Investigating the Effects of Male Circumcision on HIV Epidemics

A Microsimulation Study

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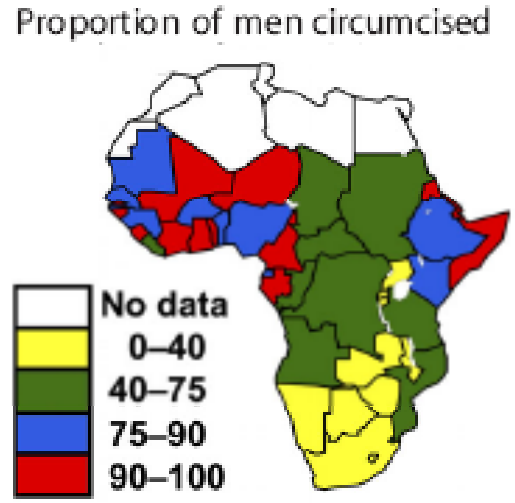
Male Circumcision & HIV

- Male circumcision (MC) first suggested as a risk factor by AJ Fink in 1986 letter to *New England Journal of Medicine*

- Approximately 40 cross-sectional, cohort, case-control studies done in 1990s (Siegfried, 2005)



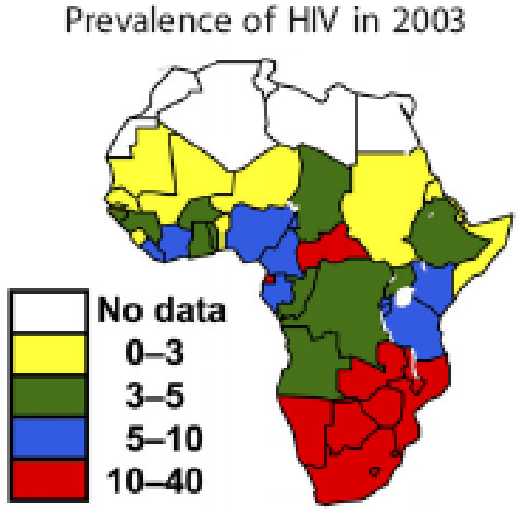


Figure: Williams B. G., J. O. Lloyd-Smith et al. "The Potential Impact of Male Circumcision on HIV in Sub-Saharan Africa." PLoS Med 3:1032-40

Biological Mechanism

- Study of 19 Australian cadavers found that the inner mucosal surface is highly concentrated with CD4+ target cells (Patterson et al, 2002)

- Foreskin specimens of 39 Kenyan men shows an abundance of CD4+ T cells and macrophages in inner mucosal surface of the human foreskin, making it highly susceptible to HIV infection (Donoval et al, 2006)

South African Clinical Trial*

- 3,274 uncircumcised men, aged 18–24 years randomized control trial
- 49 HIV infections in control group and 20 in intervention group
- After interim analysis data and safety monitoring board truncated trial as of April 30, 2007
- Crude RR = 0.40 (0.24 – 0.69 95% CI)
- **Adjusted RR = 0.39 (0.23 – 0.64 95% CI)** after controlling for behavioral covariates

- Additional trials in Kenya & Uganda have shown 53 and 48 percent reductions in HIV acquisition, respectively

* Auvert B, Taljaard D, Lagarde E, et al. (2005). " Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk." *PLoS Med* 2(11): e298

Male Circumcision as Intervention ?

- MC has an *individual-level* effect on female-to-male HIV transmission
- Scientific and policy journals, as well as popular press have advocated for immediate implementation of population-level MC interventions, and the NIH has pledged support for such interventions
- ***But***…
  - Is widespread MC socially and culturally ***acceptable*** in African communities?
  - Is there a safe and affordable surgical ***procedure*** for performing a high volume of male circumcisions?
  - Is the ***population-level effect*** on the HIV epidemic substantial enough to merit an intervention?

