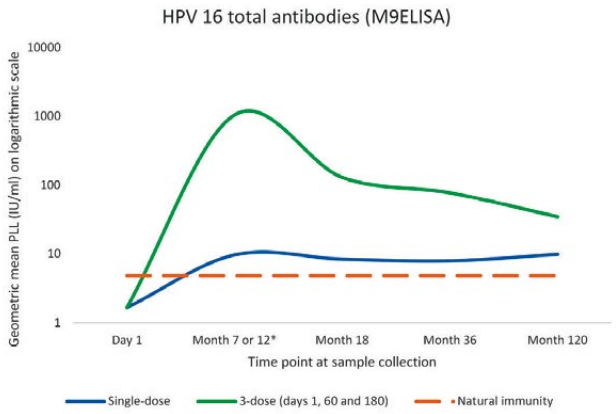
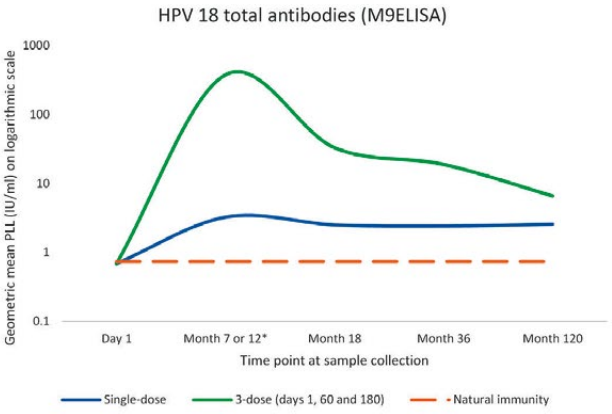
IARC's Indian HPV vaccine study has shown that the efficacy of a **single dose** against persistent **HPV 16 and 18** infections was as high as that of three doses due to high and durable antibody response in the single dose recipients 10 years post-vaccination



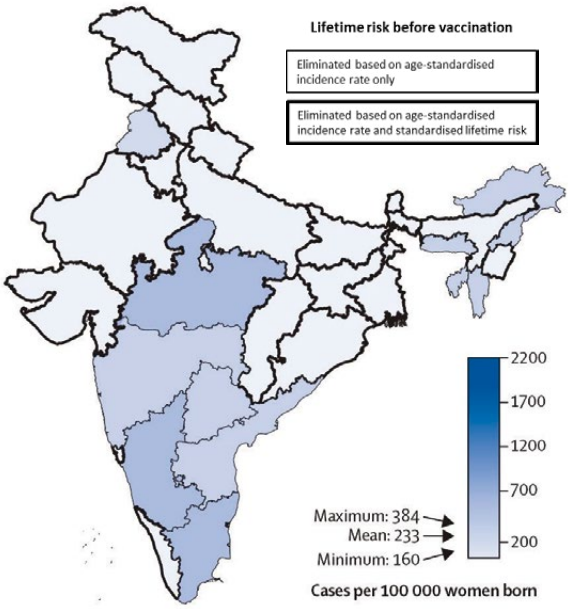


Efficacy of HPV vaccine against persistent HPV 16/18 infections in IARC India trial:

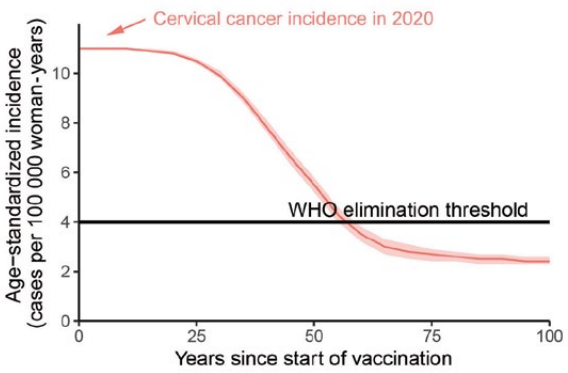
90.1% **92.7%** **90.1%**

India alone contributes to one fifth of global burden of cervical cancers

If **HPV vaccination** is introduced now in India, it could **prevent almost 1 million** cervical cancer cases among the birth cohort currently aged 10 years or younger



The introduction of single dose HPV vaccination is expected to **eliminate cervical cancer** as a public health priority in India **in 50 years**



