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Understanding the key determinants of an HPV therapeutic vaccine

A modeling analysis

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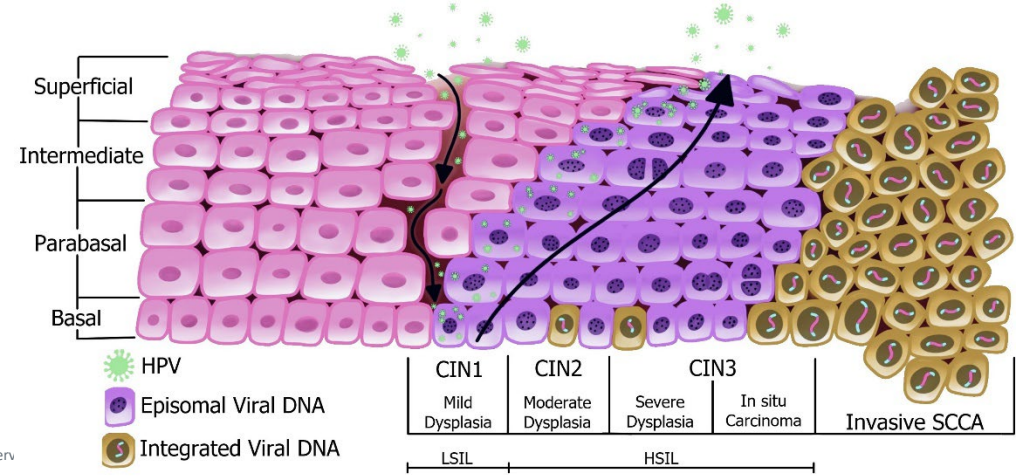
Persistent, high-risk HPV causes invasive cervical cancer

KNOWN

UNCERTAIN



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Persistent, high-risk HPV causes invasive cervical cancer

KNOWN

- 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 that can lead to invasive CC

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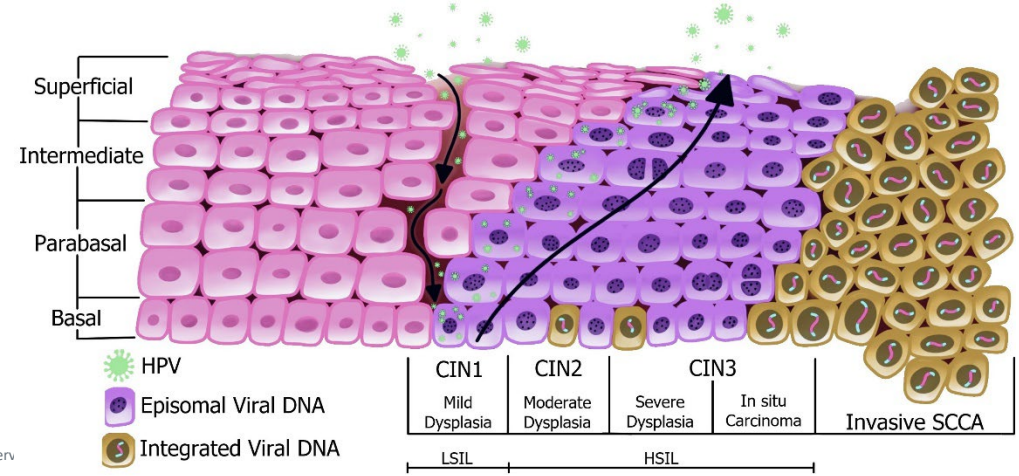