Acceptability

- Acceptability studies carried out in Malawi, South Africa, Kenya, Zimbabwe, and Botswana
- Studies found that between 51% and 87% of uncircumcised men would prefer to be circumcised if it might decrease risk of HIV acquisition
- Between 68% - 89% of women said they would circumcise a newborn son if it might decrease the risk of acquiring HIV

Procedure

- Kenya: developed procedure used to circumcise 479 males age 18-24 (Krieger, 2005)
  - Cost ~20 US Dollars
  - Median operating time 30 min (18-63 min)
  - 3.5% complication rate, no fatalities or permanent disabilities
  - 99% of study participants were satisfied with the results, all interviewed sexual partners were happy

Effect

- Individual-level effect *does not* guarantee a substantial population-level effect

> "For persons who are highly exposed to risk of HIV infection … a 60% reduction in annual risk will ultimately protect only a smaller proportion. Basic probability calculations show that in discordant couples exposed for 30 years, some 74% will contract the HIV virus if circumcised, compared with 97% if uncircumcised."
>
> – Michel Garenne (PLoS Med, Jan 2006)

- To assess the impact of various intervention scenarios …

Simulate Populations Affected by HIV …

- Individual-level (micro) simulator:
  - Individual level
  - Stochastic
  - Two sex
- Modeled processes include:
  - Fertility & Mortality
  - Marital union formation and separation
  - Non-marital union formation and separation
  - Sexual intercourse
  - HIV Transmission, vertical and horizontal (only heterosexual)
  - **Circumcisions**

Why Simulate ?

- Naturally handles different levels of analysis and interactions between levels
  - Population ⇔People ⇔ Unions, etc.
- Produces rich output that can be analyzed in many ways
- By explicitly modeling individuals, disease states, and relationships, automatically ensures *internal consistency*
  - In disease and population processes
    - HIV and fertility / mortality
    - HIV and behavioral processes
  - Between sexes in pairing dynamics

Demographic Parameters

- From Gwembe Tonga, Southern Zambia: 1957-1995
- Collected by Anthropologists as part of long-term study
- Detailed genealogy of ~15,000 people over 38 years:
  - Dates of birth and death
  - Dates of union formation and separation
  - Links between spouses
  - Links between parents and children
  - Dates of entry and exit from observation
- Use demographic data to calculate empirical hazards implemented in simulator
- All parameters allowed to vary with time, age, sex, marital/parenthood status

