



Technical Meeting:

Challenges in the HPV Screening Landscape, Triage of Screening Positive Samples, and Screening in the Era of Vaccination
Antwerp, Belgium, 27-28 August 2020 (remotely)

and rethinking

Organizing cervical cancer screening in the era of vaccination

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Disclosure (lifetime)

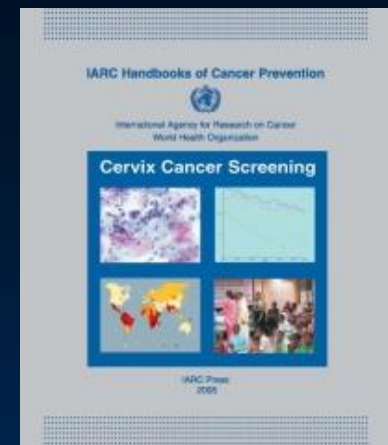
- ❖ Occasional paid consultant to Merck and GSK on HPV vaccines, to Roche, Abbott, Qiagen, and Becton & Dickinson on HPV diagnostics.
- ❖ Three unconditional grants to my institution from Merck in partial support of investigator-initiated research related to HPV in my unit (to supplement CIHR and NIH funding).
- ❖ Fees received from Elsevier to maintain editorial team for two medical journals (*Preventive Medicine* and *Preventive Medicine Reports*).
- ❖ Entire research program funded by CIHR, NIH, NCIC, CRS, CCSRI, FRQS; salary awards: CIHR Distinguished Scientist, FRSQ Chercheur National, James McGill Chair, Minda de Gunzburg Endowed Chair.

Creed: *It is an ethical duty and a privilege for experienced scientists to advise industry in bringing new technologies to advance medicine and public health. Not doing so would be detrimental to the public interest. Pharmaceutical or biotechnology companies cannot obtain the same wealth of knowledge and insights from a lay advisory board.*

Outline

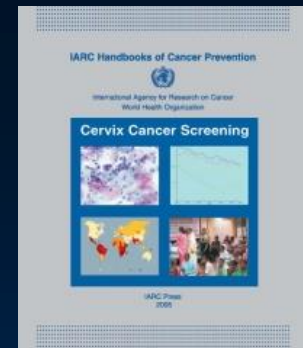
- Basic premise: cervical cancer screening based on molecular HPV testing an unequivocal improvement over the paradigm of Pap cytology
- Rationale for changing screening paradigm stronger post-HPV vaccination
- Integration of primary and secondary prevention processes brings efficiency benefits
- After 13 years, HPV vaccination has begun to change the epidemiology of cervical precancer
- How should screening be done in the future?

Conclusions of the IARC Cervix Cancer Screening Working Group (2004)



- ✓ There is *sufficient evidence* that screening by **conventional cytology** has reduced cervical cancer incidence and mortality rates.
- ✓ There is *sufficient evidence* that **testing for human papillomavirus** infection **as the primary screening modality** can reduce cervical cancer incidence and mortality rates.

IARC Cervix Cancer Screening Working Group (2004)



*“Since 1985, there have been two notable advances. The most important is the identification of certain oncogenic types of human papillomavirus (HPV) as the major cause of cervical cancer; indeed it may be that the disease does not occur in the absence of HPV infection. **With the development of vaccines against these oncogenic HPV types, it is becoming possible to envisage the primary prevention of most cases of cervical cancer. [...] It will be several decades, however, before most women in the relevant age groups will benefit from such vaccines, since they will already have been at risk of exposure to the virus.**”*