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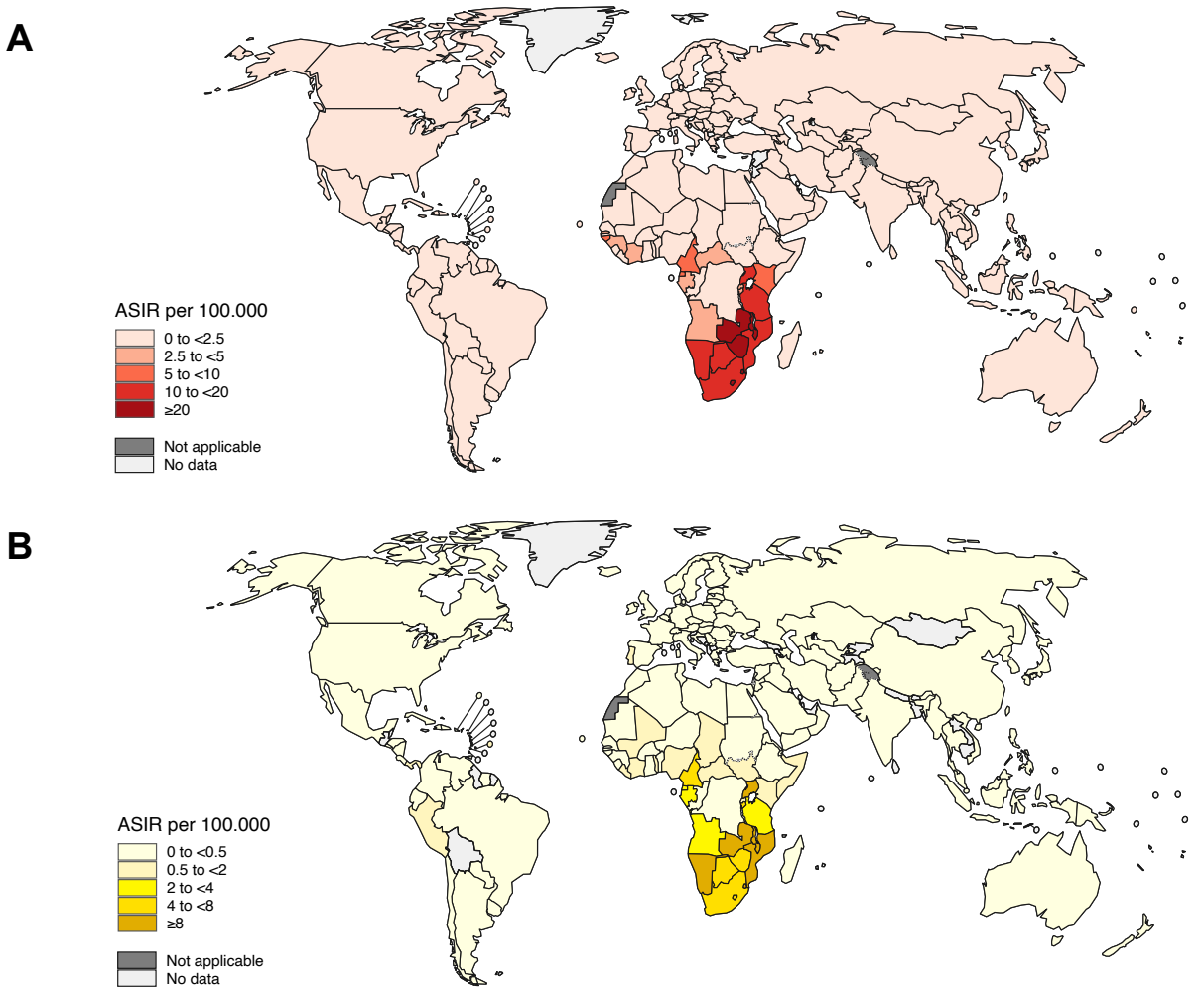
During the 2022–2023 biennium, the Early Detection, Prevention, and Infections Branch (EPR) contributed significantly to the priority research areas of the Agency to support countries to implement evidence-based interventions in cancer prevention and early detection, tailored to the local context.