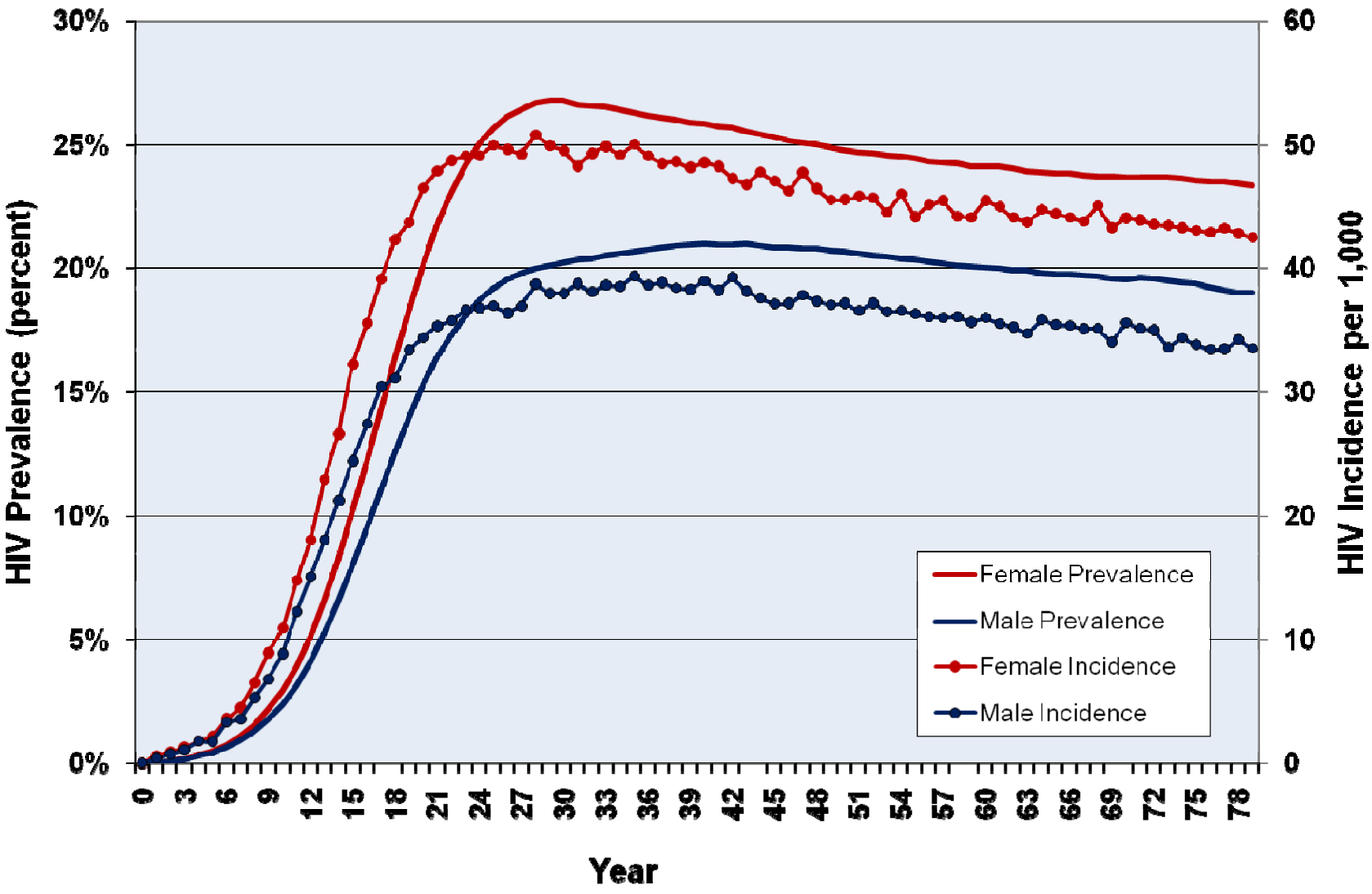
HIV Dynamics

- Each intercourse with an infected partner has probability of HIV transmission
  - Depends on duration since infection
- Duration since infection impacts other biological and behavioral dynamics:
  - Heterosexual horizontal transmission probability
  - Vertical transmission probability
  - Frequency of intercourse
  - Likelihood of forming new union or new non-marital union
  - Likelihood of dissolving unions, etc.
- HIV parameters calibrated so that:
  - Sex-specific horizontal transmission, average (both sexes) of about 6/1000 transmissions per intercourse over total period of infection (observed by Gray et al. in Uganda)
  - Vertical transmission, average of about 1 in 3 births