Policy landscape for the changes in cervical cancer screening post-vaccination

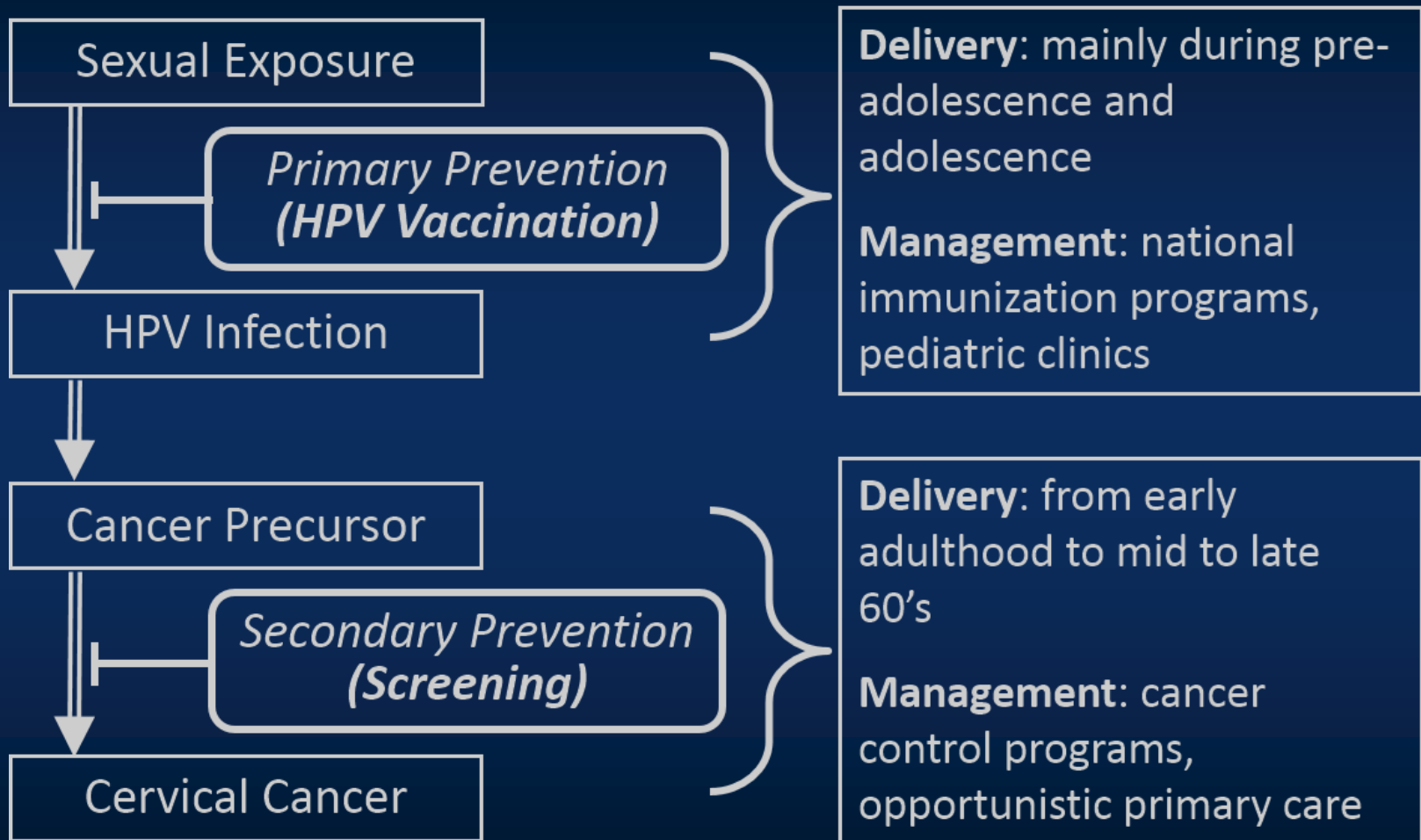
- Technology choices:
 - Cytology (LBC or conventional) alone or with HR-HPV testing for ASC-US triage
 - Cytology and HR-HPV co-testing
 - HR-HPV testing followed by triage of HPV+ cases (cytology, partial genotyping alone, partial genotyping with conditional cytology)
- Age to start screening: 18, 21, 25, 30
- Frequency of screening
 - Annual, q2, q3, q5, >q5 (technology dependent)
- Age to stop screening for cervical cancer: 65, 69, 74

