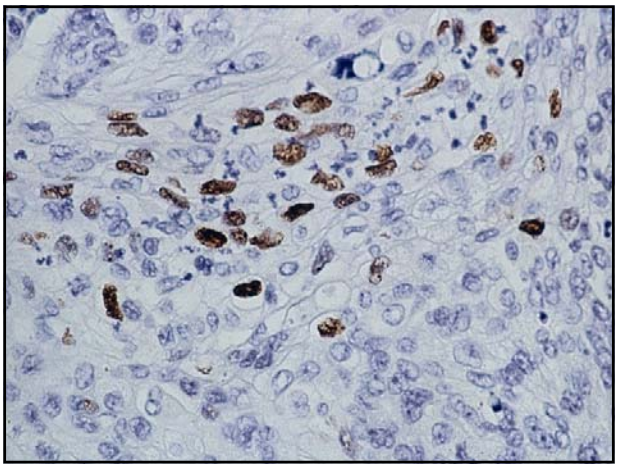
Globalni izzivi za eliminacijo raka materničnega vratu v času pandemije COVID-19 in po njej

Mario Poljak

Inštitut za mikrobiologijo in imunologijo
Medicinska fakulteta, Univerza v Ljubljani



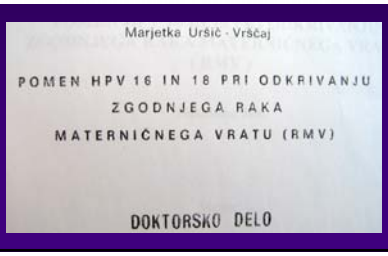
HPV research in Slovenia started in 1990 independently at:

- Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana (Jožica Marin)
- Institute of Pathology, Faculty of Medicine, University of Ljubljana (Mario Poljak)
- Institute of Oncology, Ljubljana (Marjetka Uršič-Vrščaj)

Mario Poljak

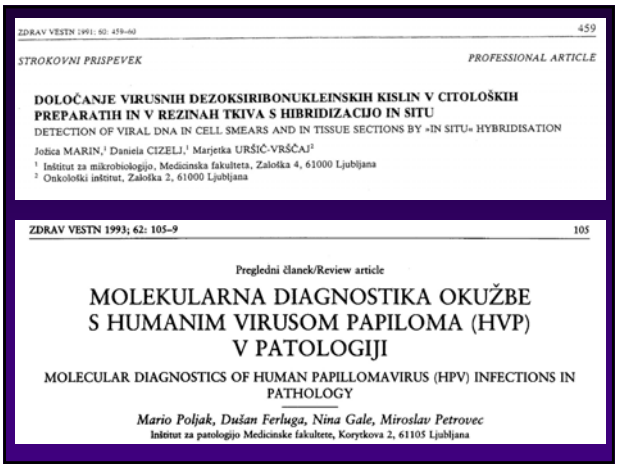
POMEN OKUŽBE S HUMANIMI VIRUSI PAPILOMA V ETIOPATOGENEZI EPITELIJSKIH NOVOTVORB GRLA IN POŽIRALNIKA

Doktorska naloga


Marjetka Uršič - Vrščaj

POMEN HPV 16 IN 18 PRI ODKRIVANJU ZGODNJEGA RAKA MATERNIČNEGA VRATU (RMV)

DOKTORSKO DELO


ZDRAV VESTN 1991; 60: 459–60 459

STROKOVNI PRISPEVEK PROFESSIONAL ARTICLE

DOLOČANJE VIRUSNIH DEZOKSIRIBONUKLEINSKIH KISLIN V CITOLOŠKIH PREPARATIH IN V REZINAH TKIVA S HIBRIDIZACIJO IN SITU

DETECTION OF VIRAL DNA IN CELL SMEARS AND IN TISSUE SECTIONS BY »IN SITU« HYBRIDISATION

Jožica MARIN,[1] Daniela CIZELJ,[1] Marjetka URŠIČ-VRŠČAJ[2]

[1] Inštitut za mikrobiologijo, Medicinska fakulteta, Zaloška 4, 61000 Ljubljana
[2] Onkološki inštitut, Zaloška 2, 61000 Ljubljana

ZDRAV VESTN 1993; 62: 105–9 105

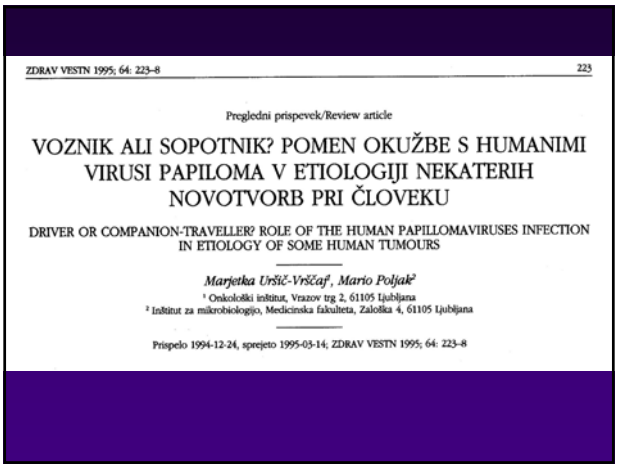
Pregledni članek/Review article

MOLEKULARNA DIAGNOSTIKA OKUŽBE S HUMANIM VIRUSOM PAPILOMA (HVP) V PATOLOGIJI

MOLECULAR DIAGNOSTICS OF HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS IN PATHOLOGY

Mario Poljak, Dušan Ferluga, Nina Gale, Miroslav Petrovec

Inštitut za patologijo Medicinske fakultete, Korytkova 2, 61105 Ljubljana


ZDRAV VESTN 1995; 64: 223–8 223

Pregledni prispevek/Review article

VOZNIK ALI SOPOTNIK? POMEN OKUŽBE S HUMANIMI VIRUSI PAPILOMA V ETIOLOGIJI NEKATERIH NOVOTVORB PRI ČLOVEKU

DRIVER OR COMPANION-TRAVELLER? ROLE OF THE HUMAN PAPILLOMAVIRUSES INFECTION IN ETIOLOGY OF SOME HUMAN TUMOURS

Marjetka Uršič-Vrščaj[1], Mario Poljak[2]

[1] Onkološki inštitut, Vrazov trg 2, 61105 Ljubljana
[2] Inštitut za mikrobiologijo, Medicinska fakulteta, Zaloška 4, 61105 Ljubljana

Prispelo 1994-12-24, sprejeto 1995-03-14; ZDRAV VESTN 1995; 64: 223–8

Eur J Gynaec Oncol 1996; 17: 368-71.

Association of risk factors for cervical cancer and human papilloma viruses in invasive cervical cancer

M. Uršič-Vrščaj[1], J. Kovačič[2], M. Poljak[3], J. Marin

Institute of Oncology, Ljubljana, Slovenia; University Department of Gynecology and Obstetrics, Ljubljana, Slovenia; Institute of Microbiology, Faculty of Medicine, Ljubljana, Slovenia

Received January 29, 1996; revised manuscript accepted for publication March 11, 1996

Summary

Our study was carried out on 70 patients with invasive squamous carcinoma of the uterine cervix (CC) or invasive adenocarcinoma of the uterine cervix at all stages, admitted to the University Department of Gynecology and/or to the Institute of Oncology in Ljubljana. The patients were not selected by age. A questionnaire on known risk factors in CC was filled in for each of the 70 patients, and two tumor smears were taken for the determination of human papilloma viruses (HPV) 16 and 18 by means of *in situ* hybridization and polymerase chain reaction (PCR). Each patient also had the serum level of vitamin A determined. The results of our study revealed a correlation between HPV 16 or 18 infection (60:40) and CC. When analysing some already known risk factors, no statistically significant difference could be established for any of the factors studied, except for the age at first birth.

Key words: Invasive carcinoma of the uterine cervix; Human papilloma viruses 16 and 18, in situ hybridization; Polymerase chain reaction; Risk factors for cervical cancer.

Večer

Stran / Page: 3
Doseg / Reach: 151.600
Država / Country: SLOVENIA
Površina prispevka / Size: 69 cm2

18.12.2006

1 / 1

Cepljenje proti raku na maternicnem vratu

Občinski svet občine Komenda je sprejel predlog župana **Tomaža Drolca**, da 1,5 milijona tolarjev namenijo cepljenju deklet v osmem in devetem razredu osnovne šole proti virusu, ki povzroča raka na maternicnem vratu. V občini Komenda je deklet v tej starosti okrog 50. Njim in njihovim staršem bodo jutri na okrogli mizi pojasnili vse o virusu, bolezni in novem cepivu. Ker je cepivo precej drago, so se v občini odločili, da bodo naprej zagotovili možnost cepljenja dekletom, ki bodo prihodnje leto šla v srednjo šolo in tako zapustila občino. Kasneje obstaja možnost, da bi cepljenje omogočili tudi drugim. V roku petih ali sedmih let naj to cepljenje ne bi bilo več samoplačniško in naj bi ga krila zdravstvena blagajna oziroma zdravstveno zavarovanje.

Cepivo deluje na dva virusa, ki ju povezujejo s tem rakom, in naj bi ženske vsaj za nekaj časa varovalo pred izbruhom bolezni. Namenjeno je zlasti dekletom do 26. leta. Pri tem velja, da je najboljši čas za cepljenje pred prvim spolnim odnosom. Cepljenje proti omenjenem virusu naj bi sicer še v tem mesecu v Sloveniji postalo dostopno vsem samoplačnikom, odločitev komendskih svetnikov, da za cepljenje namenijo občinski denar, pa je prva v Sloveniji. **(sta)**

Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, Chiacchierini LM, Jansen KU; Proof of Principle Study Investigators.

A controlled trial of a human papillomavirus type 16 vaccine.

N Engl J Med 2002; 347:1645-51

I S I S

GLASILO ZDRAVNIŠKE ZBORNICE SLOVENIJE

Leto XVI, številka 7 / 1. julij 2007 STATUS ARTIS MEDICAE

Štirivalentno cepivo proti okužbi s HPV – kaj se je zgodilo v zadnjih šestih mesecih?

Mario Poljak, Marjetka Uršič Vrščaj

Jana

Stran / Page: 52
Doseg / Reach: 143.000
Država / Country: SLOVENIA
Površina prispevka / Size: 711 cm2

12.12.2006

1 / 3

Žal bo cepljenje **samoplačniško!**

Globalni izzivi za eliminacijo raka maternicnega vratu v času pandemije COVID-19 in po njej

Mario Poljak

Inštitut za mikrobiologijo in imunologijo
Medicinska fakulteta, Univerza v Ljubljani

I have no conflicts of interest to declare.

cervical cancer is at present the best (and only) human cancer candidate for eradication

...

because it is a result of infectious disease

...

but, elimination is more realistic goal

ERADICATION

No single case of particular disease in the whole world in the last 5 years

ERADICATION

a permanent reduction to zero of the worldwide incidence of infection

intervention measures are no longer needed

ELIMINATION

achieving the measurable global targets set by WHO

control measures must be continued after elimination has been achieved

Human diseases with greatest potential for eradication

Guinea worm
Lymphatic filariasis
River blindness

Polio

Measles
Mumps
Rubella

Cervical cancer as best human cancer candidate for elimination

important public health issue (569'847 cases per year; 311'365 deaths)
GLOBOCAN 2018

infectious origin, no reservoirs outside humans

long clinical latency

acceptable and valid screening tools available

precursors lesions can be treated in a safe, effective and acceptable way

safe and effective vaccines against main etiological factor - HPV

WHO statement on cervical cancer elimination Director-General call to action

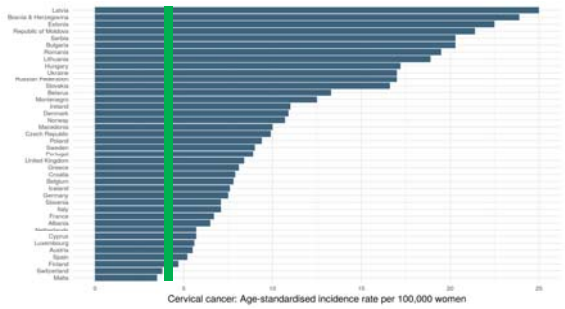
World Health Organization

"Today I am calling for coordinated action globally to eliminate cervical cancer, one of the greatest threats to women's health. We have the tools and, crucially, the political commitment to achieve it"

www.who.int/reproductivehealth/DG_all-to-action.pdf

Dr Tedros Adhanom Ghebreyesus
WHO Director General - 19 May 2018

Cervical Cancer Incidence: Europe



Globocan 2018

Elimination definition and 2030 targets

Vision: A world without cervical cancer

Goal: cervical cancer incidence below 4 cases per 100,000 woman-years

2030 TARGETS

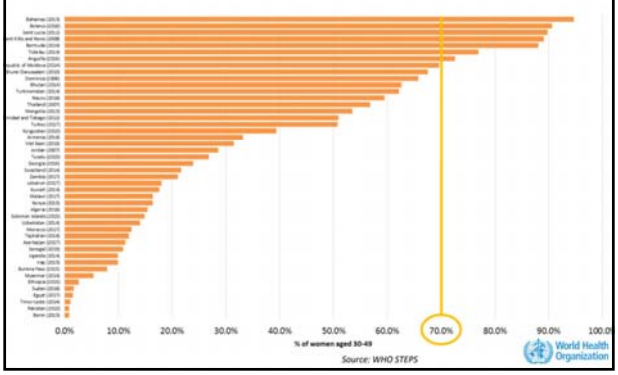
90% of girls fully vaccinated against HPV by age 15

