History of Cervical Cancer Screening

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Head Scientific Committee SCGO
20th SCGO Annual Symposium, 27 November 2021, Hyatt Regency Phnom Penh Hotel

Objectives

To highlight :

- The history of the three methods of cervical cancer screening including Cytology, VIA and HPV test and the recommendations for its use to date.

Outline

I. Burden of cervical cancer in the world and in Cambodia

II. History of cervical cancer screening methods (Pap smear, VIA and HPV test)

III. History of WHO cervical cancer screening recommendations

IV. Conclusion

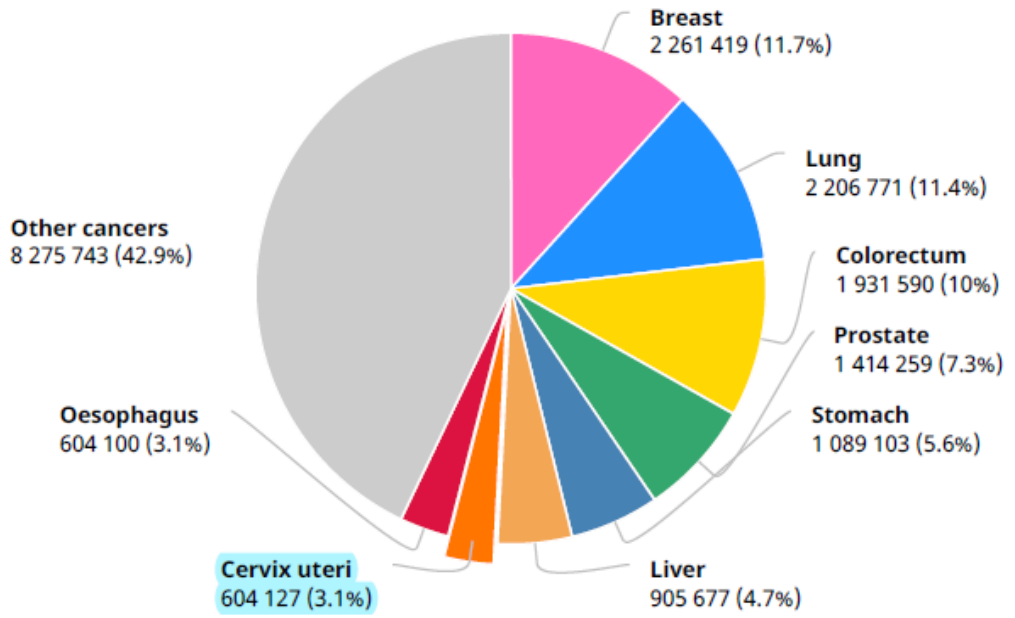
I.
Burden of cervical cancer Worldwide and in Cambodia