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KNOWN

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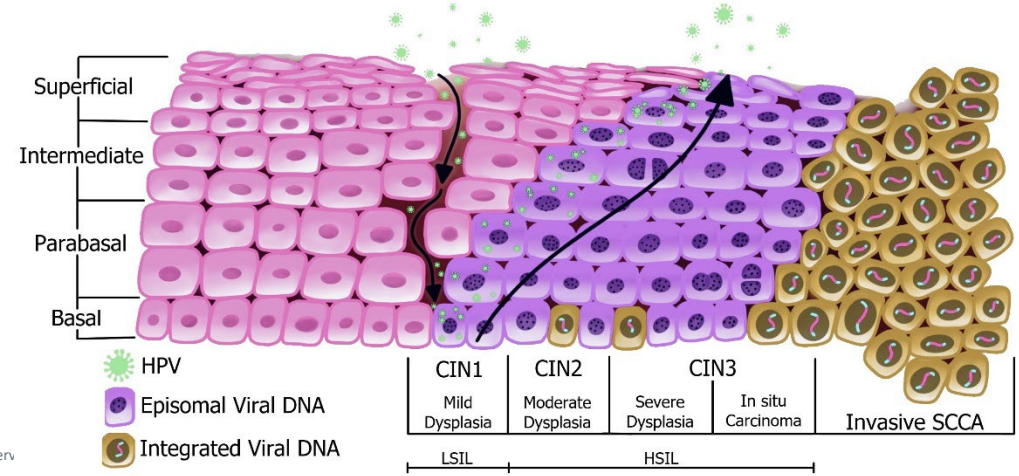
UNCERTAIN

- Why do some infections persist and others resolve?
- Does infection resolution represent true clearance or latent infection?
- What risk does latency have for future disease?



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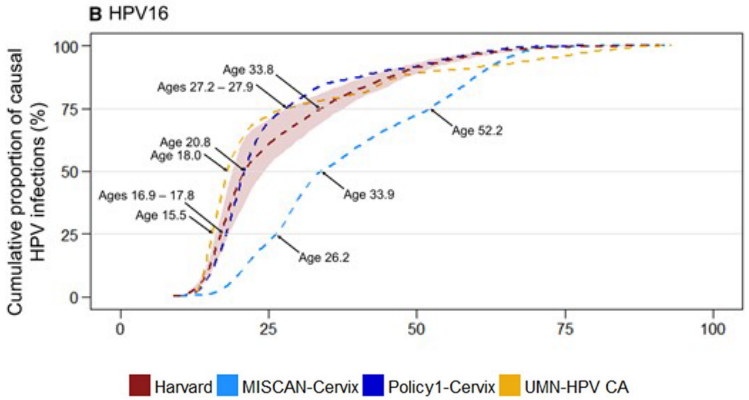
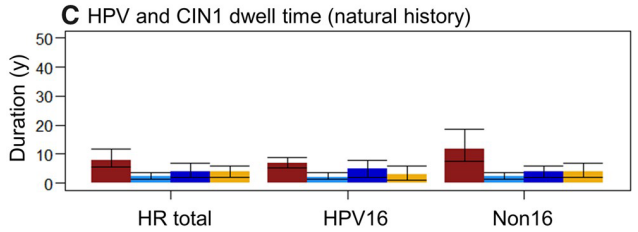
An incomplete scientific understanding of HPV

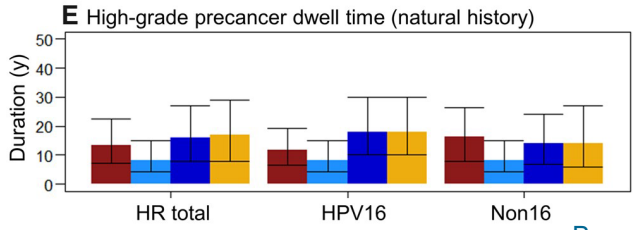
What happens between causal HPV infection and onset of cervical cancer?

- What is the rate of dysplastic cell growth?
- How much does natural history vary between individuals and across populations?
- How much does resolving this uncertainty matter for optimal decision-making?