Evidence for HPV Primary Screening is Overwhelming

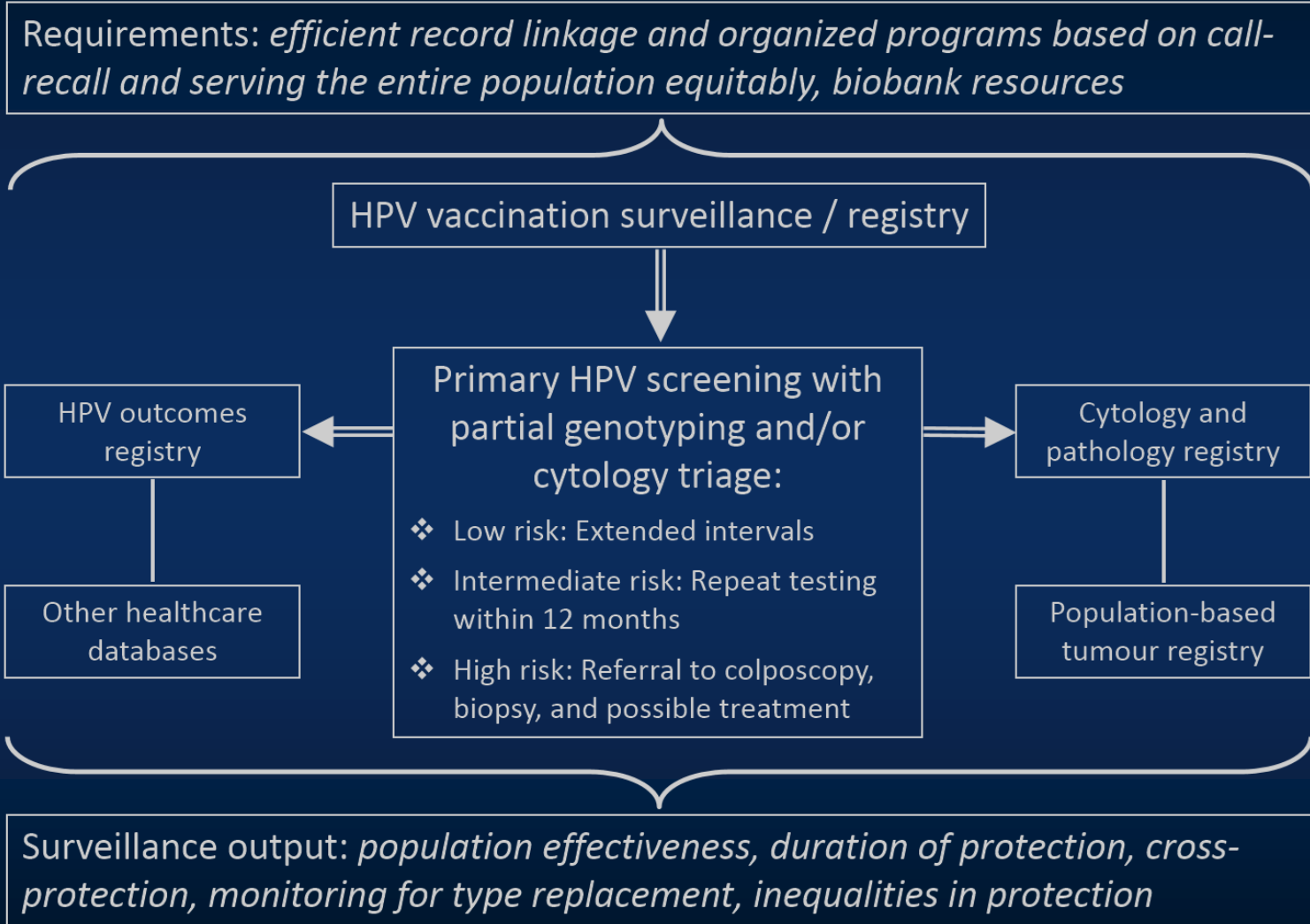
HPV primary screening is clinically superior, more cost-effective and less burdensome for women than the Pap test:

