IDM INSTITUTE FOR DISEASE MODELING

Understanding the key determinants of an HPV therapeutic vaccine: a modeling analysis

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Persistent, high-risk HPV causes invasive cervical cancer

- HPV is one of the most prevalent STIs
- 90% of infections self-resolve and provide partially protective immunity
- Persistent hr-HPV causes dysplastic cell changes and accumulation of genetic mutations that can lead to invasive cervical cancer

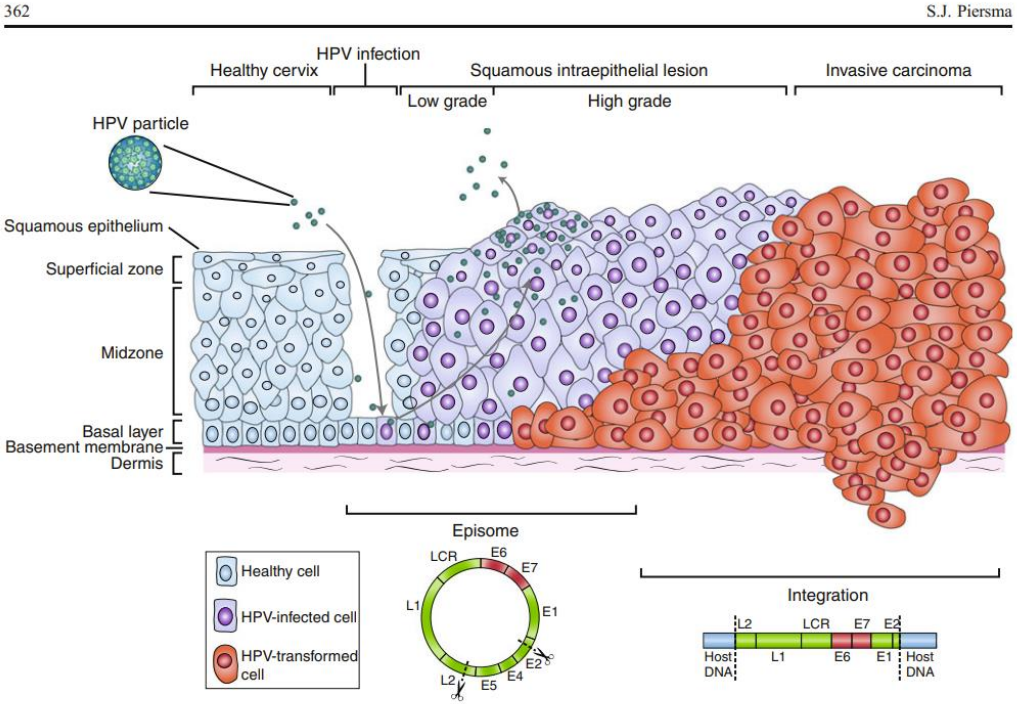
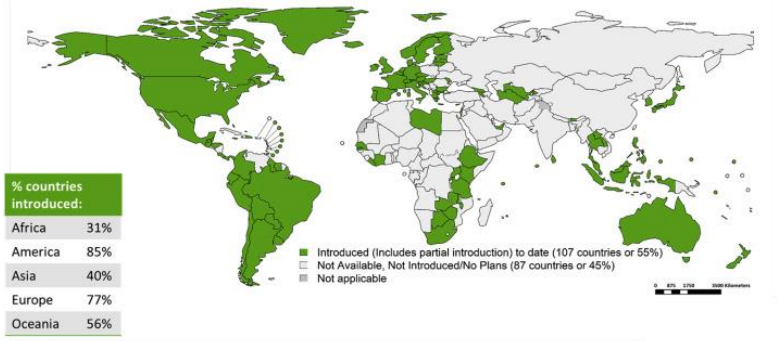