Model-based hypothesis testing can help resolve these questions







Burger, JNCI

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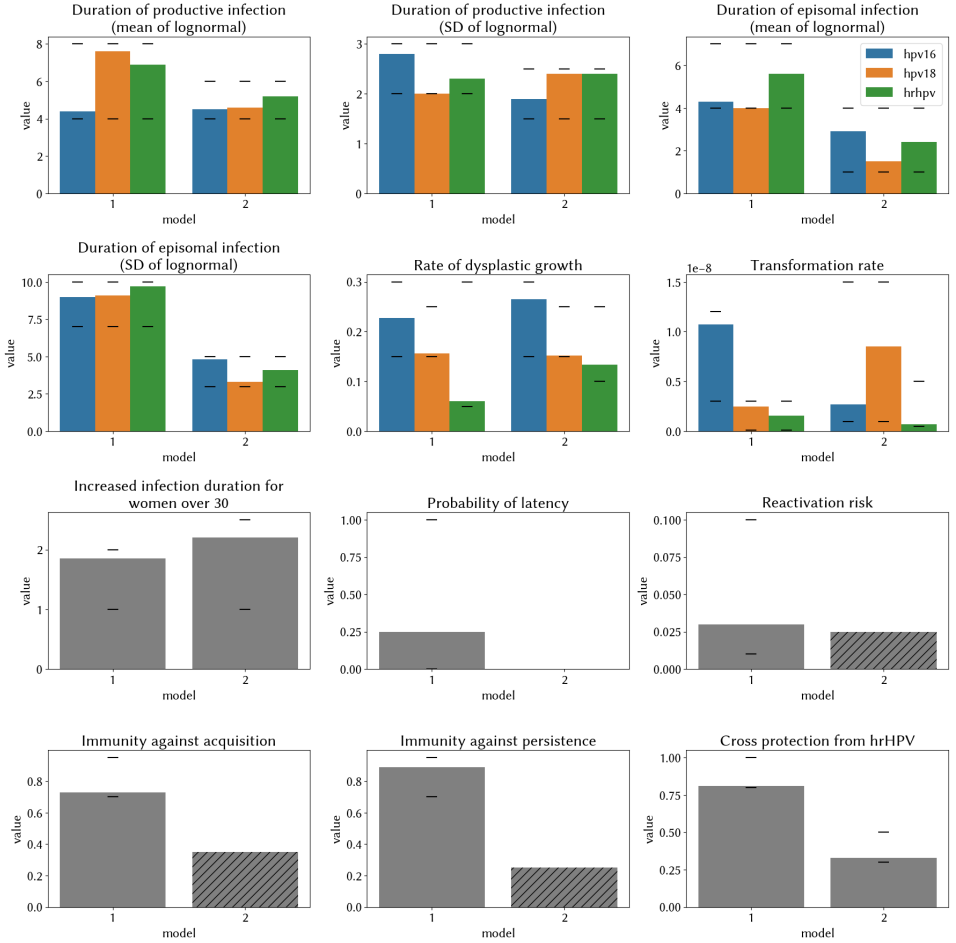
Analytic methods

1. Fit two proposed natural history models to estimated cervical cancer cases by age and HPV genotype distribution, using HPVsim



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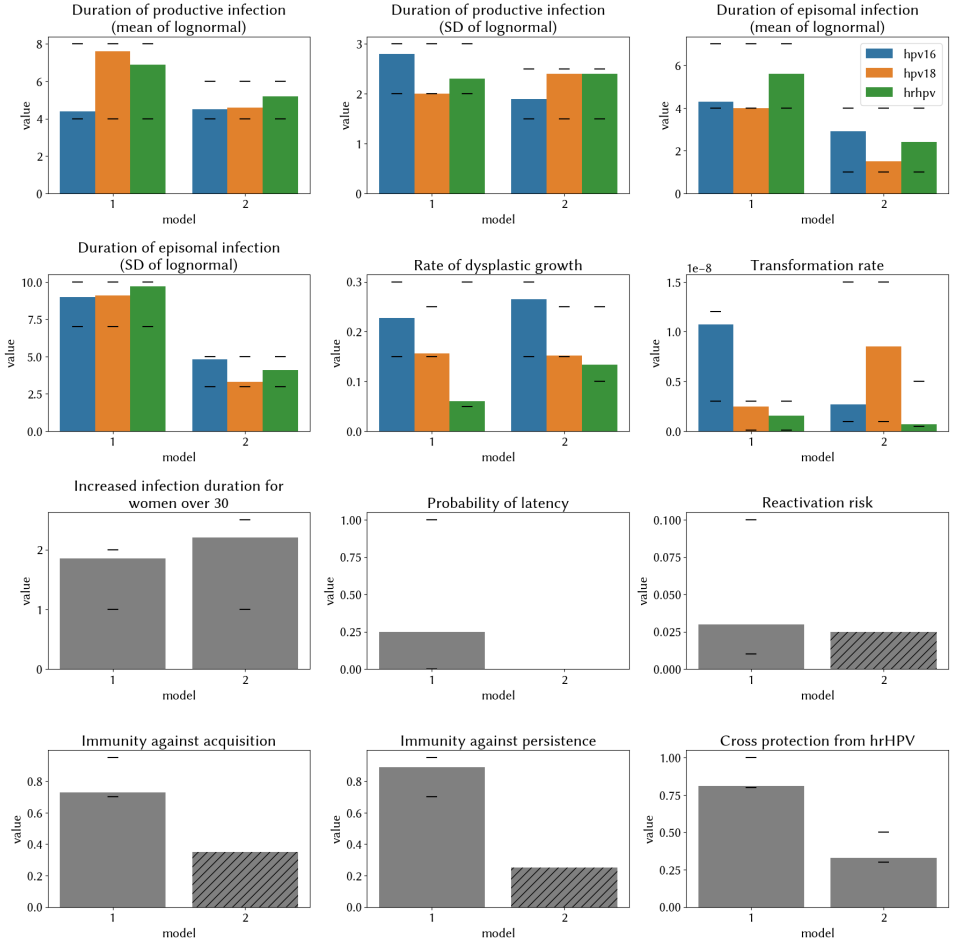
Analytic methods