Given the amenability of infections to preventive interventions, EPR continued to improve global, regional, and country-level estimates with new data and methodology, most notably expanding the cancer types considered to be causally associated with Epstein–Barr virus (EBV). In a meta-analysis of 220 studies including more than 68 000 cases of gastric adenocarcinoma, EBV prevalence in tumour cells was 7.5%, suggesting the occurrence of 81 000 EBV-associated gastric cancers worldwide annually (Hirabayashi et al., 2023a). In another meta-analysis, EBV prevalence was 11.0% in gastric diffuse large B-cell lymphoma (DLBCL) (Hirabayashi et al., 2023b). EPR's studies on the prevalence of EBV in large, representative tumour series of patients diagnosed with all types of lymphoma in France (Donzel et al., 2022) and in Rwanda (Mpunga et al., 2022) suggested an important etiological involvement of EBV in DLBCL, in addition to well-characterized associations with Hodgkin lymphoma, Burkitt lymphoma, and natural killer/T-cell lymphoma subtypes. A meta-analysis of 520 studies estimated 42% of cirrhosis globally to be attributable to hepatitis B virus and 21% to hepatitis C virus (Alberts et al., 2022); this will inform policies towards the elimination of viral hepatitis.

EPR also addressed the cancer burden attributable to HIV. For cervical cancer, 5% of the global burden was estimated to be attributable to HIV; this percentage was more than 40% in southern Africa, where the contribution of HIV was much higher in younger women (Ibrahim Khalil et al., 2022a). An estimated 19 560 HIV-attributable cases of Kaposi sarcoma are diagnosed annually in sub-Saharan Africa (~80% of the worldwide burden) versus 5064 cases of non-HIV-attributable (classic or endemic) Kaposi sarcoma (~60% of the worldwide burden) (Figure 1) (Ibrahim Khalil et al., 2022b).

Figure 1. Age-standardized incidence rates (ASIR) in 2020 by country of (A) HIV-attributable cervical cancer and (B) HIV-attributable Kaposi sarcoma, using the entire female population (for cervical cancer) or the entire population (for Kaposi sarcoma) as a denominator. (A) Reproduced from Ibrahim Khalil et al. (2022a). © 2022 World Health Organization; licensed by UICC. International Journal of Cancer published by John Wiley & Sons Ltd on behalf of UICC. (B) Reproduced from Ibrahim Khalil et al. (2022b). © 2022 World Health Organization. International Journal of Cancer published by John Wiley & Sons Ltd on behalf of UICC.

