I Codici Europei contro il cancro, con enfasi sull'HPV (alla quinta edizione, ECAC 5 2023-2025)

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Nessun Conflitto di Interesse

La mia presentazione comprenderà due parti:

1. Introduzione al prossimo Codice Europeo (**ECAC5**) contro il cancro, con enfasi su **HPV** e le possibili raccomandazioni sulla prevenzione di **altri tumori importanti causati da infezioni**;
2. Cenno a conseguenze della vaccinazione HPV sullo screening della cervice: nuovi risultati su **«UNMASKING» DA Costa Rica HPV Vaccine Trial (Shing et al, Lancet Oncol. 2022)**

International Agency for Research on Cancer

World Health Organization

2015

Codice Europeo Contro il Cancro

Italiano

Ricerca

HOME | 12 MODI | SUL CANCRO | PROVE SCIENTIFICHE | SUL CODICE

Codice Europeo Contro Il Cancro

12 MODI PER RIDURRE IL TUO RISCHIO DI CANCRO

Stampare il codice

1. Non fumare. Non consumare nessuna forma di tabacco.

2. Rendi la tua casa libera dal fumo. Sostieni le politiche che promuovono un ambiente libero dal fumo sul tuo posto di lavoro.

3. Attivati per mantenere un peso sano.

4. Svolgi attività fisica ogni giorno. Limita il tempo che trascorri seduto.

5. Segui una dieta sana:
   - Consuma molti e vari cereali integrali, legumi, frutta e verdura.
   - Limita i cibi ad elevato contenuto calorico (alimenti ricchi di zuccheri o grassi) ed evita le bevande zuccherate.
   - Evita le carni conservate; limita il consumo di carni rosse e di alimenti ad elevato contenuto di sale.

6. Se bevi alcolici di qualsiasi tipo, limitane il consumo. Per prevenire il cancro è meglio evitare di bere alcolici.

7. Evita un'eccessiva esposizione al sole, soprattutto per i bambini. Usa protezioni solari. Non usare lettini abbronzanti.

8. Osserva scrupolosamente le istruzioni in materia di salute e sicurezza sul posto di lavoro per proteggerti dall'esposizione ad agenti cancerogeni noti.

9. Accerta di non essere esposto a concentrazioni naturalmente elevate di radon presenti in casa. Fai in modo di ridurre i livelli elevati di radon.

10. Per le donne:
    - L'allattamento al seno riduce il rischio di cancro per la madre. Se puoi, allatta il tuo bambino.
    - La terapia ormonale sostitutiva (TOS) aumenta il rischio di alcuni tipi di cancro. Limita l'uso della TOS.

11. Assicurati che i tuoi figli partecipino ai programmi di vaccinazione contro:
    - l'epatite B (per i neonati)
    - il papillomavirus umano (HPV) (per le ragazze).

12. Partecipa a programmi organizzati di screening per il cancro:
    - dell'intestino (uomini e donne)
    - del seno (donne)
    - del collo dell'utero (donne).

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Cancer Epidemiology, 2015, 18 printed pages

European Code against Cancer 4th Edition: Infections and Cancer☆

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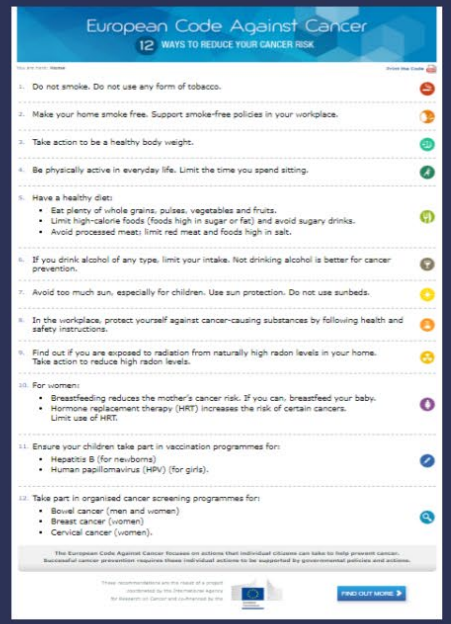
ABSTRACT

Of the 2,635,000 new cancer cases (excluding non-melanoma skin cancers) occurring in the European Union (EU) in 2012, it is estimated that approximately 185,000 are related to infection with human papillomaviruses (HPVs), hepatitis B and C viruses (HBV and HCV), and *Helicobacter pylori* (*H. pylori*). Chronic infection with these agents can lead to cancers of the cervix uteri, liver, and stomach, respectively. Chronic infection with HCV can also lead to B-cell non-Hodgkin lymphoma. Human immunodeficiency virus (HIV) infection continues to be of major public health importance in several EU countries and increases cancer risk via HIV-induced immunosuppression. The fourth edition of the European Code Against Cancer presents recommendations on effective and safe preventive interventions in order to reduce the risk of infection-related cancers in EU citizens. Based on current available evidence, the fourth edition recommends that parents ensure the participation of their children in vaccination programs against HBV (for newborns) and HPV (for girls). In the 'Questions and Answers' (Q&As) section about vaccination and infections in the website for the European Code Against Cancer, individuals who are at risk of chronic HBV or HCV are advised to seek medical advice about testing and obtaining treatment when appropriate. Individuals most at risk of HIV are advised to consult their doctor or healthcare provider to access counselling and, if needed, testing and treatment without delay. Information about *H. pylori* testing and treatment is also provided as testing might currently be offered in some high-risk areas in Europe. The rationale and supporting evidence for the recommendations on vaccination in the European Code Against Cancer, and for the main recommendations on vaccination and infection in the Q&As, are explained in the present review.