Fig. 1 Human papilloma virus (HPV)-induced malignant progression. Infection with HPV likely occurs in the basal layer of the cervical epithelium, which is exposed in a microlesion. During the productive lifecycle the early genes (E1, E2, E4, E5, E6 and E7) are expressed and viral DNA is replicated from episomal DNA. Hereafter, in the upper layers the late genes L1 and L2 are expressed and viral particles are assembled. Subsequently the virions are shed and new infection can be commenced. Low-grade squamous intraepithelial lesion (LSIL) support the production of viral particles. In a minority of infected women the lesion progresses into high-grade squamous intraepithelial lesion (HSIL). Progression towards microinvasive and invasive carcinoma is associated with the integration of the viral genome into host DNA and is frequently accompanied by loss of part of the viral genome, including disruption of the E2 gene. As a result, expression of the viral oncoproteins E6 and E7 are upregulated. LCR, long control region. Adapted by permission from Macmillan Publishers Ltd: [Nature Reviews Cancer] (Woodman et al. [130]), copyright (2007)

Cervical cancer is at a global inflection point

- **Context:**
  - Despite being preventable, there are still 600k new cases and 300k new deaths from CCx each year, 90% of which occur in LMICs
  - Modeling showed we can achieve CCx elimination by scaling up PxV and S&T → WHO 90-70-90 elimination strategy set
- **Challenge:**
  - Prophylactic vaccine supply, demand; delayed health impact
  - High-cost HPV testing, not point of care, loss to follow-up, variable performance
- **Opportunity:** New tools are necessary to enable delivery at scale, address unmet needs of women missed by PxV, and bend CCx curve

HPV vaccination introduction status, 2021



Bruni et al., 2021

Cervical cancer screening coverage, 2019

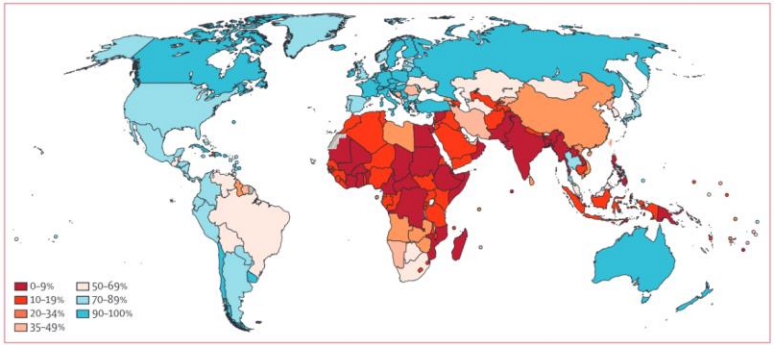


Figure 2: Ever in lifetime cervical cancer screening coverage in women aged 30-49 years in 2019 by country

Bruni et al., 2019

What is the public health value of a therapeutic HPV vaccine?