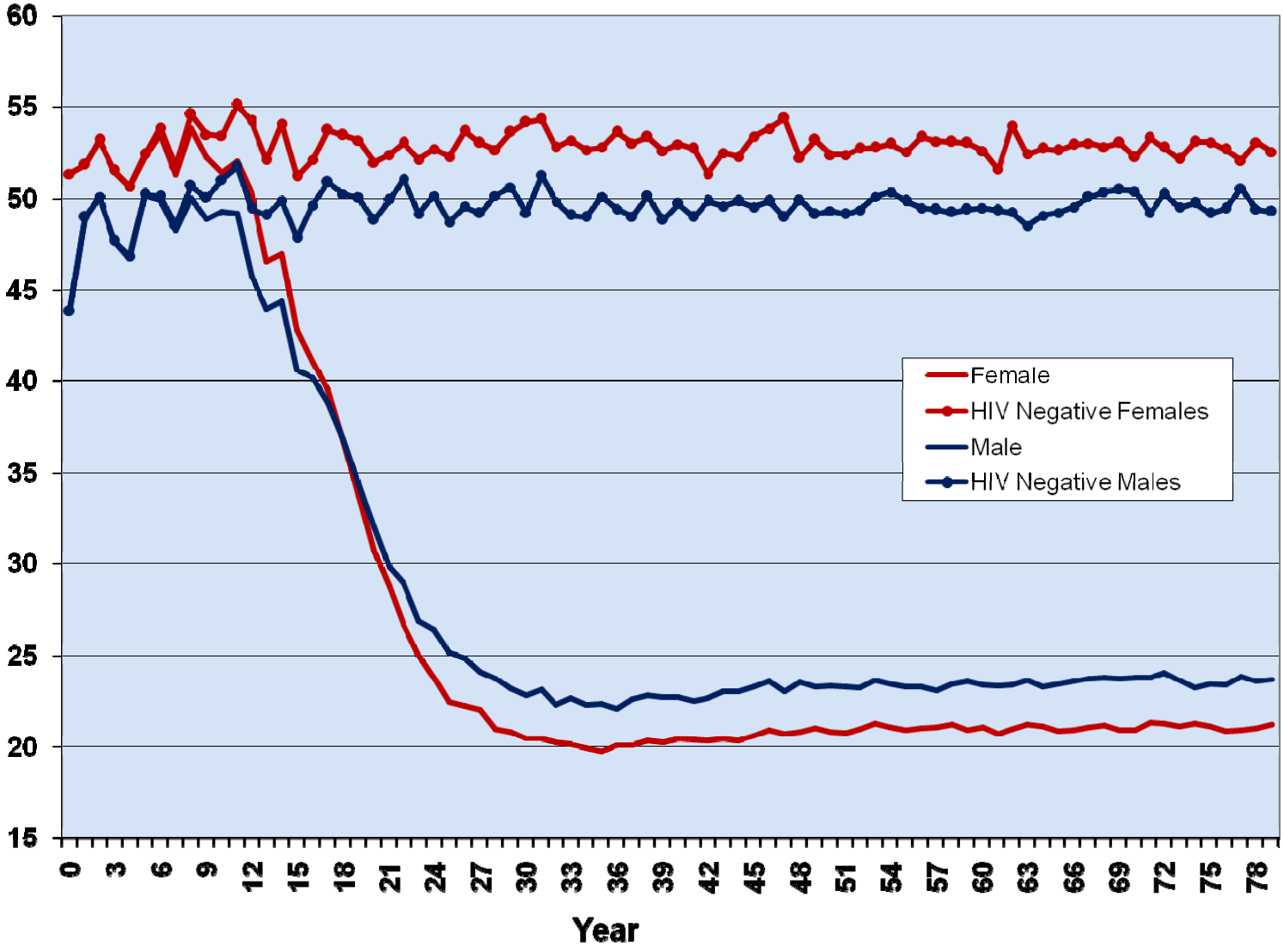
Modeling Circumcision

- Used observed cases and person years from Auvert trial to calculate reduction in monthly F → M transmission probability (~0.598) if male partner is circumcised
- Currently we model no effect on M → F transmission
  - A recent observational study in Kenya suggests there may ~30% reduction
- 25% of all males circumcised at birth (not as part of intervention)
- For interventions, every uncircumcised male in selected age range is exposed to a monthly probability of circumcision, such that after surviving the exposure period, the appropriate intervention level of circumcisions has been achieved