70% of women screened with a high precision test at ages 35 and 45

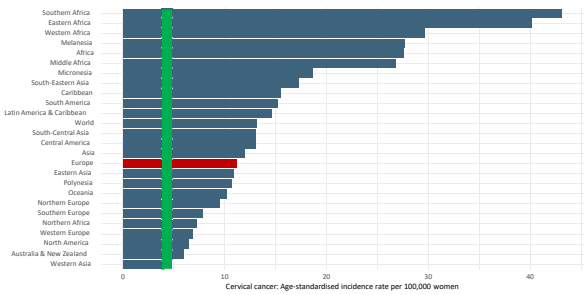
90% of women with cervical disease receive treatment and care

2030 target: 30% reduction in mortality from cervical cancer

Proportion of Women Between 30-49 Screened for Cervical Cancer At Least Once



Cervical Cancer Incidence: World regions



Source: Globocan 2018

secondary prevention (screening)
+
primary prevention (vaccination)

secondary and primary prevention act additively by intervening at different points in the natural history of cervical cancer and imply actions in women of different ages

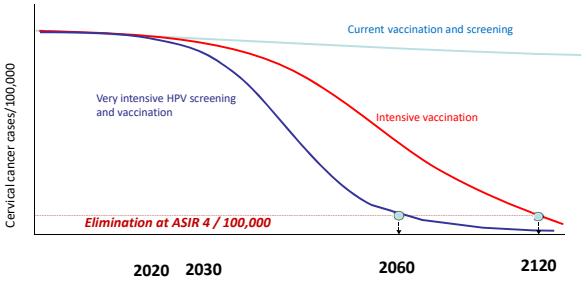
secondary & primary prevention

current status

pre-COVID-19 problems

COVID-19-related problems

Cervical Cancer Elimination: Conceptual Framework



secondary prevention (screening)

(cytology-based, **HPV-based**, cytology + HPV-based)

secondary & primary prevention

current status

pre-COVID-19 problems

COVID-19-related problems

population-based
&
organised
&
high coverage
&
high quality cytology

Status of implementation and organization of cancer screening in The European Union Member States—Summary results from the second European screening report

Partha Basu[1], Antonio Ponti[2], Ahti Anttila[3], Guglielmo Ronco[2], Carlo Senore[2], Diama Bhadra Vale[4], Nereo Segnan[2], Mariano Tomatis[2], Isabelle Soerjomataram[5], Maja Primic Žakelj[6], Joakim Dillner[7], Klara Miriam Elfström[8], Stefan Lönnberg[9] and Rengaswamy Sankaranarayanan[1]

Int J Cancer 2018; 142: 44-56

2007 ⟶ 2016

Incidence of cervical cancer in Slovenia 2003-2018

year	annual number of new cases	crude incidence rate/ 100.000	ASR (W)
2003	211	20.7	15.3
2004	198	19.4	13.7
2005	182	17.8	12.7
2006	162	15.8	11.3
2007	154	15.0	10.5
2008	130	12.6	8.8
2009	131	12.6	8.8
2010	142	13.7	9.4
2011	142	13.7	9.0
2012	118	11.4	7.7
2013	124	11.9	8.0
2014	114	11.0	6.8
2015	119	11.4	7.4
2016	123	11.8	7.8
2017	85	8.2	4.9
2018	106	10.2	6.6

opportunistic screening
- coverage app. 40%
- 170,000 smears/year

organised screening
- coverage above 70%
- 170,000 smears/year

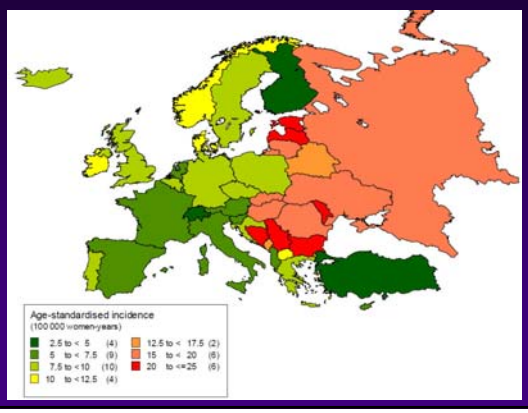
ASR (W): age-standardized rate by world population

Implementation status and the estimated target population for cervical cancer screening in the European Union – comparison between the second screening report (2016) and the first screening report (2007)

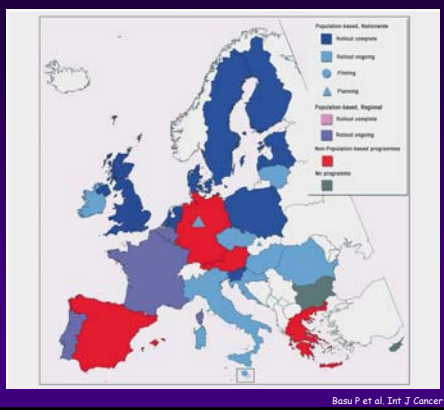
	Cervical cancer screening (target age 30–59 years)					
	Population-based programme				Non-population based programme or no programme	TOTAL
	Rollout completed	Rollout ongoing	Piloting	Planning		
Number of Member States in 2016	9	10	1	2	6	28
Number of Member States in 2007	7	5	2	3	10	27
Estimated target populations in 2016	34.7 M (32.5%)	24.1 M (22.7%)	0.02 M (0.0%)	18.2 M (17.1%)	29.5 M (27.7%)	106.5 M (100%)
Estimated target populations in 2007	24.1 M (22.7%)	21.9 M (20.6%)	5.3 M (5.0%)	3.2 M (3.0%)	51.7 M (48.7%)	106.2 (100%)

Basu P et al. Int J Cancer 2018; 142: 44-56.

Geographical distribution of the world age-standardised incidence rate of cervical cancer by country in Europe estimated for 2018 (GLOBOCAN 2018)



The type and implementation status of the cervical cancer screening programmes in the Member States of European Union (2016)



Basu P et al. Int J Cancer 2018; 142: 44-56.

Preventable fractions of cervical cancer via effective screening in six Baltic, central, and eastern European countries 2017–40: a population-based study

Salvatore Vaccarella, Silvia Franceschi, David Zaridze, Mario Poljak, Piret Veerus, Martyn Plummer, Freddie Bray

Lancet Oncol 2016; 17: 1445-1452

Summary

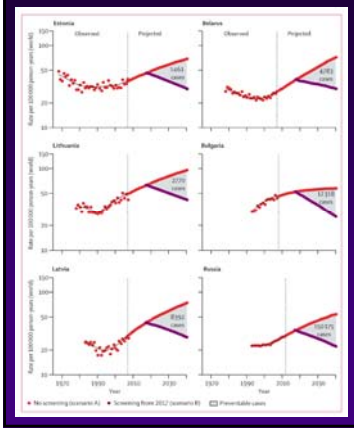
Background Cervical cancer incidence remains high in several Baltic, central, and eastern European (BCEE) countries, mainly as a result of a historical absence of effective screening programmes. As a catalyst for action, we aimed to estimate the number of women who could be spared from cervical cancer across six countries in the region during the next 25 years, if effective screening interventions were introduced.

Methods In this population-based study, we applied age-period-cohort models with spline functions within a Bayesian framework to incidence data from six BCEE countries (Estonia, Latvia, Lithuania, Belarus, Bulgaria, and Russia) to develop projections of the future number of new cases of cervical cancer from 2017 to 2040 based on two future scenarios: continued absence of screening (scenario A) versus the introduction of effective screening from 2017 onwards (scenario B). The timespan of available data varied from 16 years in Bulgaria to 40 years in Estonia. Projected rates up to 2040 were obtained in scenario A by extrapolating cohort-specific trends, a marker of changing risk of human papillomavirus (HPV) infection, assuming a continued absence of effective screening in future years. Scenario B added the effect of gradual introduction of screening in each country, under the assumption period effects would be equivalent to the decreasing trend by calendar year seen in Denmark (our comparator country) since the progressive regional introduction of screening from the late 1960s.

Findings According to scenario A, projected incidence rates will continue to increase substantially in many BCEE countries. Very high age-standardised rates of cervical cancer are predicted in Lithuania, Latvia, Belarus, and Estonia (up to 88 cases per 100 000). According to scenario B, the beneficial effects of effective screening will increase progressively over time, leading to a 50–60% reduction of the projected incidence rates by around 2040, resulting in the prevention of cervical cancer in 1500 women in Estonia and more than 150 000 women in Russia. The immediate launch of effective screening programmes could prevent almost 180 000 new cervical cancer diagnoses in a 25-year period in the six BCEE countries studied.

Interpretation Based on our findings, there is a clear need to begin cervical screening in these six countries as soon as possible to reduce the high and increasing incidence of cervical cancer over the next decades.

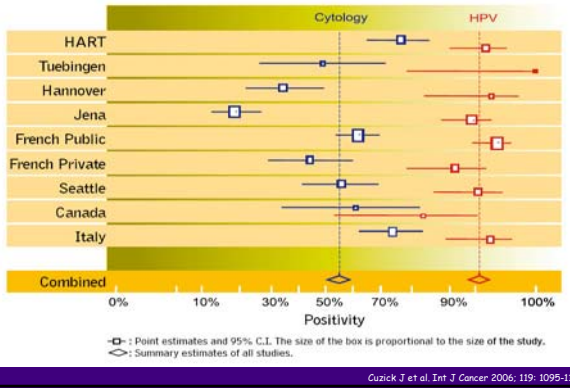
Observed and projected incidence of cervical cancer in six Baltic, central, and eastern European countries (2017-2040)



if screening had started in 2017 more than 180,000 new cases of cervical cancer could have been prevented from 2017 to 2040 in the six studied countries

Lancet Oncol 2016; 17: 1445-1452

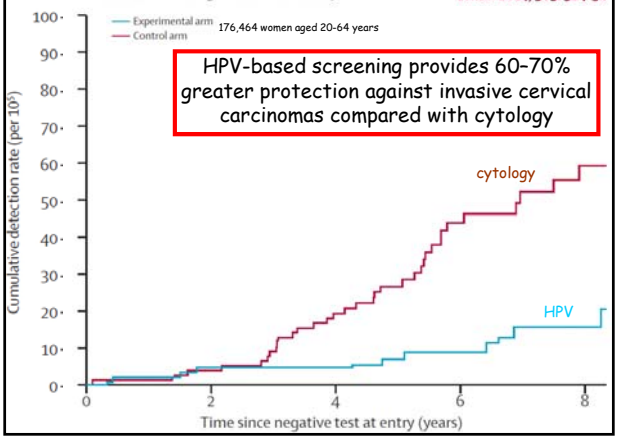
Global evaluation of the sensitivity (fraction of histology confirmed CIN 2+ detected by the test) of HPV tests as compared to cytology in studies in Europe and North America



Cuzick J et al. Int J Cancer 2006; 119: 1095-1101

Women with a negative test at entry*

Lancet 2014; 383: 524-32

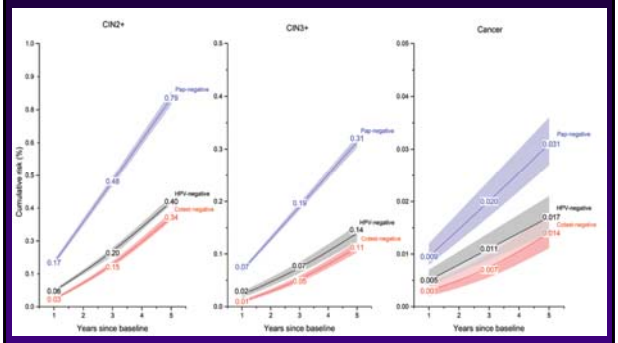


cytology-based screening

↓

HPV-based screening

Cumulative risk of CIN+2, CIN3+ and cervical cancer among 1,011,092 women aged 30 to 64 years at Kaiser Permanente Northern California by enrollment Pap and HPV test result; 2003 to 2012

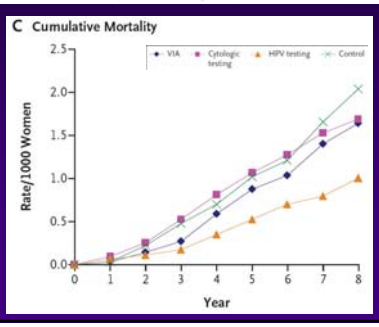


Gage JC et al. J Natl Cancer Inst 2014;106: dju153.