Cervical Cancer Worldwide 2020

International Agency for Research on Cancer
World Health Organization

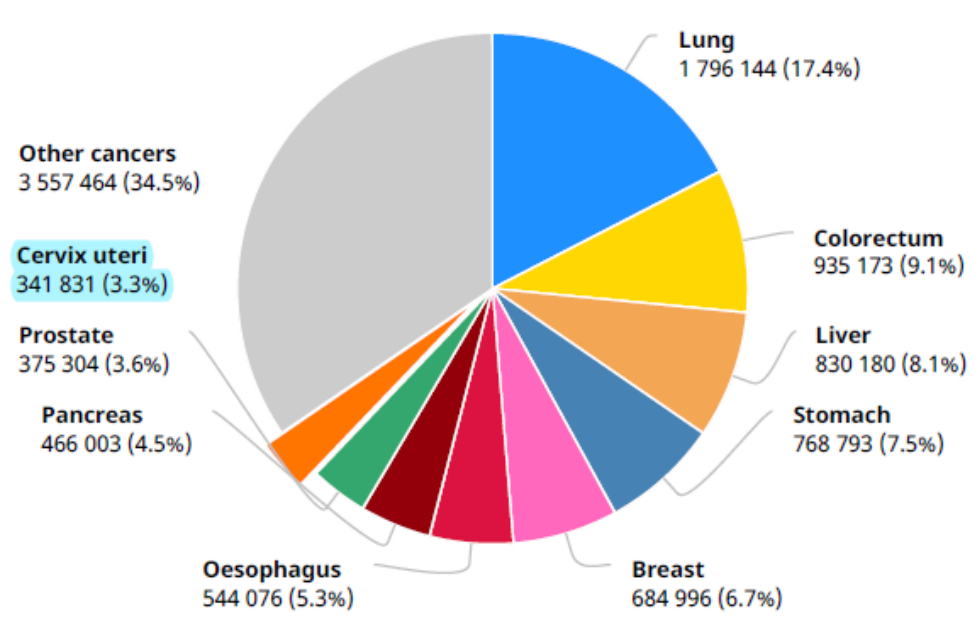
Cervix uteri
Source: Globocan 2020

Number of new cases in 2020, both sexes, all ages



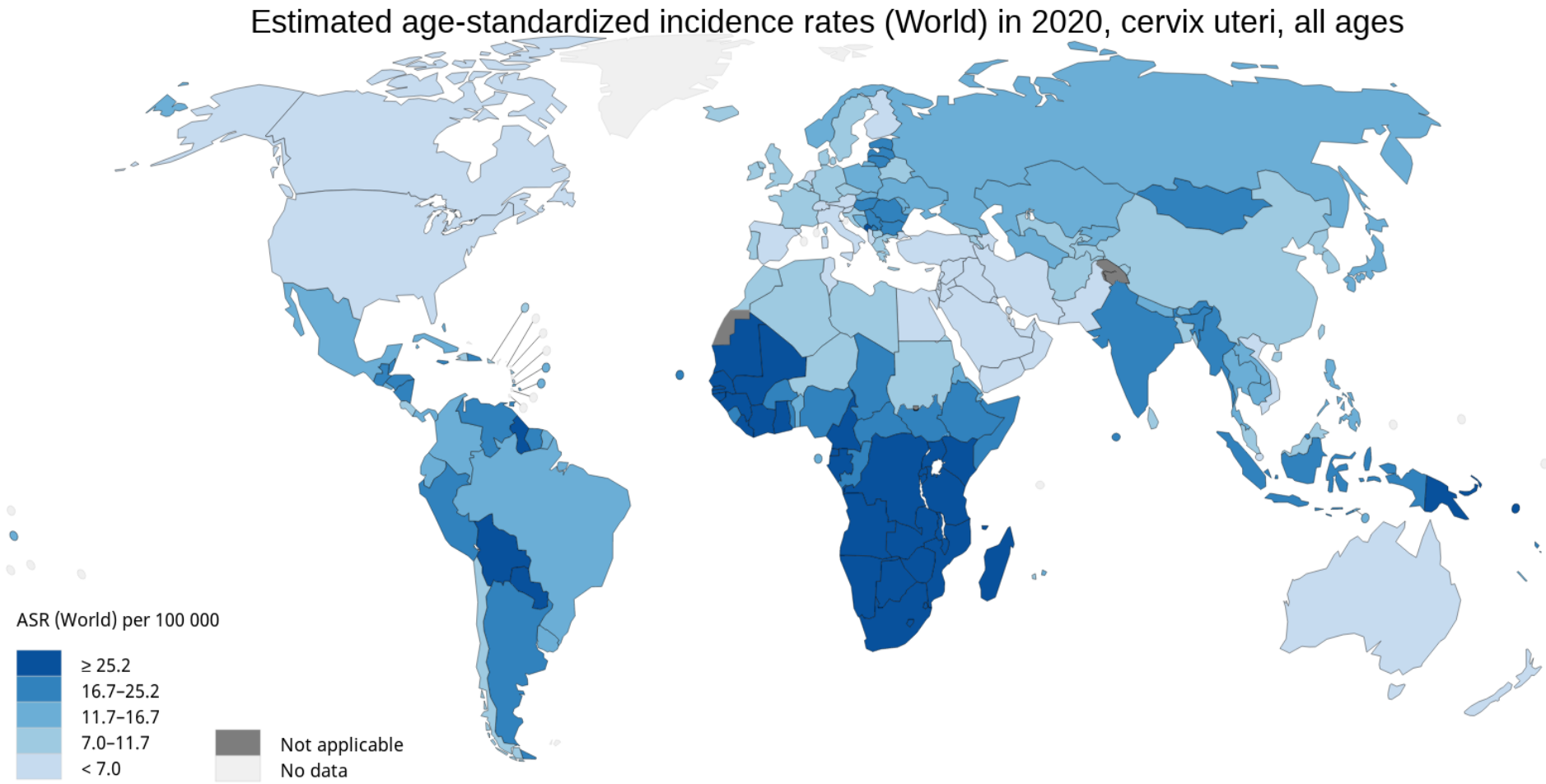
Total: 19 292 789 cases

Number of deaths in 2020, both sexes, all ages



Total: 9 958 133 deaths

Incidence of Cervical Cancer Worldwide 2020



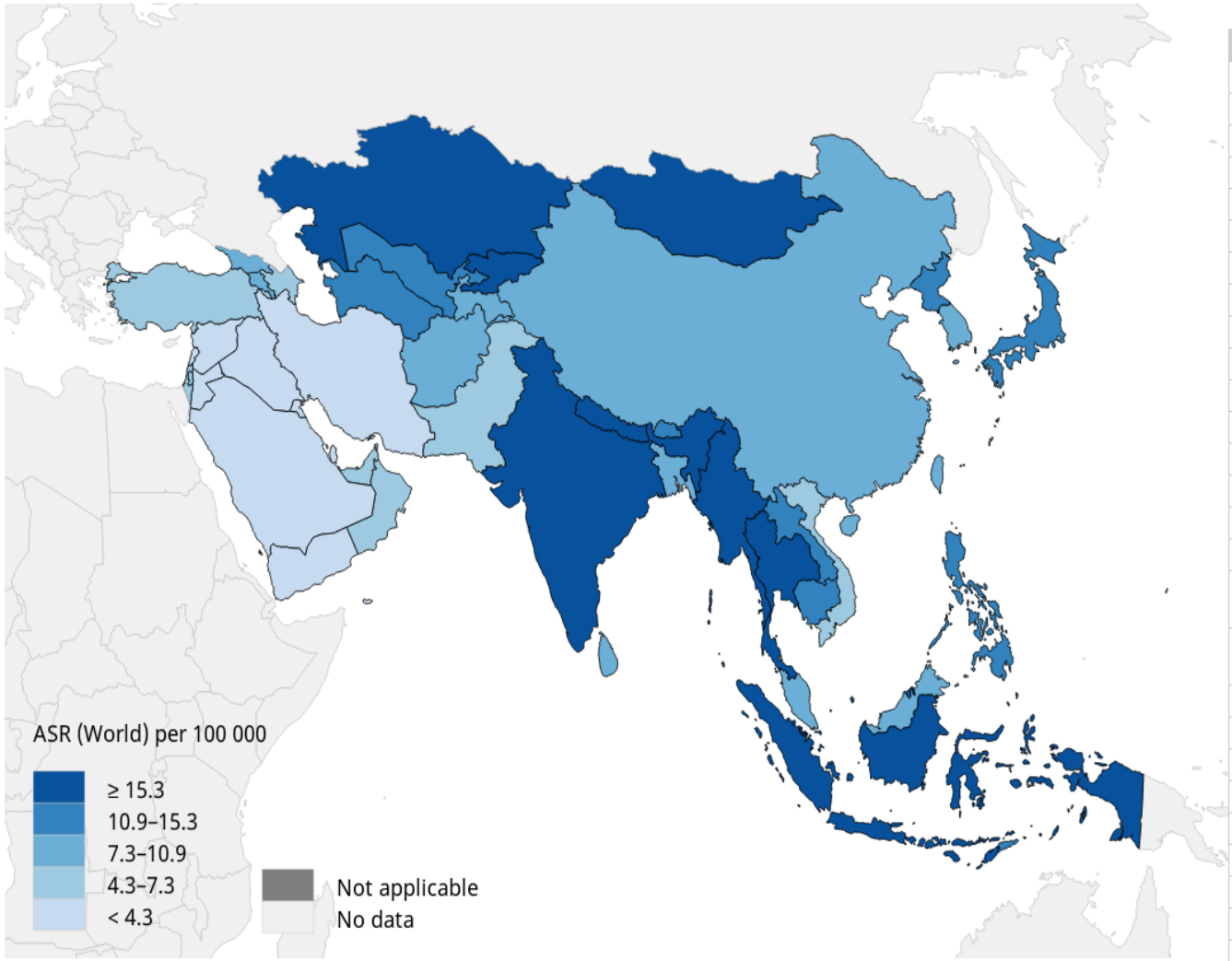
Highest incidence:

- Sub-Saharan Africa
- South America
- South-Eastern Asia
- Melanesia

Data source: GLOBOCAN 2020
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

Asia Cervical Cancer incidence 2020

Estimated age-standardized incidence rates (World) in 2020, cervix uteri, all ages



Population	ASR(W)
Maldives	24.5
Indonesia	24.4
Myanmar	22.6
Brunei Darussalam	20.8
Mongolia	19.7
India	18.0
Thailand	16.4
Nepal	16.4
Kazakhstan	15.7
Kyrgyzstan	15.4
Philippines	15.2
Japan	15.2
Turkmenistan	14.9
Bhutan	14.2
Cambodia	14.0
Timor-Leste	14.0
Lao People's Democratic Republic	12.0
Korea, Democratic Republic of	11.2
Uzbekistan	11.0
China	10.7
Bangladesh	10.6
Georgia	10.6
Afghanistan	10.4
Malaysia	10.2
Sri Lanka	9.2
Tajikistan	8.2
Korea, Republic of	8.1