- HPV testing more effective at detecting high-grade precancerous lesions and eliminates the ambiguity of equivocal smears (i.e., ASC-US).
- A negative HPV test provides greater and longer reassurance to women that they are at very low risk of cervical cancer.
- HPV testing has efficiency and quality benefits. Fewer lifetime screens with HPV screening contributes to cost-effectiveness.
- HPV testing offers greater protection against cervical adenocarcinoma.
- Self-sampling with HPV test could help reduce disparities and increase screening rates.
- Cytology will be less effective in a vaccinated population. (Franco et al., Vaccine 2006; Palmer et al., British Journal of Cancer 2016)

Interplay between primary and secondary prevention strategies for cervical cancer



Schematic rationale for an ideal integration of vaccination and screening programs in high-resource settings. The central component is a generic cervical cancer screening algorithm to inform a surveillance system post- vaccination*



* Not all record-linkage components are essential. Efficient epidemiologic surveillance can be implemented with a subset of these components.

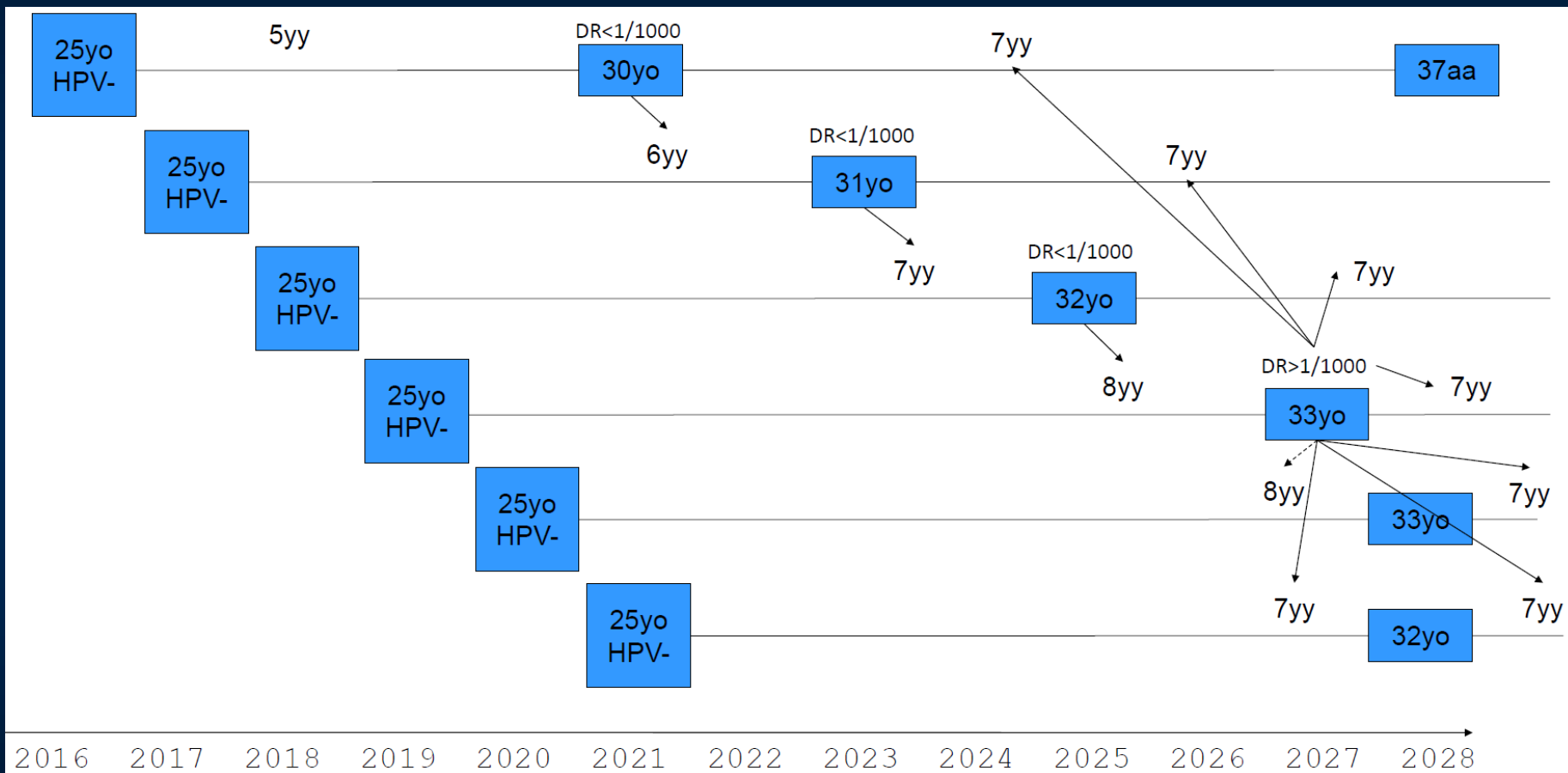
On the road to elimination...

