IDM INSTITUTE FOR DISEASE MODELING

Inferring the natural history of HPV from global cancer registries

A multi-country calibration exercise

Robyn Stuart, Jamie Cohen, Cliff Kerr,
Darcy Rao, Romesh Abeysuriya, Dan Klein,

IDM symposium 2023, Seattle, WA
23 May 2023

BILL & MELINDA GATES *foundation*

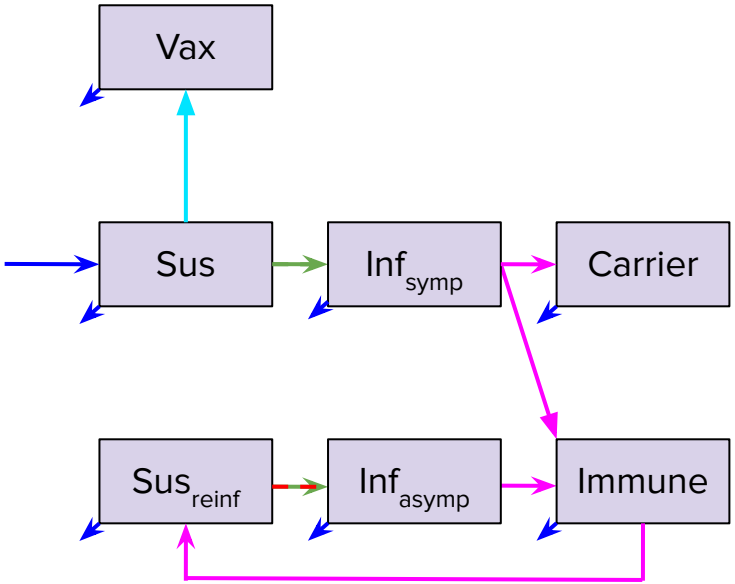
Background

Basic motivating question

- Main drivers of differences in epidemics/disease outcomes:
  - Demographic differences
  - Programmatic differences
  - Behavioral/environmental differences
  - Natural history differences?

- **How much do we expect the natural history of a disease to vary from country to country?**

Typhoid model (Bilcke et al 2019)



Bilcke, J., et al., Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study. *Lancet Infectious Diseases* **7,** 728 (2019).

How has this question been approached in the past?

- Three options for estimating natural history parameters:
  a. **Unconstrained**: parameters can vary from setting to setting depending on what best fits the data
  b. **Constrained**: parameters are fixed & identical from setting to setting
  c. **Semi-constrained**: some parameters are pooled, other free to vary

One-off models, data-driven applications

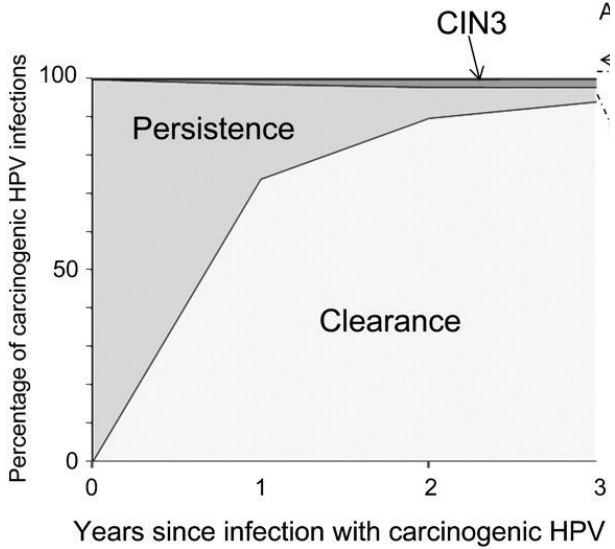
Common approach with HPV models

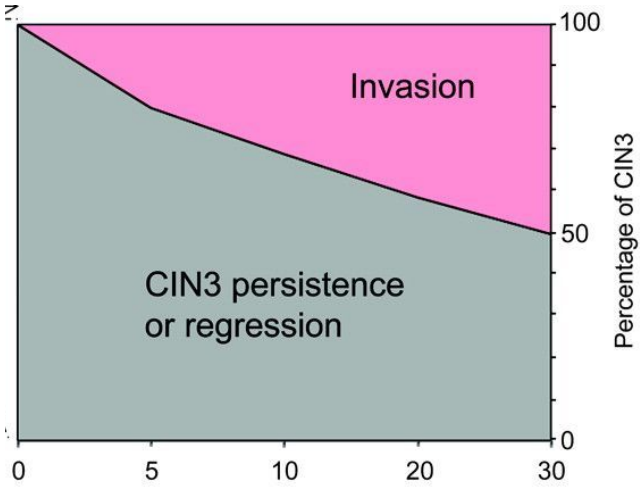
Balances flexibility & tractability

IDM INSTITUTE FOR DISEASE MODELING

A primer in HPV

- Very common STI, most people* get infected soon after sexual debut
- >50% of infections are undetectable within 6–12 months, >90% clear in 1-2y
- Persistent infection ➜ precancerous lesions on the cervix
- Precancerous lesions can clear on their own or progress to invasive cervical cancer