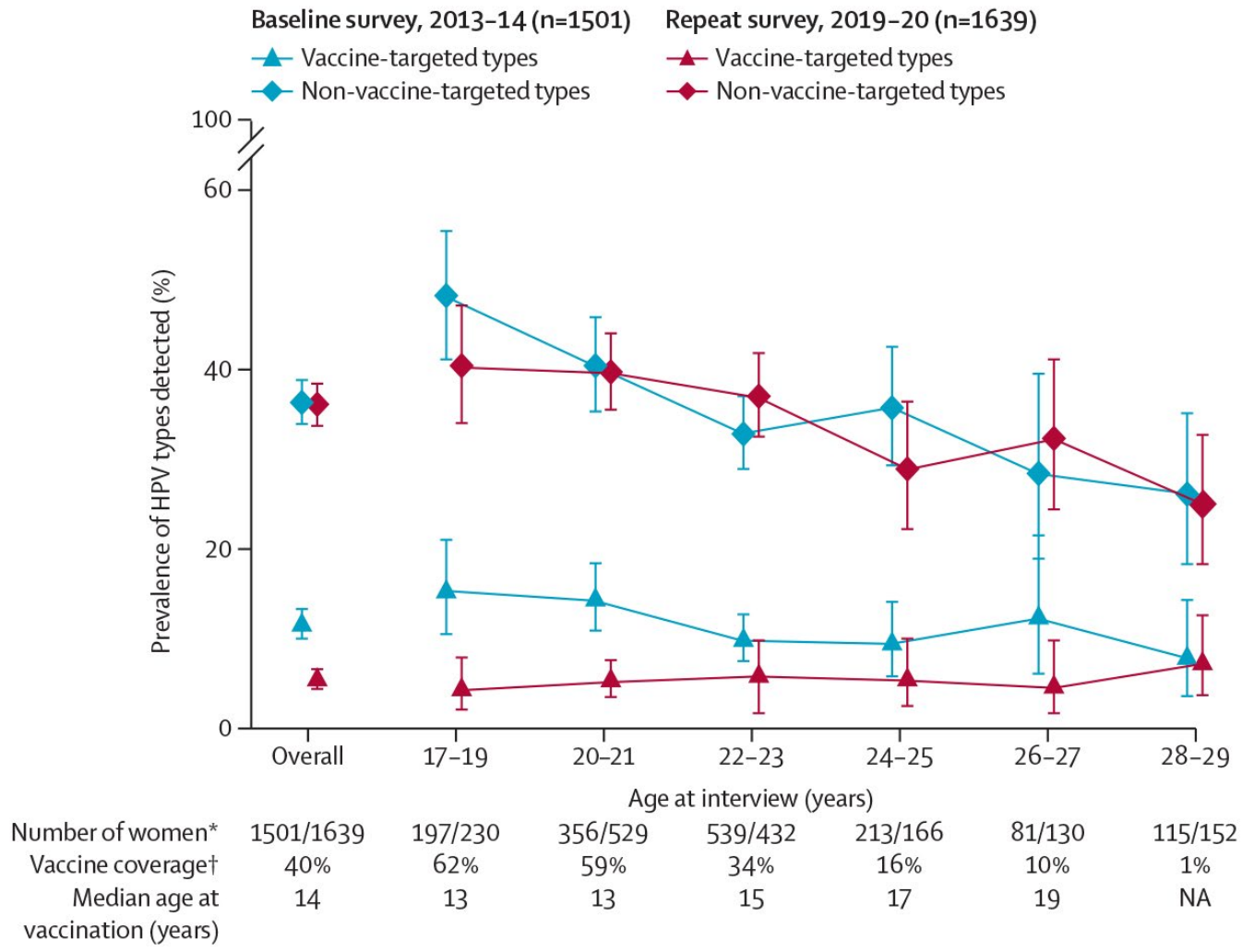


EPR studies generated valuable evidence to support the WHO advice in 2022 to opt for a single dose of human papillomavirus (HPV) vaccine. Yearly follow-up of a large cohort of females (*n* = 17 729) who received different numbers of doses of quadrivalent vaccine in India demonstrated robust immune response in single-dose recipients 10 years after vaccination and high efficacy against persistent HPV16/18 infections equivalent to that of two or three doses (Joshi et al., 2023a). By comparing antibody titres from girls aged 9–14 years in the United Republic of Tanzania who received a single dose of nonavalent vaccine with those from girls aged 10–18 years in the IARC study in India who received a single dose of quadrivalent vaccine, the Dose Reduction Immunobridging and Safety Study (DoRIS) randomized controlled trial demonstrated equivalent and sustained protection in the young Tanzanian girls (Baisley et al., 2022).

Quantifying the effectiveness of HPV vaccination is essential to reinforce the political and financial commitment of health authorities (Schulte-Frohlinde et al., 2022). Studies conducted by EPR have demonstrated the favourable impact of HPV vaccination on HPV burden at a population level in low- and middle-income countries (LMICs). Rwanda was the first African country to implement a national HPV vaccination programme, in 2011. To assess the population-level effectiveness of vaccination on HPV prevalence, cross-sectional surveys were done in 2013–2014 (baseline) and 2019–2020 (repeat) in sexually active women aged 17–29 years in Kigali, Rwanda (Figure 2) (Sayinzoga et al., 2023). Vaccine-type HPV prevalence in participants decreased from 12% in the baseline survey to 5% in the repeat survey, with an adjusted overall vaccine effectiveness of 47% (95% confidence interval [CI], 31–60%) and an adjusted indirect (due to herd protection) vaccine effectiveness of 32% (95% CI, 9–49%).

The large global burden of gastric cancer and its known principal cause, chronic infection with *Helicobacter pylori,* which is treatable, make gastric cancer a logical target for global action. EPR continues to investigate factors (e.g. salt intake) that may potentially explain regional and ethnic variations in gastric

Figure 2. Human papillomavirus (HPV) prevalence in baseline and repeat surveys in Rwanda by HPV type and age. Error bars show 95% confidence intervals. Vaccine-targeted types: HPV6, HPV11, HPV16, and HPV18. Non-vaccine-targeted types: 40 types detected by general primer (GP5+ or GP6+)-mediated polymerase chain reaction (PCR), other than the 4 vaccine-targeted types. NA, not applicable. * Baseline survey/repeat survey. † Repeat survey. Reproduced from Sayinzoga et al. (2023). © 2023 World Health Organization. Published by Elsevier Ltd.



cancer risk, using the IARC global survey, the Epidemiological Investigation of Gastric Malignancy (ENIGMA), and using biomarkers and standardized methods (Knaze et al., 2023). The GISTAR study, a collaboration with the University of Latvia, showed high compliance with the *H. pylori* test-and-treat and upper endoscopy examination among those who agreed to participate in the study, and reasons for refusal have been documented in detail, urging efforts to raise awareness (Leja et al., 2022). GISTAR also provided essential information on antibiotic resistance in those who received *H. pylori* eradication therapy, suggesting that the clarithromycin-containing regimen, unlike the amoxicillin/bismuth-containing treatment, should be avoided in a population-based setting, because the gut resistome remained increased. Correlations and temporal changes between gastric cancer and oesophageal cancer across populations worldwide were compared to inform on etiological similarities and differences (Li et al., 2023b).