N Engl J Med 2009; 360: 1385-94

HPV Screening for Cervical Cancer in Rural India

Rengaswamy Sankaranarayanan, M.D., Bhagwan M. Nene, M.D., F.R.C.P., Surendra S. Shastri, M.D., Kasturi Jayant, M.Sc., Richard Muwonge, Ph.D., Atul M. Budukh, Ph.D., Sanjay Hingmire, B.Sc., Sylla G. Malvi, M.Sc., Ph.D., Ranjit Thorat, B.Sc., Ashok Kothari, M.D., Roshan Chinoy, M.D., Rohini Kelkar, M.D., Shubhada Kane, M.D., Sangeetha Desai, M.D., Vijay R. Keskar, M.S., Raghevendra Rajeshwarkar, M.D., Nandkumar Panse, B.Com., and Ketayun A. Dinshaw, M.D., F.R.C.R.



HPV !!!

HPV test ?

HPV-based primary cervical cancer screening

PRO:

- more sensitive than cytology to detect CIN2+, CIN3+ and cervical cancer
- more accurate and less variable than cytology
- risk of CIN2+ in women who are HPV negative is substantially lower than in women who are cytologically negative = extension of screening intervals possible and safe
- possibility of self-sampling testing

CON:

- reduced specificity of HPV DNA testing requires appropriate triage

Papillomavirus Research 2015; doi:10.1016/j.pvr.2015.06.006.

European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination

Lawrence von Karsa [a,*], Marc Arbyn [b], Hugo De Vuyst [c], Joakim Dillner [d], Lena Dillner [e], Silvia Franceschi [f], Julietta Patnick [g], Guglielmo Ronco [h], Nereo Segnan [h], Eero Suonio [a], Sven Törnberg [i], Ahti Anttila [j]

HPV test choice

cervical cancer screening program should adopt a HPV primary test for use only if it has been validated by demonstrating reproducible, consistently high sensitivity for CIN2+ and CIN3+ lesions, and only minimal detection of clinically irrelevant, transient HPV infection

HPV tests (neither commercial nor in-house tests) that have not been clinically validated should not be used in clinical practice

secondary & primary prevention

current status

pre-COVID-19 problems

COVID-19-related problems

Commercially available alpha-HPV molecular tests - periodical inventories -

2010

Poljak M, Kocjan BJ. Commercially available assays for multiplex detection of alpha human papillomaviruses. Exp Rev Anti Infect Ther 2010; 8: 1139-62.

2012

Poljak M, Cuzick J, Kocjan BJ, Iftner T, Dillner J, Arbyn M. Nucleic acid tests for the detection of alpha human papillomaviruses. Vaccine 2012; Suppl 30: F100-6.

2015

Poljak M, Kocjan BJ, Oštrbenk A, Seme K. Commercially available molecular tests for human papillomaviruses (HPV): 2015 update. J Clin Virol 2016; 76: (Suppl 1): S3-S13.

2020

Poljak M, Oštrbenk Valenčak A, Gimpelj Domjanič G, Xu, L, Arbyn M. Commercially available molecular tests for human papillomaviruses: a global overview. Clin Microbiol Infect 2020; 26: 1144-50.

- not a simple addition of newly developed tests to the old list of HPV tests
- the existence of all HPV tests double-checked with manufacturers at every update round

- data retrieved from:
  - Medline/Pubmed, Web of Science, Scopus, Bing, Google Scholar, Google without language or period restrictions – September 2019 and January 2020
  - abstracts from main HPV-related conferences (2015-2020)
  - internal files
  - the Chinese National Medical Products Administration (formerly the China Food and Drug Administration) was consulted to obtain a list of HPV tests approved by agency

- conservative estimate – very likely haven't identified all HPV tests currently available

- omission of any particular commercially available HPV test was unintentional

Main groups of available commercial HPV molecular tests on the global market in 2019 (tests vs. variants)

	Tests	Variants
hr-HPV DNA screening tests	40	3
hr-HPV DNA screening tests with concurrent or reflex partial genotyping for the main hr-HPV types	41	3
HPV DNA full genotyping tests	90	21
HPV DNA type- or group-specific genotyping tests	38	89
hr-HPV E6/E7 mRNA tests	9	1
in situ hybridization DNA in mRNA based HPV tests	33	308
HPV DNA tests targeting miscellaneous HPV types	2	0
Total	253	425

Test (distinct, unique) vs. test variant

particular HPV test was considered a variant if technologically identical or very similar to the original test but targeting different HPV type(s)

Human papillomavirus 16, 18 (DNA-Technology LLC, Moscow, Russia)	DISTINCT TEST
Human papillomavirus 18, 45, 39, 59	VARIANT
Human papillomavirus 16, 31, 33, 35, 58, 52, 67	VARIANT
Human papillomavirus 6, 11	VARIANT

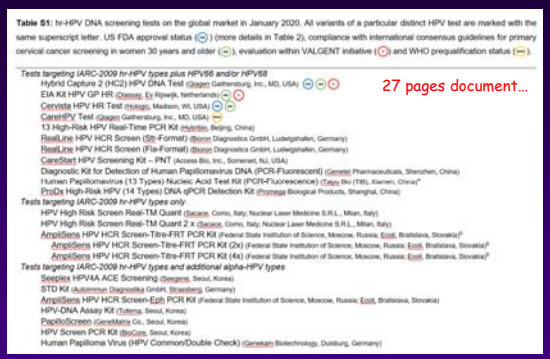


Table S1: hr-HPV DNA screening tests on the global market in January 2020. All variants of a particular distinct HPV test are marked with the same superscript letter. US FDA approval status (–)) (more details in Table 2), compliance with international consensus guidelines for primary cervical cancer screening in women 30 years and older (–), evaluation within VALGENT initiative (◯) and WHO prequalification status (—).

Tests targeting IARC-2009 hr-HPV types plus HPV66 and/or HPV68
Hybrid Capture 2 (HC2) HPV DNA Test (Qiagen Gaithersburg, Inc., MD, USA) – – ◯
EIA Kit HPV GP HR (Diassay, Ey Rijswijk, Netherlands) – ◯
Cervista HPV HR Test (Hologic, Madison, WI, USA) – –
CareHPV Test (Qiagen Gaithersburg, Inc., MD, USA) —
13 High-Risk HPV Real-Time PCR Kit (Hybribio, Beijing, China)
RealLine HPV HCR Screen (Str-Format) (Bosnir Diagnostics GmbH, Ludwigshafen, Germany)
RealLine HPV HCR Screen (Fla-Format) (Bosnir Diagnostics GmbH, Ludwigshafen, Germany)
CareStart HPV Screening Kit – PNT (Access Bio, Inc., Somerset, NJ, USA)
Diagnostic Kit for Detection of Human Papillomavirus DNA (PCR-Fluorescent) (Genetel Pharmaceuticals, Shenzhen, China)
Human Papillomavirus (13 Types) Nucleic Acid Test Kit (PCR-Fluorescence) (Talyo Bio (TIB), Xiamen, China)^
ProDx High-Risk HPV (14 Types) DNA qPCR Detection Kit (Promega Biological Products, Shanghai, China)
Tests targeting IARC-2009 hr-HPV types only
HPV High Risk Screen Real-TM Quant (Sacace, Como, Italy; Nuclear Laser Medicine S.R.L., Milan, Italy)
HPV High Risk Screen Real-TM Quant 2 x (Sacace, Como, Italy; Nuclear Laser Medicine S.R.L., Milan, Italy)
AmpliSens HPV HCR Screen-Titre-FRT PCR Kit (Federal State Institution of Science, Moscow, Russia; Ecolt, Bratislava, Slovakia)^
AmpliSens HPV HCR Screen-Titre-FRT PCR Kit (2x) (Federal State Institution of Science, Moscow, Russia; Ecolt, Bratislava, Slovakia)^
AmpliSens HPV HCR Screen-Titre-FRT PCR Kit (4x) (Federal State Institution of Science, Moscow, Russia; Ecolt, Bratislava, Slovakia)^
Tests targeting IARC-2009 hr-HPV types and additional alpha-HPV types
Seeplex HPV4A ACE Screening (Seegene, Seoul, Korea)
STD Kit (Autoimmun Diagnostika GmbH, Strassberg, Germany)
AmpliSens HPV HCR Screen-Eph PCR Kit (Federal State Institution of Science, Moscow, Russia; Ecolt, Bratislava, Slovakia)
HPV-DNA Assay Kit (Tollema, Seoul, Korea)
PapilloScreen (GeneMatrix Co., Seoul, Korea)
HPV Screen PCR Kit (BioCore, Seoul, Korea)
Human Papilloma Virus (HPV Common/Double Check) (Genekam Biotechnology, Duisburg, Germany)

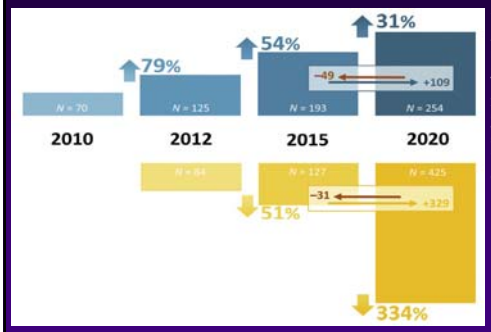
27 pages document…

2020

254 distinct commercial HPV assays
(and 425 variants)
on the global market

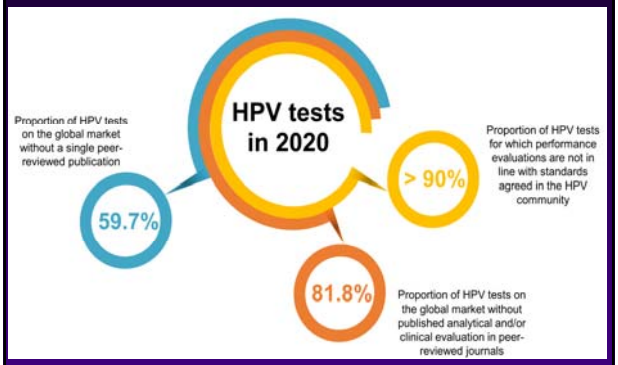
Poljak M et al. Clin Microbiol Infect 2020; 26: 1144-50

Commercially available HPV molecular tests on the global market identified in periodical inventories in 2010, 2012, 2015 and 2020



The number of identified distinct HPV tests is shown in blue bars and the number of HPV test variants in yellow bars.

In boxes are the number of HPV tests withdrawn from the market (left arrows) and number of newly identified HPV tests (right arrows) between 2015 and 2020.



