Therapeutic HPV vaccines:
PDVAC discussion 2024

Dr Sami Gottlieb, WHO
Dr Peter Dull, BMGF
9 December 2024

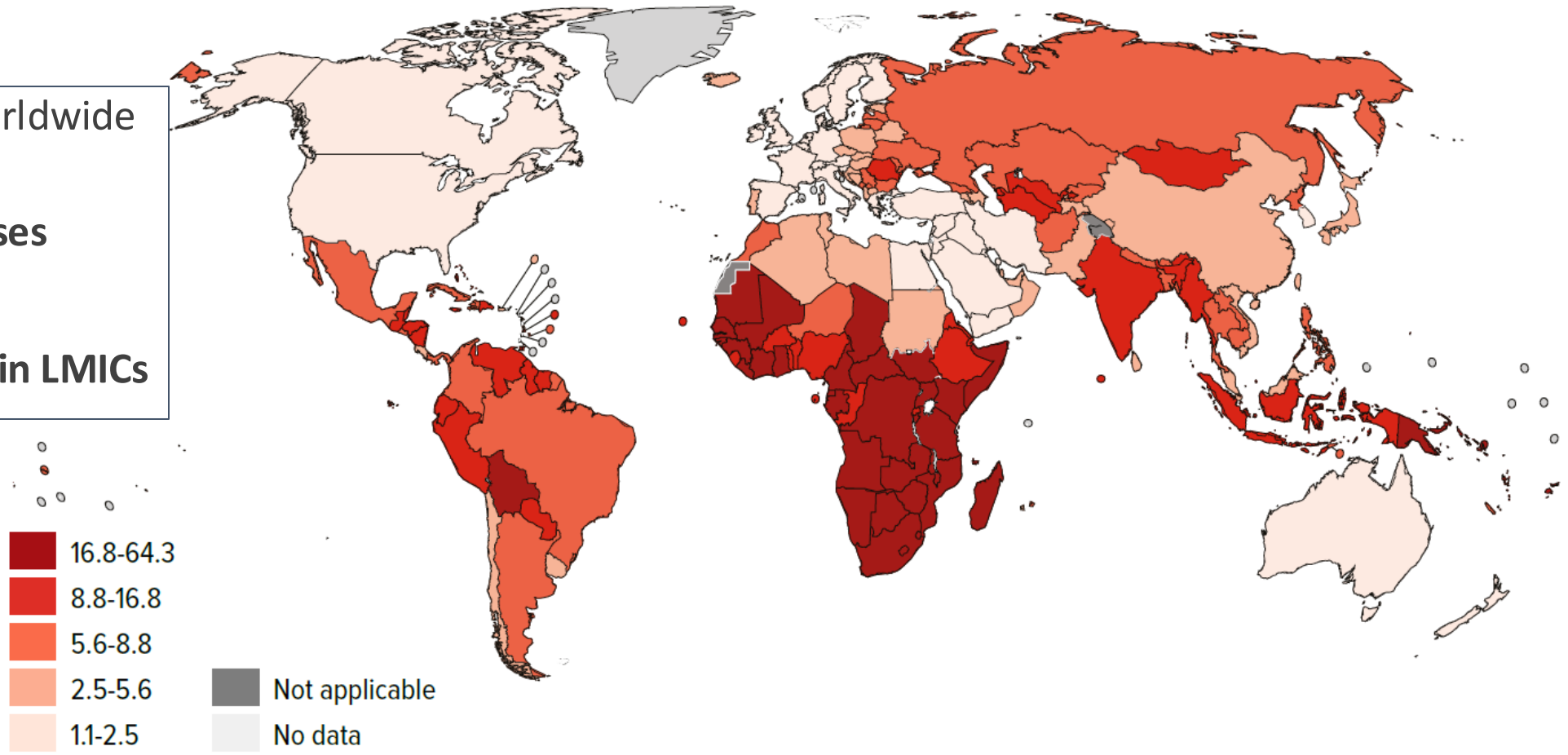
World Health Organization

human reproduction programme hrp
research for impact
UNDP · UNFPA · UNICEF · WHO · WORLD BANK

Cervical cancer is a major public health problem and reflects global inequities

Cervical cancer worldwide in 2022

- **662,000 new cases**
- **349,000 deaths**
- **>90% of deaths in LMICs**



Source: Globocan/International Agency for Research on Cancer, 2022 *(2)*.

Global strategy to eliminate cervical cancer

- “One woman dies of cervical cancer every two minutes…Each one is a tragedy, and we can prevent it.” (Dr. Tedros Adhanom Ghebreyesus, May 2018)

https://www.who.int/publications/i/item/9789240014107

human reproduction programme hrp 50
research for impact
UNDP·UNFPA·UNICEF·WHO·WORLD BANK

Global strategy targets by 2030

Threshold for elimination as a public health problem:
Age-adjusted incidence rate < 4/100,000 women

2030 Targets

SDG 2030 Target 3.4:
30% reduction in mortality from NCDs

human reproduction programme hrp 50
research for impact
UNDP·UNFPA·UNICEF·WHO·WORLD BANK

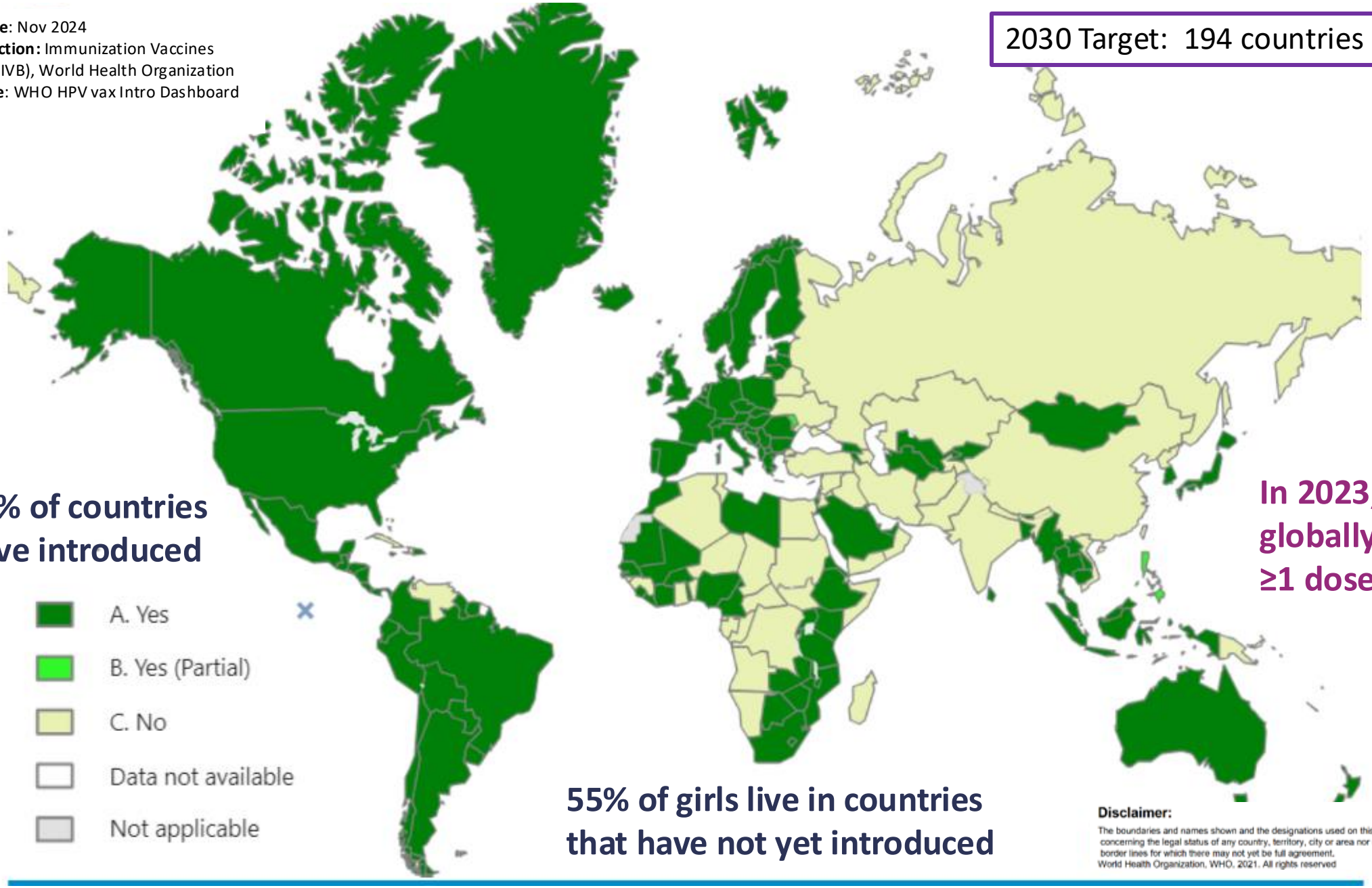
146 countries have HPV vaccine in national programme