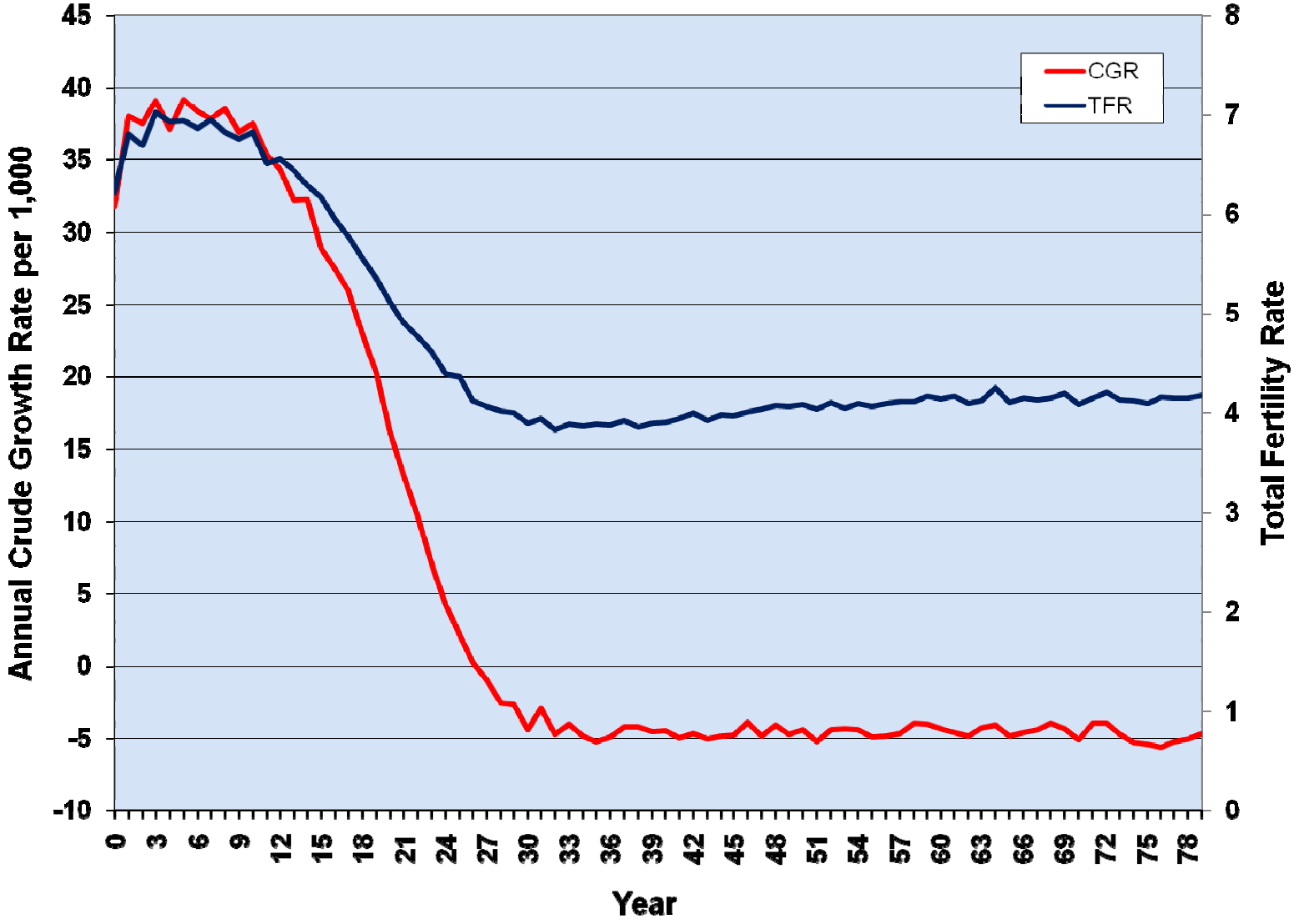
Model HIV Epidemic