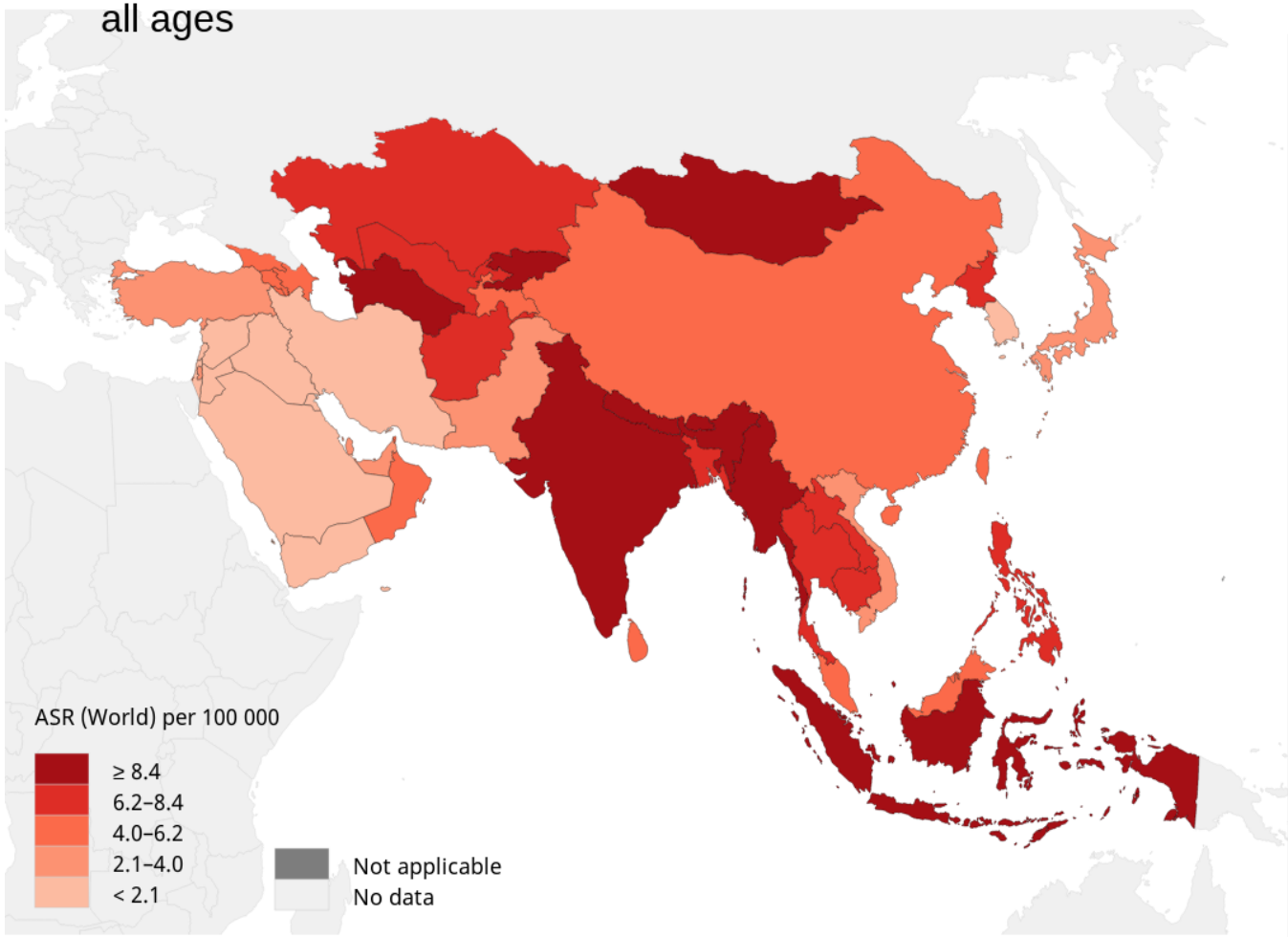
Population	ASR(W)
Armenia	7.8
Singapore	6.9
Azerbaijan	6.7
Viet Nam	6.6
Oman	6.5
United Arab Emirates	6.2
Pakistan	6.1
Israel	4.9
Gaza Strip and West Bank	4.8
Turkey	4.8
Qatar	4.1
Bahrain	3.9
Lebanon	3.4
Jordan	2.9
Syrian Arab Republic	2.8
Saudi Arabia	2.8
Kuwait	2.8
Yemen	2.5
Iran, Islamic Republic of	2.3

Data source: GLOBOCAN 2020
Graph production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization

Asia: Cervical Cancer mortality 2020

Estimated age-standardized mortality rates (World) in 2020, cervix uteri, all ages

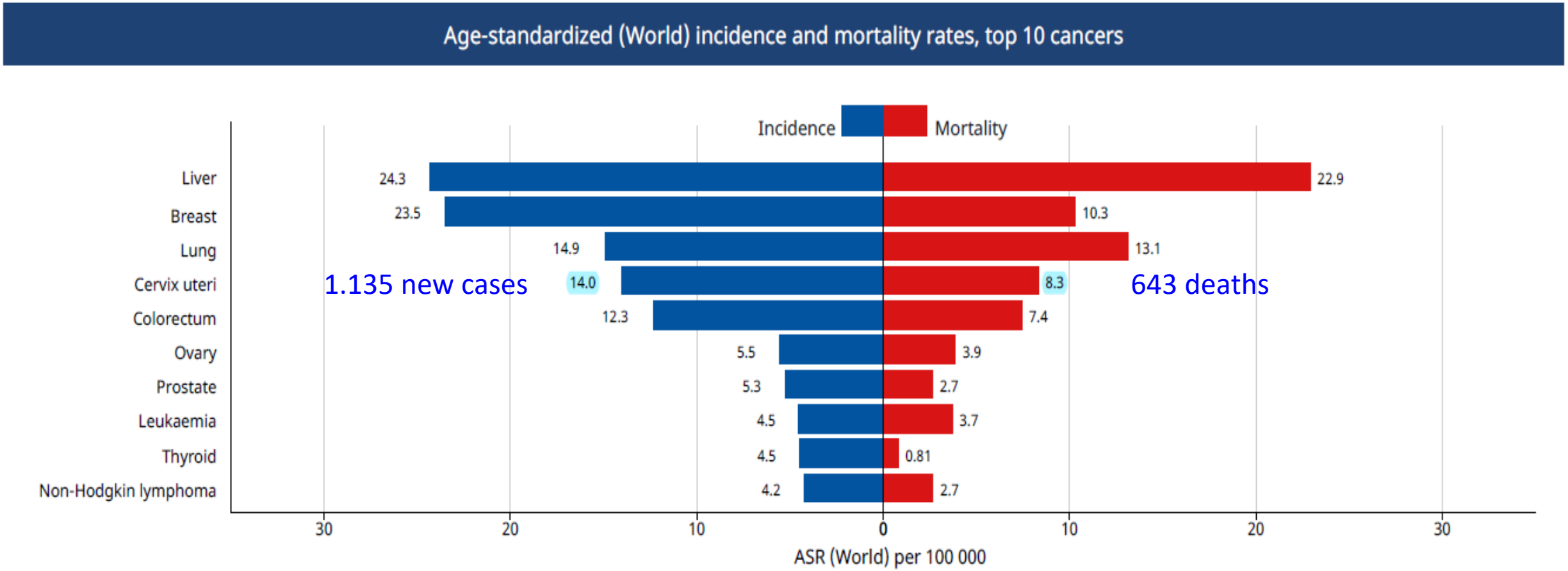


Population	ASR(W)
Myanmar	14.4
Indonesia	14.4
Maldives	14.1
Mongolia	11.6
India	11.4
Nepal	11.1
Kyrgyzstan	9.1
Turkmenistan	8.9
Timor-Leste	8.8
Bhutan	8.4
Cambodia	8.3
Philippines	7.9
Afghanistan	7.6
Thailand	7.4
Kazakhstan	7.2
Lao People's Democratic Republic	6.7
Uzbekistan	6.7
Bangladesh	6.7
Korea, Democratic Republic of	6.5
Georgia	5.9
Malaysia	5.8
Brunei Darussalam	5.7
China	5.3
Tajikistan	5.2
Sri Lanka	4.9
Armenia	4.6
Oman	4.2

