,SP
A2. GP5+/6+ PCR-EIA	Diassay, Rijkswijk, the Netherlands	None	14	16/18/31/33/35/39/45/51/52/56/58/59/66/68	No	PC,SP
B. hrHPV DNA tests validated consistently in multiple studies against standard comparator tests:						
B1. Alinity m HR HPV Assay	Abbott, Wiesbaden, Germany	Extended	14	16,18,45,31/33/52/58,35/39/51/56/59/66/68	Yes	PC
B2. Anyplex II HPV HR Detection	Seegene, Seoul, South Korea	Full	14	16,18,31,33,35,39,45,51,52,56,58,59,66,68	Yes	PC
B3. Cobas 4800 HPV Test	Roche Molecular System, Pleasanton, CF, USA	Limited	14	16,18,31/33/35/39/45/51/52/56/58/59/66/68	Yes	PC,SP
B4. HPV-Risk Assay	Self-Screen BV, Amsterdam, The Netherlands	Limited	15	16,18,31/33/35/39/45/51/52/56/58/59/66/67/68	Yes	PC,SP
B5. NeuMoDX HPV assay	Qiagen, Ann Arbor, MI, USA	Limited	15	16,18,31/33/35/39/45/51/52/56/58/59/66/68	Yes	PC
B6. Onclarity HPV Assay	BD Diagnostics, Sparks, MD, USA	Extended	14	16,18,31,45,51,52,33/58,35/39/68,56/59/66	Yes	PC,SP
B7.PapilloCheck HPV-Screening Test	Greiner Bio-One, Frickenhausen, Germany	Full	24	06,11,16,18,31,33,35,39,40,42,43,45,44/55,51,52,53,56,58,59,66,68,70,73,82	Yes	PC
B8. RealTime High Risk HPV Test	Abbott, Wiesbaden, Germany	Limited	14	16,18,31/33/35/39/45/51/52/56/58/59/66/68	Yes	PC
B9. Xpert HPV	Cepheid, Sunnyvale, CA, USA	Extended	14	16,18/45,31/33/35/52/58,51/59,39/56/66/68	Yes	PC
C. hrHPV DNA test validated consistently in multiple studies against alternative comparator test:						
C1. Cobas 6800 HPV Test	Roche Molecular System, Pleasanton, CF, USA	Limited	14	16,18,31/33/35/39/45/51/52/56/58/59/66/68	Yes	PC
D. hrHPV DNA tests evaluated in only one study against standard comparator tests:						
D1. CLART HPV4S	GENOMICA SAU, Madrid, Spain	Full	16	06,11,16,18,31,33,35,39,45,51,52,56,58,59,66,68	Yes	PC,SP
D2. OncoPredict HPV Screening	Hiantis Srl, Milan, Italy	Limited	13	16,18,31/33/35/39/45/51/52/56/58/59/68	Yes	PC
D3. REALQUALITY RQ-HPV Screen	AB ANALITICA, Padua, Italy	Limited	14	16,18,31/33/35/39/45/51/52/56/58/59/66/68	Yes	PC
E. hrHPV mRNA test:						
E1. APTIMA HPV Assay	Hologic, Bedford, MA, USA	None*	14	16/18/31/33/35/39/45/51/52/56/58/59/66/68	No	PC
F. Added since the last international publication of the list of clinically validated HPV tests						
F1. OncoPredict HPV QT	Hiantis Srl, Milan, Italy	Full	12	16,18,31,33,35,39/45,51,52,56,58,59	Yes	PC
F2. RIATOL HPV genotyping qPCR assay	AML, Antwerp, Belgium	Full	17	06,11,16,18,31,33,35,39,45,51,52,53,56,58,59,66,68	Yes	PC
F3. Allplex HPV HR Detection assay	Seegene, Seoul, South Korea	Full	14	16,18,31,33,35,39,45,51,52,56,58,59,66,68	Yes	PC
F4. Vitro HPV Screening Assay	Vitro S. A., Sevilla, Spain	Limited**	14	16,18,31/33/35/39/45/51/52/56/58/59/66/68	Yes	PC

* Another mRNA assay (APTIMA HPV16, 18/45, Hologic) can identify HPV16 and HPV18/45

** HPV Direct Flow Chip (Vitro S.A): provides full genotyping if Vitro HPV Screening shows other hrHPV (not HPV16/18)

‡ A slash "/" means that HPV types are identified as an aggregate; a comma "," means that HPV types or groups of types are identified separately

A HPV genotype in green does not belong to the IARC group I "carcinogenic types" or to group IIA "probably carcinogenic types" (Bouvard Lancet Oncol 2009[9])

¥ Amplification of human gene, which is an internal quality indicator that the specimen contains human cells

PC PreservCyt (Hologic, Bedford, MA, USA)

SP SurePath (BD Diagnostics, Sparks, MD, USA)

As of April 2024, 20 tests fulfilled the criteria for use in a cervical screening setting.