Decision-making algorithm for the WGs

Starting point

Recommendation from a previous Code to be updated, or new recommendation (takes into account other Regional Codes for guidance)



Criterion 1: Confidence in the evidence to keep, modify or add a recommendation that is relevant for the region or a large sub-region

Criterion 2: Suitability and acceptability for a broad target population of the general public in the EU

Criterion 3: Intelligibility of the formulation of the recommendation for a lay audience

Criterion 4: Availability of international polices to enable environments to comply with the recommendation

- Recommendations for the public
- Corresponding Recommendations for policy-makers

The prevention of HPV-related cancer has several other strenghts as compared to other infections

*Criterion 1 : Excellent confidence in the **scientific evidence** due to long practice in cervical cancer screening, bulk of vaccine trials, epidemiological studies and endordement from International organizations*

Criterion 1.1: **Relevance** to the region or a large sub-region: **YES**, **nowhere is HPV a rare infection** nor is restricted to underprivileged minorities;

1.Is it a **priority** for the whole region? **YES,** although incidence/mortality of cervical cancer varies a lot (due to screening history), **all EU countries are aware of the problem and consider HPV vaccination and cervical screening cost-effective**;

1.1b What would be the impact on **Equity**? **GOOD**, **experience has taught us the right ways to attenuate socio-educational gradients**;

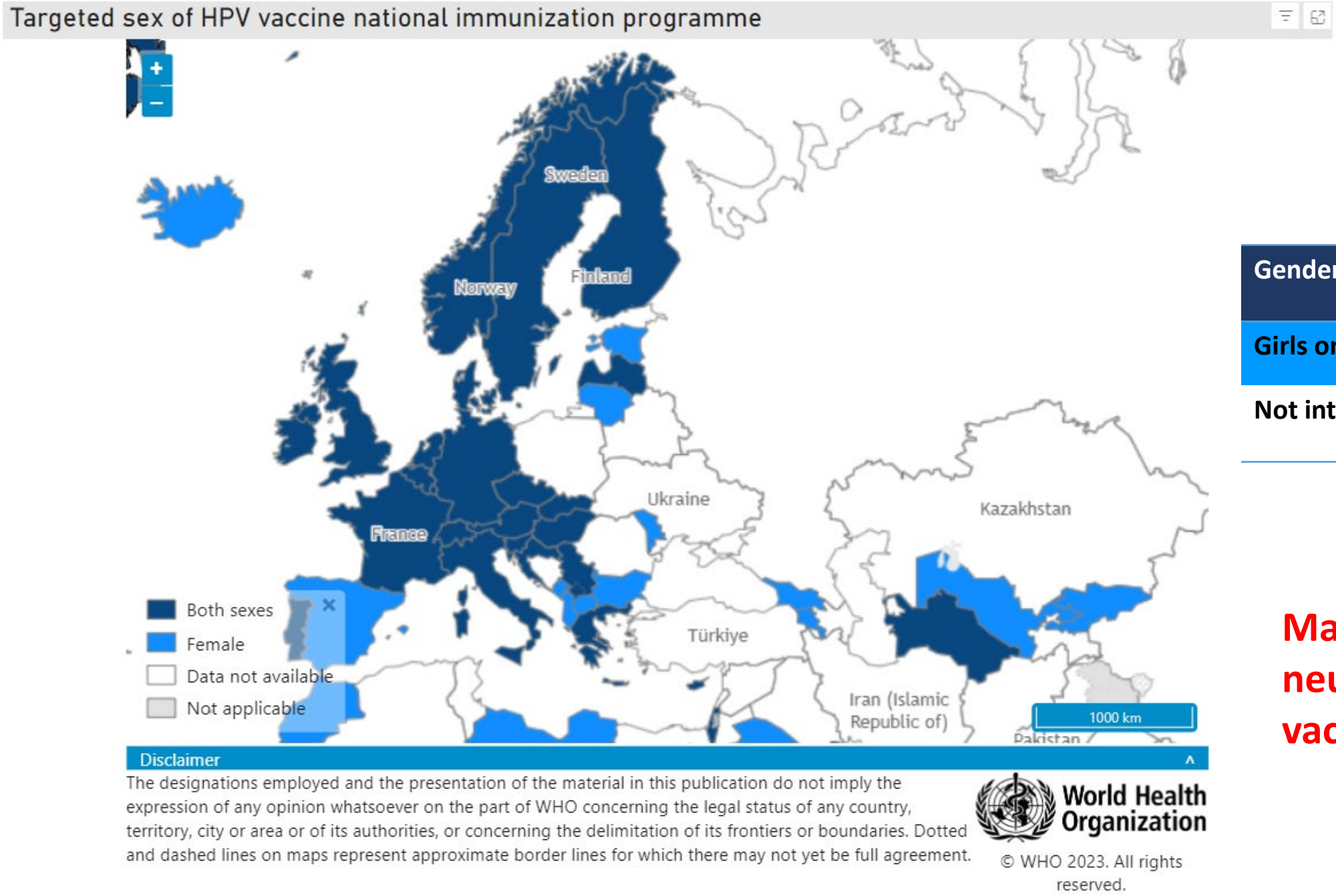
1.1c Is the intervention accessible and **feasible** to implement in the regional context? **YES**, **many success stories in the EU**

HPV - evidence presented in ECAC4, 2015

- HPV related cancer burden: Cervical, Vaginal, Anal, Penile, Oropharyngeal (2012 Globocan)
- Efficacy and safety of HPV vaccines 2 systematic reviews in F, 6 studies in M - against Cx and other cancers; (Endpoints: **HPV infection, genital warts, CIN**); duration of protection (8-10 Yrs); effectiveness by age, HPV type cross- protection
- HPV vaccines and vaccine policy: Cervarix, Gardasil & Gardasil9), Regulatory (EMA licensing); Recommended primary target (age, sex) schedule (**2-dose 9-13 yr; >14 3 dose interval**); interval (WHO PP 2014)
- Cost effectiveness (males)
- Status of introduction in EU countries, target ages (routine, catch up) & coverage & gender (**only 1 male programs in 2014**)

HPV – additional evidence/issues for ECAC5, **2024**

- Burden – update 2020 - AF different cancers (Mantel et al.)
- Vaccines: **global supply** and suppliers' landscape (WHO Market study 2022 & 2023 update (Dec 2023);
- Duration, Efficacy & effectiveness: Effectiveness data (CIN2+ and **early invasive cancers data Sweden, UK, Scotland**); Age-stratified effectiveness (diminishing ROI by age); 1-dose efficacy & duration data.
- Introduction and Coverage: scope of **males programs**, more comparable coverage trend data & regional coverage indicators (*WHO/UNICEF estimates since 2018*)
- Policy environment: 2 dose (9 to any age); option: **1 dose (9-20 yr) (WHO PP 2022)**
- **FASTER** strategies: not aware of trial data forthcoming 2023/4 however,
  - Sweden study (2-d 25-30 yr olds with HPV-DNA screening)
  - new modeling data on & impact and efficiency of catch up in secondary targets (in LMICs)
- The efficacy and cost-effectiveness of HPV vaccination after local conservative treatment for cervical intra-epithelial neoplasia: e.g. Novel trial (*only moderate-quality evidence from Cochrane Rev, Litcher et al, Obst & Gynecol, 2020*)



Status May 2023

Gender neutral	28	53%
Girls only	15	28%
Not introduced	10	19%

Mainly gender-neutral vaccination

Might the HPV-based screening experience be applied to other important cancer-causing infections?