1. Fit two proposed natural history models to estimated cervical cancer cases by age and HPV genotype distribution, using HPVsim
2. Estimate residual burden of cervical cancer over time based upon PxV and S&T scale-up
3. Evaluate potential public health value of an HPV therapeutic vaccine



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Methods details

Background PxV and S&T

- Single-dose bivalent vaccine, 9-14
- Lifelong immunity
- HPV DNA testing, 30-50 year old women, every 5 years
- 30% LTFU between screen and treatment
- Scale-up occurs immediately starting in 2025

	Prophylactic vaccination (PxV)	**Screening & treatment (S&T)**
Scenario 1	0% coverage	0% coverage
Scenario 2	50% coverage	0% coverage
Scenario 3	50% coverage	35% coverage
Scenario 4	90% coverage	70% coverage

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HPV therapeutic vaccine

- T-cell inducing vaccine, requiring 2-doses
- 1-time campaign to reach 70% of women from aged 30-50; routine administration to 70% of women aged 30. 20% LTFU between doses
- First dose achieves half the desired 2-dose effectiveness for each indication
- TxV effectiveness (clearing virus / regressing lesion)

Effectiveness	90/0	50/50	0/90
Immune memory	None	Disease	Disease + Infection

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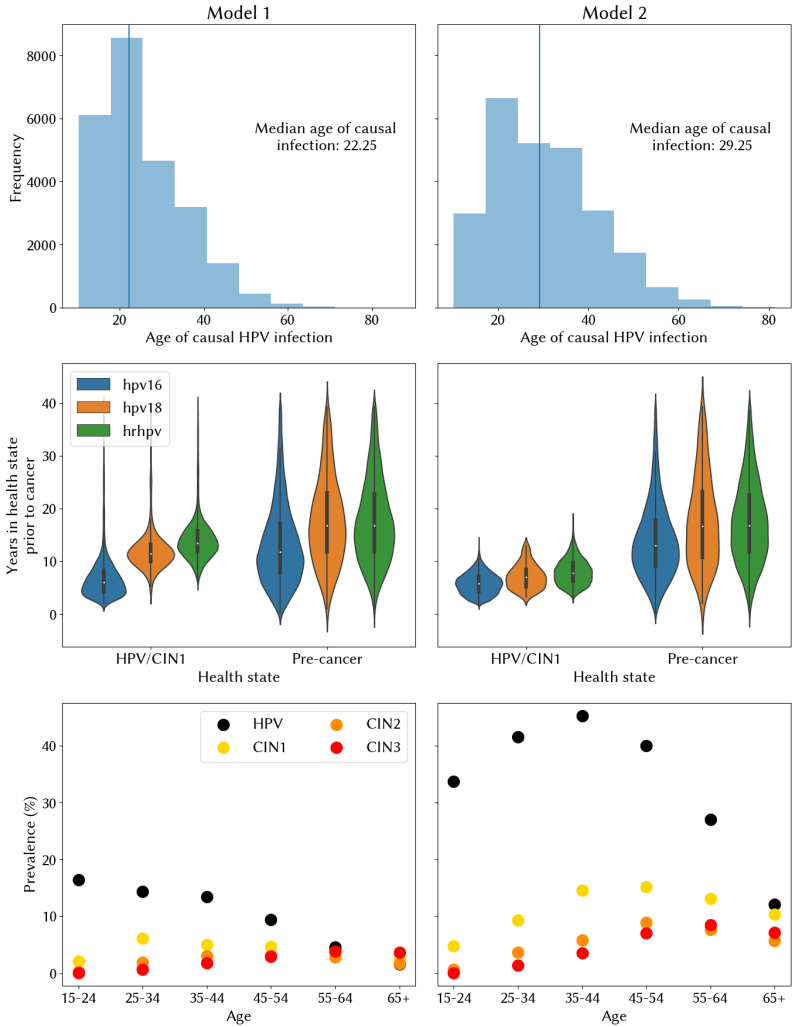
Natural history comparison