Different platforms, throughput, targets, commercial-availability, genotyping capacity etc

Only one considered point of care..

Relatively few have a formal claim for self samples, although this is increasing..

Technology…

Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2021;30:21-26
doi: 10.15570/actaapa.2021.5

Impact of the COVID-19 pandemic on human papillomavirus–based testing services to support cervical cancer screening

Mario Poljak[1], Kate Cuschieri[2], Dur-e-Nayab Waheed[3], Marc Baay[4], Alex Vorsters[3] ✉

[1]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia. [2]Scottish HPV Reference Laboratory, Royal Infirmary of Edinburgh, NHS Lothian Scotland, Edinburgh, United Kingdom. [3]Centre for Evaluation of Vaccination, Vaccine and Infectious Diseases Institute, University of Antwerp, Wilrijk, Belgium. [4]P95 Epidemiology & Pharmacovigilance, Leuven, Belgium.

acteristics required to respond to the cervical cancer elimination goal (21). The global HPV test supply needed to reach the 70% screening coverage aspiration of the WHO is estimated to be in the range of 1.4 to 1.5 billion HPV tests over a time span of 5 years (N. Broutet, personal communication).

The Covid experience

- Disruption of screening activities in a well screened population up to 9 months has little influence on cx cancer incidence and mortality rates.

However, the impact can be much larger if…

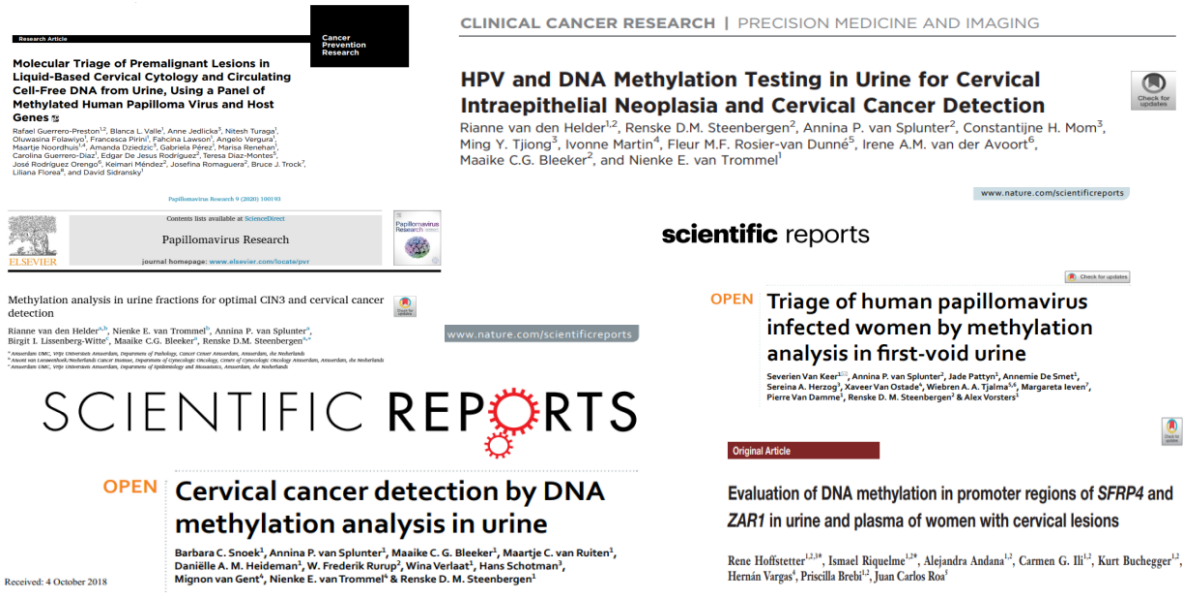
- Higher risk groups who are more affected than low risk groups
- The screening capacity remains low for a long time
- Screening before the disruption was of low quality
- Screening had not been implemented at the time of the pandemic
- Implementation is delayed in LMICS

Inge de Kok Prevention Control Board Meeting 2020

Did the Covid experience, catalyse developments for screening?*

- More point of care HPV tests?
- More self sampling?
  - Reliance on a whole molecular solution for screening
    - i.e HPV primary screen followed by extended typing and/or biomarkers

Growing evidence on the clinical performance of host and viral DNA methylation in urine for cervical cancer screening



Molecular Triage of Premalignant Lesions in Liquid-Based Cervical Cytology and Circulating Cell-Free DNA from Urine, Using a Panel of Methylated Human Papilloma Virus and Host Genes

Cancer Prevention Research

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

HPV and DNA Methylation Testing in Urine for Cervical Intraepithelial Neoplasia and Cervical Cancer Detection

Rianne van den Helder[1,2], Renske D.M. Steenbergen[2], Annina P. van Splunter[2], Constantijne H. Mom[3], Ming Y. Tjiong[3], Ivonne Martin[4], Fleur M.F. Rosier-van Dunné[5], Irene A.M. van der Avoort[6], Maaike C.G. Bleeker[2], and Nienke E. van Trommel[1]