Infections for which screen-and-treat approaches may be now possible.

HCV

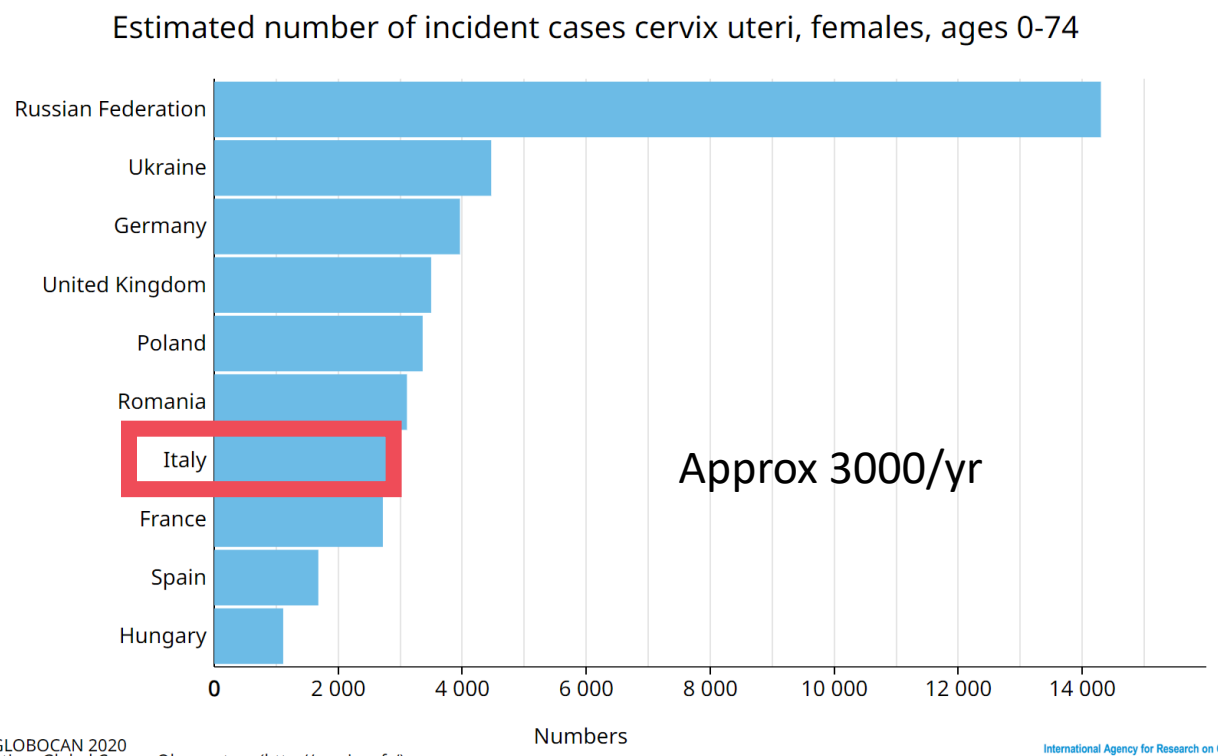
HBV

HIV

Helicobacter pylori

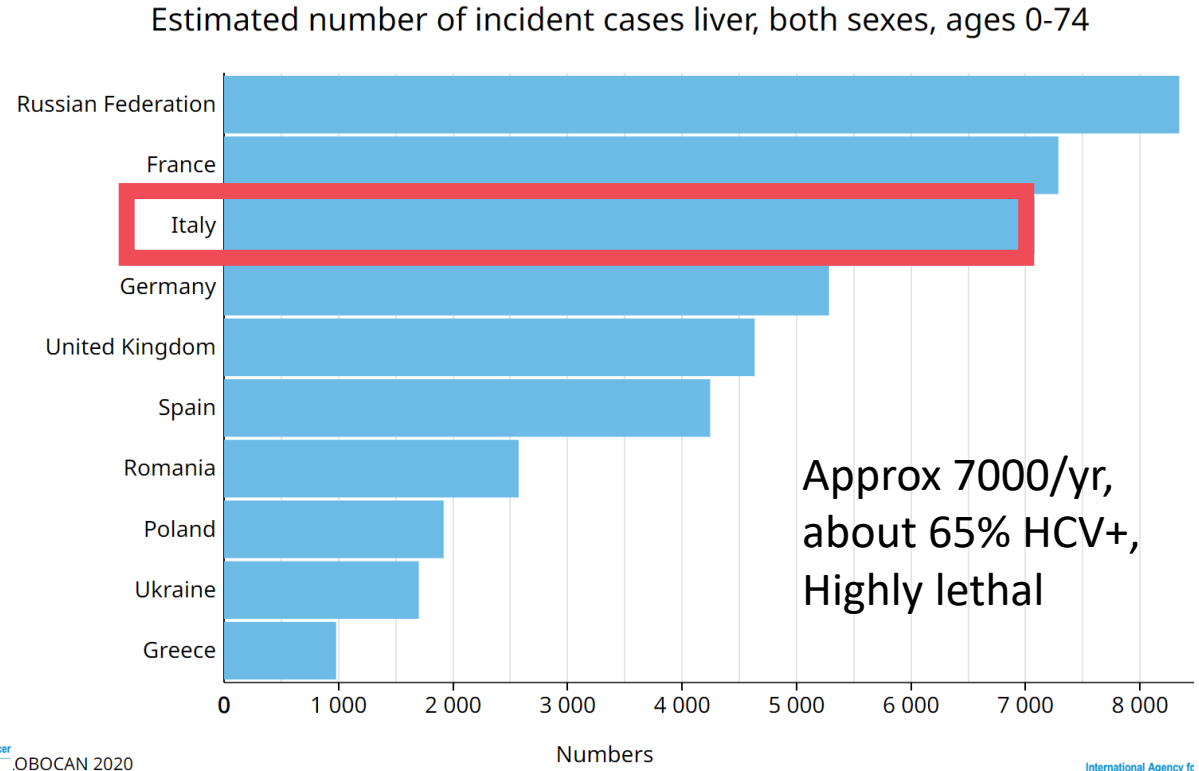
Cancer site	Agent
Stomach (mainly non-cardia)	*Helicobacter pylori,*
Liver — Hepatocellular carcinoma	Hepatitis B virus Hepatitis C virus *Opisthorchis viverrini* *Clonorchis sinensis*
Liver — Cholangiocarcinoma	Hepatitis B virus Hepatitis C virus *Opisthorchis viverrini* *Clonorchis sinensis*
Cervix uteri	Human papillomavirus, with or without HIV
Ano-genital (penile, vulva, vagina, anus)	Human papillomavirus, with or without HIV
Nasopharynx	Epstein-Barr virus
Oropharynx, Larynx, Oral Cavity	Human papillomavirus
Non-Hodgkin Lymphoma	*Helicobacter pylori* Epstein-Barr virus, with or without HIV Hepatitis C virus Human T-cell lymphotropic virus type-1 (HTLV-1)
Kaposi Sarcoma	Human herpes virus type-8 (KSHV), with or without HIV
Hodgkin Lymphoma	Epstein-Barr virus, with or without HIV
Bladder	*Schistosoma Haematobium*