- Median of age of causal infection varies by 7 years between models
- HPV prevalence by age varies 4-fold
- Parameter differences:
  - Risk of reinfection and persistence with naturally acquired immunity
  - Duration of productive and episomal HPV infection
  - Degree of latency, ~10% of cancers caused by reactivated latent infections in Model 1



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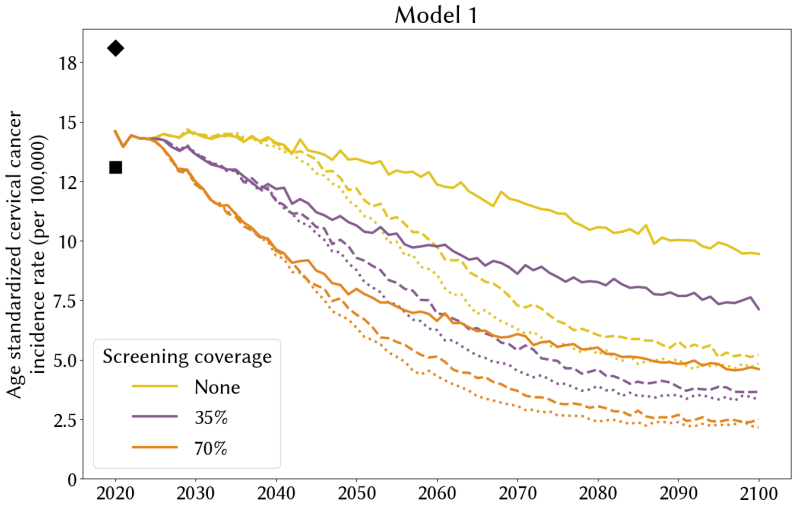
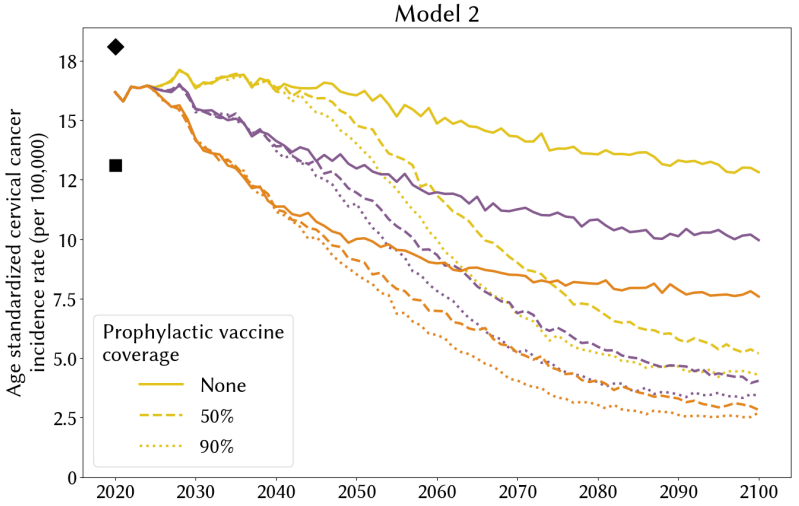
Residual burden estimation

- ASIR between 14.5 - 16 per 100,000; might capture true uncertainty
- S&T has greater near-term impact
- PxV has greater long-term impact
- S&T impact is greater in Model 1 due to longer overall dwell time (more opportunity to find women with pre-cancer) & higher naturally acquired immunity following successful treatment (benefit lasts longer).