Population	ASR(W)
Azerbaijan	4.0
Pakistan	4.0
United Arab Emirates	3.9
Viet Nam	3.4
Gaza Strip and West Bank	3.4
Singapore	3.3
Japan	2.9
Qatar	2.9
Bahrain	2.4
Turkey	2.2
Lebanon	2.0
Israel	2.0
Jordan	1.9
Syrian Arab Republic	1.9
Korea, Republic of	1.8
Yemen	1.8
Kuwait	1.8
Saudi Arabia	1.6
Iraq	1.5

Data source: GLOBOCAN 2020
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

Cambodia Cervical Cancer 2020



Problems of Cancer 19th and 20th Century (1)

- Cancer is AN OLD DISEASE
- Cancer is A FEMALE DISEASE
  - "Woman's nature": Disease of the reproductive organs
  - "*La femme est une malade*": Jules Michelet, French historian
- 1800, Herbert Snow: "a life of hard work", too frequent child-bearing and prolonged lactation
- 1907, Herbert Spencer: " mothers of large families", disease of poverty
- William Sinclair: "The chronically overworked and underfed, poor, worried, reposeless, drained by lactation…"
- Walter H. Walshe: associated with menopause (1846)
- Others: Cancer was a "Hereditary" and Incurable disease.

Source: Gender and Cancer in Britain, 1860–1910, The Emergence of Cancer as a Public Health Concern: Ornella Moscucci, DPhil, BSc 2005

Problems of Cancer 19th and 20th Century (2)

- 1830 - 1840 in and around Paris:
  - 9.118 deaths from all cancer.
  - 2.996 uterine cancer cases (Corpus and cervix)
- 1900: in the US: 40,000 women die from cervical cancer
- 1907 in England and Wales:
  - nearly 4,000 adult women die from uterine cancer than of cancer of any other part of the body" Obstetrician Herbert ».

- Over rising cancer mortality stimulated efforts to understand and control the disease

Source: Gender and Cancer in Britain, 1860–1910, The Emergence of Cancer as a Public Health Concern: Ornella Moscucci, DPhil, BSc 2005
It Happened Here: Dr. Georgios Nikolaou Papanicolaou, https://healthmatters.nyp.org/georgios-nikolaou-papanicolaou/amp/

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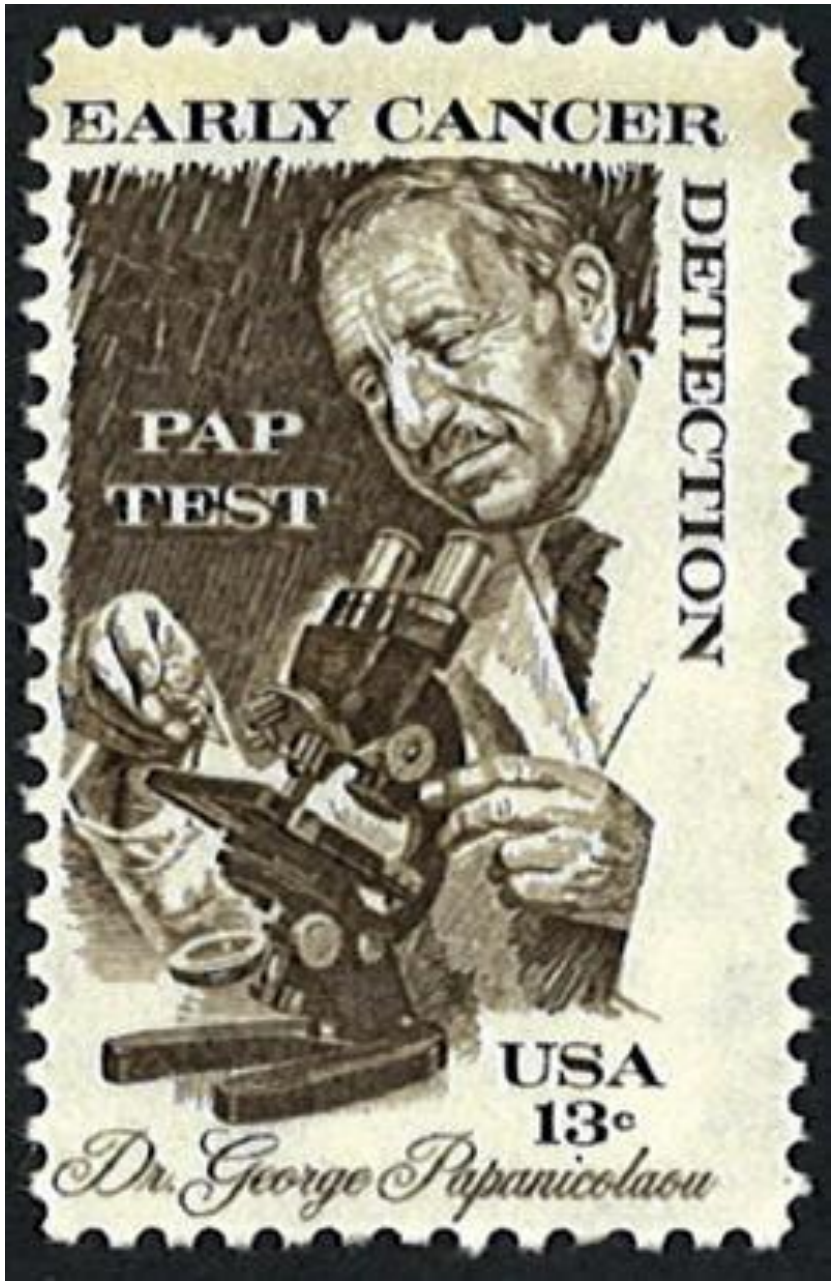
II.
History
of cervical cancer screening