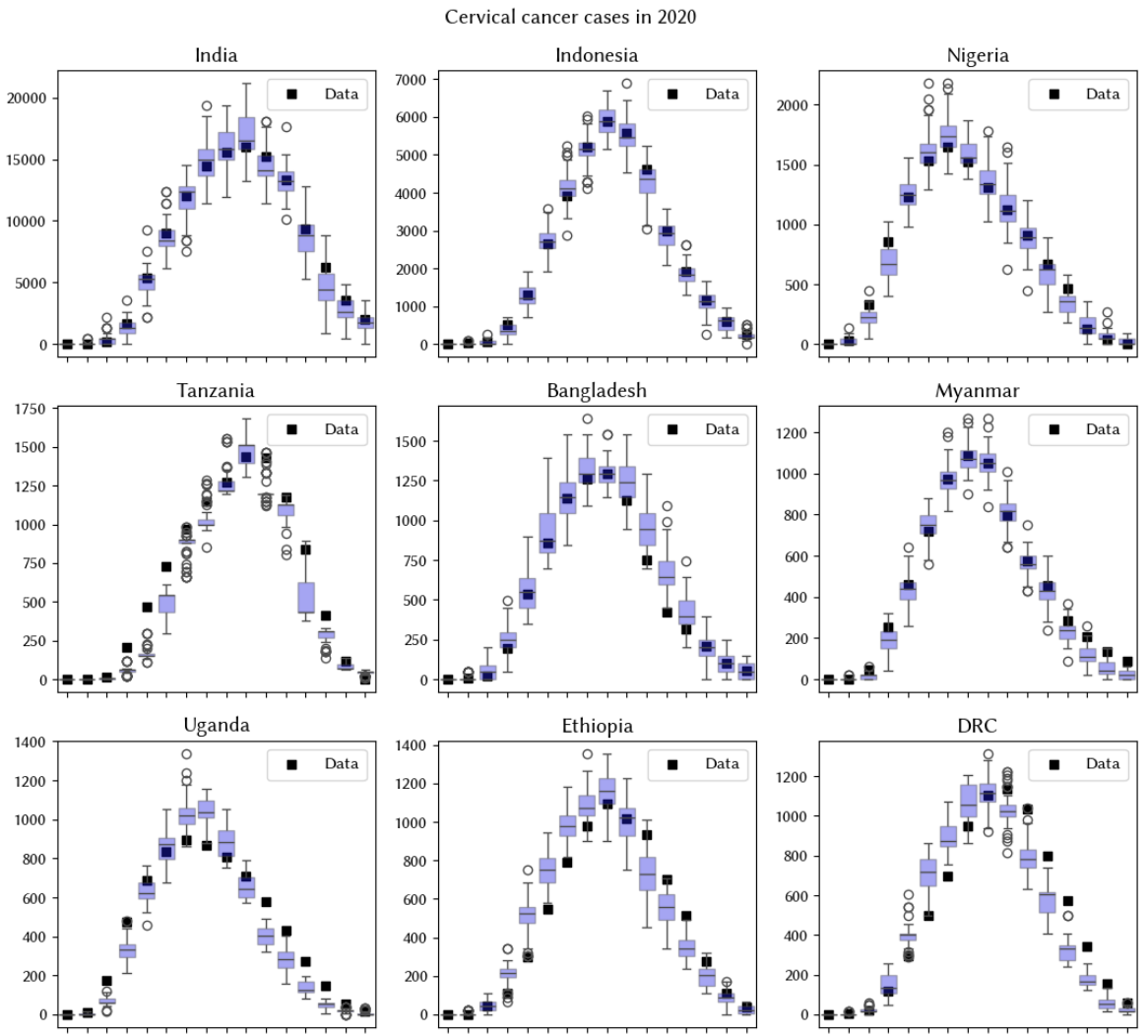
- Research question(s)
  1. Is there value in developing a therapeutic HPV vaccine?
  2. What are the key variables that influence the potential value of such a product?
  3. How much variation is there by setting?
- Methodology
  1. Calibrate models of HPV and cervical cancer epidemiology in 9-high burden LMICs using HPVsim, an open-source agent-based modeling framework for HPV transmission and progression
  2. Project residual burden of cervical cancer until 2060 with various levels of background intervention
     a. Assuming successful prophylactic vaccine scale-up (90% of 9-14 year olds)
     b. Varying S&T scale-up: 0%, 35%, 70% coverage of twice-lifetime HPV DNA screening with 10-30% treatment LTFU
  3. Evaluate therapeutic vaccine impact (cervical cancer cases, deaths, and DALYs averted)

Therapeutic vaccine assumptions

	Base case	Sensitivity
TxV effectiveness (HPV clearance/CIN2+ regression)	90/0, 70/30, 50/50, 90/50	N/A
Target age of routine administration	30, 35, 40	N/A
Age of catch-up campaign (in 1st year of introduction)	Target age – target age + 10	N/A
Coverage	70% first-dose coverage, 20% LTFU between doses	N/A
Doses	2-doses, 3 months apart	N/A
TxV immune memory	Maximum of efficacy against virus and lesion	No immune memory
Introduction year	2030	2035
Cross-protection	None	50% cross protection against all other high-risk genotypes