Papillomavirus Research

Methylation analysis in urine fractions for optimal CIN3 and cervical cancer detection

Rianne van den Helder, Nienke E. van Trommel, Annina P. van Splunter, Birgit I. Lissenberg-Witte, Maaike C.G. Bleeker, Renske D.M. Steenbergen

www.nature.com/scientificreports

scientific reports

OPEN Triage of human papillomavirus infected women by methylation analysis in first-void urine

Severien Van Keer, Annina P. van Splunter, Jade Pattyn, Annemie De Smet, Sereina A. Herzog, Xaveer Van Ostade, Wiebren A. A. Tjalma, Margareta Ieven, Pierre Van Damme, Renske D. M. Steenbergen & Alex Vorsters

SCIENTIFIC REPORTS

OPEN Cervical cancer detection by DNA methylation analysis in urine

Barbara C. Snoek, Annina P. van Splunter, Maaike C. G. Bleeker, Maartje C. van Ruiten, Daniëlle A. M. Heideman, W. Frederik Rurup, Wina Verlaat, Hans Schotman, Mignon van Gent, Nienke E. van Trommel & Renske D. M. Steenbergen

Received: 4 October 2018

Original Article

Evaluation of DNA methylation in promoter regions of *SFRP4* and *ZAR1* in urine and plasma of women with cervical lesions

Rene Hoffstetter, Ismael Riquelme, Alejandra Andana, Carmen G. Ili, Kurt Buchegger, Hernán Vargas, Priscilla Brebi, Juan Carlos Roa

Van Keer – presented at HPV Prevention and control board meeting 2022

Available strategies for triage of HPV- positive women in low resource settings

- Visual inspection after AA (VIA): Poor reproducibility and low accuracy in many settings. Leads mainly to under treatment (1)
- Visual evaluation for treatment (VAT) : Overtreatment (2)
- VIA+Enhanced visual inspection (with digital images): Unclear benefit
- VIA+ Automated reading AI (AVE): Preliminary excellent results (3)
- HPV genotype restriction: Scientifically strong added value (4)
- Multiplex of virological and cellular markers *(under evaluation) (5)*

(1) Catarino et al. 2017, Wentzensen 2017

(2) Toliman et al. 2018 (3) Hu et al. (4) Demarco et al.2020 (5) Gizaw et al. 2019

De Sanjose - https://www.hpvboard.org/meetings/

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Home / Activities / A Global Strategy for elimination of cervical cancer

? Missing Pillar

90% of women identified with cervical disease receive treatment and care

70% of women screened with a high precision (HPV) test at 35 and 45 yrs of age

90% of girls fully vaccinated with HPV vaccine by 15yrs of age

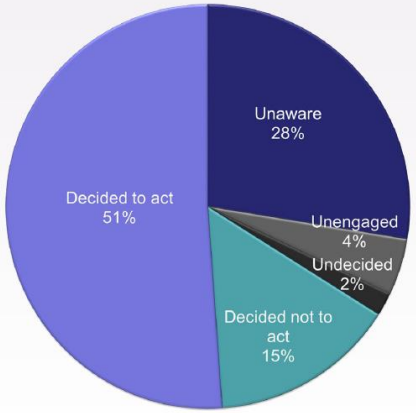
- **Social determinants of health associated with cervical cancer screening; focus on barriers/challenges/facilitators with vulnerable or marginalized women**
  Pamela Wakewich, Lakehead University (Canada)
- **Using behavioural science to increase participation in cervical cancer prevention**
  Laura Marlow, Department of Epidemiology and Public Health, UCL (UK)

Antwerp, Belgium – June 2016

Technical Meeting:

Barriers in HPV vaccination & cervical screening programmes

Identifying the main types of non-participation



Breakdown of non-maintainers (n=855)

Workshop to Develop a Culturally Appropriate Brochure

- Engaged discussions about colonial legacy, cultural sensitivity and representations of Indigenous women's bodies
- Brochure collectively designed through workshops
- Issues of age, residential school histories, privacy and the body shaped the final design

  Fully clothed woman on the outside –
  images of PAP and self-sampling on the inside -
  to protect privacy

  (Zehbe et al. 2015)

Common thread through all screening programmes is that deprivation associated with lower access/engagement

Systems that help us identify "who's not coming?" are few and far between, including in HIC

Registers & linkage

Zehbe et al. 2015 & Wakewich and Marlow : Antwerp, Belgium - 2016 - HPV Prevention and Control Board

Perspectives -

- Acceptance and implementation of HPV based screening continues at scale
- International guidance has evolved to reflect this and to support countries in their endeavours
- BUT
- Guidance needs to crystalise into action including in those countries that need it the most
    - Advocacy and gov. prioritisation
    - Robust technology
    - Improved infrastructure (digital & clinical)
    - Enhanced tailored education

HPV Prevention and Control Board

Many happy returns on your birthday

THANK YOU