1. Cytology or Pap test

George Papanicolaou



George Papanicolaou discovered Pap smear

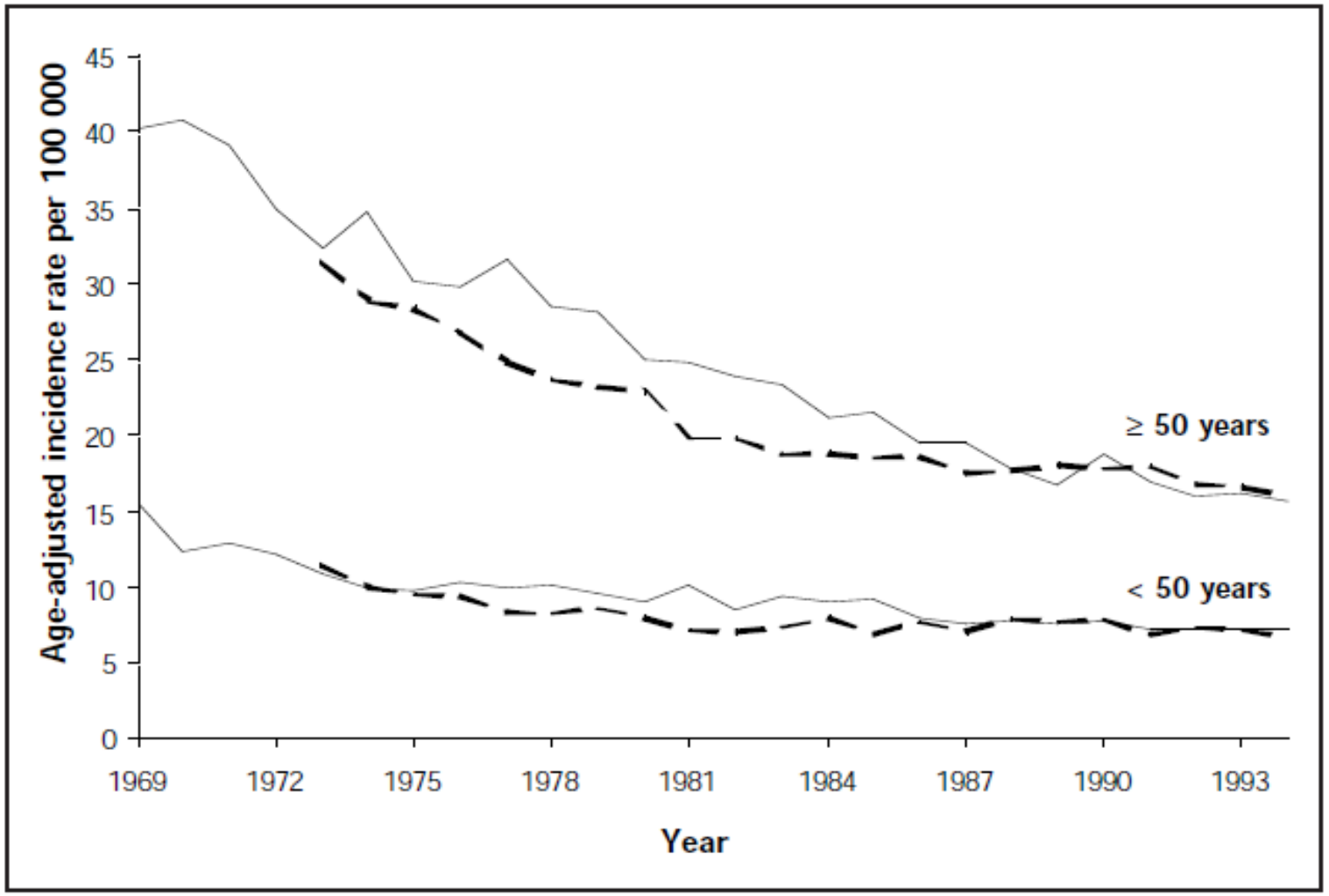
- 1916: Study with guinea pigs: Vaginal Cytology associate with physiologic change

- 1920: Study on Human: Discovered cancer cells in vaginal sample
- 1927-1929: George Papanicolaou and Aurel Babes determine cancer can be detected by inspecting cervical cells.
- 1943: His work in Collaboration with pathologist Herbert Traut published "Diagnosis of uterine cancer by the vaginal smear", become well recognized.

- 1950: Cytology first introduced in the US
- 1960: Widespread use

Source: The Great Success And Enduring Dilemma Of Cervical Cancer Screening, 2015

Cervical cancer Incidence and Mortality in the US and Canada 1969-1993



Introduction of Pap test

(Benard VB et al. 2014)

- 1950 : in the US
- Late 1950: in Canada

Fig. 3: Annual incidence rates (per 100 000 women) of invasive cervical cancer among women less than 50 years of age and among those 50 years or older in Canada (solid line) and in the United States (broken line). Rates are standardized according to age distribution of Canadian population in 1991.

Source: Cancer Bureau, Population and Public Health Branch, Health Canada, and the National Cancer Institute Statistics, Epidemiology, and End Results (SEER) program.

Cervical cancer: Epidemiology, prevention and the role of humanpapillomavirus infection, Eduardo L. Franco 2001

Pap Smear in developing countries

Women screened positive with cytology are investigated with colposcopy and directed biopsies to diagnose high-grade CIN and treated with LEEP for CIN in a 3-visit strategy (Screen, Diagnostic and Treat)

- Middle-income countries have performed suboptimally in reducing cervical cancer burden due to complexity of the test, lake of laboratories, human resources and well-organized screening programs…
- This led to the evaluation of alternative screening approaches such as VIA for Screen-and-Treat" approach with single-visit.

Screening for Cancer in Low- and Middle-Income Countries R. Sankaranarayanan, MD 2014]

Successful Cytology screening

- The successes of cytology programs in reducing the burden of cervical cancer in selected countries and regions:
  - Organized cytology screening programs
  - Repeated screening over short intervals (annual, biennial and triennial)

- However, the successes of cytology programs must be juxtaposed with rising of cervical cancer incidence and mortality rates in the other parts of the world.

Limitation of Pap smear

- *WHO 2006,* Wide variability in sensitivity for detection of pre-cancer and cancer:
  - Under the best conditions in developed countries or research settings, conventional cytology can detect up to 84% of precancer and cancer.
  - Under poor conditions its sensitivity can be as low as 38%.
- Subjective nature of the cytological interpretation.
- ASCUS led to over-referral to colposcopy and potentially over-treatment

- A single negative test does not provide long-term reassurance that cancer will not develop and has major medical, economic and legal implications or leading reason for medical malpractice litigation.

- Thus, it is important to recognize the limitations of cytology-based programs, which arguably have reached their maximum impact for global cervical cancer prevention.

2. Visual Inspection with Acetic acid (VIA)

- VILI, Visual inspection of cervix after application of Lugol's iodine , first method used for cervical cancer screening was introduced by Dr. Walter Shiller in 1930-1940.
- Discontinued after the advent of cytology

- VIA reemerged and become an alternative method for cervical cancer screening in low resource setting due to contraints of implementing cytology-based.

Cervical cancer screening in developing countries, Report of a WHO Consultation 2002

Sensitivity and Specificity of VIA

Table 1-4. Test Qualities of VIA when Performed as Primary Screening Method in Low-Resource Settings

STUDY	COUNTRY	NUMBER OF CASES	DETECTION OF HGSIL[a] AND CANCER	
			SENSITIVITY[b]	SPECIFICITY[b]
Belinson (2001)	China	1,997	71%	74%
Denny et al. (2000)	South Africa	2,944	67%	84%
Sankaranarayanan et al. (1999)	India	1,351	96%	68%
University of Zimbabwe/JHPIEGO (1999)	Zimbabwe	2,148	77%	64%
Sankaranarayanan et al. (1998)	India	2,935	90%	92%
Megevand et al. (1996)	South Africa	2,426	65%	98%
Sankaranarayanan and Wesley (unpublished)	India	2,462	84%	90%
Sankaranarayanan et al. (2004)	India	56,939	76.8%	85.5%

[a] HGSIL = high-grade squamous intraepithelial lesion

[b] Estimated from the number provided in the manuscript and does not reflect adjustment(s) for verification bias.