Number of cancer of the **cervix** (~3000/yr) and liver (~7000/yr) in Italy and other European countries, *Globocan, 2020*



:GLOBOCAN 2020
uction: Global Cancer Observatory (http://gco.iarc.fr/)
onal Agency for Research on Cancer 2023

International Agency for Research on Cancer
World Health Organization



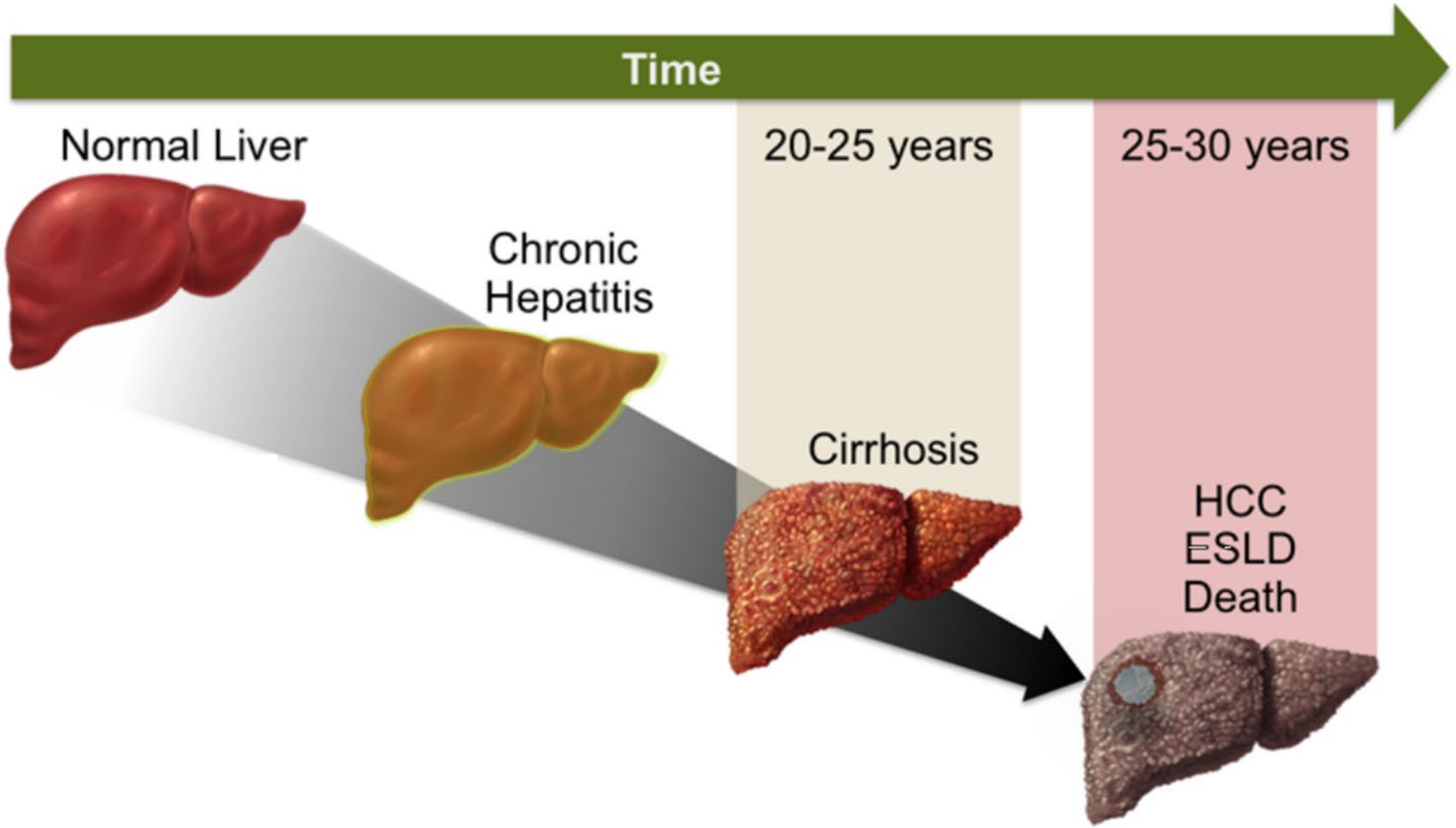
OBOCAN 2020
on: Global Cancer Observatory (http://gco.iarc.fr/)
l Agency for Research on Cancer 2023

International Agency fo
World Health Organization

In Italy and in many EU countries number of liver cancer is higher than cervical cancer (both sexes).