As members of the WHO Guidelines Development Group for cervical cancer screening and treatment, EPR researchers identified the priority implementation research questions in the population-level introduction of the new screening algorithms, including primary HPV DNA and messenger RNA (mRNA) testing with or without triage (Broutet et al., 2022). EPR studies continued to generate evidence to inform the WHO living guidelines. The performance of visual inspection after application of acetic acid (VIA) and colposcopy as triage techniques was assessed in the ESTAMPA multicentre study in Latin America, in which more than 40 000 women aged 30–64 years were screened with HPV testing. Although the results varied greatly between examiners and study sites, both triage methods showed high sensitivity for the detection of cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) (84.5% for VIA and 91.2% for colposcopy), with an almost 50% reduction in referrals (Baena et al., 2023b; Valls et al., 2023). A longitudinal study involving 9526 women in China demonstrated that women with positive results on self-sampled HPV tests could be very effectively triaged with a combination of HPV16/18 genotyping and human gene methylation testing (with HPV16/18-positive women referred for colposcopy and non-HPV16/18-positive women tested for methylation). Such a triage strategy had a sensitivity of 96.6% and a specificity of 58.3% to detect CIN2+ lesions, and the colposcopy referral rate was reduced by half (Zhang et al., 2022a). Genotyping of cervical samples from 1252 participants (including 398 women with CIN2+ lesions) in the ESTAMPA study demonstrated that genotypic diversity (the prevalence of multiple infections of HPV types) gradually decreased with higher grade of lesions: 43% for ≤ CIN2, 28% for CIN3, and 8% for cancers (Basiletti et al., 2022; Correa et al., 2022).

Based on a longitudinal follow-up of 1153 women living with HIV (WLHIV) in India, EPR demonstrated that the women with persistent HPV infection had a 138-fold increased risk of CIN2+ lesions compared

Figure 3. Essential criteria to be fulfilled by a screening programme to be considered as organized. Through a systematic review and an expert consensus, 16 essential criteria were identified. Reproduced from Zhang et al. (2022b). © Zhang et al., 2022.