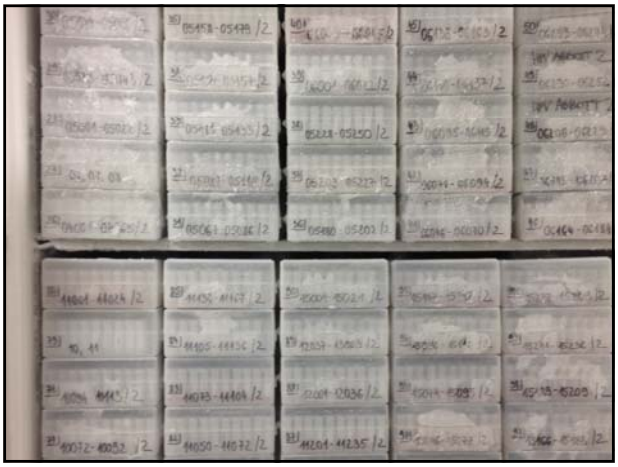
Poljak M at al. Clin Microbiol Infect 2020; 26: 1144-50

- 102/253 (40.3%) of HPV tests with at least one publication

BUT

- 46/253 (18.2%) of HPV tests with published performance evaluation (analytical and/or clinical)
- 56/253 (22.1%) of HPV tests cross-sectional descriptive studies only - no data for key test performance characteristics (sensitivity, specificity, reproducibility)

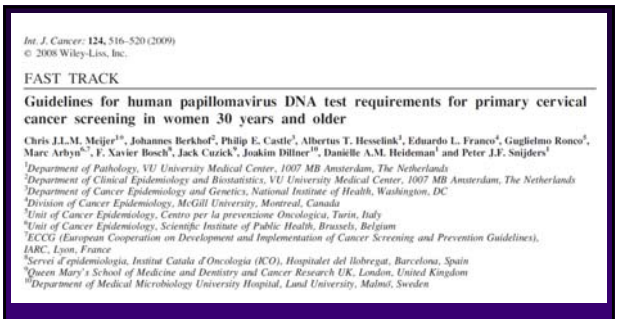
- "test A versus test B" approach with no reference standard
- ad hoc collections of heterogeneous clinical samples without follow-up
- various target population (including several non-genital)



No.	DNA chip assay	Bioneer result
1	16	16
3	others	53
2	54	54
4	Others	33
Negative sample	Negative	Negative

The clinical evaluation of the *AccuPower*® HPV Genotyping Kit was performed on 5 clinical samples. *AccuPower*® HPV Genotyping Kit is more sensitive than DNA chip assay.

http://eng.bioneer.com/diagnostic/HumanMDxkits/HPV-Genotyping-technical.aspx



Int. J. Cancer: **124**, 516–520 (2009)
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FAST TRACK

Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older

Chris J.L.M. Meijer[1]*, Johannes Berkhof[2], Philip E. Castle[3], Albertus T. Hesselink[4], Eduardo L. Franco[4], Guglielmo Ronco[5], Marc Arbyn[6,7], F. Xavier Bosch[8], Jack Cuzick[9], Joakim Dillner[10], Danielle A.M. Heideman[1] and Peter J.F. Snijders[1]

[1]Department of Pathology, VU University Medical Center, 1007 MB Amsterdam, The Netherlands
[2]Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, 1007 MB Amsterdam, The Netherlands
[3]Department of Cancer Epidemiology and Genetics, National Institute of Health, Washington, DC
[4]Division of Cancer Epidemiology, McGill University, Montreal, Canada
[5]Unit of Cancer Epidemiology, Centro per la prevenzione Oncologica, Turin, Italy
[6]Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium
[7]ECCG (European Cooperation on Development and Implementation of Cancer Screening and Prevention Guidelines), IARC, Lyon, France
[8]Servei d'epidemiologia, Institut Catala d'Oncologia (ICO), Hospitalet del llobregat, Barcelona, Spain
[9]Queen Mary's School of Medicine and Dentistry and Cancer Research UK, London, United Kingdom
[10]Department of Medical Microbiology University Hospital, Lund University, Malmö, Sweden

relative clinical accuracy compared to either of two HPV tests which demonstrated lower cumulative incidence of cervical cancer 5 years after a negative HPV test than 3 years after a normal cytology in four large European randomized trials

Int. J. Cancer: **124,** 516–520 (2009)

FAST TRACK

Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older

Chris J.L.M. Meijer[1]*, Johannes Berkhof[2], Philip E. Castle[3], Albertus T. Hesselink[1], Eduardo L. Franco[4], Guglielmo Ronco[5], Marc Arbyn[6,7], F. Xavier Bosch[8], Jack Cuzick[9], Joakim Dillner[10], Danielle A.M. Heideman[1] and Peter J.F. Snijders[1]

Requirements for HPV tests in primary cervical screening

1. A clinical sensitivity for CIN2+ not less than 90% of the clinical sensitivity of the hc2 in women of at least 30 years.

2. A clinical specificity for CIN2+ not less than 98% of the clinical specificity of the hc2 in women of at least 30 years of age.

3. Intra-laboratory reproducibility and inter-laboratory agreement with a lower confidence bound not less than 87%.

Validation for clinical accuracy (September 2020)

Evaluated assay	Study	Evaluated assay		Comparator assay			Evaluated/comparator assay		Non-inferiority test*		Validation level[1]
		Absolute		Comparator assay	Absolute		Relative				
		sensitivity	specificity		sensitivity	specificity	sensitivity	specificity	p_{non}	p_{sup}	
GP5+/6+ EIA	Meijer, 2009[9]	98.7%	96.0%	HC2*	98.7%	94.1%	1.00	1.02	0.0037	<0.0001	⊕⊕⊕⊕
PapilloCheck	Hesselink, 2014[20]	95.8%	96.7%	GP5+/6+ EIA	96.4%	97.7%	0.99	0.99	<0.0001	0.0072	⊕⊕⊕
	Heard, 2016 [84]	96.1%	89.7%	GP5+/6+ EIA	94.1%	90.4%	1.02	0.99	0.0002	0.0970	
Abbott RT hrHPV test	Carozzi, 2011[21]	96.4%	92.3%	HC2	97.6%	92.6%	0.99	1.00	0.0040	0.0087	⊕⊕⊕
	Poljak, 2011[22]	100.0%	93.3%	HC2	97.4%	91.8%	1.03	1.02	0.0112	0.0000	
	Hesselink, 2013[27]	95.6%	92.0%	GP5+/6+ EIA	98.5%	91.8%	0.97	1.00	0.0278	0.0003	
cobas 4800	Heideman, 2011[24]	90.0%	94.6%	HC2	91.7%	94.4%	0.98	1.00	0.0216	0.0009	⊕⊕⊕
	Lloveras, 2013[25]	98.3%	86.2%	HC2	98.3%	85.3%	1.00	1.01	0.0093	0.0012	
	Ejegod, 2020[89]	92.6%	91.2%	GP5+/6+ EIA	92.6%	89.2%	1.00	1.02	0.0006	<0.0001	
cobas 6800	Saville, 2019[87]	98.3%	88.4%	cobas 4800	100.0%	89.4%	0.98	0.98	0.0157	.0442	⊕⊕⊕
	Frayle, 2019[88]	98.3%	92.8%	cobas 4800	100.0%	92.1%	0.98	0.99	0.0157	0.0056	
RIATOL qPCR	Depuydt, 2012[26]	93.5%	95.6%	HC2	83.9%	94.4%	1.11	1.01	0.0001	<0.0001	⊕⊕
	Benoy, 2019[89]	96.0%	89.5%	GP5+/6+ EIA	96.0%	89.7%	1.00	1.00	0.0006	0.0069	
APTIMA	Heideman, 2013[27]	95.5%	94.5%	GP5+/6+ EIA	100.0%	93.6%	0.96	1.01	0.0394	0.0002	-
Cervista	Boers, 2014[28]	89.0%	91.2%	HC2	93.4%	88.8%	0.95	1.03	0.0043	<0.0001	⊕
	Alameda, 2015[29]	93.4%	85.2%	HC2	100.0%	86.4%	0.98	0.99	0.0122	0.3170†	
BD Onclarity	Ejegod, 2014[30]	92.9%	87.7%	HC2	94.2%	88.8%	0.99	0.99	0.0009	0.0216	⊕⊕⊕
	Cuschieri, 2015 [90]	96.7%	89.6%	HC2	98.4%	89.9%	0.98	1.00	0.0245	0.0155	
	Ejegod, 2016 [91]	96.1%	89.7%	GP5+/6+ PCR	94.1%	90.4%	1.02	0.99	0.0002	0.0970	
	Bonde, 2019[112]	92.6%	92.6%	GP5+/6+ EIA	92.6%	89.6%	1.00	1.04	<0.0001	<0.0001	
HPV-Risk assay	Hesselink, 2014[20]	97.1%	94.3%	GP5+/6+ EIA	97.1%	94.1%	1.00	1.00	0.0056	0.0003	⊕⊕⊕
	Polman, 2017[93]	93.7%	91.8%	HC2	96.1%	89.9%	0.98	1.02	<0.001	<0.001	
	Heideman, 2019[94]	93.4%	92.6%	GP5+/6+ EIA	92.6%	89.5%	1.01	0.99	0.0006	<0.0001	
Anyplex II HPV HR	Hesselink, 2016 [95]	98.3%	93.6%	GP5+/6+ PCR	98.3%	94.1%	1.00	0.99	0.0052	0.0232	⊕⊕⊕
	Jung, 2016 [96]	92.5%	81.7%	HC2	87.5%	81.8%	1.06	1.00	0.0067	0.0354	
	Ostrbenk, 2018[97]	96.9%	94.1%	HC2	95.9%	92.7%	1.01	1.01	0.001	<0.0001	

64

D:\project\Kankercentrum\IMC_introHPVscreen\TechnicalReport\Report IKW introduction HPV screening ver9.docx

VALGENT 1
5 HPV assays - samples derived from a Belgian biobank

VALGENT 2
6 HPV assays - samples derived from Scottish HPV archive

VALGENT 3
14 HPV assays – samples derived from Slovenian national cohort

VALGENT 4
11 HPV assays – samples from Copenhagen, Denmark

Issues to be resolved…

we need complete HPV diagnostic assays including sample extraction procedure !

manufacturers should put more effort into evaluating their HPV products

manufacturers should seek advice from established HPV researchers in the very early phase of development on:
- how to properly design a novel test
- define intended use of future test (clinical, epidemiological, research…)
- how to evaluate test performance that the HPV community will accept evaluation/validation results

manufacturer-independent evaluations and publication of results in peer-reviewed journals are crucial

evaluation on alternative clinical specimens needed (self-collected cervicovaginal lavage specimens, vaginal swabs, other self-collected samples, tissues, urine…)

more competitively priced HPV tests needed !

Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening?

Clin Microbiol Infect 2015;21:817-26

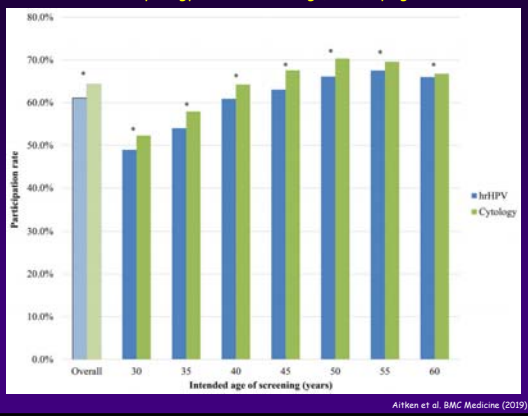
M. Arbyn[1], P. J. F. Snijders[2], C. J. L. M. Meijer[2], J. Berkhof[2], K. Cuschieri[4], B. J. Kocjan[5] and M. Poljak[5]

1) Unit of Cancer Epidemiology and Belgian Cancer Centre, Scientific Institute of Public Health, Brussels, Belgium, 2) Department of Pathology, 3) Department of Clinical Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, The Netherlands, 4) Scottish HPV Reference Laboratory, Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK and 5) Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

UPDATE OF THE LIST OF HPV ASSAYS THAT FULFILL REQUIREMENTS FOR PRIMARY CERVICAL CANCER SCREENING

M. Arbyn[1], M. Poljak[2], C.J.L.M. Meijer[3], P.J.F. Snijders[3], J. Berkhof[4], K. Cuschieri[5], I. Heard[6], J. Bogers[7,8], C. Depuydt[7], D. Vanden Broeck[7,8], I. Benoy[7,8], J. Bonde[9], T. Gheit[10], M. Tommasino[10], M. Pawlita[11], I. Iftner[12], P. Sasieni[13], D. Geraets[14], W. Quint[14] submitted

Participation rate in Dutch hrHPV-based screening (2017) and in cytology-based screening (2015) by age



Aitken et al. BMC Medicine (2019) 17:228

secondary & primary prevention

current status

pre-COVID-19 problems

COVID-19-related problems

200 Million Monthly COVID-19 Tests Needed in US, Report Says

Sep 09, 2020 | staff reporter

Save for later

NEW YORK – To open safely and in stages, a US nationwide screening strategy will require about 200 million tests each month for students and staff at the nation's primary and secondary schools, as well as residents and staff at nursing homes, according to a report released on Wednesday.

UK Government Unveils Plan to Run 500,000 COVID-19 Tests Per Day

Sep 10, 2020 | staff reporter

Save for later

NEW YORK – The UK government plans to ramp testing for SARS-CoV-2 to half a million kits processed per day by the end of October in a bid to reopen the country after months of social distancing measures to control the virus, which causes the disease COVID-19.