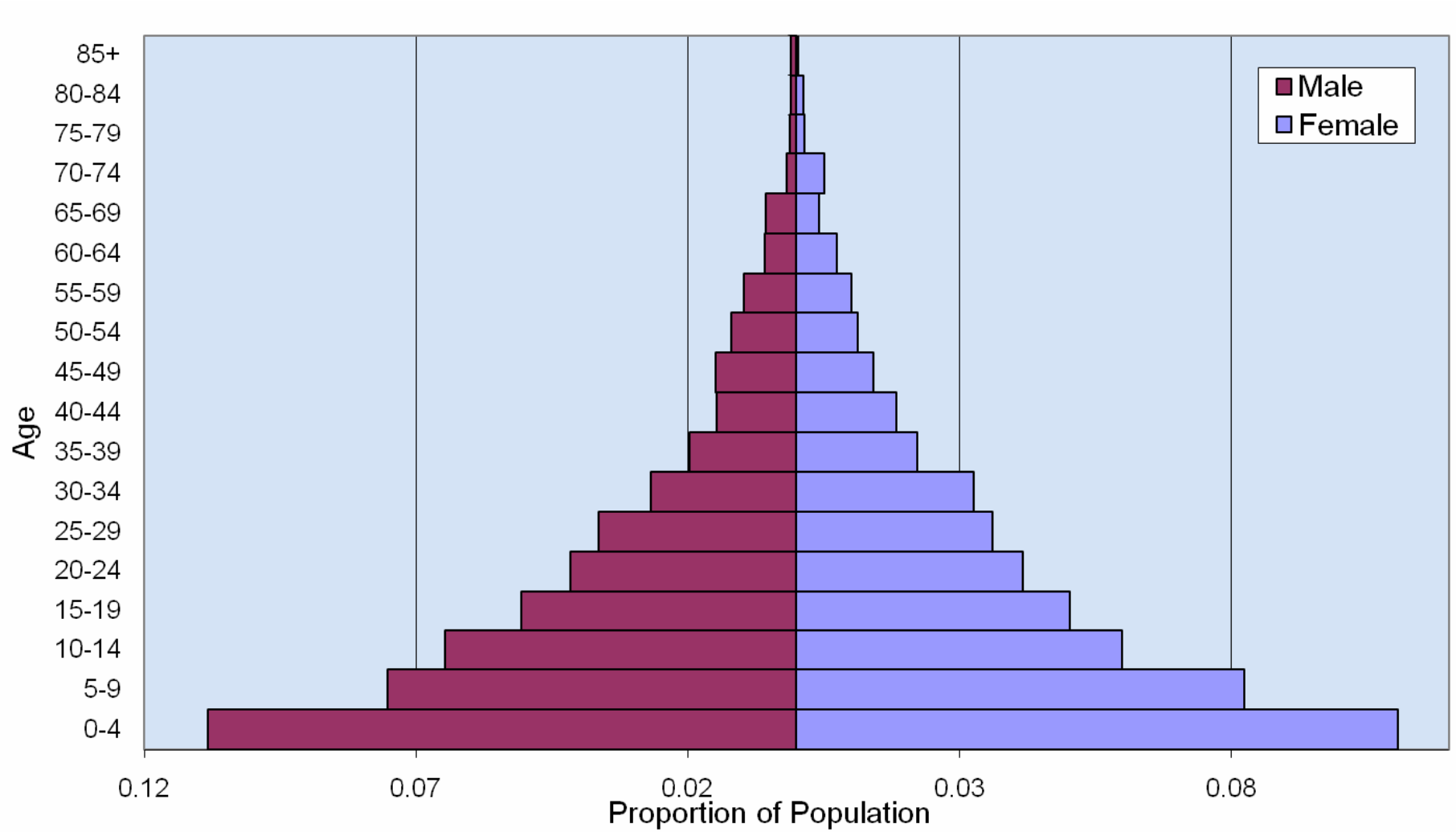
Expectation of Life at Birth (years)