- Vaccination has reduced the incidence (and prevalence) of cervical precancers caused by vaccine-targeted HPV types.
- In consequence, it is having an impact on screening performance and practices shifting the balance of benefits to harms.
- Can screening begin later in life, be done less frequently, and be stopped earlier in populations with high vaccination coverage?
- Should policies differ between vaccinated and unvaccinated?
- Modelling studies: combining vaccination and screening is cost effective and good value for money but screening would have to start later in life, e.g., 30 years for the 2valent or 4valent vaccines and 35 years for the 9valent and be done less frequently (Kim et al., 2017; Pedersen et al., 2018).
- Lesion management guidelines will also need to be relaxed: risk of cervical precancer post-LSIL is lower among vaccinated than among unvaccinated (Castle et al., 2019).

On the road to elimination...

- In the past 10 years, screening guidelines have gradually shifted to favour molecular HPV testing (ASCCP/ASCP/ACS 2012; USPSTF 2012; ASCO 2016; ASCCP 2019; ACS 2020; as well as European guidelines of 2015, etc.)
- Yet, except for Italy, countries are opting for a one-size-fits-all screening strategy irrespective of vaccination history.
- No country or professional organization has recommended variations in screening or management policies to reflect individual vaccination status or for populations with high vaccination coverage.

Rossi, PG, Carozzi F, Federici A, Ronco G, Zappa M, Franceschi S, et al. Cervical cancer screening in women vaccinated against human papillomavirus infection: Recommendations from a consensus conference. *Prev Med* 2017;98:21-30).



Detection rate will be evaluated at their second screening episode. If DR is below 1/1000 the interval will be increased by one year. If DR is not below 1/1000 the interval will be fixed at the length of the previous cohort