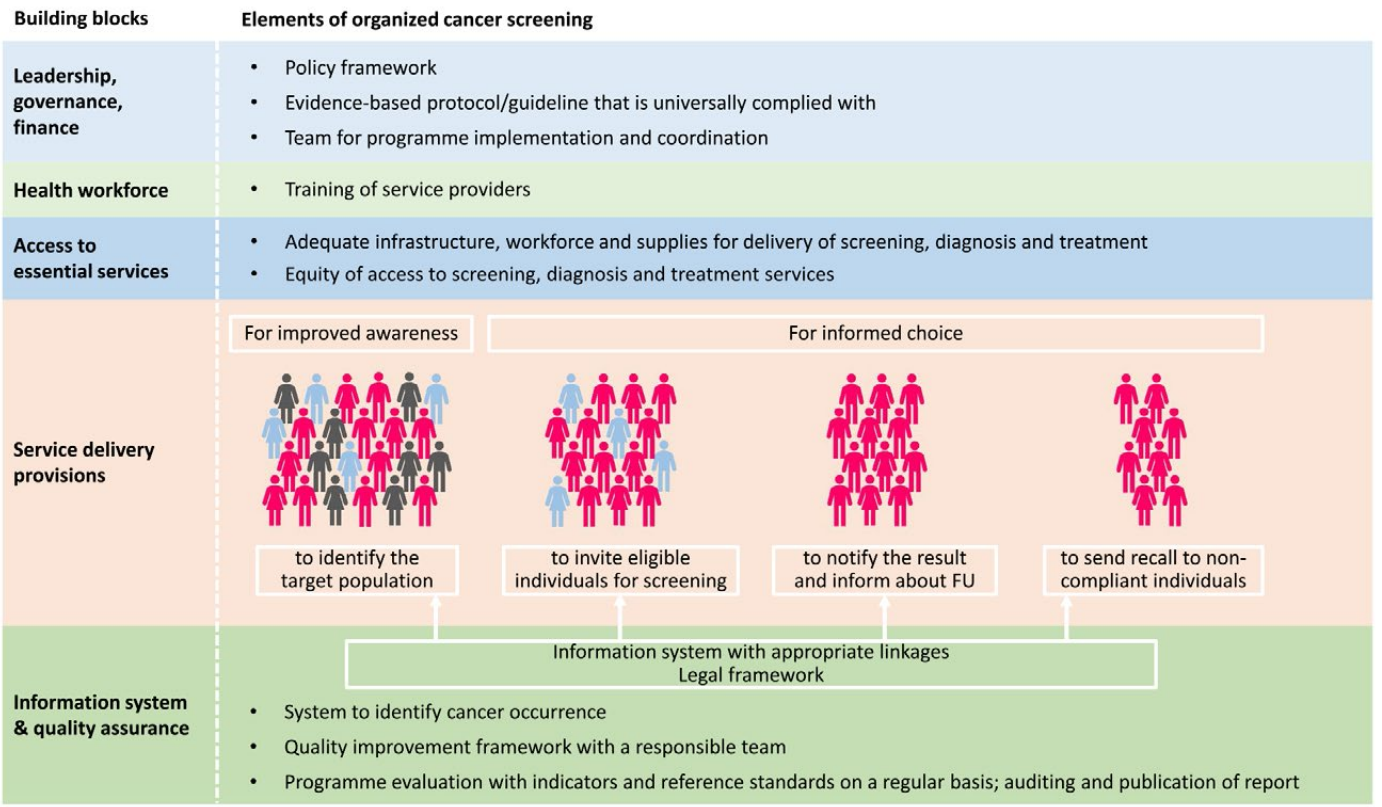


Figure 4. In collaboration with the Department of Health and the Health Service Executive of Ireland, EPR defined the key issues in the practice of cancer audits in cervical screening programmes. © IARC.

with the HPV-negative women. The HPV-negative WLHIV have nearly zero risk of developing CIN2+ in the next 3.5 years, thus providing supporting evidence to the WHO recommendation to extend the screening interval to 3–5 years in WLHIV despite their significant risk of developing cervical cancer (Joshi et al., 2023b).

The efficacy and safety of thermal ablation and cryotherapy for cervical precancers were studied in a large randomized trial in Zambia (Mwanahamuntu et al., 2022), and a systematic review of the evidence was performed (Zhang et al., 2023a). Another study, conducted in Benin, Cote d'Ivoire, and Senegal, demonstrated the feasibility of screening a large number of women opportunistically through primary care settings and the high acceptance (88%) of same-day ablative treatment. The most significant implementation challenge was low compliance (66.1%) of the women referred to higher-level facilities for excisional treatment or for further investigation due to suspected cancer (Selmouni et al., 2022a).

Studies are continuing in EPR to evaluate the effectiveness of screening for cancer sites other than the cervix (breast, colorectum, lung, prostate, and stomach). Clinical breast examination was evaluated as a screening test for women aged 35–69 years in a randomized controlled trial in India. Long-term (14-year) follow-up of 115 290 participants demonstrated a significantly higher age-standardized incidence rate of early-stage cancers (relative risk [RR], 1.4; 95% CI, 1.1–1.8) in the screened women compared with the unscreened women, without any difference in the mortality rate (RR, 1.1; 95% CI, 0.8–1.5) (Ramadas et al., 2023).

A demonstration project implemented in Morocco in collaboration with the Ministry of Health screened 10 000 men and women aged 50–75 years for colorectal cancer with the faecal immunochemical test (FIT) through primary health care (Selmouni et al., 2022b). Among the 4.7% FIT-positive individuals, compliance with colonoscopy was only 62.6%, which was directly linked with the lengthening of the waiting time as endoscopy services became overwhelmed. The detection rate of colorectal cancer was low (0.5 per 1000 screened).

An EPR study reported quantitative estimates of the impact of the COVID-19 pandemic on cancer screening programmes in selected LMICs (Argentina, Bangladesh, Colombia, Morocco, Sri Lanka, and Thailand). Compared with 2019, there was a significant reduction in 2020 in the volume of tests (the reduction ranged from 14.1% in Bangladesh to 72.9% in Argentina for cervical screening), the number of diagnostic evaluations of screen-positive individuals, and the detection rates of precancers (e.g. a reduction of 45.4% in the detection rate of CIN2/3 in Argentina) and cancers (e.g. a reduction of 19.1% in breast cancer detection in Morocco) (Lucas et al., 2023).