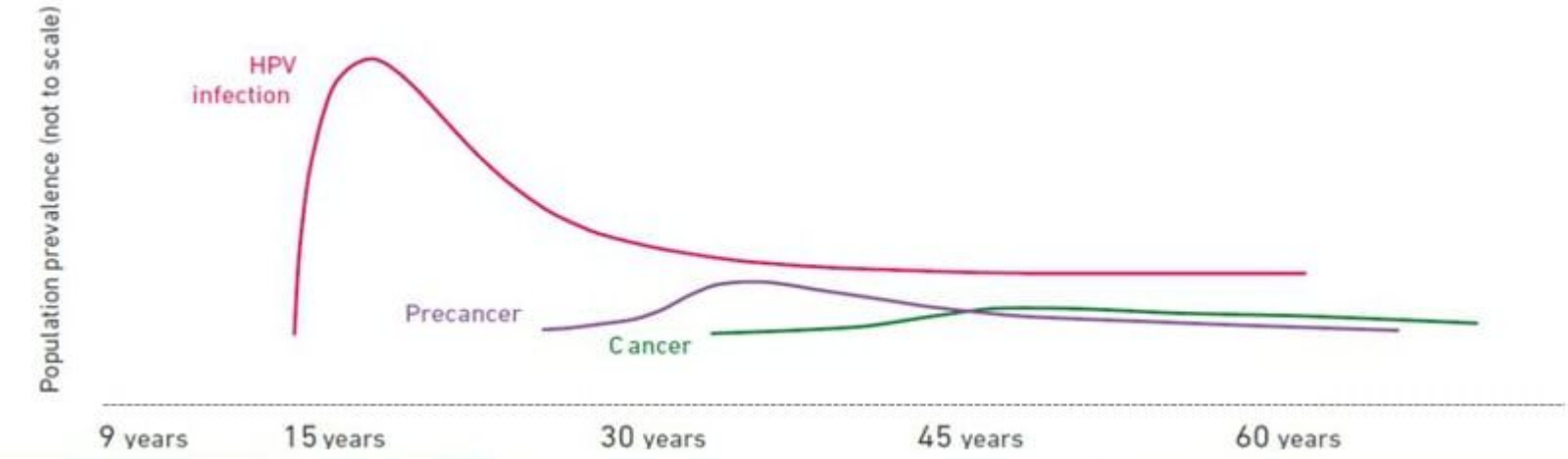


* in absence of vaccination

Figure source: Schiffman, M. et al, Human Papillomavirus Testing in the Prevention of Cervical Cancer, Journal of the National Cancer Institute **103**, 368–383,

HPV at a population level

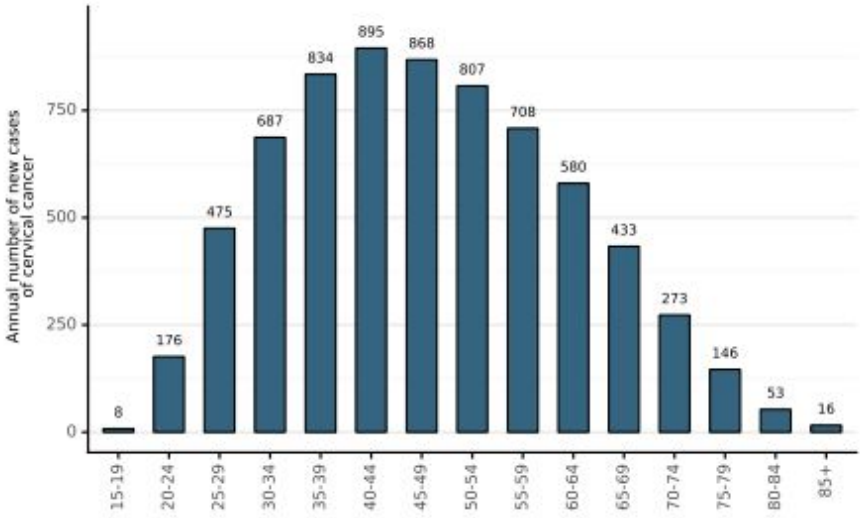
- Incident HPV infections peak shortly after sexual debut
- High-grade precancerous lesions peak ~**10-15** years later
- Invasive cancers peak **???** years after that



IDM INSTITUTE FOR DISEASE MODELING

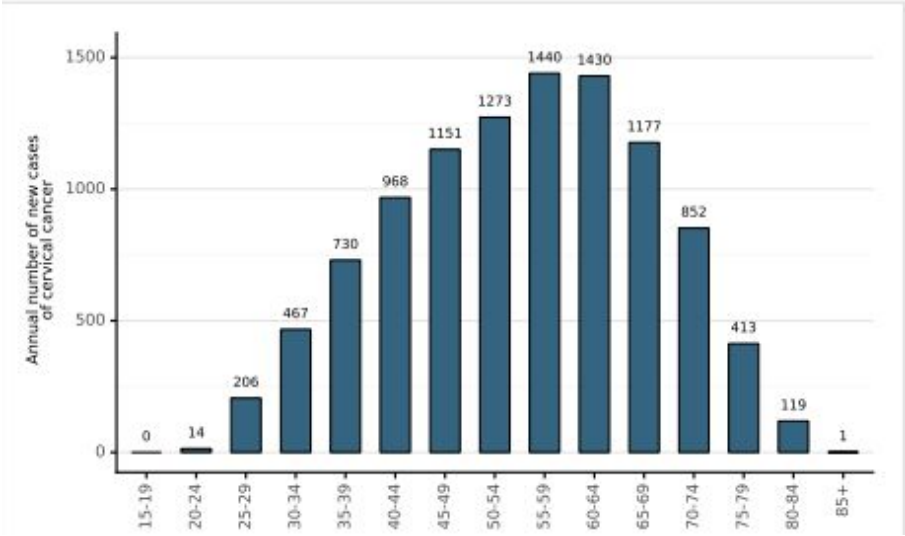
Age distribution of cervical cancer cases

UGANDA: cancers peak at 40-44



- Life expectancy: **63**
- Births/woman: **4.7**
- HIV prevalence F15-49: **6.6%** (UNAIDS)
- Median age of debut: **16.9** (2016 DHS)