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HPV TxV impact

- More value to regression of CIN2+ than viral clearance in short-term
- Overlapping in long term with a catch-up after ~10 years due to targeting women at an earlier stage in the natural history.
- Relative value of immune memory is ~2x higher in Model 2
- Impact of immune memory grows over time

	Prophylactic vaccination	Screening & treatment (S&T)
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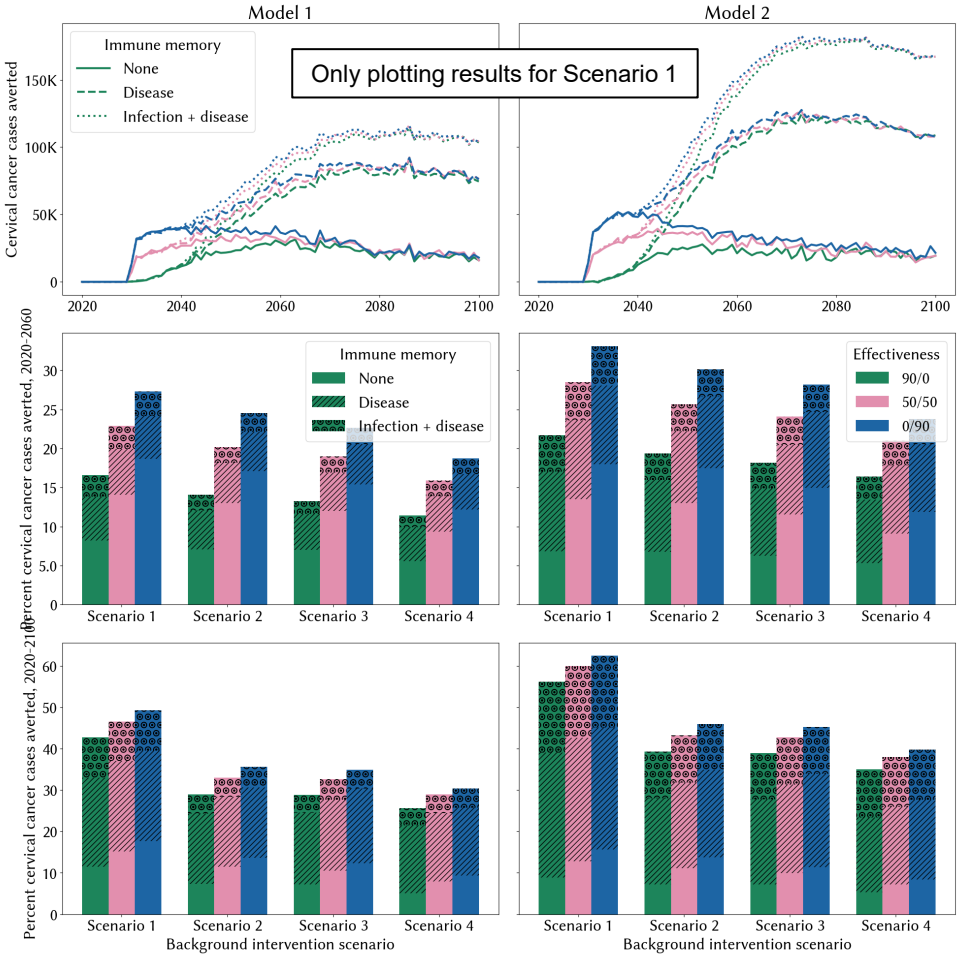

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Conclusions

- Greatest health impact levers:
  - Short-term (next 30 years): Effectiveness at regressing CIN2+
  - Long-term (next 70 years): Level of immune protection
- Even with the most optimistic PxV and S&T scale-up, TxV might avert >= deaths/FVP as MenA, rotavirus, yellow fever, PCV and Hib
- Natural history parameterization influences the relative benefit of product attributes and delivery strategies, including immune memory and age of administration
- This exercise illustrates that cervical cancer modeling has a non-identifiability issue which may meaningfully impact decisions about product development and delivery
  - More and better data collection can help reduce/constrain the uncertainty space, but much of uncertainty is not observable ethically, so will need to be propagated through modeling

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Acknowledgements

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