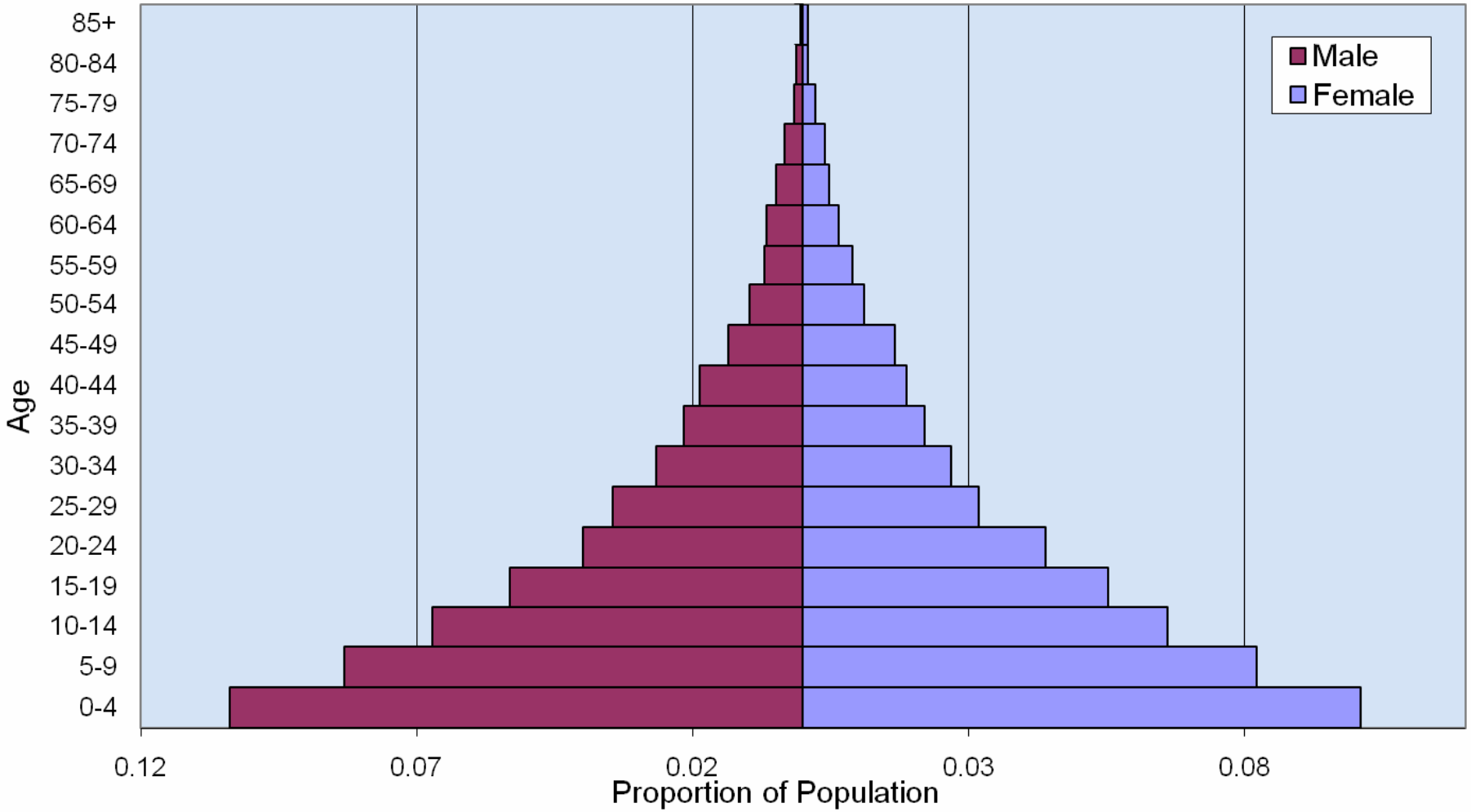
TFR & CGR


CGR
TFR
Annual Crude Growth Rate per 1,000
Total Fertility Rate
Year
45
40
35
30
25
20
15
10
5
0
-5
-10
8
7
6
5
4
3
2
1
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63 66 69 72 75 78