Providing evidence-based guidance to countries to implement cancer screening programmes with high quality remained one of the key research focuses of EPR (Figure 3 and Figure 4).

Cancer Screening in Five Continents (CanScreen5) (Zhang et al., 2023b) is a global cancer screening data repository, which reported the status and

Table 1. Comparison of organization, protocol, and quality assurance mechanisms of the cervical cancer screening programmes by continent, based on information collected by the CanScreen5 project. Reproduced from Zhang et al. (2023b). © Zhang et al., 2023.

Question	Response	Percentage by continent					*P* value
		Africa (*n* = 15)	Americas (*n* = 22)	Asia (*n* = 8)	Europe (*n* = 27)	Oceania (*n* = 1)	
Organization of screening							
Is there a person responsible for management or coordination of the cancer screening activities?	Yes	86.7	77.3	100	74.1	100	0.423
Does the health authority allocate a budget to cancer screening?	Yes	53.3	63.6	100	85.2	100	**0.001**
Is there a policy document that recommends cancer screening?	Yes	100	100	100	96.3	100	0.733
What is the type of the policy document?	Law	0	13.6	25.0	25.9	0	**< 0.001**
When was the screening programme initiated?	Before 2000	6.7	40.9	25.0	33.3	100	**0.042**
Are the screening tests available free of charge?	Yes	80.0	90.9	87.5	88.9	100	0.542
Are the diagnostic tests available free of charge?	Yes	46.7	63.6	50	74.1	0	0.056
Information system and data collection							
Are the screening-related data collected on an individual basis?	Yes	20.0	59.1	75.0	70.4	100	**0.001**
Are screening data linked with population-based cancer registries?	Yes	0	9.1	25.0	66.7	0	**< 0.001**
Screening protocol							
What is the primary screening method?	VIA	93.3	46.7	20.0	0	0	NA
	Cytology	26.7	95.5	62.5	100	0	
	HPV	26.7	27.3	25.0	11.1	100	
	Co-test	0	18.2	0	0	0	
Invitations for screening and further assessment							
Is there a system to send individual invitations to the eligible population?	Yes	0	27.3	62.5	77.8	100	**< 0.001**
Are the screen-positive individuals actively contacted for further assessment?	Yes	73.3	50.0	87.5	51.9	100	0.197
Quality assurance of screening activities							
Is there a documented guideline or policy for quality assurance?	Yes	46.7	63.6	75.0	55.6	100	**< 0.001**
Is there a person responsible for quality assurance?	Yes	53.3	50.0	87.5	66.7	100	0.083
Are there specified performance indicators?	Yes	73.3	77.3	100	55.6	100	**< 0.001**
Were the performance reports published?	Yes	33.3	31.8	75.0	59.3	100	**0.074**

HPV, human papillomavirus; NA, not applicable; VIA, visual inspection after application of acetic acid.

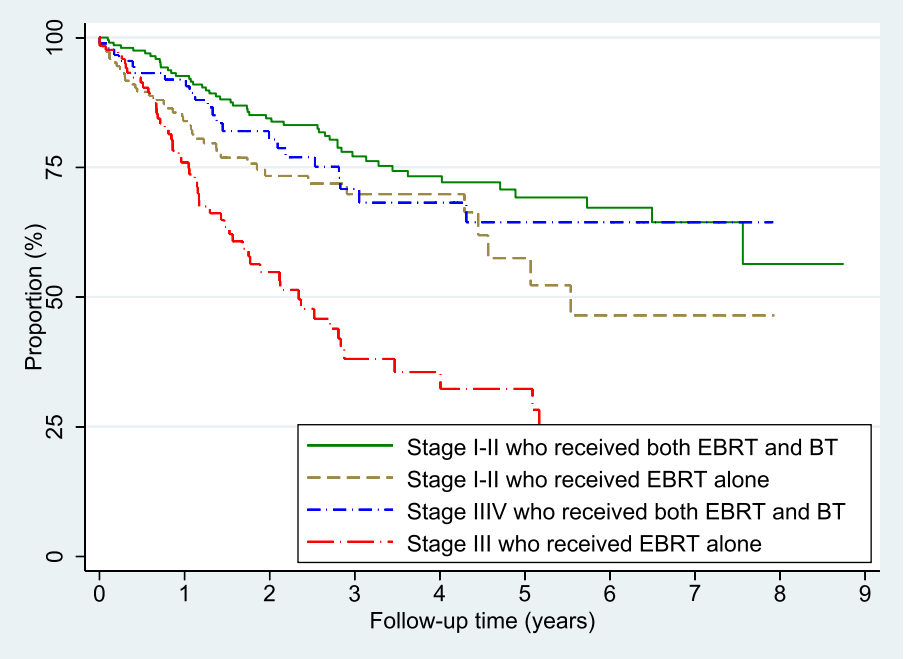
performance of breast cancer (*n* = 57), cervical cancer (*n* = 75), and colorectal cancer (*n* = 51) screening programmes in 84 countries in 2023 (Table 1). Data collected mainly from the ministry of health in each country, using a harmonized set of criteria and indicators, were made publicly available through a web-based portal (https://canscreen5.iarc.fr/).