About 65% of liver cancer are associated with HCV +/- HBV

The natural history of chronic viral hepatites C is well-understood



http://www.hepatitisc.uw.edu/pdf/evaluation-staging-monitoring/natural-history/core-concept/all

Screen-treat HCV to prevent liver cancer is conceivable

Affordable Test

HCV RNA

or (less well) HCV core antigen

Sustained virological response (SVR)

can be achieved

Affordable new treatment

Direct-acting antiviral agents (DAA)

including NS3/4A protease inhibitors, NS5A protein inhibitors, NS5B nucleoside (NPIs), and nonnucleoside (NNPIs)polymerase inhibitors administered for at least 12 weeks and delivered in the following fixed-dose combinations:

e.g., -Sofosbuvir/daclatasvir

-Paritaprevir/ritonavir-ombitasvir & dasabuvir

-Sofosbuvir/velpatasvir

-Ledipasvir/sofosbuvir

-elbasvir/grazoprevir

-glecaprevir/pibrentasvir

-Sofosbuvir/velapatasvir/voxilaprevir

-Paritrapevir/ritonavir-ombitasvir

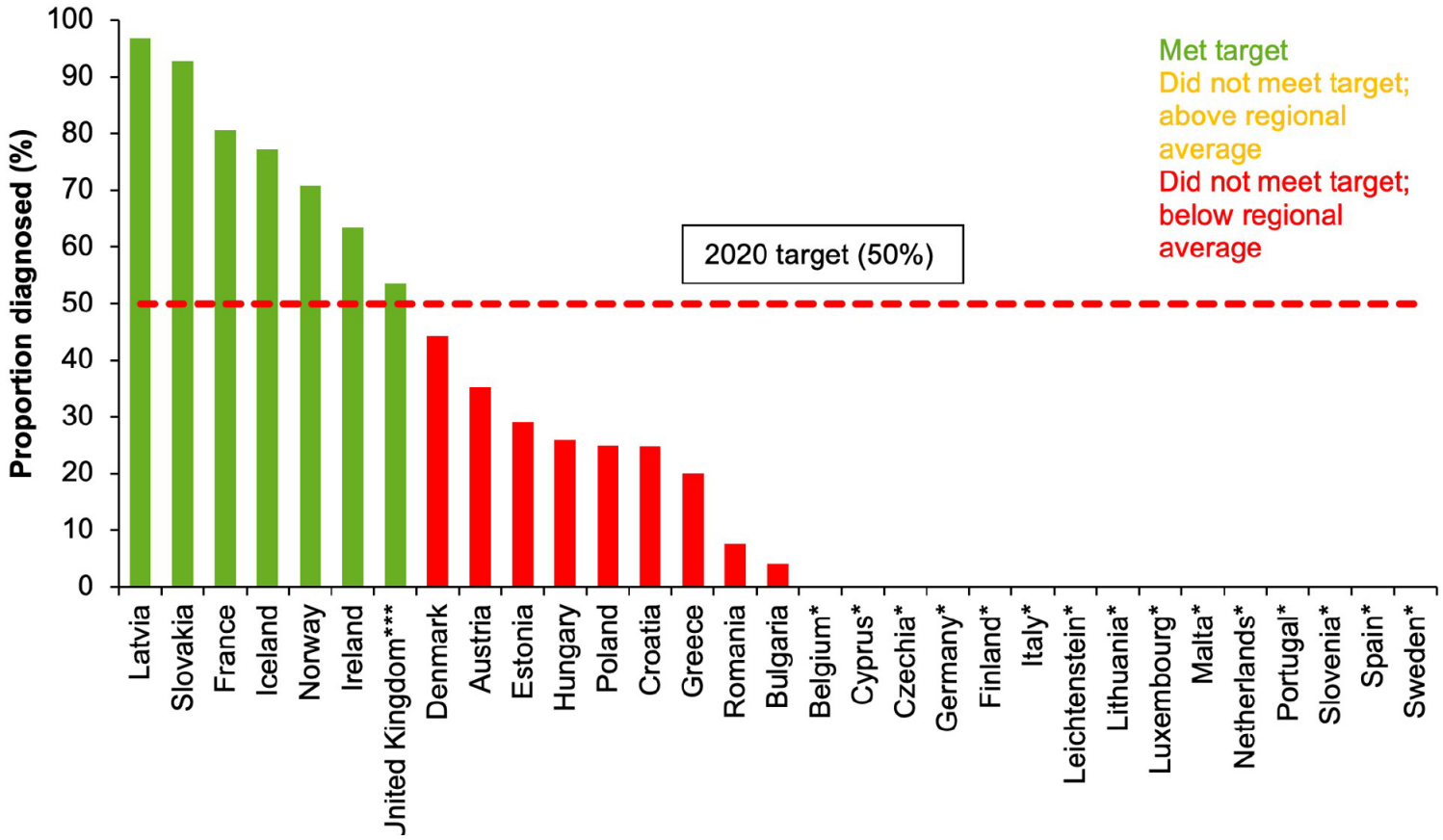
-Asunaprevir/daclatasvir/beclabuvir

Table 1. Core indicators for measuring progress towards the SDG targets and related 2020 targets.

Indicator	WHO European Region Action Plan Target for 2020	WHO GHSS Target for 2020
Prevention		
HBV: Coverage with three doses of the HBV vaccine among 1 year olds in countries that implement universal childhood HBV vaccination	95% vaccinated	90% vaccinated
HCV: Harm reduction for people who inject drugs (PWID) • Coverage of clean needle and syringe programmes (NSP) • Coverage of opioid substitution therapy (OST)	• 200 syringes distributed per PWID per year; • 40% of opioid dependent PWID receiving opioid substitution therapy	200 sterile needles and syringes provided per PWID per year
The continuum of care for HBV and HCV		
Percent of those with chronic infection tested and aware of their diagnosis	50% diagnosed*	30% diagnosed
Percent of those aware of their HBV diagnosis on treatment, among those eligible for treatment** Percent of those aware of their HCV diagnosis started on treatment	75% on treatment/started on treatment***	5 million people receiving HBV treatment 3 million people have received HCV treatment
Percent of those on treatment achieving viral suppression (HBV) or of those on treatment achieving sustained viral response (HCV)	90% achieve viral suppression (HBV) or sustained viral response (HCV)	NA

Example of Criterion 1c: Feasibility

People (%) living with chronic HCV infection who had been diagnosed in EU/EEA countries, 2017(*Sharrock et al, PLOS GPH, 2022*) *no data from ITALY*



Target:

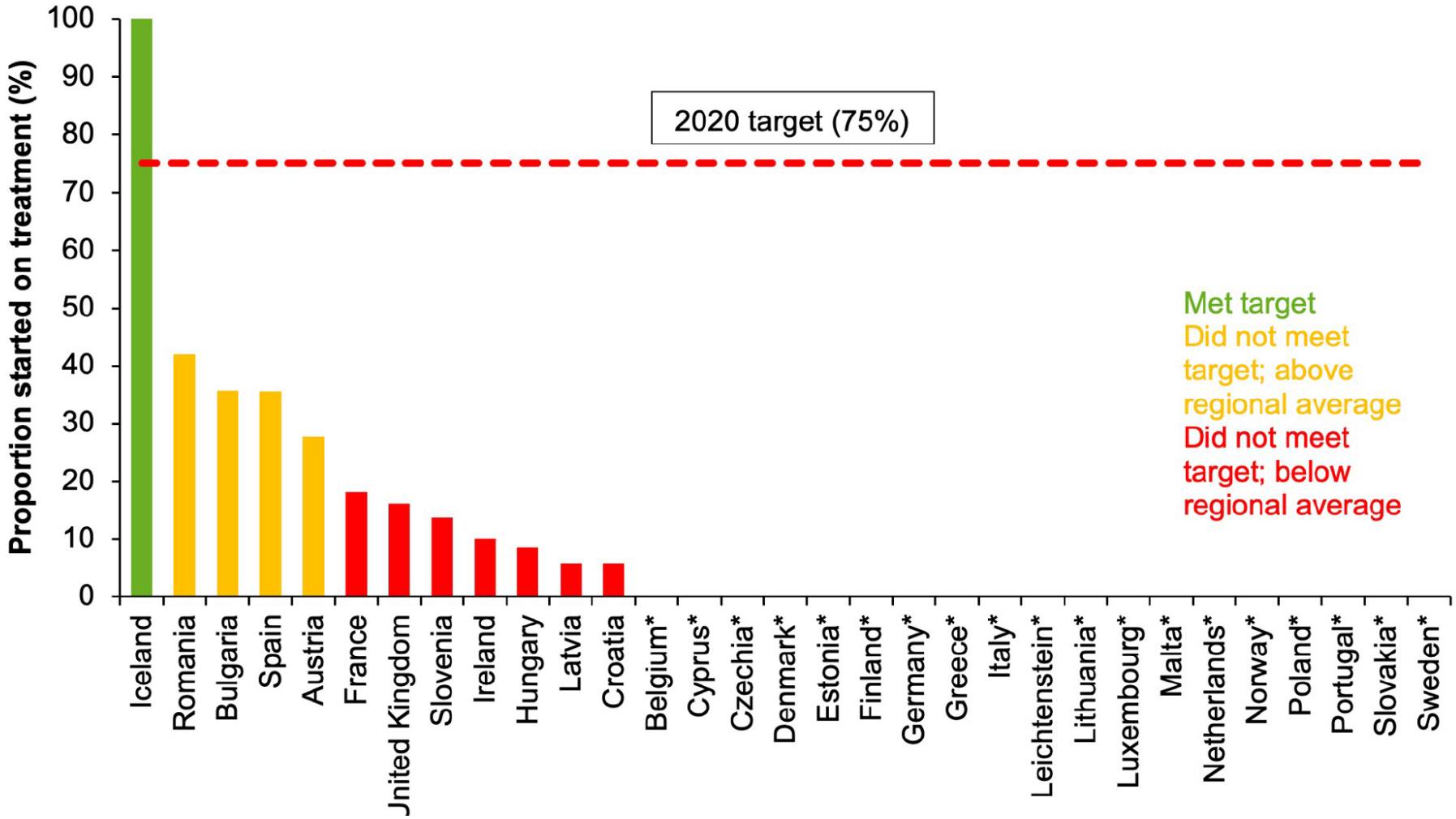
50% diagnosed
75% treated
90% responses

Few countries met the treatment target:

4/12 for HBV
7/16 for HCV

Example of Criterion 1c: Feasibility

People (%) diagnosed with chronic HCV infection who have been started on treatment in 2017 in EU/EEA and the UK (*Sharrock et al, PLOS GPH, 2022*) *no data from ITALY*



Target:

50% diagnosed
75% treated
90% responses

Few countries met the treatment target:

4/12 for HBV
7/16 for HCV

Ministero della Salute

Ma nelle **LINEE DI INDIRIZZO NAZIONALI SUI PERCORSI DIAGNOSTICO TERAPEUTICI ASSISTENZIALI PER L'INFEZIONE DA VIRUS DELL'EPATITE C del 2022** i soggetti senza segni/sintomi non erano elegibili alla terapia antivirale. **No real population-based approach.**

Comunicato stampa n. 21

Data comunicato: **29 aprile 2021**

Epatite C, Speranza e Franco firmano il decreto per lo screening nazionale gratuito: stanziati 70 milioni di euro per il 2020-2021

Il Ministro della Salute, Roberto Speranza, e il Ministro dell'Economia e delle Finanze, Daniele Franco, hanno firmato il decreto per lo Screening nazionale gratuito per il virus dell'Epatite C (HCV). Grazie alle risorse stanziate, pari a circa 70 milioni di euro per il biennio 2020-2021, il provvedimento mira a migliorare la possibilità di diagnosi e trattamento precoce della malattia, nonché ad interrompere la circolazione del virus impedendo nuove infezioni.

"Il decreto approvato oggi rappresenta uno strumento prezioso per il miglioramento della diagnosi precoce dell'epatite C – afferma *il ministro Speranza –. Una terapia tempestiva, grazie ai farmaci di ultima generazione, può portare alla guarigione ed evitare l'insorgenza di nuovi casi. Continuiamo a lavorare ogni giorno per una sanità pubblica sempre più vicina alle persone".*

Le operazioni di screening saranno rivolte a tutta la popolazione nata negli anni tra il 1969 e il 1989, ai soggetti seguiti dai servizi pubblici per le Dipendenze (SerD) e ai detenuti in carcere.

Per un'ampia adesione all'iniziativa, saranno avviate campagne di informazione rivolte alla cittadinanza sull'importanza della diagnosi precoce dell'epatite C e specifiche iniziative di formazione per il personale sanitario coinvolto.

Obstacles: **screen-and treat for non so frequent infections**
(HCV infection but also HBV and HIV)

Pros

Effective and safe **Direct-acting antiviral** (DAA) agents for hepatitis C virus (HCV) infection.