Adapted from: Belinson et al. (2001); Denny et al. (2000); Megevand et al. (1996); Sankaranarayanan et al. (1999); Sankaranarayanan et al. (1998); Sankaranarayanan and Wesley (unpublished); and University of Zimbabwe/JHPIEGO Cervical Cancer Project (1999).

Screening using VIA and treatment with cryotherapy

A demonstration project in six African countries:

(Malawi, Madagascar, Nigeria, Uganda, the United Republic of Tanzania, and Zambia)

WHO 2012

Figure 3. Summary of the final results of the demonstration project in six countries

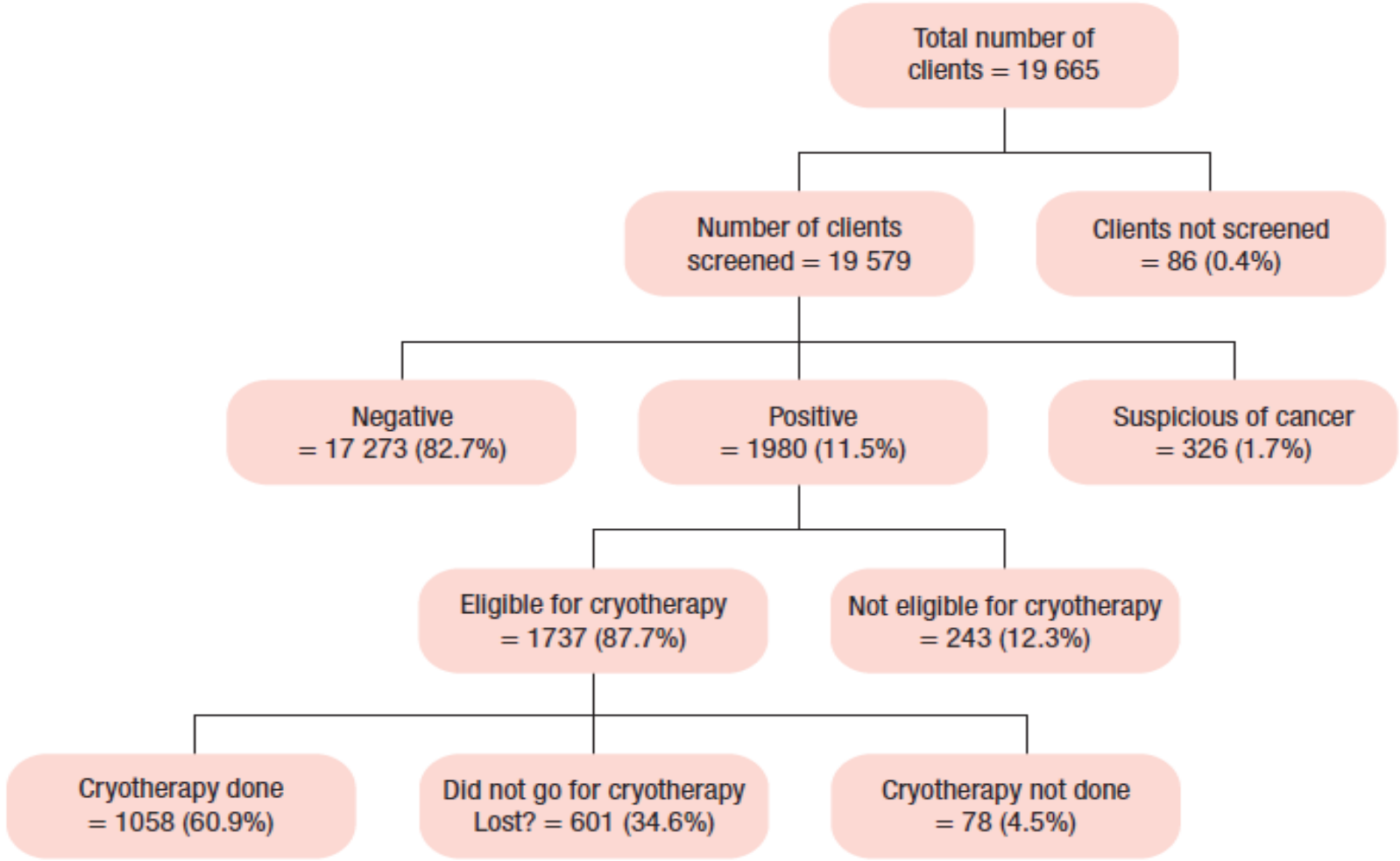
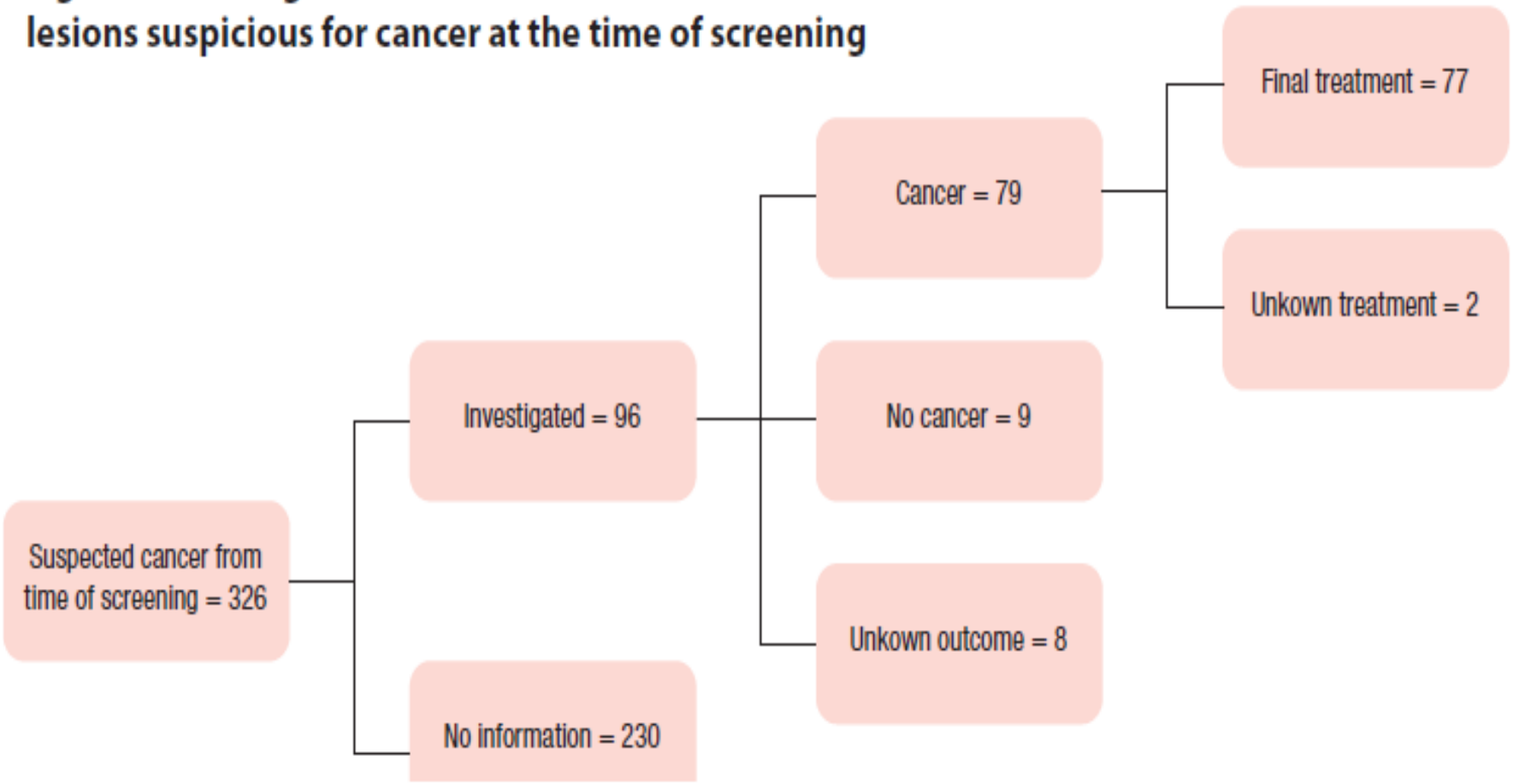