TANZANIA: cancers peak at 55-59



- Life expectancy: **66**
- Births/woman: **4.8**
- HIV prevalence F15-49: **5.7%** (UNAIDS)
- Median age of debut: **17.2** (2016 DHS)

IDM INSTITUTE FOR DISEASE MODELING

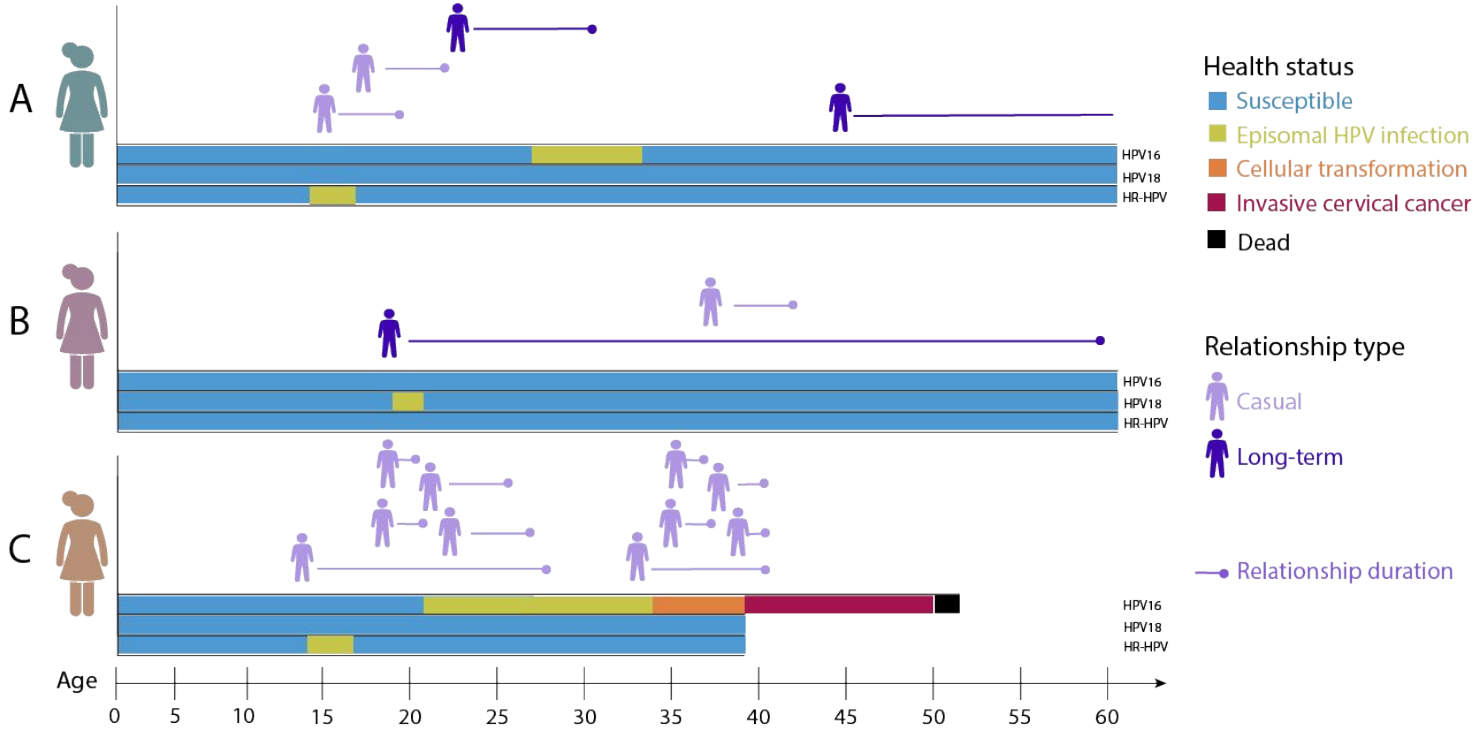
Goal of this work

- **Objective**: determine whether the differences in the age distribution of cervical cancers across SSA can be explained *without* varying natural history parameters
- **Study design**: simulation study using an agent-based HPV model
- **Setting**: 30 SSA countries [insert pic of pop size/burden]