Rapid Test (point –of-care, HCV RNA or, less good, HCV core antigen)

International Recommendations for population-based for access to DAAs

Cons

Prevalence of **«only» about 1-2%** in Italy

Highest prevalenve in EU regions (**South Italy**) and in generations born between **1930s-1950s** (unsafe blood/needles)

In younger generations current/past IVD users predominate

Highest prevalence among drug users, prisoners and migrants

Efficacy is high but effectiveness is uncertain due to a lack of hepatologists and the difficulty of targettng high-risk groups

Interesting examples of screen- and treat for HCV in primay care centers

Australia, *Yee et al, Hepatology Commun, 2022) National observational cohort of **96 clinical services** including specialist clinics and general practice)*

- no restriction on liver disease stage or drug/alcohol use; **diagnostic test available at no cost to all >18yrs and recommended for any history of exposure/liver symptom; general practitioners can prescribe DAA;**
- effectiveness per protocol and by intention to treat were compared overall by patient's characteristics and service type in such as general practice and were high inevery setting and high-risk groups.

Spain, *Martínez-Sanz et al, Madrid, Spain, J Viral Hepat, 2021) 4 primary care centres health*

Cluster randomized trial of a risk-assessment questionnaire and HCV/HIV rapid tests in high-risk subjects vs only the educational intervention in care-givers. Coverage and treatment improved 17 times in the intervention group

Conclusions on real-world effectiveness in «selective» screening

- Targeting sub-populations defined by more than age and gender is sometimes necessary but **coverage evaluation and call/recall system are challenging**;
- Other examples of «selective screening»: **familiar predisposition; HIV-pos individuals; and men-having sex with men**.
- Population **registries** can sometimes allow selective invitations, e.g., women vaccinated against HPV;
- Italy and most EU have health databases and regulations (**PRIVACY**) that do not allow to track sub-populations participation and evaluate screening **coverage** and **EQUITY**;

- Can the extraordinary linkage tools used by MoH for **COVID** vaccine (*Mateo-Urdiales et al, Lancet Infect Dis*) and AIFA for COVID treatment (*Torti et al, Lancet Reg. Health – Europe, 2023*) represent a **precedent**?

Consequences of HPV vaccination and HPV screening

Recommended reading

Published in final edited form as:
Lancet Oncol. 2022 July ; 23(7): 940–949. doi:10.1016/S1470-2045(22)00291-1.

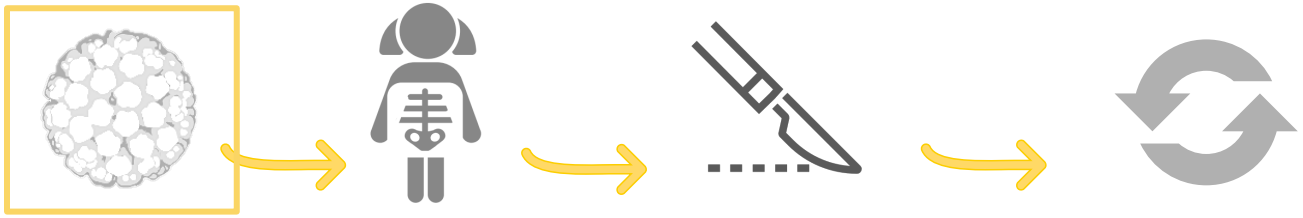
Precancerous cervical lesions caused by non-vaccine-preventable HPV types after vaccination with the bivalent AS04-adjuvanted HPV vaccine: an analysis of the long-term follow-up study from the Costa Rica HPV Vaccine Trial

Jaimie Z Shing, PhD[*],
Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

What is “clinical unmasking” *(By courtesy of J. Shing)*

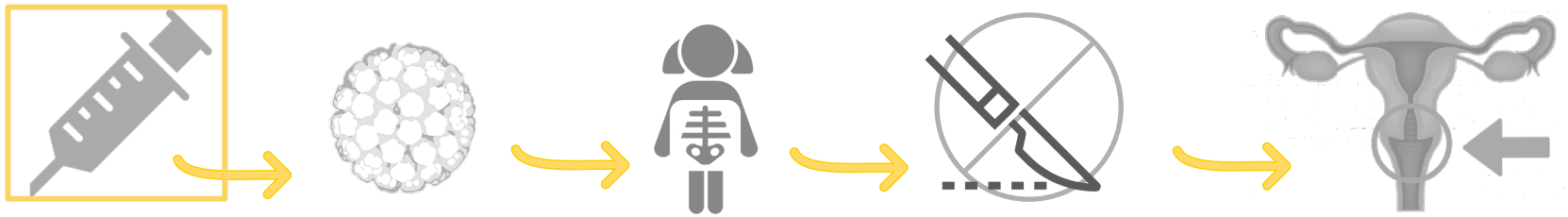
Scenario of a women who is co-infected with HPV 16 and 52

Pre-vaccine era in screened populations (or unvaccinated women in vaccine era)



HPV exposure	Screened (short-term)	Clinical treatment	Long-term
HPV 16 (infected)	Detected (pre-cancer)	Treated	Potentially acquire new HPV infections (but does not progress b/c no intact transformation zone)
HPV 52 (infected)	Undetected	Inherently removed (does not progress)	

Vaccinated women in vaccine era in screened population



Bivalent HPV vaccine	HPV exposure	Screened (short-term)	Clinical treatment	Long-term
Protected against 16/18 (and 31/33/45)	HPV 16 (vaccine-protected)	--	--	--
	HPV 52 (infected)	Undetected	--	Progress to pre-cancer

NCI Costa Rica HPV Vaccine Trial (CVT) and Long-Term Follow-Up

Pre-Specified Aim

To evaluate HPV vaccine efficacy against high-grade cervical lesions attributed to **non-vaccine-preventable** HPV types through 11 years post-vaccination

Our pre-specified hypothesis was that the clinical unmasking phenomenon would be observed in the long-term follow-up period, but NOT in earlier years due to the longer time to progression for non-vaccine-preventable HPV types

An increase in high-grade cervical lesions caused by non-vaccine-preventable types in vaccinated women was NOT observed during shorter term follow up

HPV 16/18 vaccine efficacy against CIN2+ in years 1-4 (mITT cohort)

Rates expressed as per 1,000 women

	HPV Vaccine (N = 3467)		Hepatitis A vaccine control (N = 3492)		Vaccine Efficacy	Absolute Rate Difference
HPV Type	**#**	**Rate (95% CI)**	**#**	**Rate (95% CI)**	**% (95% CI)**	**Δ (95% CI)**
HPV 16/18	38	11 (8, 15)	83	24 (19, 29)	**54% (33%, 69%)**	**-12.8 (-18, 7)**
HPV 31/33/45	21	6 (4, 9)	27	8 (5, 11)	22% (-39%, 56%)	-1.7 (-5, 2)
Non-Preventable Types	43	12 (9, 17)	43	12 (9, 16)	-1% (-54, 34%)	0.1 (-5, 5)
All CIN2+ irrespective of type	102	29 (24, 36)	153	44 (37, 51)	**33% (14%, 48%)**	**-14.4 (-23, -5)**