GLOBAL

Date of slide: Nov 2024
Map production: Immunization Vaccines Biologicals (IVB), World Health Organization
Data Source: WHO HPV vax Intro Dashboard

2030 Target: 194 countries

WHO HPV Dashboard

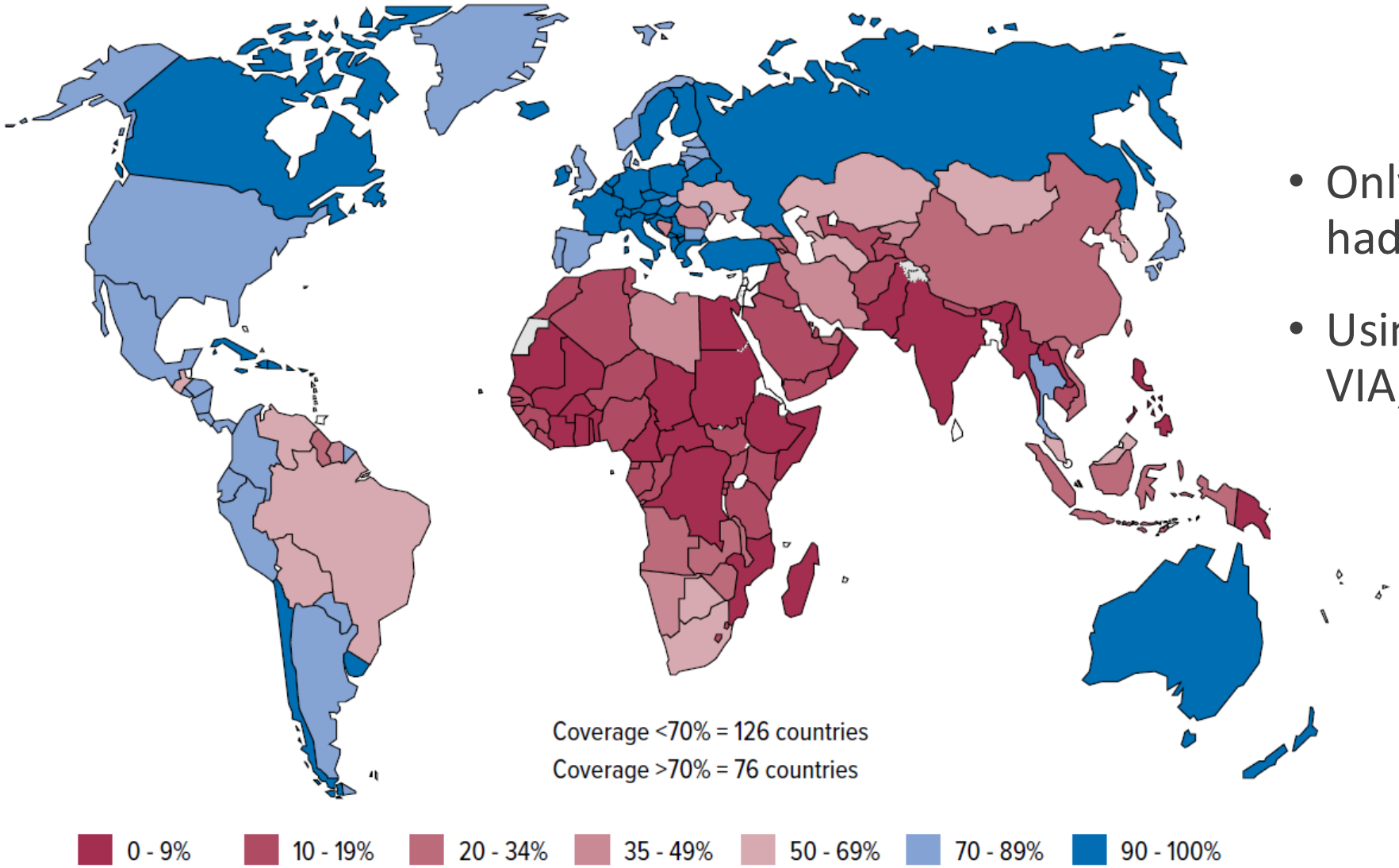


75% of countries have introduced

In 2023, 27% of girls globally had received ≥1 dose of vaccine

55% of girls live in countries that have not yet introduced

Ever in lifetime screening coverage, women 30-49y (2019)



- Only ~10% of women in LMICs had ever had screening
- Using any method, including VIA, which is inaccurate

Source: Adapted from Bruni et al., Lancet Global Health, 2022 *(6)*.

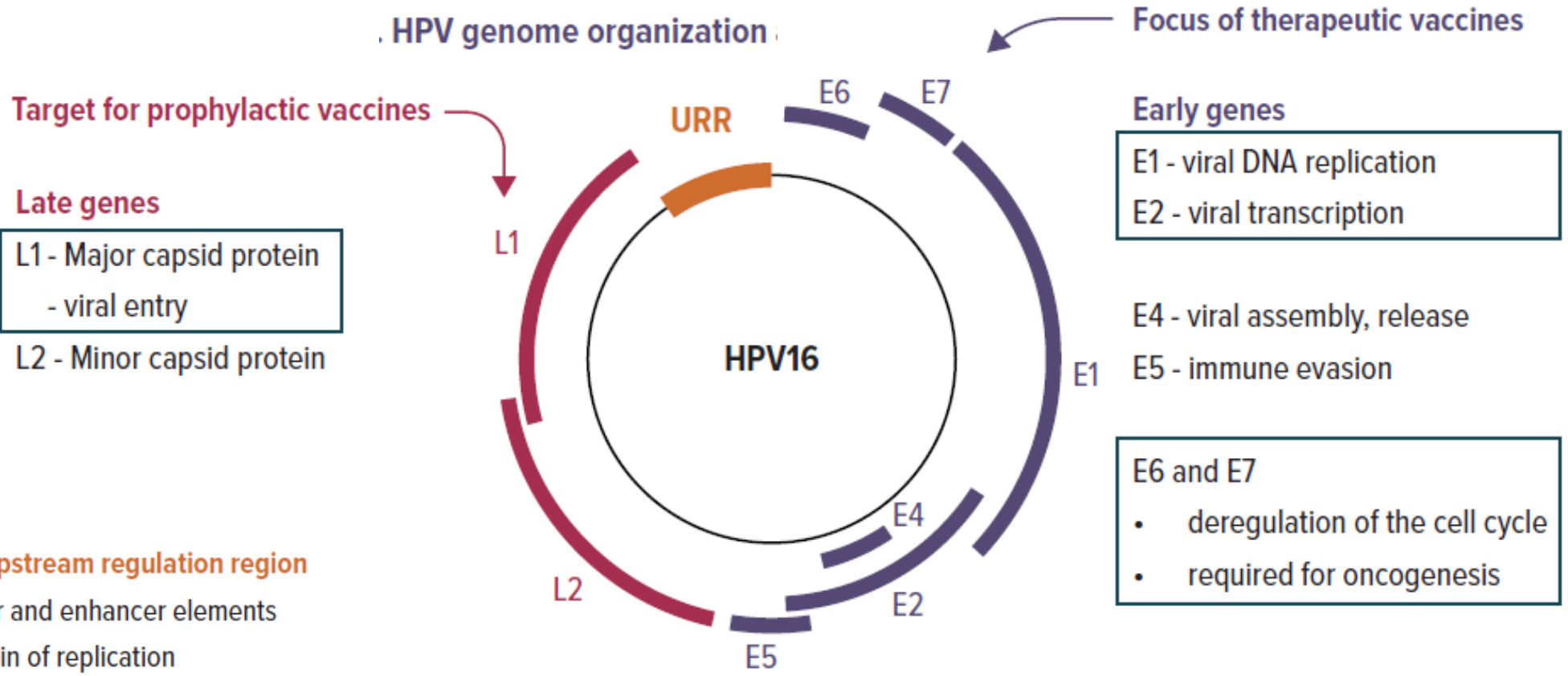
New innovations in the cervical cancer response