COVID-19-related problems arising

- unprecedented health and economic impact of the COVID-19 pandemic
- due to the COVID-19 pandemic, cervical cancer prevention activities have been disrupted in many countries; in May 2020, 46% of the 122 countries included in a WHO survey report closure of population-level screening activities; ICSN found that cancer screening services were suspended in 88% of the settings
- extraordinary demand on a global scale for sampling devices, reagents, consumables, and diagnostic instruments needed for timely diagnosis of SARS-CoV-2 infection
- manufacturer's shift toward new niche market with unprecedented market growth opportunity
- serious COVID-19-related supply chain problems (reagents and consumables)
- preexisting microbiology lab employee shortage, then COVID-19 pandemic hit
- shifted interest of public, agencies and medical journals ("nothing is important but COVID-19")
- "new normal"; unclear future; potential of second, third, fourth… waves of pandemic

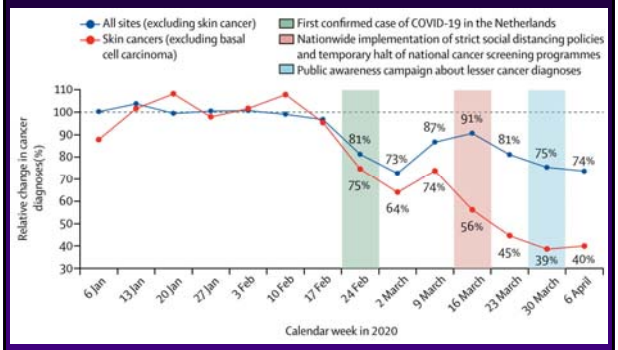
Panther (Hologic)

about 1,100 instruments across U.S.

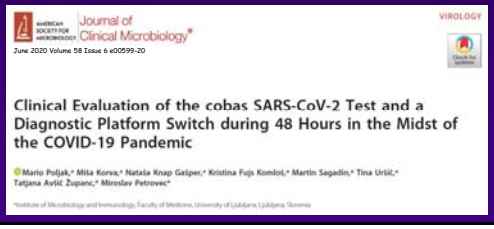
at full tilt, the machines could process about 33 million tests per month, but the company makes roughly 4.8 million

https://www.reuters.com/article/us-health-coronavirus-usa-testing-insight-idUSKCN24S19H

Number of cancer diagnoses by week in the Netherlands in the period between Jan 6, 2020 (calendar week 2) and April 12, 2020 (calendar week 15)



Dinmohamed AG et al. Lancet Ocology 2020


Journal of Clinical Microbiology
June 2020 Volume 58 Issue 6 e00599-20
VIROLOGY

Clinical Evaluation of the cobas SARS-CoV-2 Test and a Diagnostic Platform Switch during 48 Hours in the Midst of the COVID-19 Pandemic

Mario Poljak,[a] Miša Korva,[a] Nataša Knap Gašper,[a] Kristina Fujs Komloš,[a] Martin Sagadin,[a] Tina Uršič,[a] Tatjana Avšič Županc,[a] Miroslav Petrovec[a]
[a]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

25,000 machines worldwide

company is making about 2 million tests per month - enough to run two or three tests globally per machine each day

Cepheid is working on millions of new cartridges but does not expect a dramatic supply boost until June 2021

https://www.reuters.com/article/us-health-coronavirus-usa-testing-insigh-idUSKCN24S19H

only clinically validated HPV tests should be used in cervical cancer screening

PQDx 0268-070-00 WHO PQ Public Report December 2017/ version 3.0

WHO Prequalification of In Vitro Diagnostics
PUBLIC REPORT

Product: Xpert® HPV
WHO reference number: PQDx 0268-070-00

Xpert® HPV with product code **GXHPV-CE-10** manufactured by **Cepheid AB, CE marked regulatory version**, was accepted for the WHO list of prequalified in vitro diagnostics and was listed on 21 December 2017.

Intended use:
The Xpert® HPV assay is a qualitative in vitro test for the detection of the E6/E7 region of the viral DNA genome from high risk Human Papillomavirus (HPV) in patient specimens. The test carries out multiplexed amplification of target DNA by real-time Polymerase Chain Reaction (PCR) of 14 high risk HPV types in a single analysis. Xpert® HPV specifically identifies types HPV 16 and HPV 18/45 in two distinct detection channels, and reports 11 other high risk types (31, 33, 35, 39, 51, 52, 56, 58, 59, 66 and 68) in a pooled result. Specimens are limited to cervical cells collected in PreservCyt® Solution (Hologic Corp.). Cervical specimens collected in PreservCyt Solution that have been pretreated with Glacial Acetic Acid (GAA) to lyse excess red blood cells for cytology review have also been validated for use with the Xpert® HPV assay.

Conclusions (secondary prevention)

254+ commercial HPV assays (and 425+ variants) on the global market

60% of HPV tests on the global market without a single peer-reviewed publication

81% of HPV tests on the market without published performance evaluation (analytical and/or clinical) in peer-reviewed journals

great majority of performance evaluations not in line with standards agreed in the HPV community

several clinically unvalidated HPV assays are used worldwide in daily practice - only a small subset of HPV tests on the market has validated clinical performance

2 + 11 HPV assays fulfil cross-sectional criteria for primary screening

2 + 3 HPV assays have at least 36+ months longitudinal data

serious COVID-19-related supply chain problems arising

COVID-19 pandemic's negative impact on cancer control creates the opportunity to make self-sampling a standard to empower women everywhere

Elimination definition and 2030 targets

Vision: A world without cervical cancer

Goal: cervical cancer incidence below 4 cases per 100,000 woman-years

2030 TARGETS

90% of girls fully vaccinated against HPV by age 15

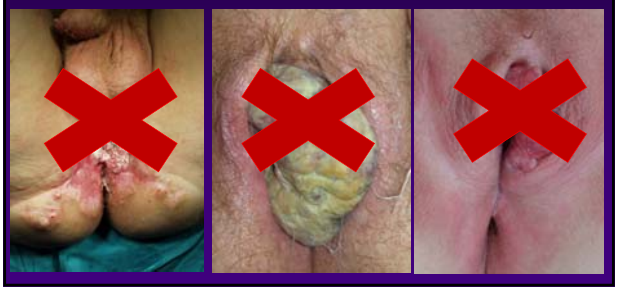
70% of women screened with a high precision test at ages 35 and 45

90% of women with cervical disease receive treatment and care

2030 target: 30% reduction in mortality from cervical cancer

100 Countries Included HPV Vaccine in the National Immunization Program (Nov 2019)

98-100% efficacy against anogenital lesions (cervical, vulvar, vaginal, and anal) caused by targeted HPV types in several large international randomized, double-blind trials



secondary & primary prevention

current status

pre-COVID-19 problems

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American Academy of Pediatrics

Recommended Childhood and Adolescent Immunization Schedule—United States, 2017

COMMITTEE ON INFECTIOUS DISEASES

Annals of Internal Medicine

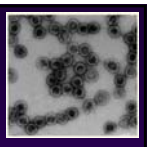
CLINICAL GUIDELINE

Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017*

Two doses are recommended for persons starting the series before their 15th birthday.

Three doses are recommended for those who start the series on or after their 15th birthday and for persons with certain immunocompromising conditions.

Prophylactic HPV vaccines



L1 viral like particles

2vHPV: 16 and 18 with AS04

4vHPV: 6, 11, 16 and 18 with aluminium

9vHPV: 6, 11, 16, 18, 31, 33, 45, 52 and 58 with aluminium

Randomized controlled efficacy trial in Costa Rica to test efficacy of 1 dose vs. 2 doses (NCI & Gates Foundation)

4-arm non-inferiority trial in 12-16 year old girls:

- 1 dose and 2 doses of bivalent vaccine and 9-valent vaccine
- unethical to have a placebo arm

Main hypothesis:

- protection induced by 1 dose is not inferior to 2 doses

Second hypothesis:

- protection will be similar for 1 dose of either vaccine
- potential difference due to adjuvant: alum vs. AS04

clinicaltrials.gov: identifier NCT03180034

Avis sur le calendrier de vaccination contre les virus du papillome humain (VPH)

Dépôt légal – 2e trimestre 2018

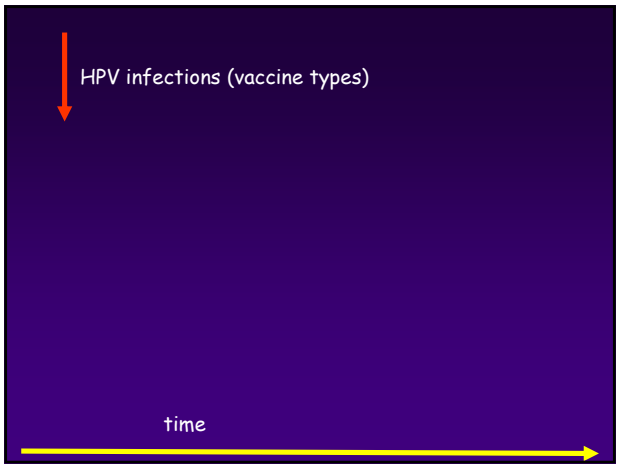
COMITÉ SUR L'IMMUNISATION DU QUÉBEC

a two-vaccine mixed schedule:
- one dose of 9v vaccine followed by one dose of 2v vaccine

rationale: to maximize the immune response against HPV-16 and HPV-18 while ensuring good immunity against the other seven HPV types included in 9v-vaccine

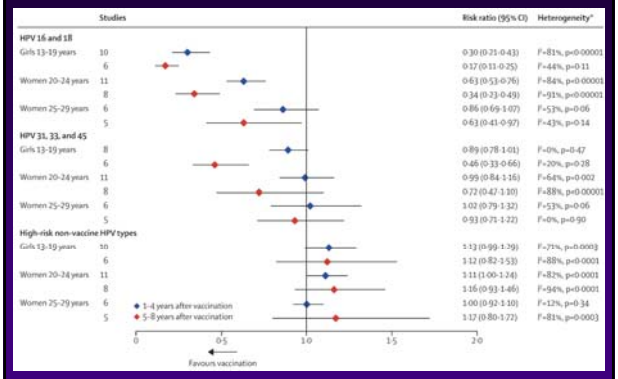
only for girls and boys aged 9 to 17 years in good health

for individuals aged 18 and over as well as for other groups (e.g. immunocompromised), the vaccination schedule remains unchanged (2 doses of 9v vaccine)



Real life efficacy data

Changes in the prevalence of HPV infections between pre-vaccination and post-vaccination periods



Drolet M et al. Lancet 2019;394:497-509.

Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis

Mélanie Drolet, Élodie Bénard, Norma Pérez, Marc Brisson, on behalf of the HPV Vaccination Impact Study Group

Lancet 2019;394:497-509

studies published between Feb 1, 2014, and Oct 11, 2018

updated systematic review and meta-analysis includes data from 60 million individuals and up to 8 years of post-vaccination follow-up

Quadrivalent vaccine-targeted human papillomavirus genotypes in heterosexual men after the Australian female human papillomavirus vaccination programme: a retrospective observational study

Lancet Infect Dis 2017;17:68-77

Eric P F Chow, Dorothy A Machalek, Sepehr N Tabrizi, Jennifer A Danielewski, Glenda Fehler, Catriona S Bradshaw, Suzanne M Garland, Marcus Y Chen, Christopher K Fairley

Retrospective, observational study of urine and urethral swab specimens from heterosexual men aged 25 years or younger (2004-2015), who tested positive for *Chlamydia trachomatis*

Australian-born men:
4vHPV-targeted genotype prevalence decreased from 20% to 3%

Australian-born men aged 21 years or younger:
4vHPV-targeted genotype prevalence decreased from 31% to 0%

herd protection of mainly unvaccinated men from the vaccinated females

HPV infections (vaccine types)

genital warts

time

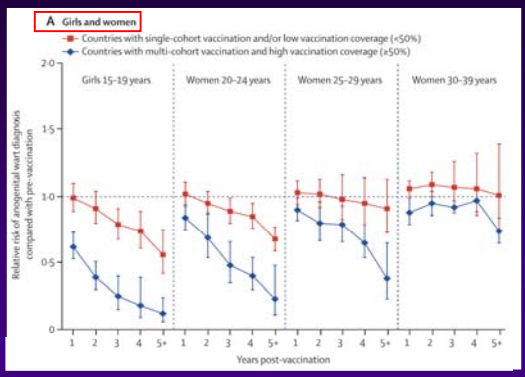
HPV infections (vaccine types)

genital warts

CIN 2/3

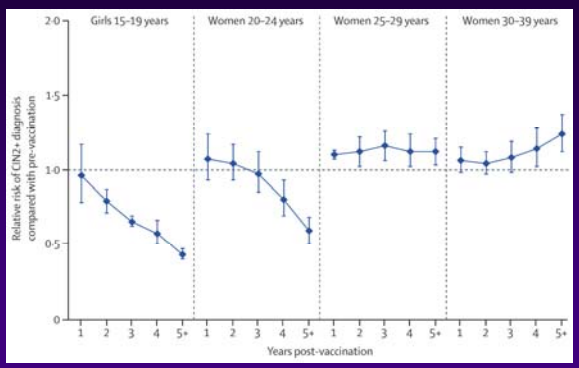
time

Changes in anogenital wart diagnoses during the 8 years after the introduction of girls-only HPV vaccination in countries using the quadrivalent vaccine



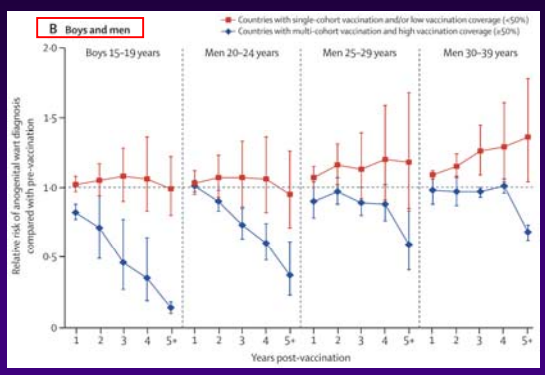
Drolet M et al. Lancet 2019;394:497-509.