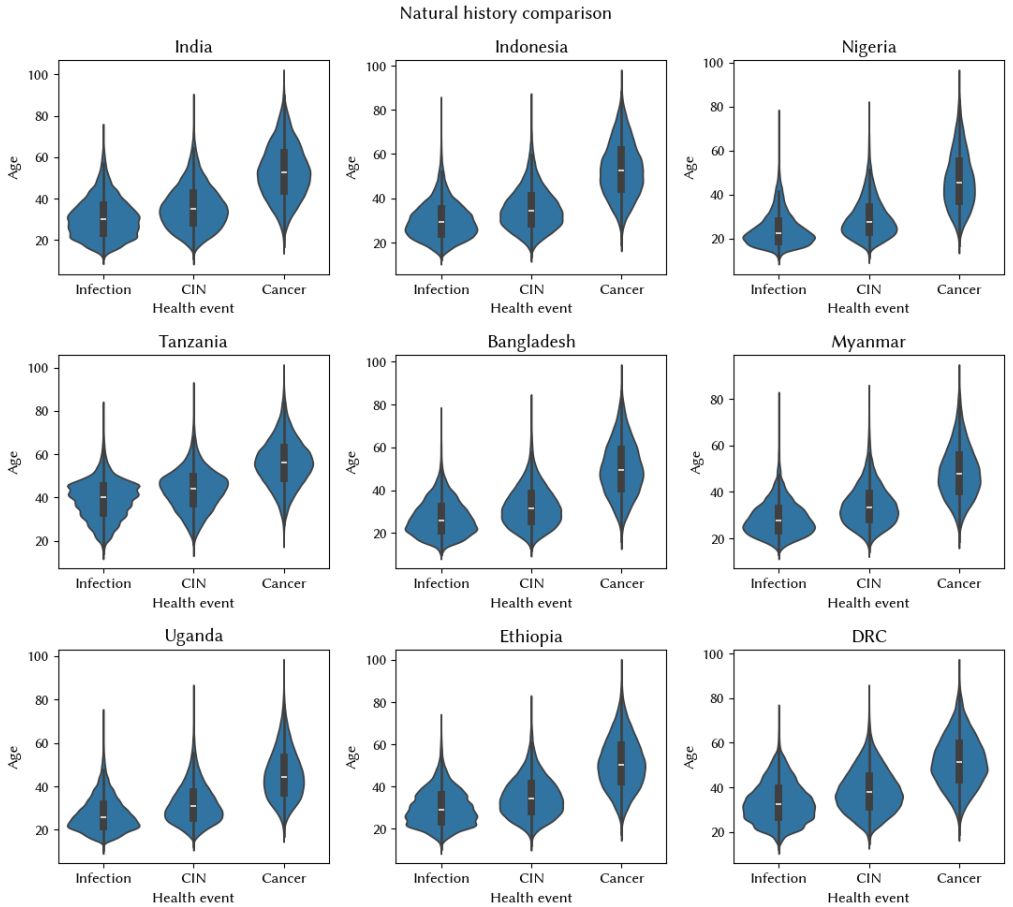
Calibration

- Calibrated HPVsim to cancers by age (and, where possible, genotype distribution in pre-cancer/ cancer) by adjusting:
  - Sexual behavior (distribution of extra-marital partners)
  - Duration of CIN2+ prior to regression or oncogenesis
  - Rate of oncogenesis



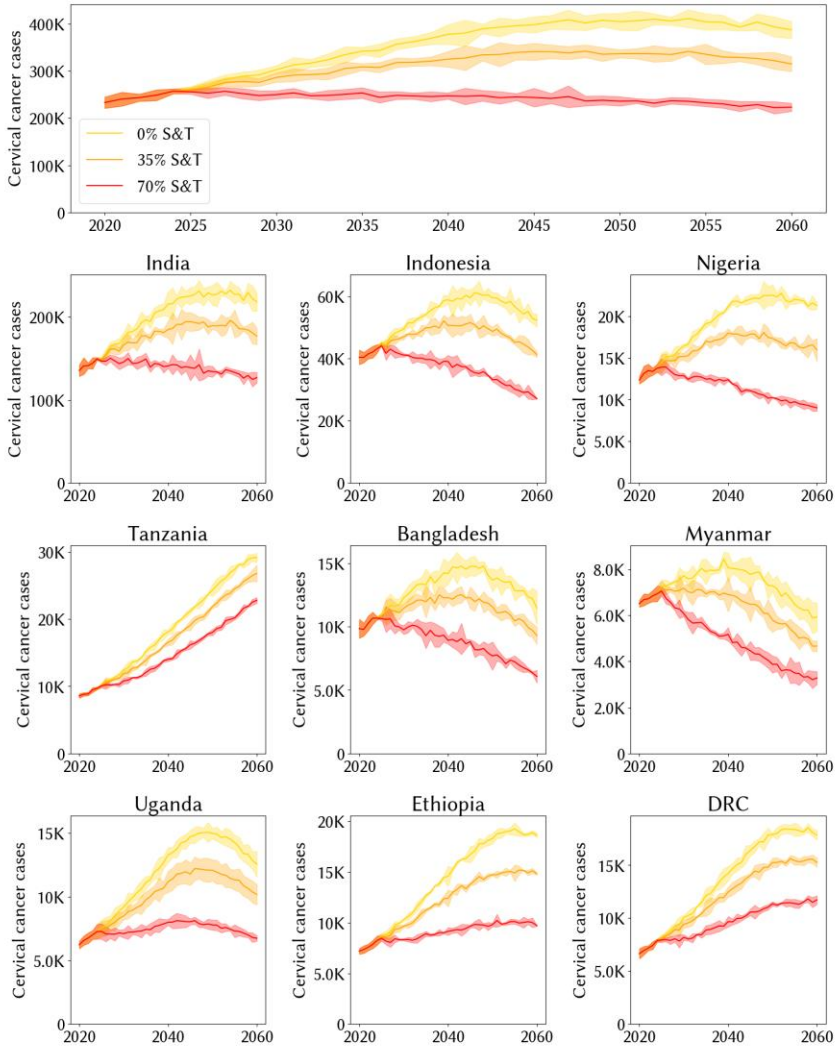
Natural history variation across settings