- **Challenges in reaching targets** of WHO cervical cancer elimination strategy
  - Millions of women have already acquired HPV infection
  - Complexity of HPV screening/treatment approaches in many settings

- As we **scale up existing interventions**, also **scanning horizon for new innovations** that might enhance existing efforts or address specific gaps

Therapeutic HPV vaccines

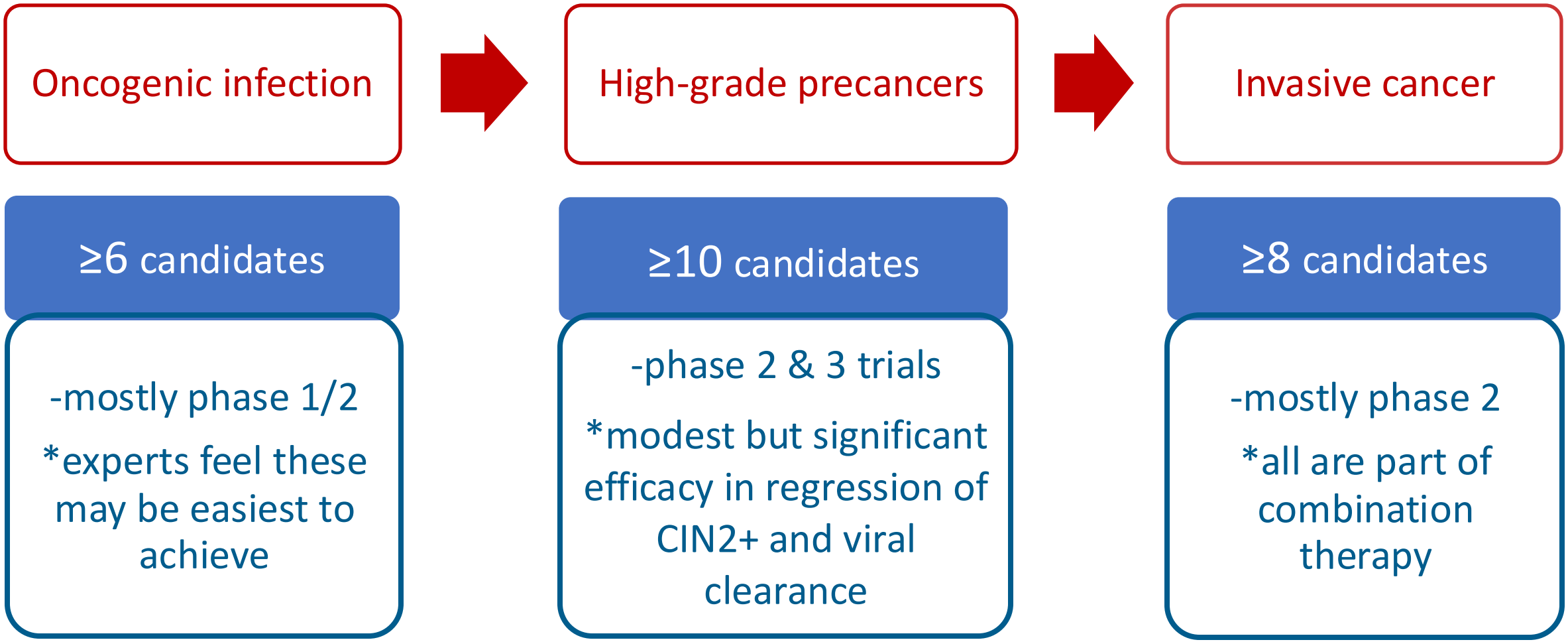
- Differ from prophylactic vaccines: **therapeutic vaccines** are designed to work in people **who already have infection**



Source: Adapted with permission from Stanley M, Clin Microbiol Rev, 2012 *(68)*.

Active pipeline of therapeutic HPV vaccines

Focusing on different phases of the natural history



Listed on clinicaltrials.gov; Mo et al, Front Cell Molec Infect 2022; Khalil et al, BMJ Open 2023; Dull et al, Vaccine 2024

Can therapeutic HPV vaccines address gaps?

WHO workstreams on vaccine development

Preferred product characteristics (PPCs)

- What should the vaccine look like to optimize its benefits?
- Who will get it and how will it be used?

PDVAC = WHO Product Development for Vaccines Advisory Committee

- WHO PPC document

Value of vaccines assessments

- What is the public health need the vaccine would address?
- How valuable would the vaccine be?

IVIR-AC = WHO Immunization and Vaccines Implementation Research Advisory Committee

- Initial modeling
- End-user assessment

Research and development pathways

- What will it take to develop an effective vaccine?
- How can we facilitate the research and development?

- 2023 meeting on clinical endpoints, regulatory pathways

- **Interconnected and iterative** workstreams
- Contribute to WHO **full value of vaccines assessment** (FVVA)

human reproduction programme hrp 50
research for impact
UNDP·UNFPA·UNICEF·WHO·WORLD BANK

Development of PPC document

>80 experts/stakeholders contributed directly, from all WHO regions

First expert consultation Oct 2021

Second consultation Nov 2022

IPVC workshop Modelling Apr 2023

Public consultation Sep 2023

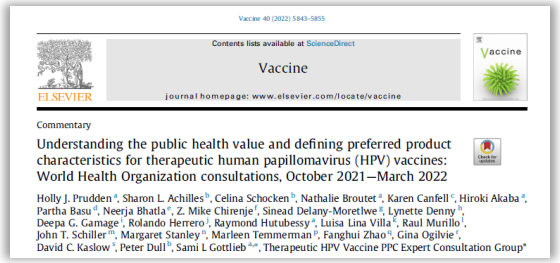
Final WHO publication Jul 2024

Several rounds input Meeting report

PDVAC input Dec 2022

Several rounds input Draft PPC document

PDVAC input Dec 2023


Vaccine 40 (2022) 5843–5855

Contents lists available at ScienceDirect

Vaccine

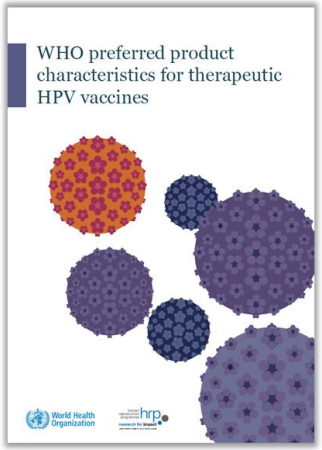
journal homepage: www.elsevier.com/locate/vaccine

Commentary

Understanding the public health value and defining preferred product characteristics for therapeutic human papillomavirus (HPV) vaccines: World Health Organization consultations, October 2021—March 2022

Holly J. Prudden [a], Sharon L. Achilles [b], Celina Schocken [b], Nathalie Broutet [a], Karen Canfell [c], Hiroki Akaba [a], Partha Basu [d], Neerja Bhatla [e], Z. Mike Chirenje [f], Sinead Delany-Moretlwe [g], Lynette Denny [h], Deepa G. Gamage [i], Rolando Herrero [j], Raymond Hutubessy [a], Luisa Lina Villa [k], Raul Murillo [l], John T. Schiller [m], Margaret Stanley [n], Marleen Temmerman [o], Fanghui Zhao [a], Gina Ogilvie [c], David C. Kaslow [p], Peter Dull [p], Sami L Gottlieb [a,*], Therapeutic HPV Vaccine PPC Expert Consultation Group*