Methods

Modeling framework: HPVsim

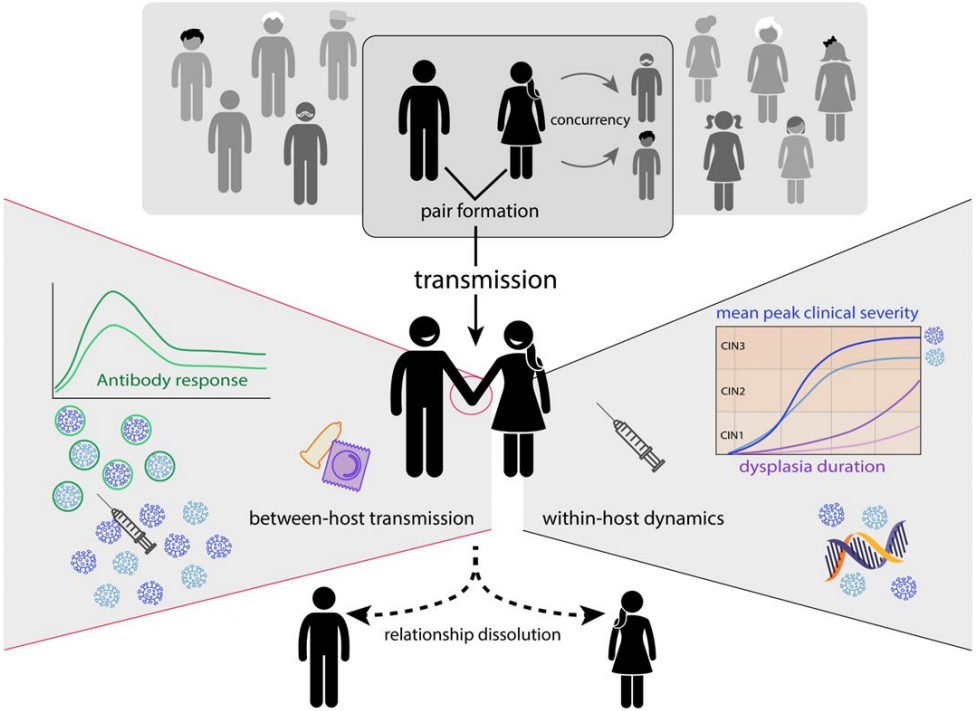
- Agent-based model



IDM INSTITUTE FOR DISEASE MODELING

Modeling framework: HPVsim

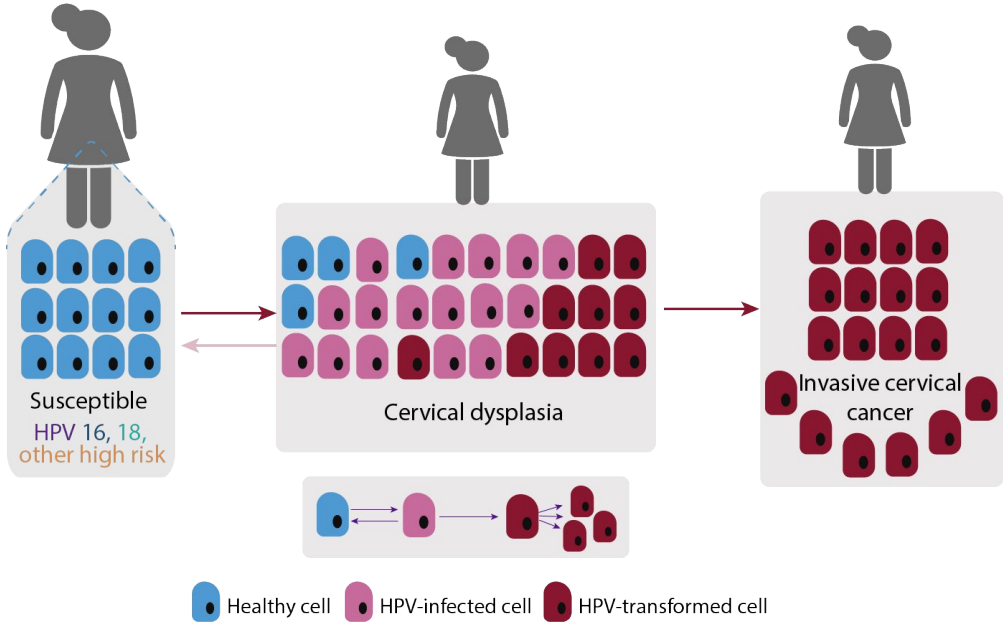
- Agent-based model
  - captures HPV transmission



IDM INSTITUTE FOR DISEASE MODELING

Modeling framework: HPVsim

- Agent-based model
  - captures HPV transmission
  - simulates progression



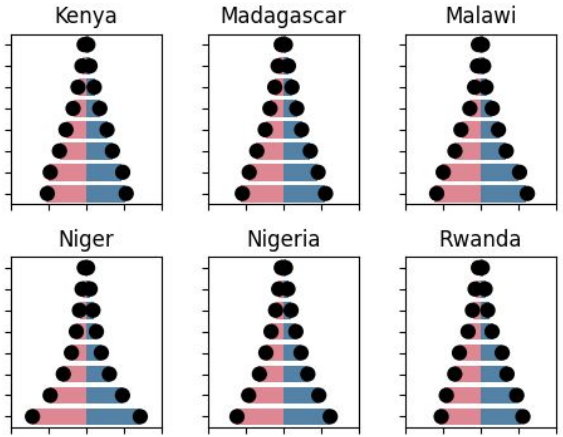
IDM INSTITUTE FOR DISEASE MODELING

Modeling framework: HPVsim

- Agent-based model
  - captures HPV transmission
  - simulates progression
- Software details:
  - Implemented in pure Python
  - Open source (MIT license)
  - Easy to use
  - Online tutorials
  - Documentation
  - Fast (aim: <1 min/simulation)

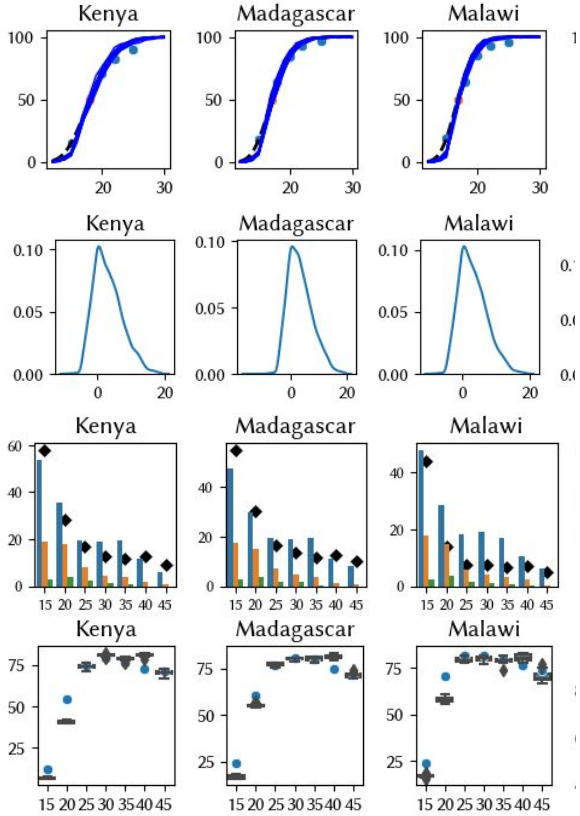
Account for demographic, behavioral, and programmatic differences