The cancer burden, prevalence of cancer risk factors, existing national cancer control plans, and health system capacities of fragile states were reviewed in a collaborative study with WHO (Mosquera et al., 2022). Countries with a Fragile States Index (FSI) score of ≥ 90.0 for at least 10 years during the period 2006–2020 (*n* = 31) were included. The proportion of cancers attributable to infections was significantly higher in these 31 states than in non-fragile states. Despite the growing prevalence of risk factors and cancer burden, only 6 of the 31 states had implemented more than one of the WHO MPOWER measures for tobacco control, and only half had an updated cancer control plan.

EPR scientists have strongly advocated for implementation research studies to improve cancer control (Basu et al., 2022). Such studies conducted by EPR are aimed at identifying context-appropriate solutions to improve participation in cancer screening, especially of socio-economically disadvantaged populations (Oommen et al., 2023). Some of these solutions include having dedicated policies to improve coverage among disadvantaged populations and using innovative methods to minimize the structural barriers. As part of one such study in the European Union, a survey was conducted among 31 screening programme managers from 22 countries to identify existing policies focused on improving participation of vulnerable women in cervical screening. The results of this survey suggested that although many countries identify lower coverage among vulnerable population subgroups as a public health problem, few have developed dedicated policies to broaden coverage in these subgroups (Mallafré-Larrosa et al., 2023).

EPR studied the effectiveness of patient navigation to improve access to cancer screening through a systematic review of evidence (Mosquera et al., 2023a). The review found that patient navigation could increase screening participation by up to 250% compared with usual care. However, only one of the 44 studies included in the review was conducted in LMICs. Patterns-of-care studies reported the impact of delays and abandonment of cancer care in selected LMICs (Figure 5).

Figure 5. In a patterns-of-care study on patients with cervical cancer in Morocco, EPR demonstrated that more than half of the patients did not have a full course of radiation (external-beam radiotherapy [EBRT] and brachytherapy [BT]), and they had significantly lower survival compared with patients with the same stage of disease who completed the full course of radiation. Reproduced from Benider et al. (2022). © Benider et al., 2022.



	2-year		5-year	
	No. at risk	Survival proportion (%)	No. at risk	Survival proportion (%)
Radiotherapy type by stage at diagnosis				
EBRT and brachy therapy among stage I-II patients	133	84.4	46	69.2
EBRT alone among stage I-II patients	61	73.3	12	57.5
EBRT and brachy therapy among stage III patients	51	80.4	18	64.4
EBRT alone among stage III patients	35	54.8	9	32.3

CanScreen5

Capacity-building is at the core of developing and upholding the CanScreen5 network. In the short term, it assists public health officials and researchers in understanding how to evaluate and ensure quality assurance of screening programmes. Over time, it stimulates countries to collect and share precise information about their cancer screening initiatives. These data are subsequently used to review and enhance the quality improvement of these programmes.

The CanScreen5 framework involves a training programme organized by IARC, geared towards imparting foundational cancer screening principles and quality improvement. Training of Trainers was provided to 44 countries (17 in Africa and 27 in the Community of Latin American and Caribbean States [CELAC]), with participants nominated by the health authorities of each country.

The next step involves helping Master Trainers to spread the training to health-care providers and screening managers in their respective countries. To ensure the long-term sustainability of the CanScreen5 capacity-building initiative, EPR is proposing to establish training hubs worldwide, managed by regional organizations or institutions. These hubs will encompass a customized Training of Trainers programme rooted in the regional and local context. This vision ensures the sustainability and lasting impact of the CanScreen5 capacity-building programme.

Participants in the in-person session of the CanScreen5 Training of Trainers Learning Programme in Sharjah (United Arab Emirates), 17–19 May 2022. © IARC.