Shing and Hu et al. Lancet Oncol. 2022.

mITT = modified Intention-to-treat

Clinical unmasking of high grade cervical lesions caused by non-vaccine-preventable types was observed in the CVT long-term follow-up

HPV 16/18 vaccine efficacy against CIN2+ in years 7-11 (mITT cohort)

Rates expressed as per 1,000 women

	HPV Vaccine (N = 2767)		Unvaccinated Control Group (N = 2563)		Vaccine Efficacy	Absolute Rate Difference
HPV Type	**#**	**Rate (95% CI)**	**#**	**Rate (95% CI)**	**% (95% CI)**	**Δ (95% CI)**
HPV 16/18	5	2 (1, 4)	47	18 (14, 24)	**90% (77%, 97%)**	**-17 (-19, -13)**
HPV 31/33/45	14	5 (3,8)	29	11 (8, 16)	**55% (16%, 77%)**	**-6 (-10, -1)**
Non-Preventable Types	61	22 (17, 28)	33	13 (9, 18)	**-71% (-164%, -13%)**	**9 (2, 16)**
All CIN2+ irrespective of type	80	29 (23, 36)	109	43 (35, 51)	**32% (9%, 49%)**	**-14 (-23, -4)**

= -23 per 1,000

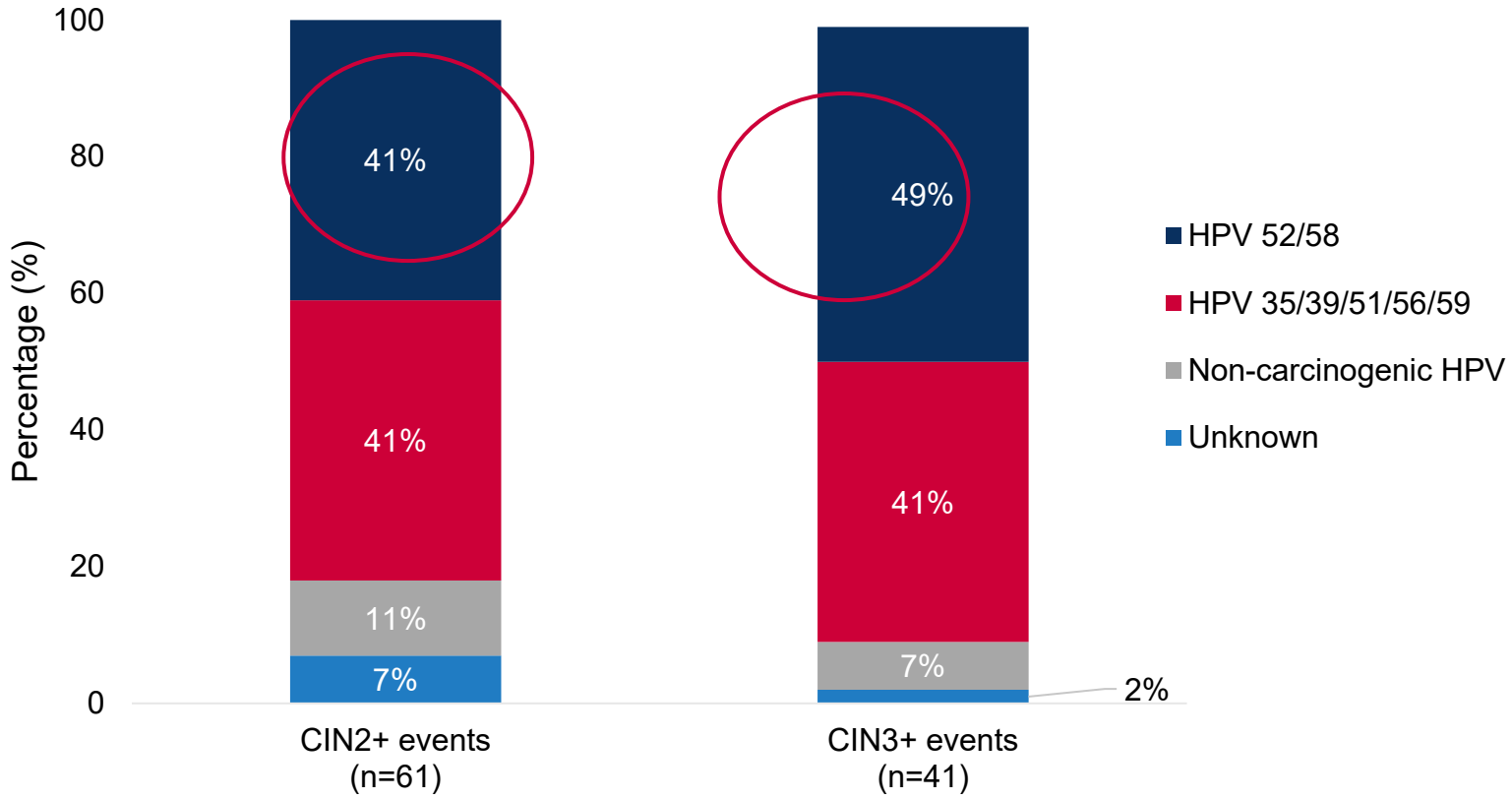
+ 9 per 1,000

Shing and Hu et al. Lancet Oncol. 2022.

mITT = modified Intention-to-treat

A large proportion of the unmasked lesions were caused by HPV types targeted by the nonavalent HPV vaccine

HPV type distribution of unmasked cervical lesions during years 7-11



Shing and Hu et al. Lancet Oncol. 2022.

Important takeaways and things to consider

The HPV vaccine's protection outweighs the additional risk of cervical lesions caused by non-preventable HPV types

Non-vaccine-preventable types have a lower risk of progression to invasive cancer due to their slow growing nature

Increased valency of HPV vaccines may reduce the burden of unmasked lesions in vaccinated populations

Continued cervical cancer screening may reduce the unmasking potential

Cervical cancer screening is moving toward more HPV-based testing (increased specificity) and may aid in detecting HPV infections

Grazie per l'invito e l'attenzione