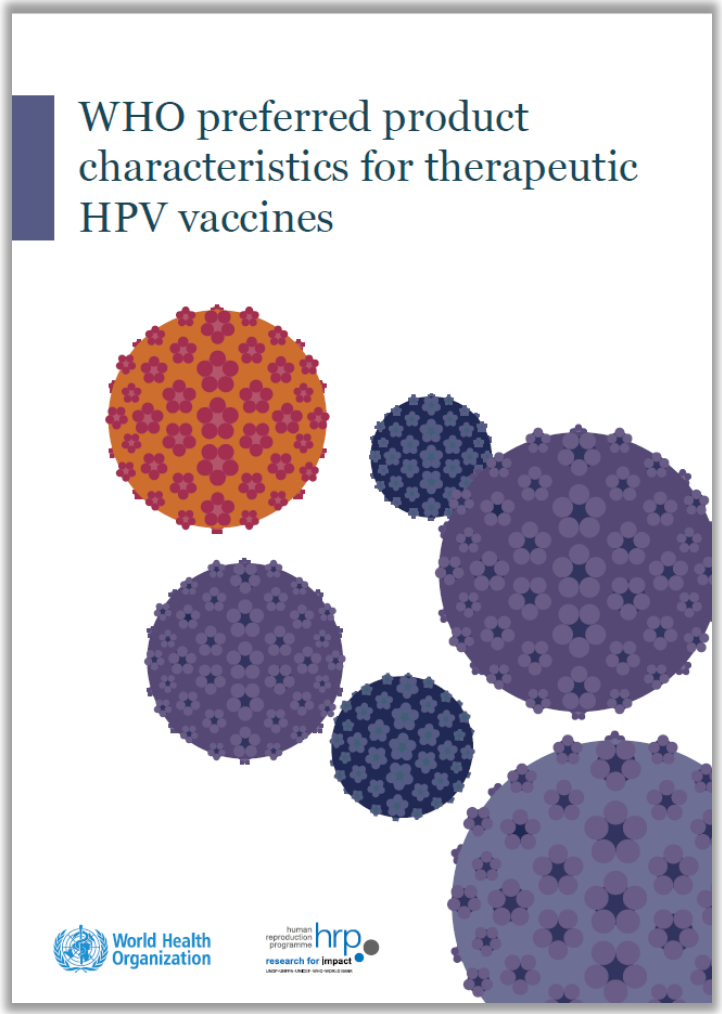
PDVAC = WHO Product Development for Vaccines Advisory Committee



https://doi.org/10.1016/j.vaccine.2022.08.020

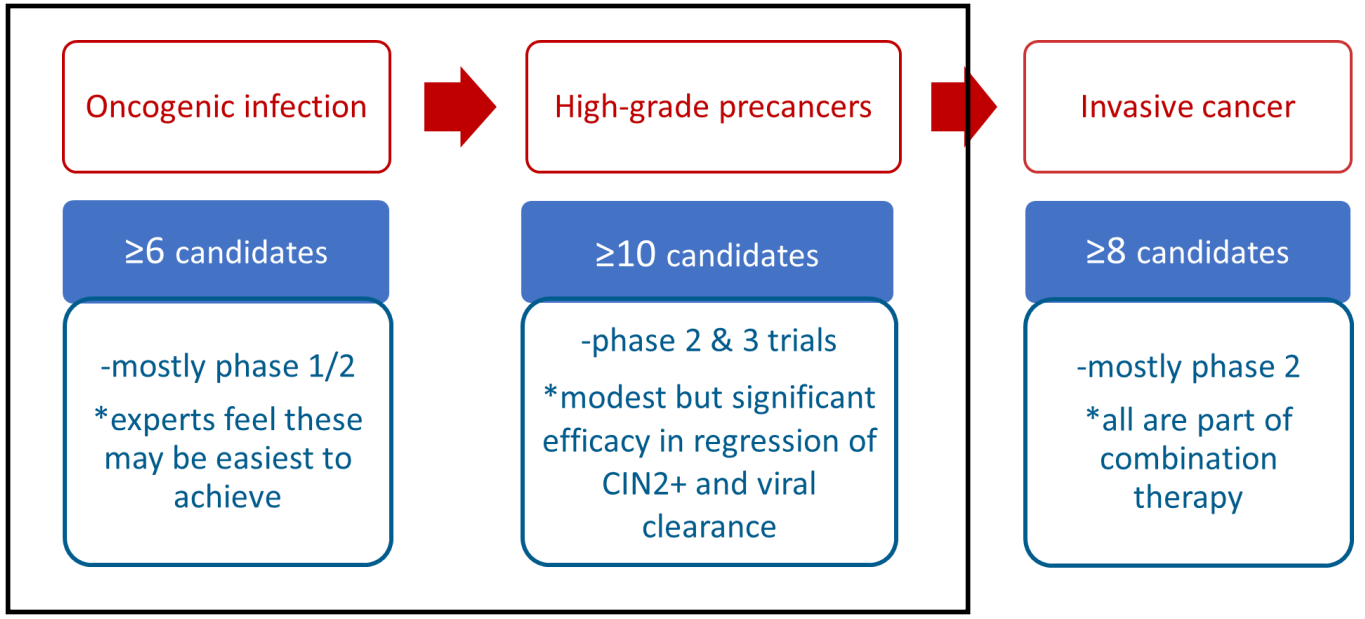
https://www.who.int/publications/i/item/9789240092174

WHO preferred product characteristics (PPCs) for therapeutic HPV vaccines, July 2024



PPC document

WHO webstory



https://www.who.int/publications/i/item/9789240092174

Public health need for therapeutic HPV vaccines

- Experts focused on **reducing cervical cancer deaths over next 30-40 years**

Waiting room of gynaecologic health outpatient department – Nepal.

- Difficulties in **scaling up screening and treatment in LMICs**
  - In many settings, S&T has been **difficult to scale up at all**: complexity, costs, need for multiple visits, lack of delivery infrastructure
  - Even in settings with some S&T implementation/testing capacity**: large loss to follow-up (LTFU)** between screening and treatment or **reduced access to treatment**
- Extra considerations for **women living with HIV**
  - Lower effectiveness/increased recurrences after existing treatment
  - Need for more frequent follow-up

human reproduction programme hrp 50
research for impact
UNDP·UNFPA·UNICEF·WHO·WORLD BANK

Alignment of public health need and vaccine approaches

- Both types of vaccines could play a role in addressing the public health need
- Ideally the vaccines would have activity against both infection and precancers
- Individual vaccines may have differential activity against these outcomes and thus different considerations

Clearance of HPV infection

Regression of high-grade precancer

To be illustrative, separate PPCs were developed for each

PPC 1: Vaccines that primarily clear oncogenic HPV infection

Indication	First generation vaccines Clearance of oncogenic infection, at a minimum HPV types 16 and 18 Increased public health value Regression of cervical precancers OR clearance of additional oncogenic HPV types OR prolonged effects against reinfection or recurrence
Target population	Adult women* (e.g., ages 25 to 49 years) esp in settings where high proportion have not received Px HPV vaccine nor been screened
Delivery strategy	Population-based delivery, with no requirement for preceding test OR Targeted vaccination based on positive test results

*The PPCs are intended to be inclusive of all people who can get cervical cancer, including cisgender women as well as transgender men and other gender diverse people who may be at risk.

PPC 2: Vaccines that primarily treat high-grade precancers

Indication	Regression of high-grade cervical precancers, at a minimum those due to HPV types 16 and 18 Regression of precancers due to other types or clearance of additional HPV types would add benefit
Target population	Those with a positive cervical cancer screening test according to current screening guidelines
Delivery strategy	Alignment with existing cervical cancer screening and treatment infrastructure HPV testing and vaccination may occur outside of structured screening programmes

Additional notes: PPCs for therapeutic HPV vaccines

- Therapeutic HPV vaccines may be **preferable to existing treatments** considering not just efficacy, but also safety, cost, deliverability, or acceptability
- Might also provide benefit as an **adjunct to existing treatments** to improve efficacy or reduce recurrences – may be particularly important for **WLHIV**
- A **"test and vaccinate" approach** – HPV testing followed by immediate vaccination for those testing positive – can be done in a variety of settings
- Primary indication for cervical infection, but additional **efficacy against HPV infections at other sites** (e.g. anal, vaginal, oropharyngeal) would be valuable