- Age of causal HPV infection youngest in settings with younger age of cancer (Nigeria, Uganda) and oldest in settings with older age of cancer (India, Tanzania)
  - Function of sexual behavior differences (debut, concurrency)
  - Non-identifiable with durations/ progression rates (i.e., earlier/later age of causal infection vs. shorter/longer dwelltime)



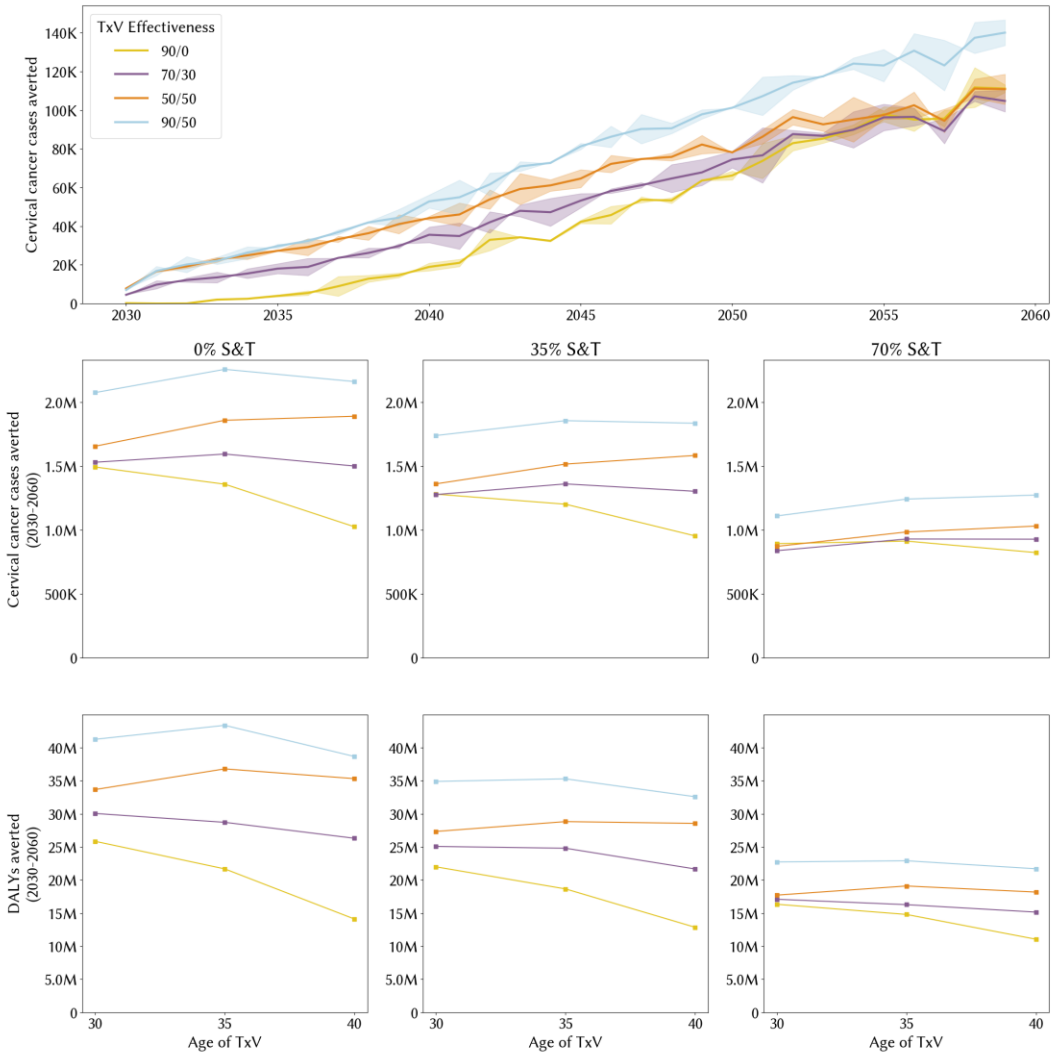
Residual burden

- Significant residual burden over next 35 years, even with optimistic PxV and S&T scale-up