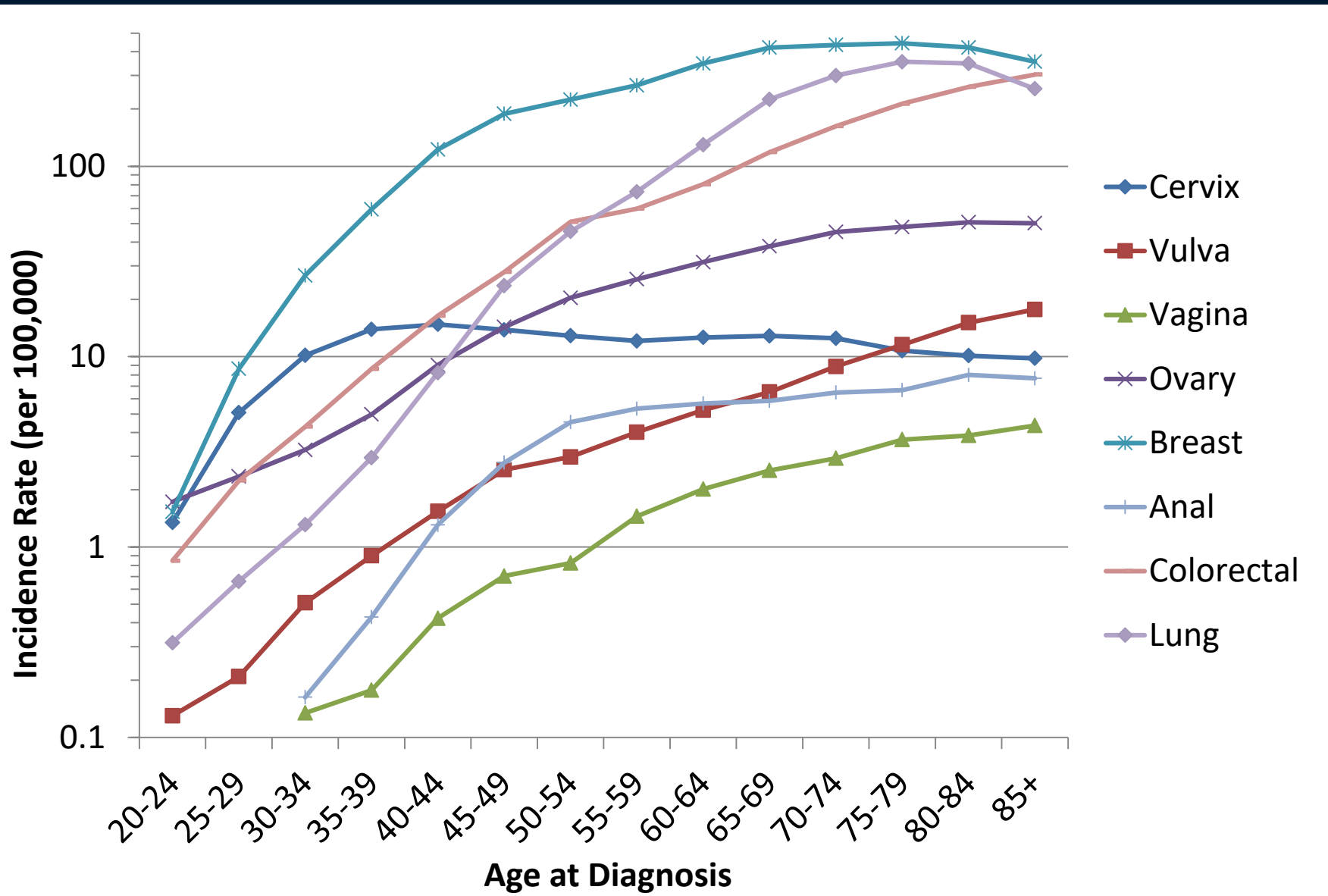
There is urgency to change the screening paradigm now but how will screening perform in the future?

- With high vaccination coverage in all age cohorts, cross-protection, and herd immunity, HPV transmission will be kept at a minimum.
- Molecular tests (HPV) may eventually lose its clinical utility in identifying disease that has become so rare relative to (false) positive findings (El-Zein et al., *J Clin Virol* 2016).
- Cervical cancer screening is not devoid of immediate and long-term risks for women's reproductive health.
- Today, such risks are far outweighed by the benefits of screening.
- The question is: will that balance change in the future?