Preliminary modeling of therapeutic HPV vaccine impact

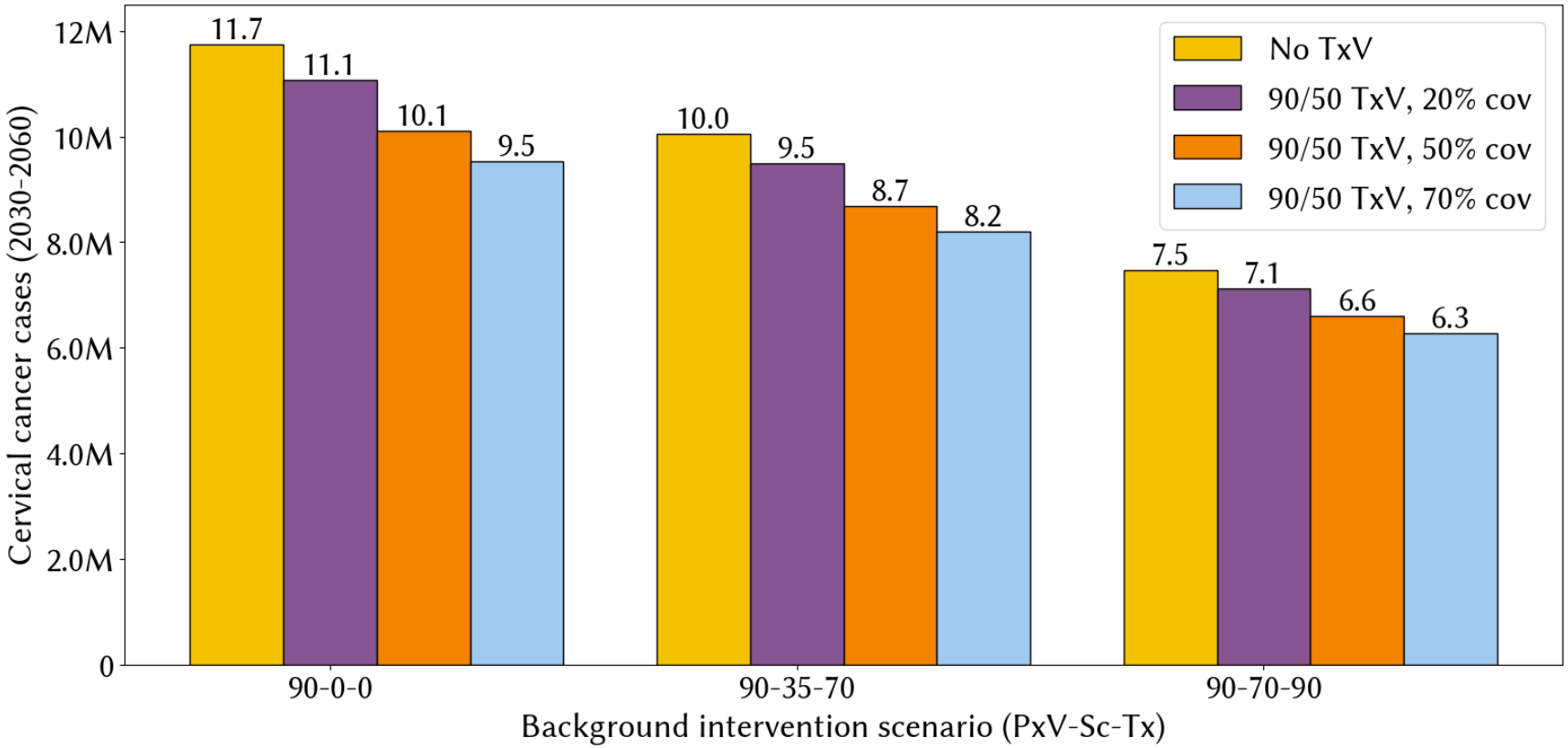
- Three models: mass vaccination with vaccines clearing infection
- Models showed therapeutic vaccines can accelerate reductions in cervical cancer burden, especially with action against both infection and high-grade precancers
  - Most optimistic assumptions: up to 25% CxCa cases averted over 30 years

- Added benefits of Tx HPV vaccines drop
  - as background scale-up of interventions approaches 90-70-90 targets
  - as therapeutic vaccine licensure is delayed
- Added benefits increase
  - with some efficacy against precancers
  - cross-protection
  - long-lasting immune memory

Canfell et al 2024; https://daffodilcentre.org/wp-content/uploads/2024/01/TxV-modelling-report_25Jan2024.pdf
Cohen et al 2024; https://www.medrxiv.org/content/10.1101/2023.12.04.23299403v1
Spencer et al, 2020; Int J Cancer 2022

human reproduction programme hrp 50
research for impact
UNDP·UNFPA·UNICEF·WHO·WORLD BANK

Modeled impact of Tx HPV vaccine in 9 high-burden LMICs



Tx HPV 16/18 vaccine:

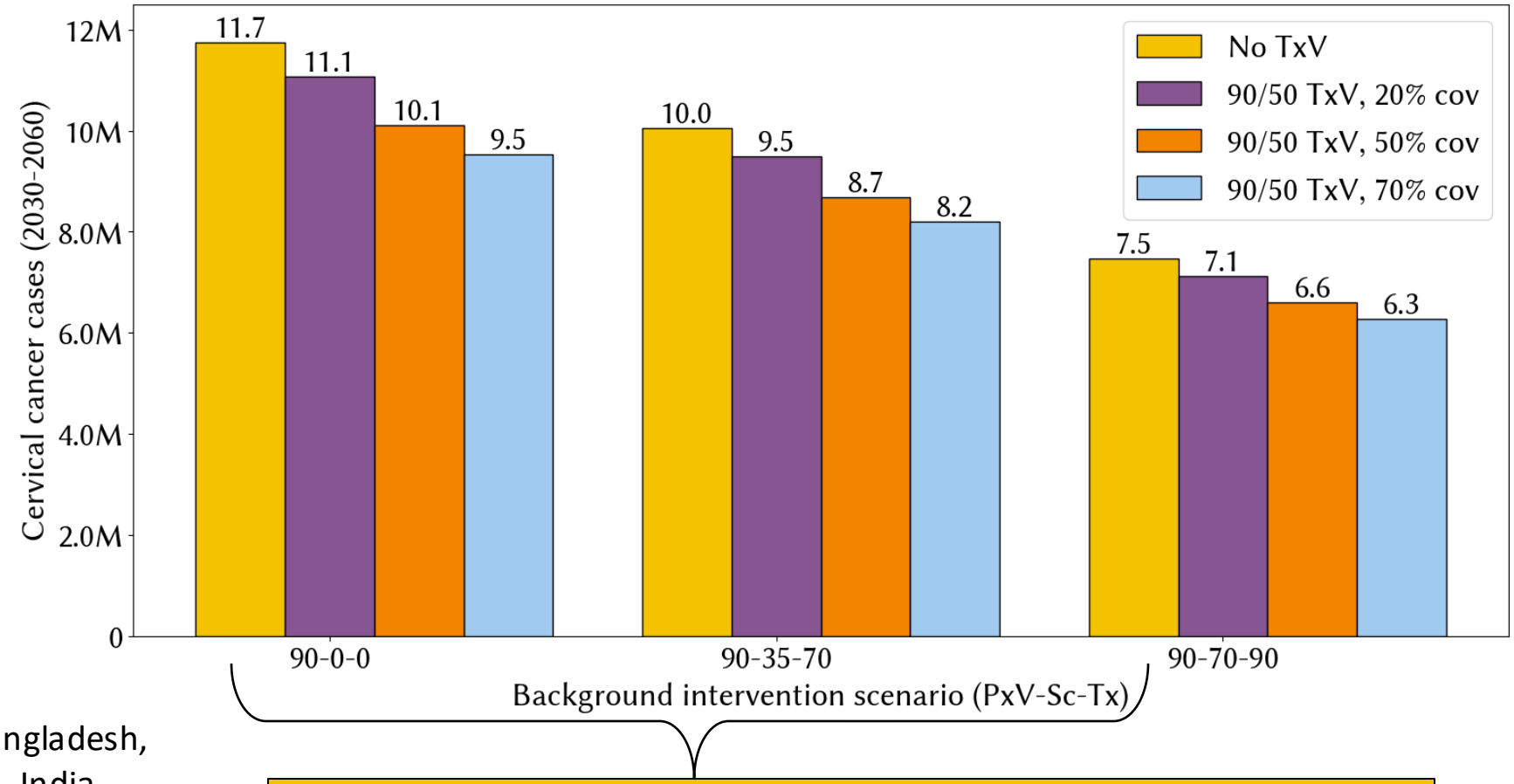
- Efficacy 90% HPV, 50% CIN2/3
- Introduced 2030
- Mass administration to 30-40yo women
- No cross protection
- Lifelong immune memory