- Over 200,000 cases annually in 9 high-burden countries
- >50% of burden driven by India



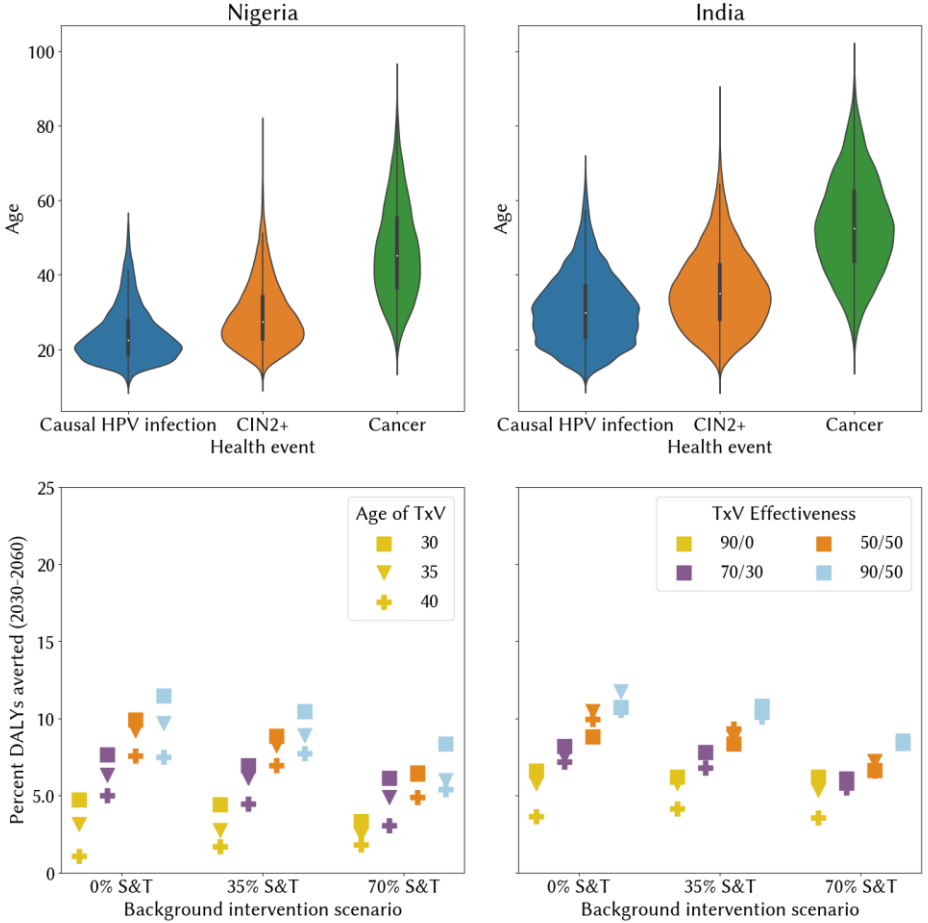
TxV could avert ~40 million DALYs

- Effectiveness against CIN2+ has biggest impact over short term and virus over long term, mirroring delayed impact of PxV
- TxV could optimistically avert 45 million DALYs over 30 years in 9 high-burden countries
- There is more value to regressing CIN2+ if administered to older vs. younger women
  - Optimal age target based upon product profile