Figure 4. Investigation and treatment outcomes of clients who had lesions suspicious for cancer at the time of screening



Study conclude that VIA is an alternative simple and safe, simplify the process and render it feasible and acceptable to women and providers in low-resource settings.

Advantages of VIA

- Application of 3–5% acetic acid, minimal test and consumables
- Identify Acetowhite lesions 1mn after
- Naked-eye examination of the uterine cervix under bright light
- Easy to perform, safe and affordable.
- Can be performed at all levels of the health-care system and all levels of health care providers and in particular low-resource settings
- Short period of training in cryotherapy as an outpatient procedure
- See and Treat in one visit

Limitation of VIA

- Subjective: high variability of results between providers.
- Lack of a diagnostic step can result in false-positive results and overtreatment
- Not appropriate for many post-menopausal women.

- *Jhpiego 2005: VIA* Sensitivity 65-96% ; Specificity 64-98% in detection of HSIL.
- M. Arbyn 2020: VIA Sensitivity 22-91%; Specificity 47-99%.

VIA proved to be a cost-effective approach in low-resources setting.

*Cervical cancer screening in developing countries, Report of a WHO Consultation 2002

3. Human Papillomavirus

Harald zur Hausen (1936-)

Dr. Harald zur Hausen (Source: German Cancer Research Center)

Harald zur Hausen discovered Human Papillomavirus (HPV)

Papillomavirus caused cancer in animals and commonly produced warts in the genital tract

- 1970: Hausen hypothesized that HPV might be responsible for cervical cancer.
- 1980 -1982: Discovered HPV 6 and 11 in wart samples.
- 1983 -1984: Discovered HPV 16 and 18, in the CxCa tumor samples

Harald zur Hausen (1936-)By: Grace Kim Published: 2017-07-24

HPV test in the US

- 1999: First introduced in the US
  - As Triage method for cytology positive with ASCUS (*Saraiya M et al. 2013).*
  - Women aged 30 years and older who test positive for high-risk HPV will need to be referred for colposcopy and biopsy.
  - Advantage in reducing the number of colposcopies
- 2003: Co-testing with Cytology:
  - Extend interval to every 3 years if both tests have negative results.
- 2014: Primary screening for women over the age of 25 years

Source: [Point-Counterpoint: Cervical Cancer Screening Should Be Done by Primary Human Papillomavirus Testing with Genotyping and Reflex Cytology for Women over the Age of 25 Years, Mark H. Stoler, R. Marshall Austin, Chengquan Zhao]

Introduction of HPV test in Mexico

- Study in rural Mexico, 2006-2007: 12 330 women aged from 25 to 65 years were randomly allocated to HPV screening and 12 731 to cervical cytology.
  - HPV testing identified 117·4 women with CIN 2 or worse per 10 000 and 30.4 invasive cancer per 10 000.
  - Cytology identified 34·4 women with CIN 2 or worse per 10 000 and 7.2 invasive cancer per 10 000.

- HPV test was found to detect 3.4 times CIN 2 or worse and 4.2 times more invasive cancer than when using the Pap test.
- 2009-2010 Expansion to 21 states, 32 states.

Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial. Prof Eduardo Lazcano-Ponce, PhD. Lancet 2011]

HPV testing in China

- China study 2015- 2017 included 1,160,981 women aged 35–64 years of whom 833,469 underwent HPV testing and 327,512 underwent cytology:
  - HPV testing detected 3 860 CIN2+ (5.5 per 1000) and
  - Cytology detected 1 222 CIN2+ (4.4 per 1000).

- HPV testing could improve CIN2+ detection rate supporting the introduction of primary screening with high-risk HPV testing in China and similar middle-income countries.

Real-world effectiveness of primary screening with high-risk human papillomavirus testing in the cervical cancer screening programme in China: a nationwide, population-based study. Yanxia Zhao 2021

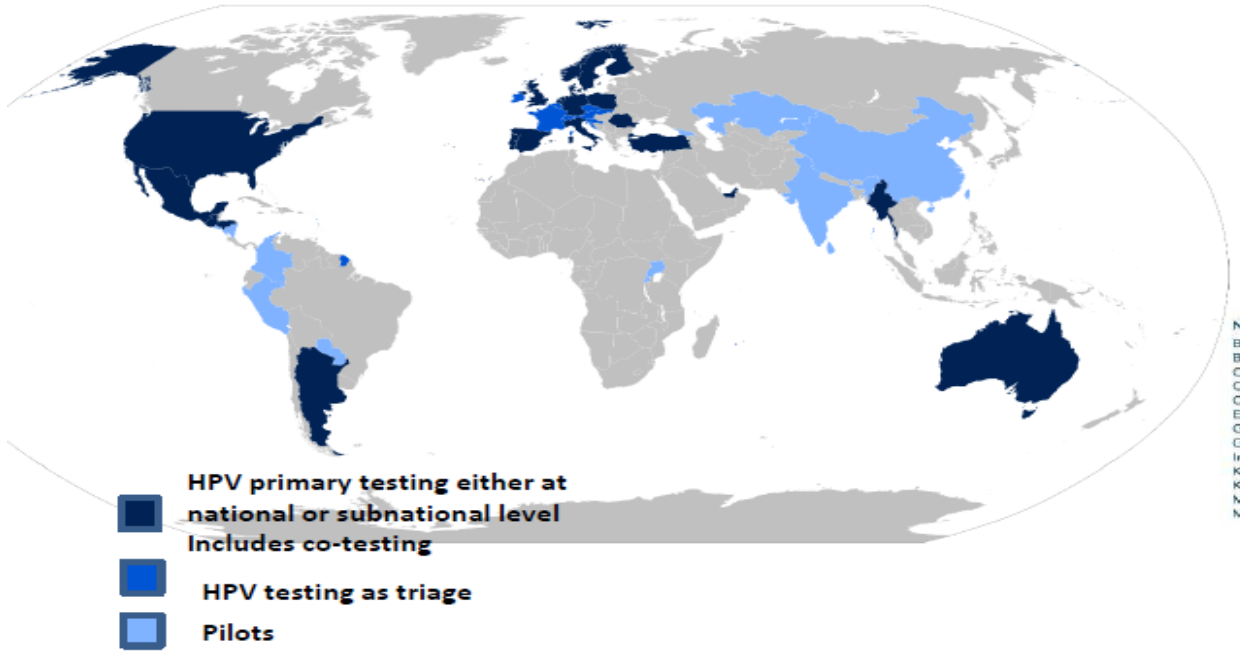
Advantages of HPV test

- HPV testing provides an Objective outcome, highly Reproducible, more Easily monitored.
- HPV testing is more sensitive and reliable for detection of precancerous lesions and cervical cancer than cervical cytology