Countries: Bangladesh, DRC, Ethiopia, India, Indonesia, Myanmar, Nigeria, Tanzania, Uganda

Unpublished data; https://www.medrxiv.org/content/10.1101/2023.12.04.23299403v1

Slide courtesy of Jamie Cohen, Institute for Disease Modelling

Modeled impact of Tx HPV vaccine in 9 high-burden LMICs



Tx HPV 16/18 vaccine:

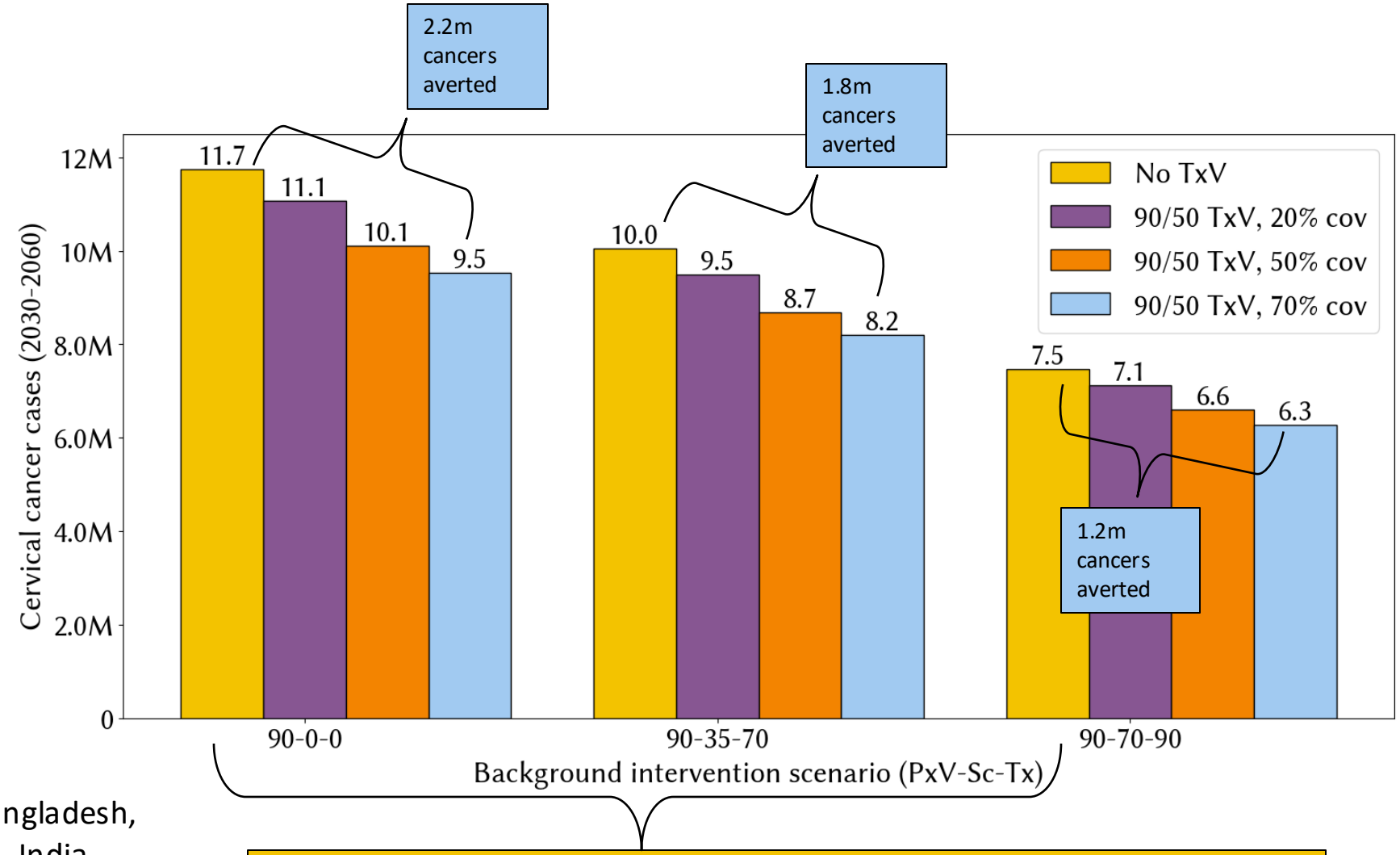
- Efficacy 90% HPV, 50% CIN2/3
- Introduced 2030
- Mass administration to 30-40yo women
- No cross protection
- Lifelong immune memory

Countries: Bangladesh, DRC, Ethiopia, India, Indonesia, Myanmar, Nigeria, Tanzania, Uganda

Scale-up to 70% screen coverage and 90% treatment can avert 4.2 million cancers (11.7 → 7.5), though may be infeasible without new tools

Slide courtesy of Jamie Cohen, Institute for Disease Modelling

Modeled impact of Tx HPV vaccine in 9 high-burden LMICs



Tx HPV 16/18 vaccine:

- Efficacy 90% HPV, 50% CIN2/3
- Introduced 2030
- Mass administration to 30-40yo women
- No cross protection
- Lifelong immune memory

Countries: Bangladesh, DRC, Ethiopia, India, Indonesia, Myanmar, Nigeria, Tanzania, Uganda

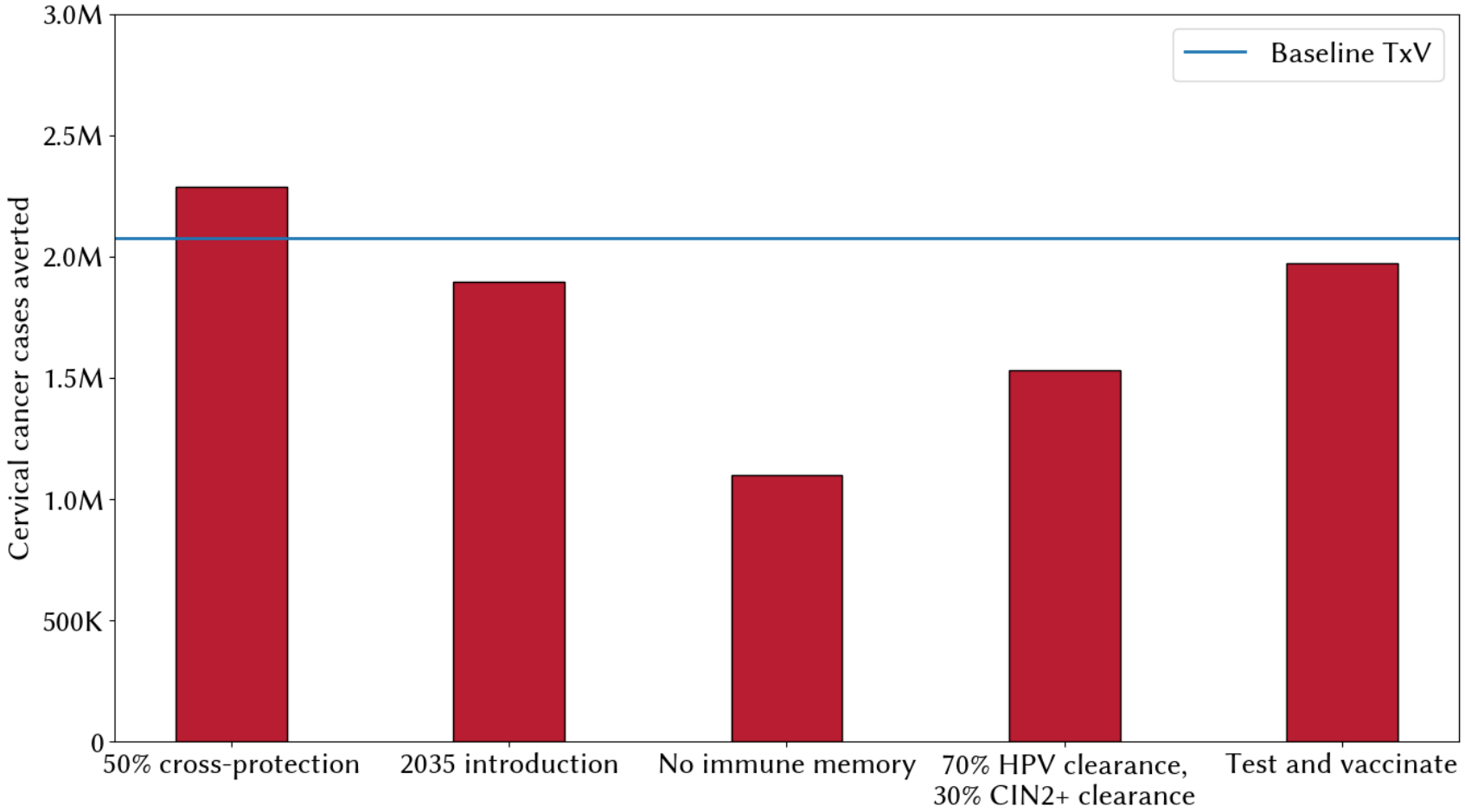
Scale-up to 70% screen coverage and 90% treatment can avert 4.2 million cancers (11.7 → 7.5), though may be infeasible without new tools