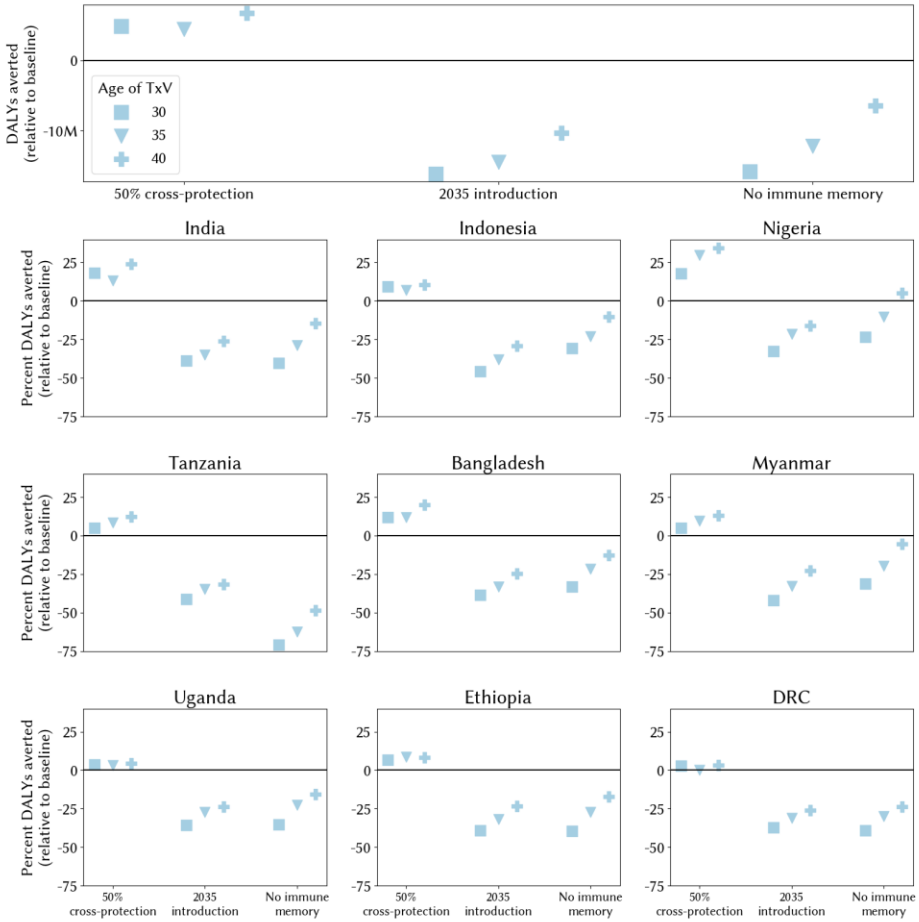
Country comparisons: age of infection/cancer

- Age that maximizes DALYs averted is younger in Nigeria than in India for every product profile and background level of screening and treatment coverage.
- In Nigeria it is always optimal to target 30 year-old women for routine administration of TxV
- The optimal age in India depends upon the TxV effectiveness against virus and lesion as well as background level of screening and treatment coverage.



Sensitivity analysis reveals more nuance

- 50% cross-protection would avert an additional 5-10 million DALYs over 30 years
  - CP would increase DALYs averted in Nigeria by up to 30% and would have a negligible impact on DALYs averted in DRC & Uganda
- Delaying TxV introduction by 5 years would result in a larger loss in impact, with less variation by age of administration and by country.
- Lack of immune memory results in variable loss by age of TxV administration and country
  - Larger loss for 30 than 35 or 40 year-olds
  - Smallest loss in Nigeria, largest in Tanzania



Conclusion

- An HPV therapeutic vaccine could have significant impact over the next 30 years
- Efficacy against CIN2+ will accelerate burden reduction
- Immune memory will sustain long-term impact
- Screen and treat scale-up can also bend burden curve, thereby reducing size of TxV impact – all shots on goal must be pursued
- Optimal age target will depend upon the attributes of the product and setting-specific factors

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