Demography (WPP):
match pop distributions



Behavior (DHS):

- age of debut
- partner age differences
- proportion of women with >1 casual partner
- proportion of women married



Programmatic: assume no significant differences

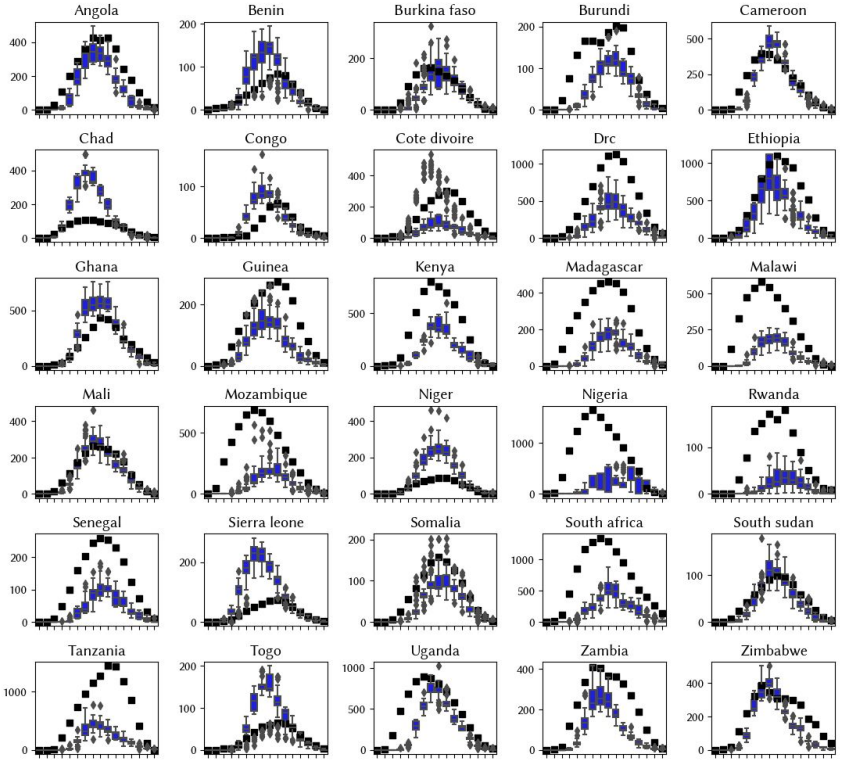
Calibration

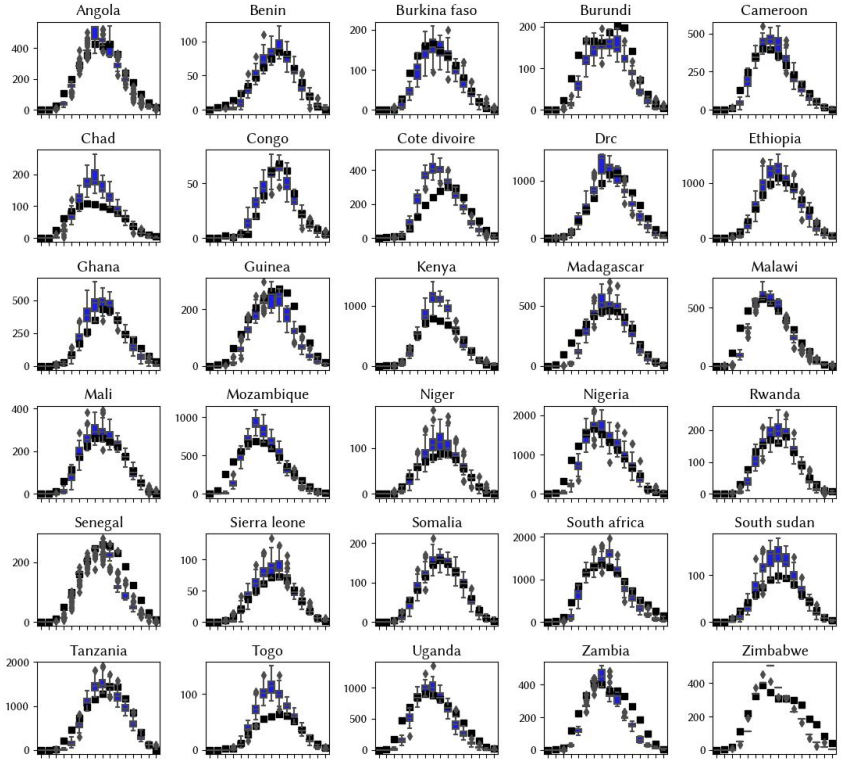
1. Immuno-varying
   - Natural histories do not change, but each population has a “rel_sev” parameter that scales their immune response
     - e.g., say an HPV16 infection will, on average, progress to level X with 6 years; with rel_sev = 1.2 an individual would reach this level in 5 years
2. Unconstrained NH:
   - calibrate all 30 countries individually, all natural histories free to vary
3. Constrained NH:
   - calibrate 30 countries simultaneously, all natural histories the same, no variation in responses