Slide courtesy of Jamie Cohen, Institute for Disease Modelling

Sensitivity analyses

Unpublished data;
https://www.medrxiv.org/content/10.1101/2023.12.04.23299403v1

- Benefit of 50% cross-protection
- Small cost of delayed introduction due to slowly accruing impact of PxV (residual burden 2035-2065 < 2030-2060)
- Impact highly sensitive to immune memory and reduced efficacy
- Test and vaccinate strategy: small reduction in cancers averted



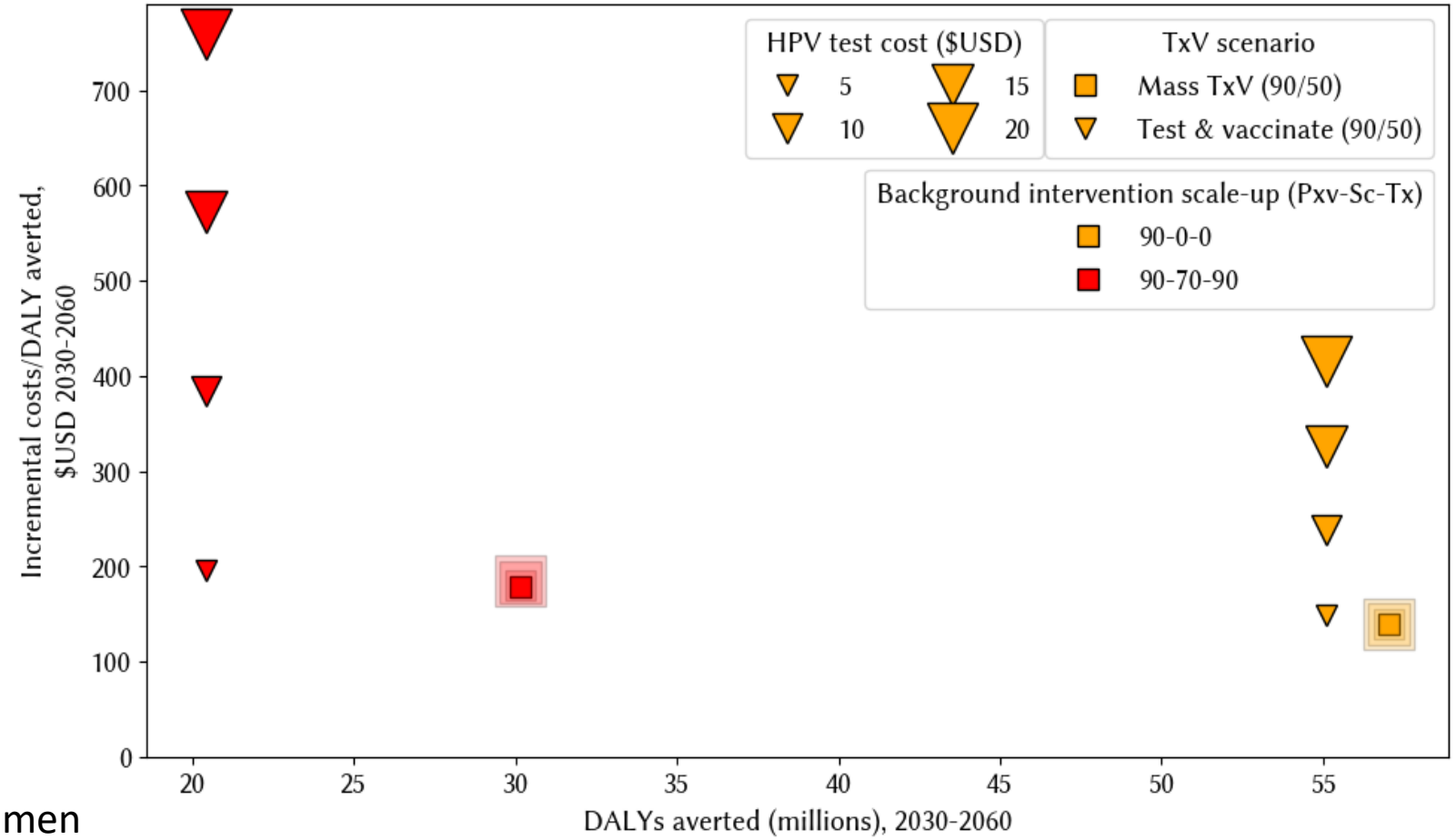
Baseline TxV scenarios: 70% coverage, efficacy: 90% HPV, 50% CIN2+, introduced in 2030 via mass administration; no cross protection; durable immune memory.

Assuming 90-0-0 background PxV/S&T scale-up.

Slide courtesy of Jamie Cohen, Institute for Disease Modelling

Cost-effectiveness analysis reveals important nuance

- Mass vaccination could avert up to 57 million DALYs at a cost of $140/DALY averted
- DALY impact falls nearly 50% if S&T reaches WHO 90-70-90 targets by 2030; cost/DALY averted increases
- Delivery via mass vaccination is more impactful and costs less per DALY averted than via test-and-vaccinate, unless cost of HPV test is < $5



TxV delivered 70% of 30-40 year old women starting in 2030

Unpublished data; https://www.medrxiv.org/content/10.1101/2023.12.04.23299403v1

Slide courtesy of Jamie Cohen, Institute for Disease Modelling

End-user assessment: therapeutic HPV vaccines.

Study objective:

To gain early understanding of the **potential value** of an HPV therapeutic vaccine, its **future use cases**, and **optimal characteristics** from the perspective of end users including **women, healthcare professionals** and **programme managers** using human-centered design methods

Part 1 **In-depth qualitative participatory research in Kenya**

- women aged 20-40 (n=35)
- healthcare workers (n=17)
- program managers (n=7)

Part 2 **Global remote key informant interviews and workshops**

- national program managers for immunisation and cervical cancer and implementing partners across all WHO regions (n=45)

SCOPE IMPACT

Insights from end-user assessment.

Preliminary; unpublished data

Opportunities for HPV TxV

Improved patient experience:

- Offer **relief** from fears through immediate and accessible treatment.
- Ease the process of care, by making it more **convenient** and **straightforward**.
- Contribute to addressing women's concerns about **privacy and discomfort** associated with gynecological exams.

Ease the process of providing cervical cancer services::

- Offer a **simplified** treatment process requiring fewer skills.
- Improve **continuity** of care if it requires less complicated follow-up for referrals.
- Create health system **efficiencies** in terms of the cost of and time required for providing care.
- Extend **reach** to women who may currently lack access.