Changes in CIN2+ among screened girls and women during the first 7 years after the introduction of girls-only HPV vaccination, in countries with multi-cohort vaccination and high vaccination coverage



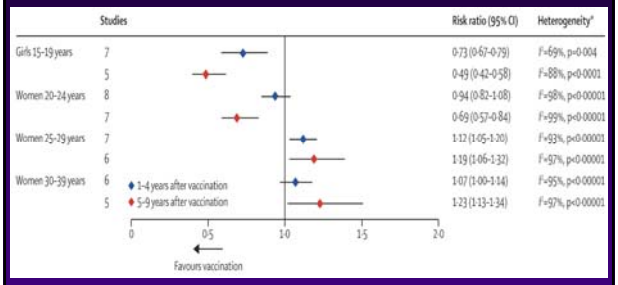
Drolet M et al. Lancet 2019;394:497-509.

Changes in anogenital wart diagnoses during the 8 years after the introduction of girls-only HPV vaccination in countries using the quadrivalent vaccine



Drolet M et al. Lancet 2019;394:497-509.

Changes in CIN2+ among screened girls and women between the pre-vaccination and post-vaccination periods



Drolet M et al. Lancet 2019;394:497-509.

Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study

BMJ 2019;365:l1161

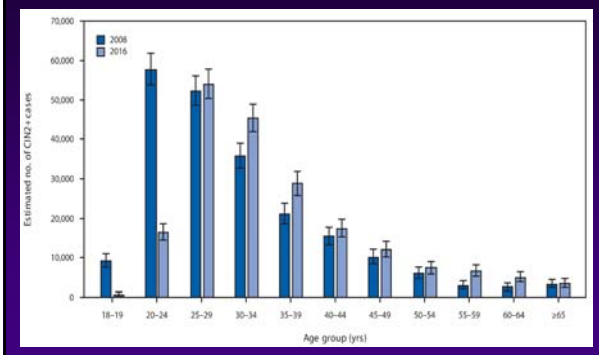
Tim Palmer,[1] Lynn Wallace,[2] Kevin G Pollock,[3,4] Kate Cuschieri,[5] Chris Robertson,[3,6,7] Kim Kavanagh,[7] Margaret Cruickshank[8]

retrospective population study, 1988-96

national vaccination and cervical screening programmes in Scotland

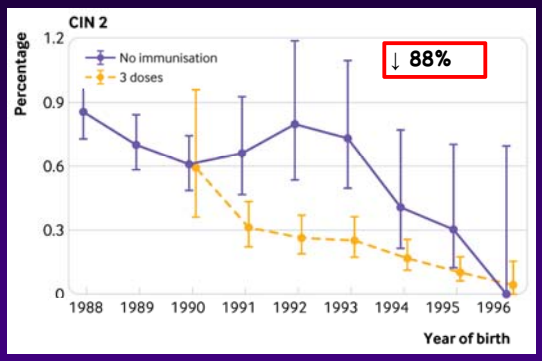
138,692 women

Estimated number of diagnosed CIN2+ cases, by age group
United States, 2008 and 2016



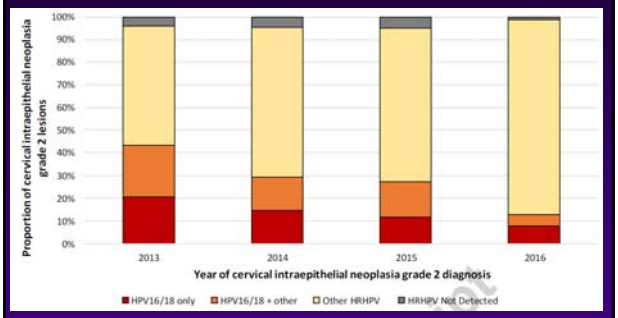
McClung NM, et al. MMWR Morb Mortal Wkly Rep 2019;68:337-43.

Histological abnormality (% of women screened) by year of birth and immunisation status; 1988-90=pre-immunisation programme cohort; 1991-94=catch-up cohort; 1995-96=routinely immunised cohort



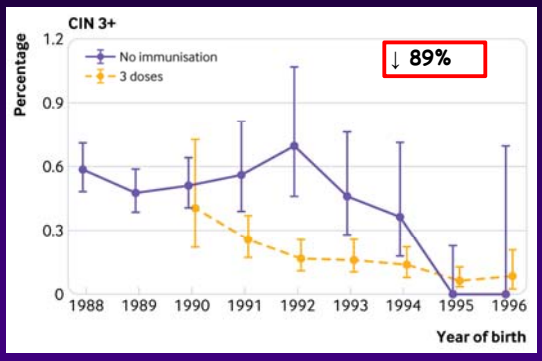
Palmer T et al. BMJ 2019;365:l1161

Changes in HPV genotypes associated with CIN2+ lesions in a cohort of young women, New Zealand, 2013-2016

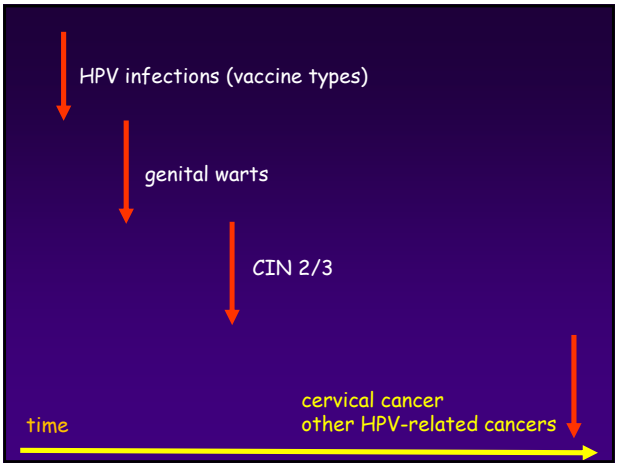


Innes CR et al. Papillomavirus Res 2018; 77-82.

Histological abnormality (% of women screened) by year of birth and immunisation status; 1988-90=pre-immunisation programme cohort; 1991-94=catch-up cohort; 1995-96=routinely immunised cohort



Palmer T et al. BMJ 2019;365:l1161



Vaccination protects against invasive HPV-associated cancers

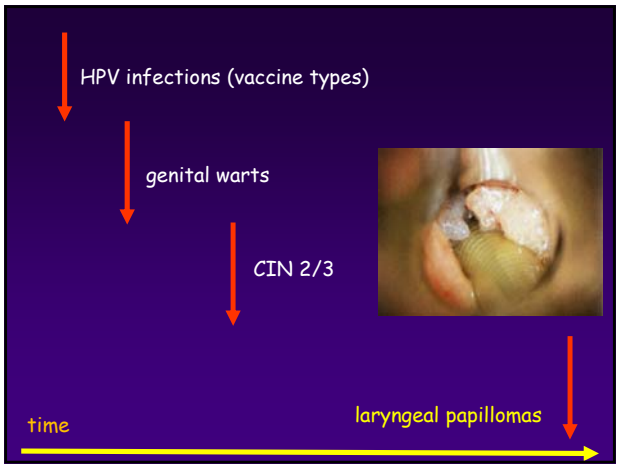
Tapio Luostarinen[1-3], Dan Apter[3], Joakim Dillner[3], Tiina Eriksson[4], Katja Harjula[4], Karl Natunen[4], Jorma Paavonen[5], Eero Pukkala[1,4] and Matti Lehtinen[2,4]

[1]Finnish Cancer Registry, Helsinki, Finland
[2]Department of Laboratory Medicine, Karolinska Institute, Stockholm, Sweden
[3]VL-Medi, Helsinki, Finland
[4]School of Health Sciences, University of Tampere, Tampere, Finland
[5]Department of Obstetrics and Gynecology, University of Helsinki, Helsinki, Finland

Int J Cancer 2018; 142: 2186–2187

Numbers and incidence rates (per 100,000 woman-years) of HPV-associated invasive cancers in cluster randomized cohorts of 9,529 14- to 17-year-old female vaccine (bHPV and qHPV) recipients and 17,838 non-HPV vaccinated, originally 14- to 19-year-old women. Passive follow-up using population-based Finnish Cancer Registry.

	HPV vaccinated women			Non-HPV vaccinated women		
Malignancy	Person years	*n*	Rate (95% CI)	Person years	*n*	Rate (95% CI)
Cervix cancer	65,656	0	-	124,245	8	6.4 (3.2, 13)
Vulva cancer	65,656	0	-	124,245	1	0.8 (0.1, 5.7)
Oropharyngeal cancer	65,656	0	-	124,245	1	0.8 (0.1, 5.7)
Other HPV cancers[1]	65,656	0	-	124,245	0	-
All HPV associated invasive cancers	65,656	0	-	124,245	10	8.0 (4.3, 15)



Scotland - Carcinoma in situ of the cervix uteri: ICD-10 D06

Numbers	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Under 5	-	-	-	-	-	-	-	-	-	-	-
5-9	-	-	-	-	-	-	-	-	-	-	-
10-14	-	-	-	1	-	-	-	-	-	-	-
15-19	1	-	-	-	1	-	-	-	-	-	-
20-24	8	1	11	4	7	13	11	11	8	4	4
25-29	23	34	25	34	26	33	24	38	39	43	9
30-34	39	38	39	37	43	37	37	58	52	47	47
35-39	42	44	36	43	30	39	32	53	47	36	43
40-44	34	41	46	41	36	28	49	47	44	44	32
45-49	24	30	29	44	35	29	34	41	36	43	33
50-54	21	25	27	20	27	26	33	37	28	17	30
55-59	15	21	29	26	24	17	22	19	25	30	21
60-64	13	17	12	22	22	22	14	13	22	25	15
65-69	26	18	21	14	13	20	16	19	17	15	14
70-74	13	19	14	16	18	13	16	15	17	14	11
75-79	17	12	19	16	17	12	11	10	18	14	8
80-84	10	4	12	10	12	7	13	15	15	7	3
85-89	3	8	7	5	6	7	3	11	9	1	4
90+	4	2	1	-	1	1	4	1	4	4	2
All Ages	293	314	328	333	318	304	319	388	381	344	276

https://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Female-Genital-Organ/

A Prospective Study of the Incidence of Juvenile-Onset Recurrent Respiratory Papillomatosis After Implementation of a National HPV Vaccination Program

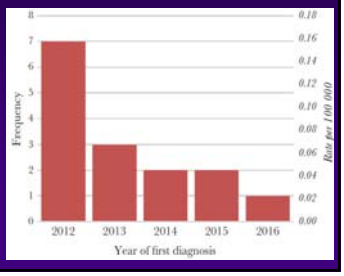
Daniel Novakovic,[1] Alan T. L. Cheng,[1,2] Yvonne Zurynski,[1,3] Robert Booy,[4] Paul J. Walker,[5] Robert Berkowitz,[6] Henley Harrison,[7] Robert Black,[8] Christopher Perry,[9] Shyan Vijayasekaran,[9] David Wabnitz,[10] Hannah Burns,[9] Sepehr N. Tabrizi,[11,12] Suzanne M. Garland,[11,12] Elizabeth Elliott,[1] and Julia M. L. Brotherton[13,14]

J Infect Dis 2018; 217: 208–212

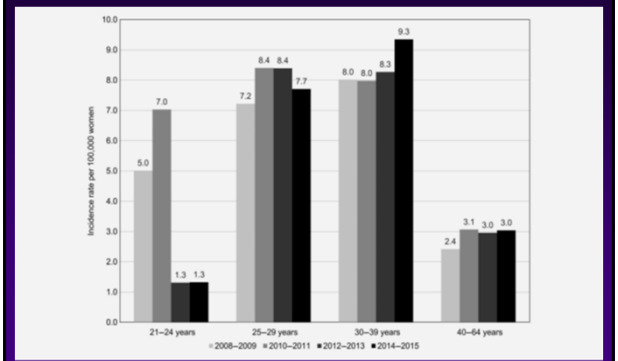
national incidence of juvenile onset recurrent respiratory papillomatosis

15 incident cases

- all mothers not vaccinated
- 20% history of genital warts
- 13/15 born by vaginal delivery



Adenocarcinoma in situ average annual 2-year incidence rates per 100,000 women, by age group, United States, 2008–2015



Cleveland AA et al. Int J Cancer 2020; 146: 810-8.