For all 3, we match to cancers by age in 2020, age-standardized rate of cancer incidence, and the type distribution in cancers

Results

Calibrations - constrained vs unconstrained

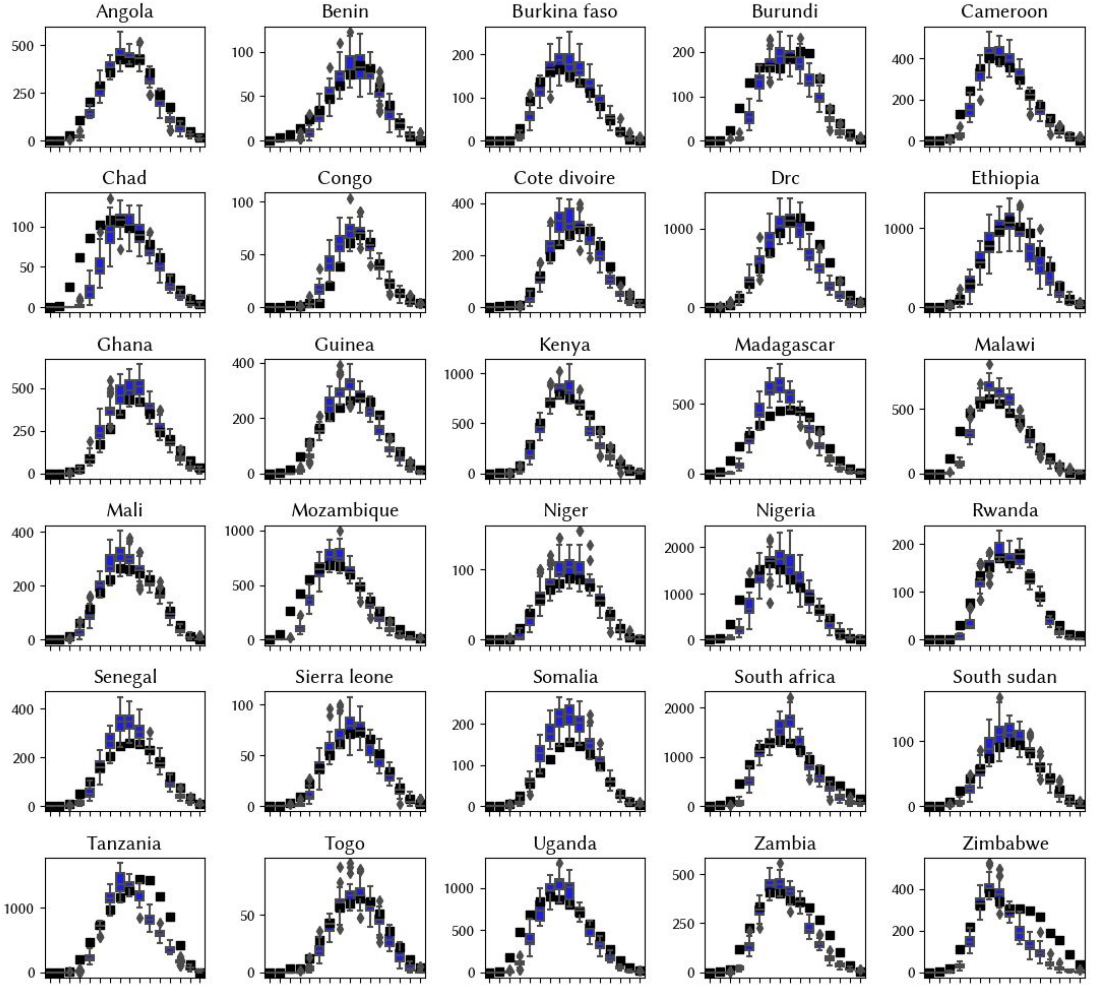




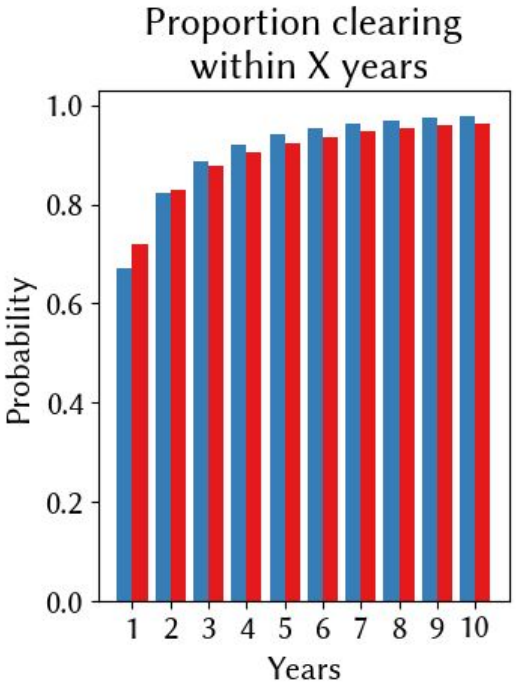
IDM INSTITUTE FOR DISEASE MODELING

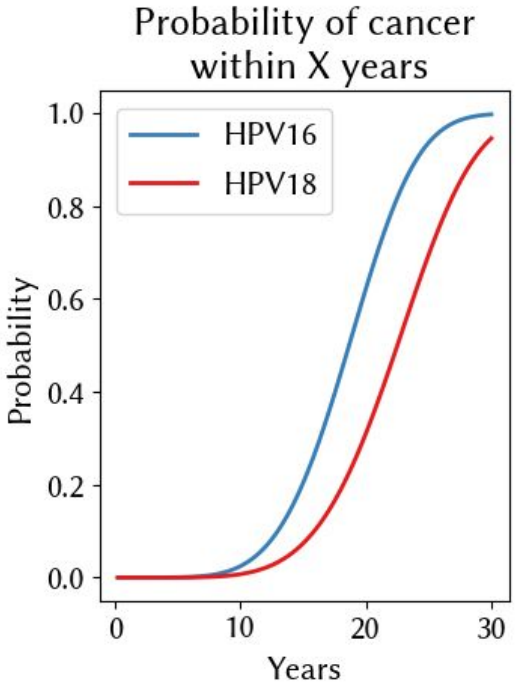
Calibration - immuno-varying

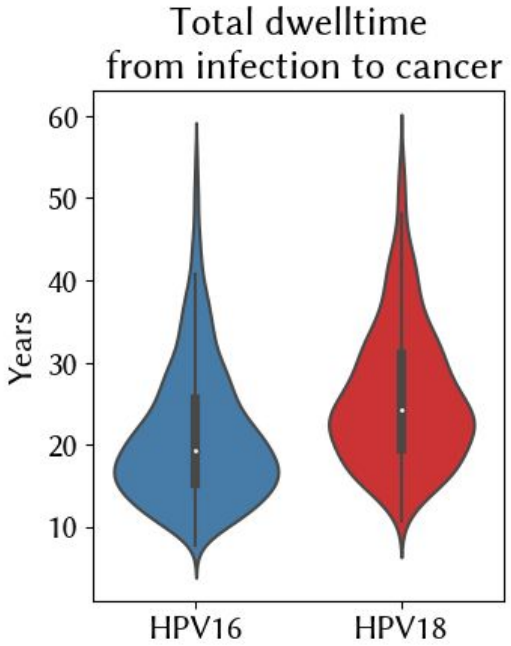
- One size not not fit all, but does fit most