Overall value of contributing to public health impact

Preferences for HPV TxV

Women and healthcare providers prefer:

- Communication about therapeutic vaccines that **reduce confusion** about what they do and how they work
- Is it a **treatment or vaccine**? Distinguishing from PxV

Program managers delivery strategy perspectives:

- Population-based approach:
  - Concerns about **population skepticism, hesitancy** in uptake of new vaccines
  - **Resource constraints** in LMICs for vaccinating full population, viewed as more **unrealistic** approach
  - Concerns about **"wasting" vaccines** since most HPV clears on its own compared with preceding test
- Screening/testing-based approach:
  - Considered **more viable** and realistic approach
  - Vaccine hesitancy less of an issue **after positive test**
  - Simpler, but subject to some **similar challenges** faced by the system now, such as trained health workforce, costs of tests, etc

HPV THERAPEUTIC VACCINES – PRODUCT DEVELOPMENT "CHALLENGES AND OPPORTUNITIES"

Peter Dull (BMGF)

December 9, 2024

PDVAC

HPV TX VACCINE – REGULATORY ENDPOINTS MEETING REPORT PUBLISHED

Vaccine 42 (2024) 126100

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Conference report

Meeting report: Considerations for trial design and endpoints in licensing therapeutic HPV16/18 vaccines to prevent cervical cancer

Peter M. Dull [a,1,*], Sharon L. Achilles [a], Rafi Ahmed [b], Ruanne V. Barnabas [c,d,e], Nicole G. Campos [e], Keith Chirgwin [f], Jamie A. Cohen [a], Silvia de Sanjosé [g,h], John Doorbar [i], Mark H. Einstein [j], Claudia I. Emerson [k], Sami L. Gottlieb [l], Allan Hildesheim [m], Youlin Qiao [n], Paul Ruff [o], Joshua N. Sampson [h], Peter Sasieni [p], Mark Schiffman [q], Haina Shin [a], Margaret A. Stanley [i], Cornelia L. Trimble [r], Nicholas Wentzensen [q], Angelika B. Riemer [s,t,1,2], John T. Schiller [u,1,2], Aimée R. Kreimer [q,1,2]

- Gaps identified and discussed
  - Natural history of HPV infection incompletely understood
  - Surrogate for true viral “clearance” (2 negative tests)
  - Implications for different follow-up designs (negative HPV test vs. lack of lesion progression)
- Study size estimates for efficacy (success criteria)
- Implications of target indication
  - Among HPV / CIN positive vs
  - Among “at risk” population

HPV TX VACCINE – "CLEARANCE" STUDIES ARE FEASIBLE

3b. Sample size estimates for study of treatment of women with HPV16/18 prevalent infection, evaluation at 2 years post vaccination (Primary study objective). Range of clearance probabilities derived from published and unpublished data reported in Table 2

Probability of clearance in unvaccinated (at 2 years)	True VE	VE to exclude (LL95%CI)	Sample size (per arm) with 80% power	Sample size (per arm) with 90% power
90%	90%	70%	500	630
90%	90%	60%	280	370
90%	90%	50%	200	260
70%	90%	70%	150	200
70%	90%	60%	90	110
70%	90%	50%	70	80

3c. Sample size estimates for study of prevention of progression to cervical pre-cancer among women with HPV16 prevalent HPV infection, evaluation at 2 years post vaccination (Secondary study objective). Range of progression probabilities from Costa Rica Vaccine Trial (CVT) [39]

Probability of progression to CIN2+ among unvaccinated (at 2 years)	True VE	VE to exclude (LL95% CI)	Sample size (per arm) with 80% power	Sample size (per arm) with 90% power
6.7%	90%	70%	730	950
6.7%	90%	60%	430	550
6.7%	90%	50%	310	410
4.2%	90%	70%	1180	1560
4.2%	90%	60%	680	890
4.2%	90%	50%	490	620

DS, dual stain; HPV, human papilloma virus.
HPV, human papilloma virus; VE, vaccine efficacy; LL95%CI, Lower limit of 95% Confidence interval.
CIN, cervical intraepithelial neoplasia; VE, vaccine efficacy, LL95%CI, Lower limit of 95% Confidence interval.

- Phase 3 studies can be "reasonably" sized (range 300 – 1000 per group) with Phase 2b PoC based on "negative HPV" significantly smaller

- High complexity studies (i.e., high per subject cost) and duration requires negotiation

HPV THERAPEUTIC VACCINE – WHAT IS NEXT?

2024: Another year for learning but pipeline growing

- How do we facilitate developer engagement?
  - Better delineate / socialize high- / low-income market opportunities
    - China example driving domestic developers (mRNA, sa-mRNA, vector platforms) into clinical studies
  - Full Value of Vaccine Assessment
- What is the target launch for an HPV therapeutic vaccine (i.e., is 2030 realistic) and how important is it?

  Multiple dependencies: Lack of PoC clinical study for a clearance vaccine; Lack of "major pharma" engagement; Lack of funding path in LMIC setting; Operational learnings for study conduct shared

Summary

- Therapeutic HPV vaccines are in clinical development and might be an additional tool in efforts to eliminate cervical cancer and save lives
- Therapeutic vaccines that clear infection and cause regression of high-grade precancers could both play a role in prevention programmes
- Must not diminish the urgency around current scale-up, but therapeutic HPV vaccines remain a promising innovation
- Additional work is still needed to better quantify added value

The Teal Sisters, Zambia, survivors and advocates for cervical cancer elimination

Evidence needs and possible next steps

- Better understanding of value – which components of FVVA most important?
  - Further evaluation of current models and cross-model comparisons (with IVIR-AC)
  - Specific trade-off analyses, e.g.:
    - the time to licensure after which it doesn't make sense to pursue therapeutic vaccines
    - investment in therapeutic vaccines vs expanding prophylactic use to more age cohorts
    - for S&T scenario: how much lower can efficacy be if accessibility is increased?
  - Adequate assessment of HIV, country archetypes, economic modeling
- Better understanding of the pipeline – alignment with global needs and realistic timelines to licensure
- Better understanding of end use – how likely to be able to scale up therapeutic vaccines in the different use cases, programmatic needs

human reproduction programme hrp 50
research for impact
UNDP·UNFPA·UNICEF·WHO·WORLD BANK

For discussion with PDVAC

- What role should WHO play in advancing therapeutic HPV vaccine development?
- Should an FVVA be done now? Full FVVA or certain components?

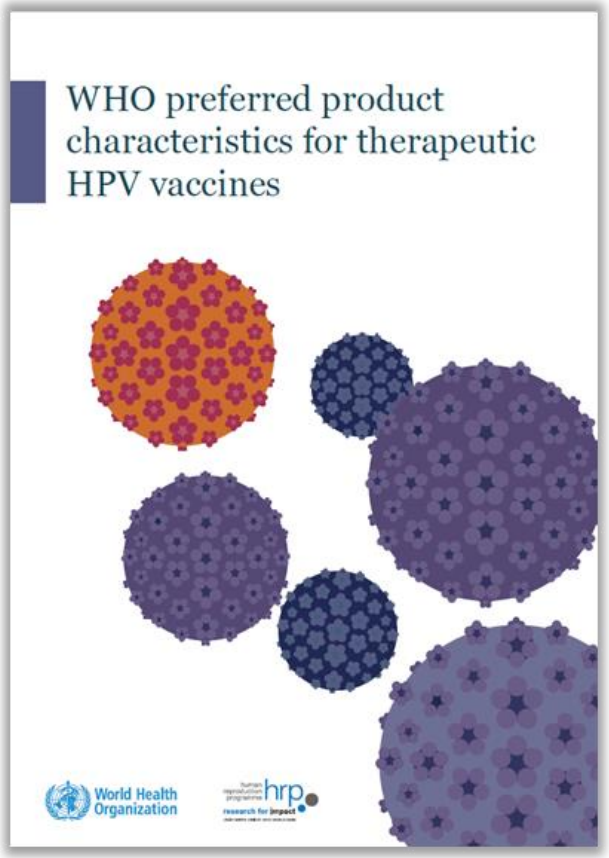
Thank you!

Sincere thanks to the many colleagues participating in these efforts, and the Bill & Melinda Gates Foundation for support. Special thanks to:

Sharon Achilles
Maribel Almonte
Partha Basu
Karen Canfell and team
Jamie Cohen
David Kaslow
Nelly Mugo
Gina Ogilvie
Holly Prudden
John Schiller
Celina Schocken
Margaret Stanley

World Health Organization

human reproduction programme hrp research for impact
UNDP · UNFPA · UNICEF · WHO · WORLD BANK



PPC document

WHO webstory