Has Human Papillomavirus (HPV) Vaccination Prevented Adverse Pregnancy Outcomes? Population-Level Analysis After 8 Years of a National HPV Vaccination Program in Australia

Yuill S et al. J Infect Dis 2020;222:499–508

Susan Yuill,[1,2,3] Sam Egger,[1] Megan Smith,[1,2,3] Louiza Velentzis,[1,2,3] C. David Wrede,[4,5] Deborah Bateson,[6,7] and Karen Canfell[1,2,3]

[1]Cancer Research Division, Cancer Council NSW, Sydney, Australia, [2]School of Public Health, University of Sydney, Sydney, Australia, [3]Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia, [4]Department of Oncology & Dysplasia, Royal Women's Hospital, Melbourne, Australia, [5]Department of Obstetrics and Gynaecology, Melbourne Medical School, University of Melbourne, Melbourne, Australia, [6]Family Planning NSW, Sydney, Australia, [7]Discipline of Obstetrics, Gynaecology and Neonatology, The University of Sydney School of Medicine, Sydney, Australia

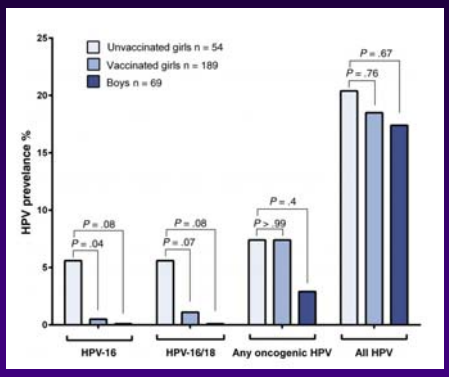
Background. Human papillomavirus (HPV) infection, and its sequelae of precancerous cervical lesions and their subsequent treatment, have been linked with an increased risk of adverse pregnancy outcomes. Publicly funded HPV vaccination of female adolescents began in Australia in 2007 with initial catch-up to age 26 years.

Methods. Using data from the National Perinatal Data Collection we compared rates of preterm births and small-for-gestational-age infants born in Australia 2000–2015. We used generalized linear models, assuming a Poisson distribution and log link function, with single-year categories of infant birth year, maternal age, and age-specific HPV vaccination coverage as independent variables.

Results. In maternal cohorts with 60%–80% HPV vaccination coverage as achieved in Australia, there was a relative rate reduction of 3.2% (95% confidence interval, 1.1%–5.3%) in preterm births and 9.8% (8.2% to 11.4%) in small-for-gestational-age infants, after adjustment for infant's birth year and maternal age.

Conclusion. This analysis provides provisional population-level evidence of a reduction in adverse pregnancy outcomes in cohorts of women offered HPV vaccination. Confounding by smoking or other variables and/or ecological analysis limitations, however, cannot be excluded. These findings indicate potential broader benefits of HPV vaccination than have been documented to date.

Oropharyngeal HPV prevalence in unvaccinated females, vaccinated females, and unvaccinated males aged 12–14 years, by vaccination status and HPV type



Mehanna H et al. Clin Infect Dis 2019;69:1296-302

Human papillomavirus vaccines in 2020

Highly efficacious

Extremely safe

Underutilized

(especially in males)

(exceptionally used in HIV+ individuals)

Post-licencing real life safety data

secondary & primary prevention

current status

pre-COVID-19 problems

COVID-19-related problems

Global Advisory Committee on Vaccine Safety (GACVS):
- an independent expert clinical and scientific advisory body
- provides WHO with scientifically rigorous advice on vaccine safety issues

over 270 million doses of HPV vaccines have been distributed

first safety review in 2007, and subsequent in 2008, 2009, 2013, 2014 and 2015

the risk of anaphylaxis characterized as app. 1.7 cases per million doses

syncope established as a common anxiety or stress related reaction to injection

no other adverse reactions identified - HPV vaccines are extremely safe

Influence of vaccine safety rumors on vaccination coverage

Japan	70% (2013)	→	0.6% (2015)
Denmark	90% (2012)	→	44% (2015)
Ireland	87% (2013)	→	49% (2016)
Columbia	88% (2012)	→	5% (2016)

Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modelling study

Kate T Simms*, Sharon J B Hanley*, Megan A Smith*, Adam Keane, Karen Canfell

Summary

Background Funding for human papillomavirus (HPV) vaccination in Japan began in 2010 for girls aged 12–16 years, with three-dose coverage initially reaching more than 70%. On June 14, 2013, 2 months after formal inclusion in Japan's national immunisation programme, proactive recommendations for the HPV vaccine were suspended following reports of adverse events since found to be unrelated to vaccination, but which were extensively covered in the media. Vaccine coverage subsequently dropped to less than 1% and has remained this low to date. We aimed to quantify the impact of this vaccine hesitancy crisis, and the potential health gains if coverage can be restored.

Methods In this modelling study, we used the Policy1-Cervix modelling platform. We adapted the model for Japan with use of data on HPV prevalence, screening practices and coverage, and cervical cancer incidence and mortality. We evaluated the expected number of cervical cancer cases and deaths over the lifetime of cohorts born from 1994 to 2007 in the context of the vaccine hesitancy crisis. We assessed a range of recovery scenarios from 2020 onwards, including a scenario in which routine coverage is restored to 70%, with 50% catch-up coverage for the missed cohorts (aged 13–20 years in 2020). To estimate the impact of the vaccine crisis to date, we also modelled a counterfactual scenario in which 70% coverage had been maintained in 12-year-olds from 2013 onwards.

Findings The vaccine crisis from 2013 to 2019 is predicted to result in an additional 24 600–27 300 cases and 5000–5700 deaths over the lifetime of cohorts born between 1994 and 2007, compared with if coverage had remained at around 70% since 2013. However, restoration of coverage in 2020, including catch-up vaccination for missed cohorts, could prevent 14 800–16 200 of these cases and 3000–3400 of these deaths. If coverage is not restored in 2020, an additional 3400–3800 cases and 700–800 deaths will occur over the lifetime of individuals who are 12 years old in 2020 alone. If the crisis continues, 9300–10 800 preventable deaths due to cervical cancer will occur in the next 50 years (2020–69).

Interpretation The HPV vaccine crisis to date is estimated to result in around 5000 deaths from cervical cancer in Japan. Many of these deaths could still be prevented if vaccination coverage with extended catch-up can be rapidly restored.

Lancet Public Health 2020; S: e223-34
Published Online February 10, 2020
https://doi.org/10.1016/S2468-2667(20)30010-4
See Comment page e184

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Correspondence to: Dr Karen Canfell, Cancer Research Division, Cancer Council NSW, Sydney, NSW 2011, Australia karen.canfell@nswcc.org.au

Association between quadrivalent human papillomavirus vaccination and selected syndromes with autonomic dysfunction in Danish females: population based, self-controlled, case series analysis

BMJ 2020;370:m2930

Anders Hviid,[1,3] Nicklas M Thorsen,[1] Palle Valentiner-Branth,[2] Morten Frisch,[1,3] Kåre Mølbak[2,4]

869 patients with autonomic dysfunction syndromes from a cohort of 1,375,737 Danish born female participants aged 10 to 44 years during 2007-2016:

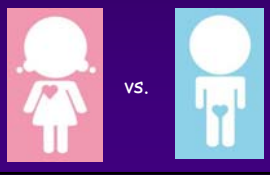
- 136 with chronic fatigue syndrome
- 535 with complex regional pain syndrome
- 198 with postural orthostatic tachycardia syndrome

Quadrivalent HPV vaccination did not statistically significantly increase the rate of a composite outcome of all syndromes with autonomic dysfunction in a 365 day risk period following vaccination (rate ratio 0.99, 95% CI 0.74 to 1.32) or the rate of any individual syndrome in the risk period:

- chronic fatigue syndrome (0.38, 95% CI 0.13 to 1.09)
- complex regional pain syndrome (1.31, 95% CI 0.91 to 1.90)
- postural orthostatic tachycardia syndrome (0.86, 95% CI 0.48 to 1.54)

Wealth inequity

Gender inequity



Simon Harris T.D.
Minister of Health
Ireland

I am here to demonstrate my trust in HPV immunisation and how it protects women from developing cancer later in their lives.

We all know that the vaccine works and that it works very well.

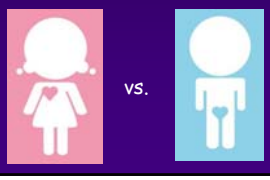
No serious side effects in any country can be scientifically attributed to this vaccine.

Thanks to the HPV vaccine, Ireland's daughters, mothers, wives, sisters and loved ones can live long and fulfilling lives without living in fear of cervical cancer.

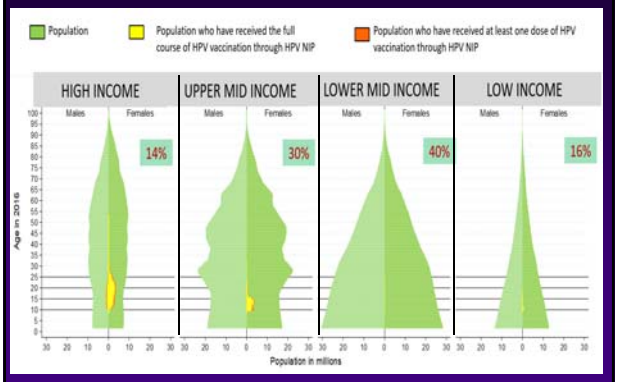
I, as Minister of Health continue to pledge my full support to the HPV vaccination program and the tremendous work carried out by many people sitting here in this room today.

Wealth inequity

Gender inequity



Population pyramids and the number of people vaccinated through national HPV vaccination programmes by income (by the end of 2016)



Courtesy of Laia Bruni, ICO, Barcelona

Why to vaccinate males against HPV ?

inability of natural anti-HPV antibodies to prevent HPV reinfection in males

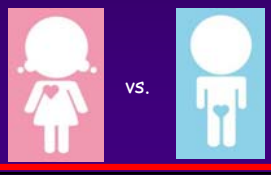
HPV vaccination is the only reliable method to ensure immune protection against new HPV infections and subsequent HPV-induced cancers in males

vaccination of males further increases protection of women against HPV-induced cancers by transmission interruption (herd protection)

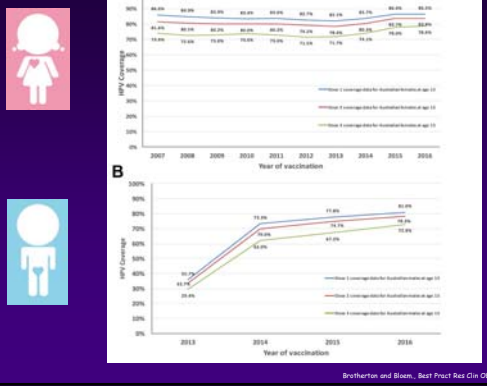
Male HPV vaccination protects also against cervical cancer!

Wealth inequity

Gender inequity



Trend in HPV vaccine coverage at age 15 in Australia, 2013-2016



78.6%

72.9%

Brotherton and Bloem., Best Pract Res Clin Obstet Gynaecol 2017, in press.