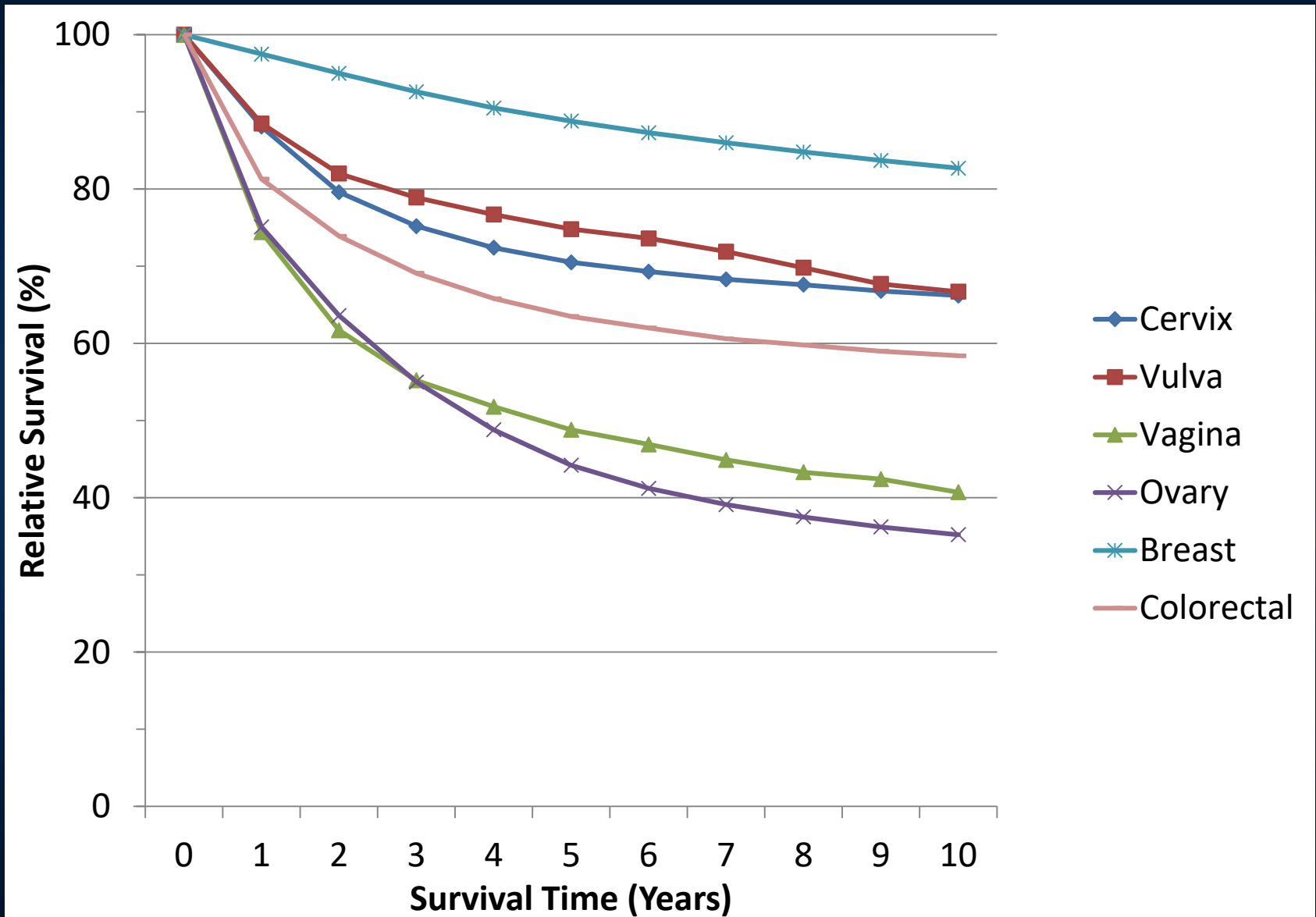
One way to know when screening should stop?

- Risk tolerance will vary among populations; there will be a need for benchmarks of acceptable disease risk.
- Some countries may decide to phase out screening based on consensus that an acceptably low level of cervical cancer risk has already been attained, e.g., much below WHO's target.
- Comparison of the projected post-vaccination incidence of cervical cancer with that of cancers for which screening is possible or standard practice.
- Compare the case-fatality/prognosis of different cancers.
- Examples of benchmarks: Vaginal and vulvar cancers (both amenable to be detected early via cytology)

Age-specific incidence rates of selected cancers in women in the United States (SEER program 2007-11)



Survival rates for selected cancers in women in the United States (SEER program 1988-2010)



Conclusions and conjectures

- ✓ Incorporation of molecular HPV testing in cervical cancer screening is no longer questioned as the way forward.
- ✓ Many challenges remain for equitable implementation of HPV vaccination and molecular screening technologies.
- ✓ As the prevalence of cervical precancerous lesions continues to fall the ratio of benefits to harms from screening will decline dramatically.
- ✓ Defining benchmarks of tolerable risk via analogy with other cancers may help deciding in 30-40 years on abolishing cervical cancer screening or doing only once or twice during a lifetime.
- ✓ COVID-19 pandemic's negative impact on cancer control creates the opportunity to make self-sampling a standard to empower women everywhere.