- HPV negative means that a woman are very low risk of precancer for next several year (Natural history of HPV infection).

Countries Introducing Screening with HPV Testing and VIA Testing

Global Progress in HPV DNA Testing for Cervical Cancer Screening Status: June 2019



Global Progress in Visual Inspection (VIA) for Cervical Cancer Screening Status: June 2019

National programs

Bangladesh, Bolivia, Cambodia, China, Colombia, El Salvador, Guatemala, Guyana, Indonesia, Kenya, Kiribati, Malawi, Morocco, Mozambique, Nicaragua, Panama, Paraguay, Peru, Philippines, Rwanda, Suriname, Tanzania, Thailand, Uganda, Vietnam, Zambia

Pilot programs

Angola, Benin, Bhutan, Botswana, Burkina Faso, Cameroon, Côte d'Ivoire, Ethiopia, Gambia, Ghana, Grenada, Guinea, Haiti, Honduras, India, Lesotho, Madagascar, Maldives, Mali, Mauritania, Myanmar, Namibia, Nepal, Niger, Nigeria, Republic of Congo, Senegal, Sierra Leone, South Africa, St. Lucia, Sudan (North), Togo, Turkey, Vanuatu, Zimbabwe

**[41] Work in progress, some geographical regions not fully updated

Data sources: Cervical Cancer Action, HPV Information Centre, Chrysostomou 2018, Personal comunications

PATH

3.

History of WHO cervical cancer screening recommendations

Frequency of Pap test

Table 1-2. Reduction in Cumulative Cervical Cancer Rate with Different Frequencies of Screening

FREQUENCY OF SCREENING* IN YEARS	REDUCTION (%) IN CUMULATIVE RATE
1	93.5
2	92.5
3	90.8
5	83.6
10	64.1

* Screening all women age 35–64 *who have had at least one previous negative Pap smear.*

Source: IARC 1986.

WHO 1992

- Cytology:
- Stepwise approach for cost-effectiveness based on resources available:
  - Target group : 40 years
  - Resources limited : Once in her lifetime
  - Resources available : Every 10y , every 5y (35-55y)
  - Resources are high : first extend to 25y and 60y
  - Additional resources : Every 3 years for 25-60y

Source: *Cervical Cancer Screening Programmes: Managerial Guidelines*. Geneva: World Health Organizations (1992) Miller AB.

WHO 2006

- Cytology is recommended for large-scale cervical cancer screening programs, if sufficient resources exist.

- HPV DNA test in conjunction with cytological (sufficient resources exist)
- HPV DNA tests as primary screening methods (only in pilot projects)

  (Not before 30 years of age)

- Visual screening methods (VIA and VILI) only in pilot projects.

Source: WHO Comprehensive cervical Cancer Control A guide to essential practice 2006

WHO 2013-2014

Cytology, HPV test and VIA are the 3 main methods of cervical cancer screening.

VIA become most recommended for LMIC

- Screen, Diagnostic and Treat: Screen-positive women are investigated with colposcopy and directed biopsies to diagnose high-grade CIN and treated with LEEP in a 3-visit strategy.
- The Screen-and-Treat approach eliminates diagnostic step and extra visits:
  - One initial test positive:
    - VIA+ follow by Cryotherapy
  - Two tests positive:
    - HPV test+ and VIA+ follow by Cryotherapy

- *WHO* ***Comprehensive Cervical Cancer Control*** *A guide to essential practice 2014*
- ***WHO*** *Comprehensive cervical cancer prevention and control: a healthier future for girls and women 2013*
- WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention 2013

WHO 2013- 2014

- Target women :
  - 30–49 years old
  - Can be extended age <30 if high risk for CIN2+.

- Interval of screening:
  - VIA or cytology : Interval of 3 to 5 years.
  - HPV testing: interval of 5 years
  - Cytology every 3 years

  - At least once for every woman in a lifetime

- *WHO C**omprehensive Cervical Cancer Control** A guide to essential practice 2014*
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WHO 2021

Screening and treatment approaches

- In the **"screen-and-treat approach"**, the decision to treat is based on a positive primary screening test only.
- In the **"screen, triage and treat approach"**, the decision to treat is based on a positive primary screening test followed by a positive second test (a "triage" test), with or without histologically confirmed diagnosis.

WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition 2021

Summary recommendation for the general population of women

WHO suggests using either of the following strategies for cervical cancer prevention among the general population of women:

- HPV DNA detection in a **screen-and-treat** approach starting at the **age of 30 years** with regular screening **every 5 to 10 years**.
- HPV DNA detection in a **screen, triage and treat** approach starting at the **age of 30 years** with regular screening **every 5 to 10 years**.

Summary recommendation for women living with HIV

WHO suggests using the following strategy for cervical cancer prevention among women living with HIV:

- HPV DNA detection in a **screen, triage and treat** approach starting at the **age of 25 years** with regular screening **every 3 to 5 years**.

WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition 2021

Cytology, HPV test and VIA remains the 3 main methods of cervical cancer screening

HPV test is recommended as primary screening method

Table 2.2. The seven algorithms considered

Screen-and-treat approaches:	
1	VIA as the primary screening test, followed by treatment
2	HPV DNA detection (self- or clinician-collected) as the primary screening test, followed by treatment
Screen, triage and treat approaches:	
3	Cytology as the primary screening test, followed by colposcopy triage, followed by treatment
4	HPV DNA detection as the primary screening test, followed by HPV16/18 triage (when already part of the HPV test), followed by treatment, and using VIA triage for those who screen negative for HPV16/18
5	HPV DNA detection as the primary screening test, followed by VIA triage, followed by treatment
6	HPV DNA detection as the primary screening test, followed by colposcopy triage, followed by treatment
7	HPV DNA detection as the primary screening test, followed by cytology triage, followed by colposcopy and treatment

WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition 2021

4. CONCLUSION

- Methods of cervical cancer screening used with flexibility depending to the resources available in different settings of each country are key of success.

- Evolution of screening methods lead to:
  - improvement the quality of test, more accurate, faster and least expansive and accessible worldwide.
  - support to the WHO Global Strategy for the Elimination of Cervical Cancer.