Number of people vaccinated through HPV national vaccination programmes globally (2018)

86 million girls/women have received at least one-dose of HPV vaccine through national HPV vaccination programmes

14 million boys/men have received at least one-dose of HPV vaccine through national HPV vaccination programmes

Bruni L. et al. IPV Meeting 2018, unpublished data

Vaccination With Moderate Coverage Eradicates Oncogenic Human Papillomaviruses If a Gender-Neutral Strategy Is Applied

J Infect Dis 2020;222:948-56

Simopekka Vänskä,[1,2,3] Tapio Luostarinen,[1] Iacopo Baussano,[4] Dan Apter,[5] Tiina Eriksson,[6] Kari Natunen,[6] Pekka Nieminen,[7] Jorma Paavonen,[7] Ville N. Pimenoff,[2,8,9] Eero Pukkala,[8,11] Anna Söderlund-Strand,[3] Gary Dubin,[10] Geoff Garnett,[10] Joakim Dillner,[2] and Matti Lehtinen[2,8,12]

[1]Infectious Disease Control and Vaccinations, Finnish Institute for Health and Welfare, Helsinki, Finland, [2]Department of Laboratory Medicine, Karolinska Institute, Stockholm, Sweden, [3]Finnish Cancer Registry, Helsinki, Finland, [4]International Agency for Research on Cancer, Lyon, France, [5]VL-Medi Oy, Helsinki, Finland, [6]Tampere University, Tampere, Finland, [7]University of Helsinki, Helsinki, Finland, [8]Catalan Institute of Oncology, Bellvitge Biomedical Research Institute, Barcelona, Spain, [9]Department of Clinical Microbiology, Skåne University Hospital, Lund, Sweden, [10]Takeda Pharmaceuticals International, Zurich, Switzerland, [11]Gates Foundation, Seattle, Washington, USA, [12]Deutsches Krebsforschungszentrum, Heidelberg, Germany

(See the Editorial Commentary by Sanjose and Bruni, on pages 888–9.)

Background. Human papillomavirus (HPV) vaccination of girls with very high (>90%) coverage has the potential to eradicate oncogenic HPVs, but such high coverage is hard to achieve. However, the herd effect (HE) depends both on the HPV type and the vaccination strategy.

Methods. We randomized 33 Finnish communities into gender-neutral HPV16/18 vaccination, girls-only HPV16/18 vaccination, and hepatitis B virus vaccination arms. In 2007–2010, 11 662 of 20 513 of 40 852 of 39 420 resident boys/girls from 1992 to 1995 birth cohorts consented. In 2010–2014, cervicovaginal samples from vaccinated and unvaccinated girls at age 18.5 years were typed for HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59/66/68. Vaccine efficacy for vaccinated girls, HE for unvaccinated girls, and the protective effectiveness (PE) for all girls were estimated. We extended the community-randomized trial results about vaccination strategy with mathematical modeling to assess HPV eradication.

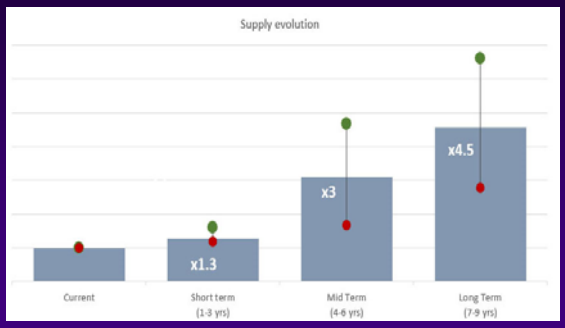
Results. The HE and PE estimates in the 1995 birth cohort for HPV18/31/33 were significant in the gender-neutral arm and 150% and 40% stronger than in the girls-only arm. Concordantly, HPV18/31/33 eradication was already predicted in adolescents/young adults in 20 years with 75% coverage of gender-neutral vaccination. With the 75% coverage, eventual HPV16 eradication was also predicted, but only with the gender-neutral strategy.

Conclusions. Gender-neutral vaccination is superior for eradication of oncogenic HPVs.

Merck quadruples Gardasil supply in China contract but still might not meet full demand

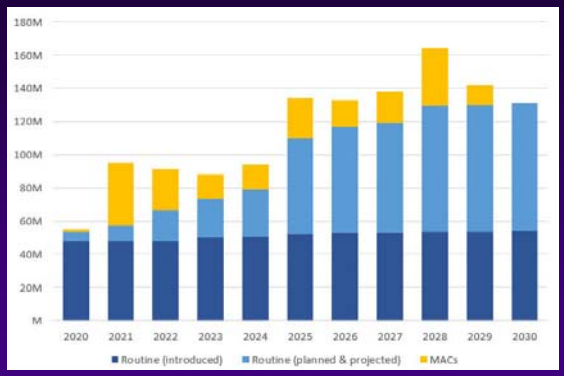
by Angus Liu | Nov 12, 2018 10:38am

Supply to slowly grow in the short term, followed by steep ramp up from year 4-5



Source: MI4A market study, December 2019

Scenario 1 - routine 2-dose vaccination (current recommendation)

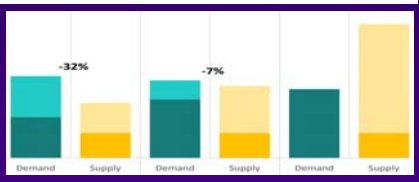


MAC = multi-age cohort

Source: MI4A market study, December 2019

Dynamic supply-demand balance

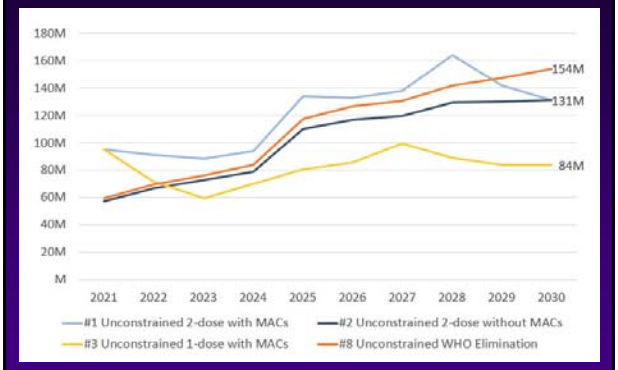
	Base Supply		
Demand Scenarios	**Short-Term (1-3)**	**Mid-Term (4-6)**	**Long-Term (6-9)**
#1 2-dose + MACs	20 countries delayed		
#2 2-dose No MACs			
#3 1-dose + MACs*	7 countries delayed		



MAC = multi-age cohort

Source: MI4A market study, December 2019

Dose requirement across four different scenarios



MAC = multi-age cohort

Source: MI4A market study, December 2019

SAGE recommendations on HPV vaccination (October 2019)

In the context of a limited supply of HPV vaccine, SAGE recommended the following additional strategies:

1. All countries should temporarily pause implementation of boy, older age group (>15 years) and multi-age cohort (MAC) HPV vaccination strategies until vaccine supply allows equitable access to HPV vaccine by all countries.

2. To try to reach girls before they age out of the recommended primary target population, countries could target girls who are 13 or 14 years old or in the equivalent school grade for 2-dose vaccination

3. Countries could adopt an extended interval of 3-5 years between the 2 doses, with the first dose being given to younger girls

secondary & primary prevention

current status

pre-COVID-19 problems

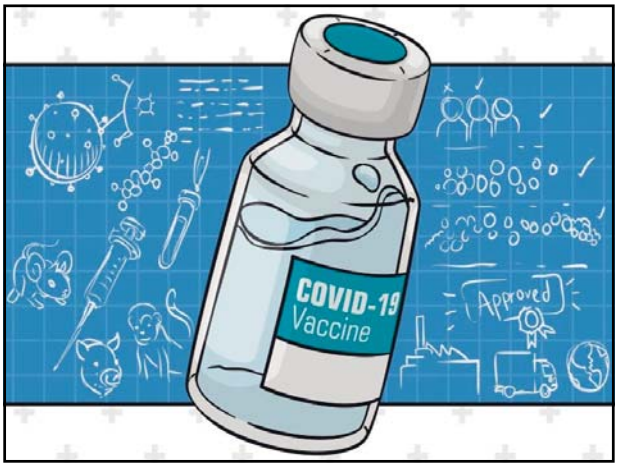
COVID-19-related problems

Dynamic supply-demand balance

	Base Supply			Low Supply		
Demand Scenarios	Short-Term (1-3)	Mid-Term (4-6)	Long-Term (6-9)	Short-Term (1-3)	Mid-Term (4-6)	Long-Term (6-9)
#1 2-dose + MACs	20 countries delayed					
#2 2-dose No MACs						
#3 1-dose + MACs*	7 countries delayed					

MAC = multi-age cohort

Source: MI4A market study, December 2019

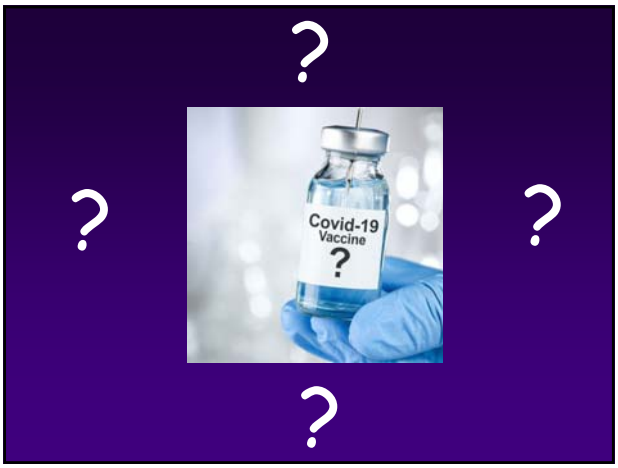


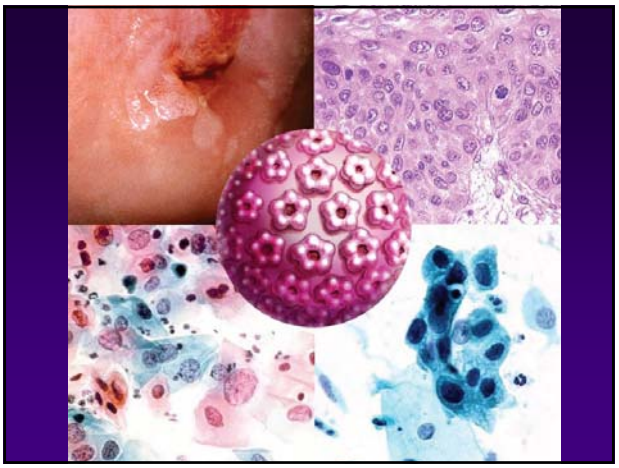
Conclusions (primary prevention)

in the 13 years since its introduction, HPV vaccination has seen many positive developments: a reduced number of doses and more flexible schedules have reduced cost and facilitated program implementation

2vHPV, 4vHPV and 9vHPV vaccines are extremely safe, highly effective but underused (especially in males and only exceptionally used in HIV+ individuals)

as both genders are responsible for HPV transmission, both genders should get vaccinated to share the burden in reducing the risk of HPV-related disease, as well as have equal access to direct vaccine benefits





Conclusions GENERAL

the magnitude of prevention potential of HPV-related cancers is currently not rivalled for any other neoplastic disease in humans

only integration of primary and secondary prevention brings efficieny benefits

HPV-based screening is beneficial over cytology-based screening

only gender-neutral vaccination will lead to control of HPV-related diseases in both genders and maximize prevention of cervical cancer

failure to implement HPV-based screening and gender-neutral, age-extended and global HPV vaccination looks like a missed public health opportunity

several pre-COVID-19 and COVID-19-related problems arrising

GIVE LOVE NOT HPV

We know HPV is causing cervical cancer

We have excellent HPV screening tests and HPV vaccines

We can envisage cervical cancer elimination

ipvs International Papillomavirus Society

Although we are in a COVID-19 pandemic,

we are also in an HPV pandemic!


Tackling cervical cancer in Europe amidst the COVID-19 pandemic

Arbyn M, Bruni L, Kelly D, Basu P, Poljak M, Gultekin M, Bergeron C, Ritchie D, Weiderpass E
Tackling cervical cancer in Europe amidst the COVID-19 pandemic.
Lancet Public Health 2020; 5: e425.

the COVID-19 pandemic might also generate opportunities for more efficient prevention, by promoting more cost-effective, evidence-based protocols, by focusing on women who are at high-risk, extending HPV testing on self-collected samples, and discouraging inefficient policies, such as screening with two tests.