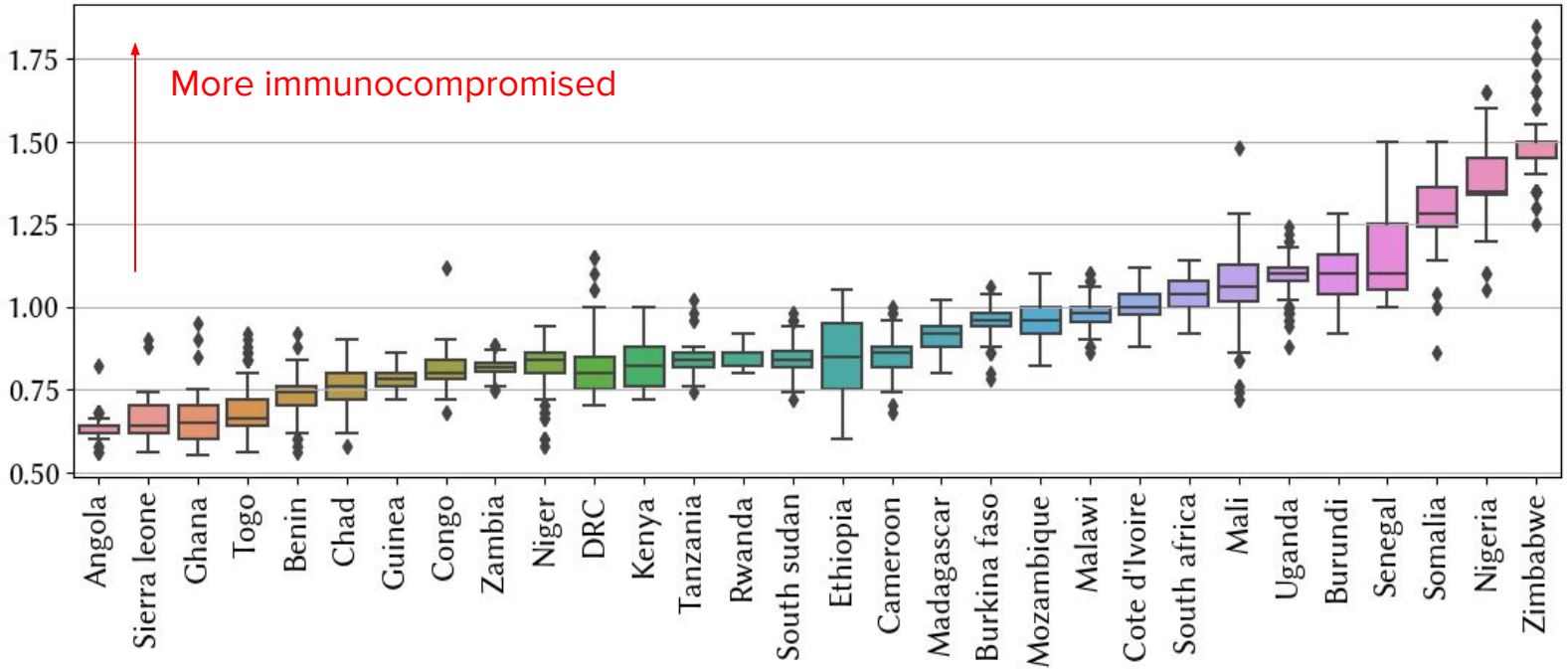
Implied natural histories



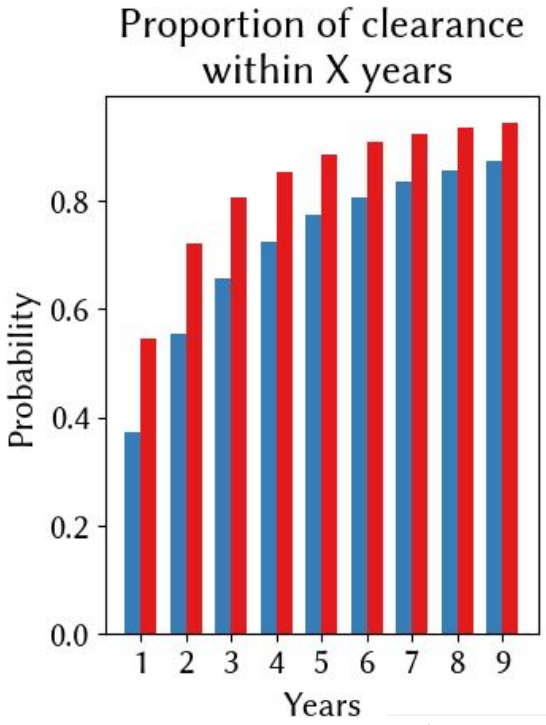


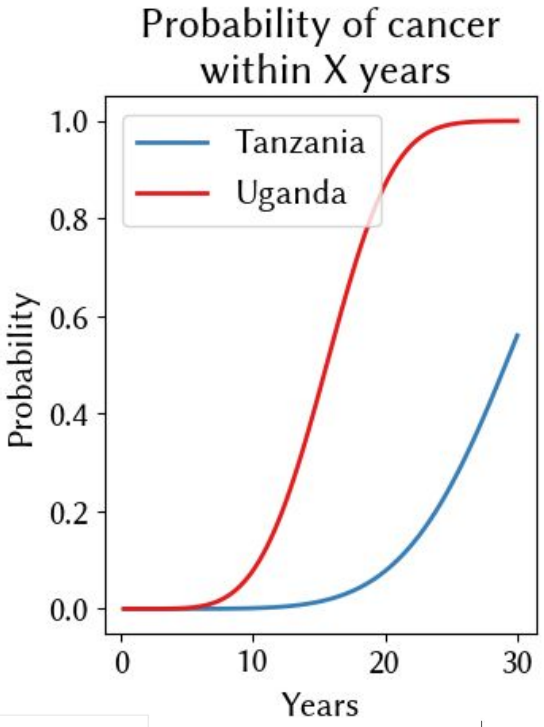


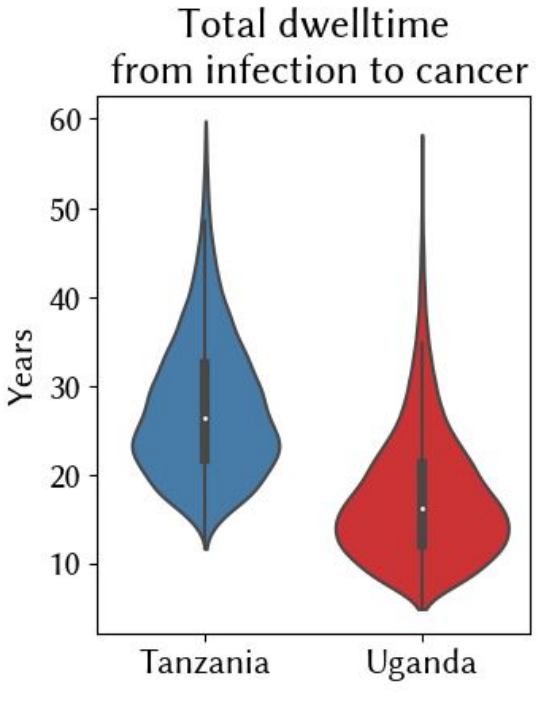
Immunocompromise levels

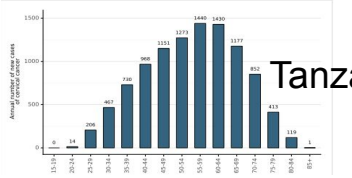


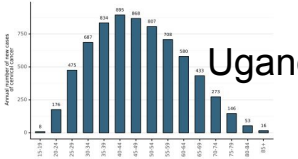
Pitfalls of unconstrained approach











IDM INSTITUTE FOR DISEASE MODELING

Conclusions

What we found

- We were unable to explain the differences in the data on the age distribution of cervical cancer cases via demographic and behavioral differences alone.
- When we did not constrain the natural history parameters to be the same across all countries, we were able to calibrate our model to the data, but at the expense of having a reliable and consistent understanding of the disease's natural history.

What this means

- Many possible interpretations:
  - Insufficient data for calibrating to - justifies using estimates from HIC?
  - Insufficient models - many factors that contribute to variations in natural history that are NOT captured by models
- There's a trade-off between a consistent understanding of how a disease behaves, and designing a model that replicates the particulars of a country's epidemic
- Jamie's talk (up next!) investigates how different models of HPV's natural history might influence modeled impact of interventions.

Acknowledgements

HPVsim model development has been led by Jamie Cohen, Robyn Stuart, Romesh Abeysuriya, and Cliff Kerr. This project is sponsored by Hao Hu and Daniel Klein.

We thank our expert advisers for their frequent and helpful consultations on model conceptualization and development. These include but are not limited to Sharon Achilles, Maike Scharp, Celina Schocken, Peter Dull, John Schiller, Chris Karp, and Holger Kanzler. Mark Jit, David Wilson, Sherrie Kelly, Jasmina Panovska-Griffiths, Andrew Shattock, Edinah Mudimu, Michelle O'Brien, Richard Gray, Helen Olsen, and Greer Fowler provided editing and informal review. Erin Ingle provided valuable literature review support to inform model parameters. Tremendous gratitude to Mandy Izzo for her graphical content and editing support.

IDM INSTITUTE FOR DISEASE MODELING