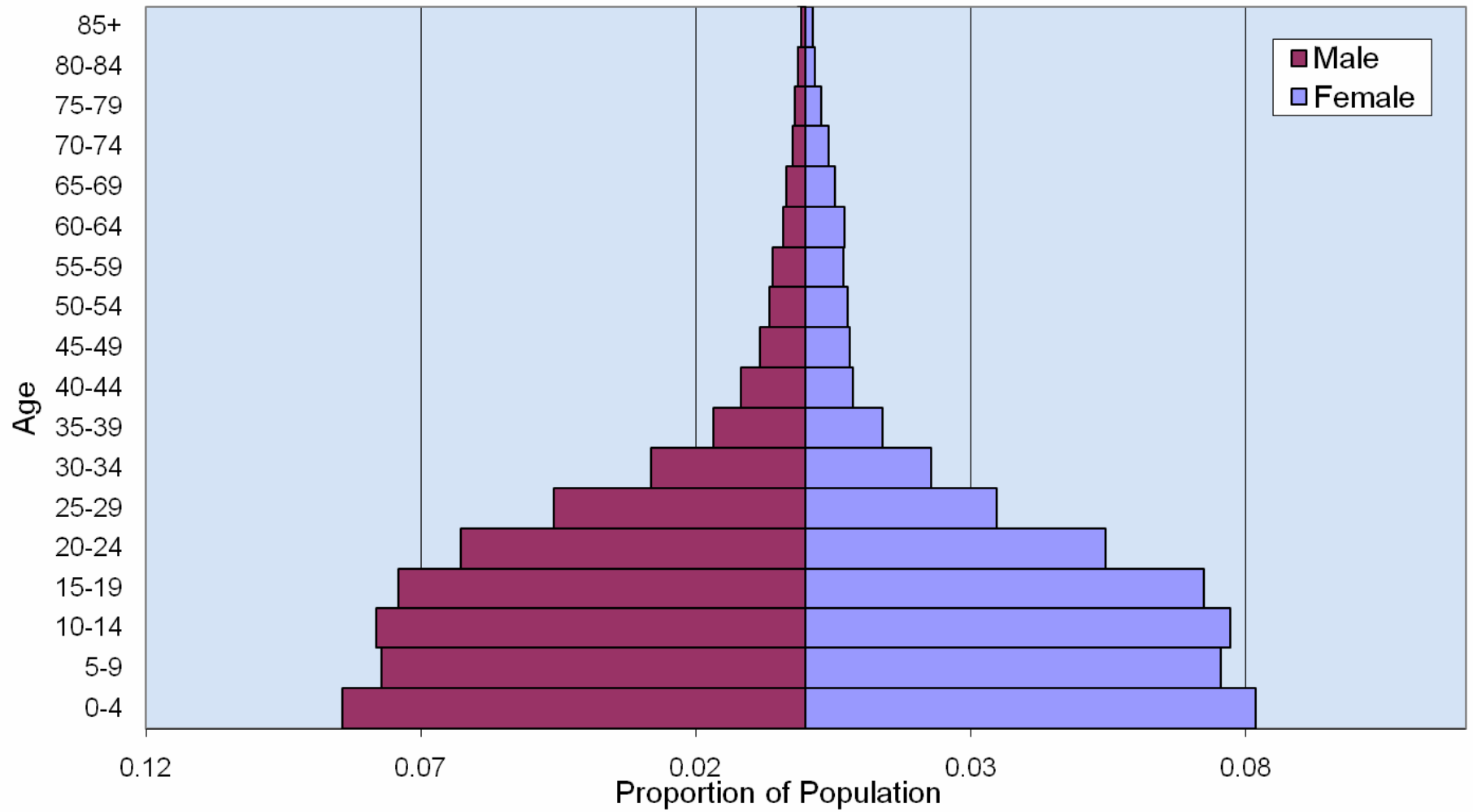
Population Pyramid: Pre-HIV



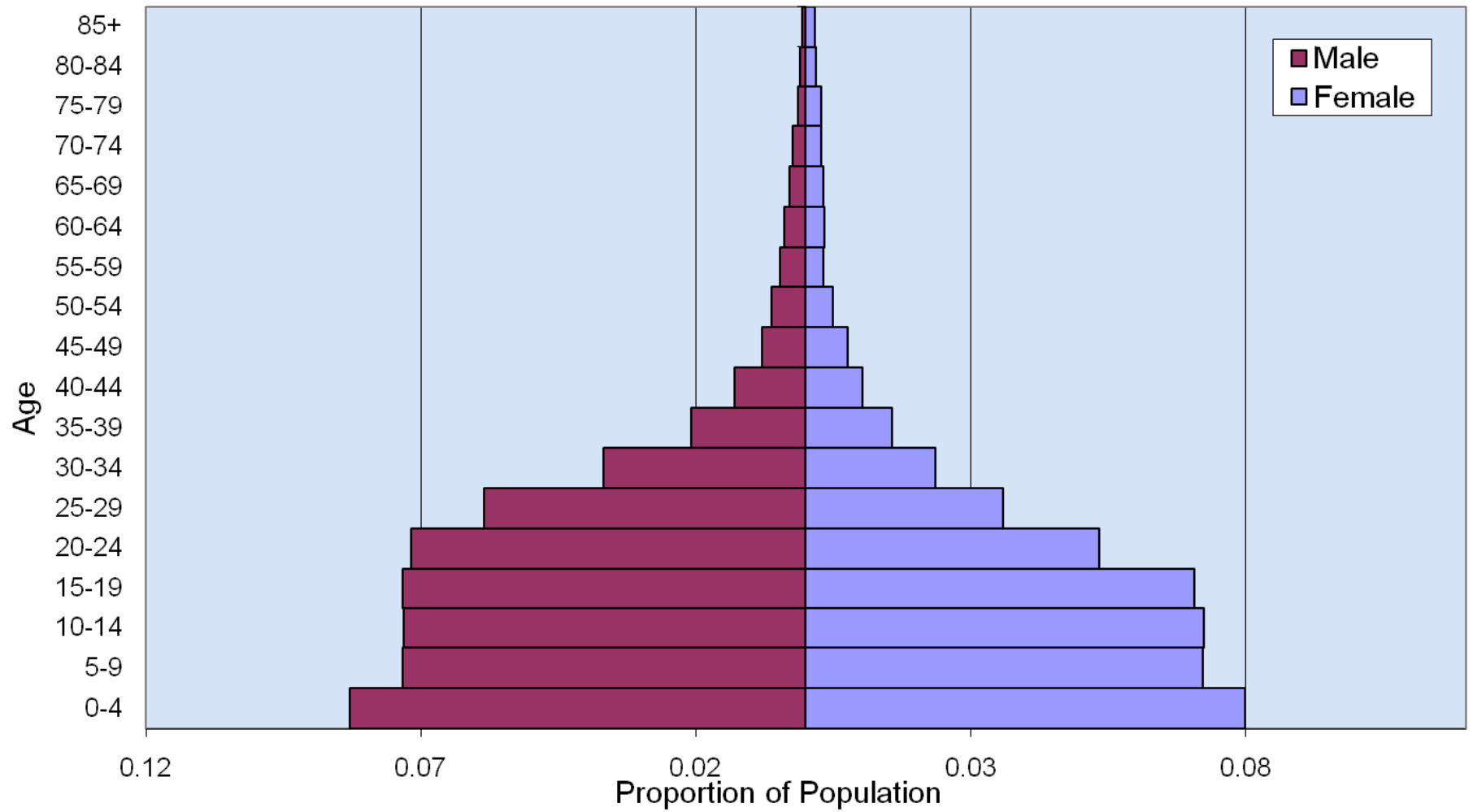
15 Years into Epidemic



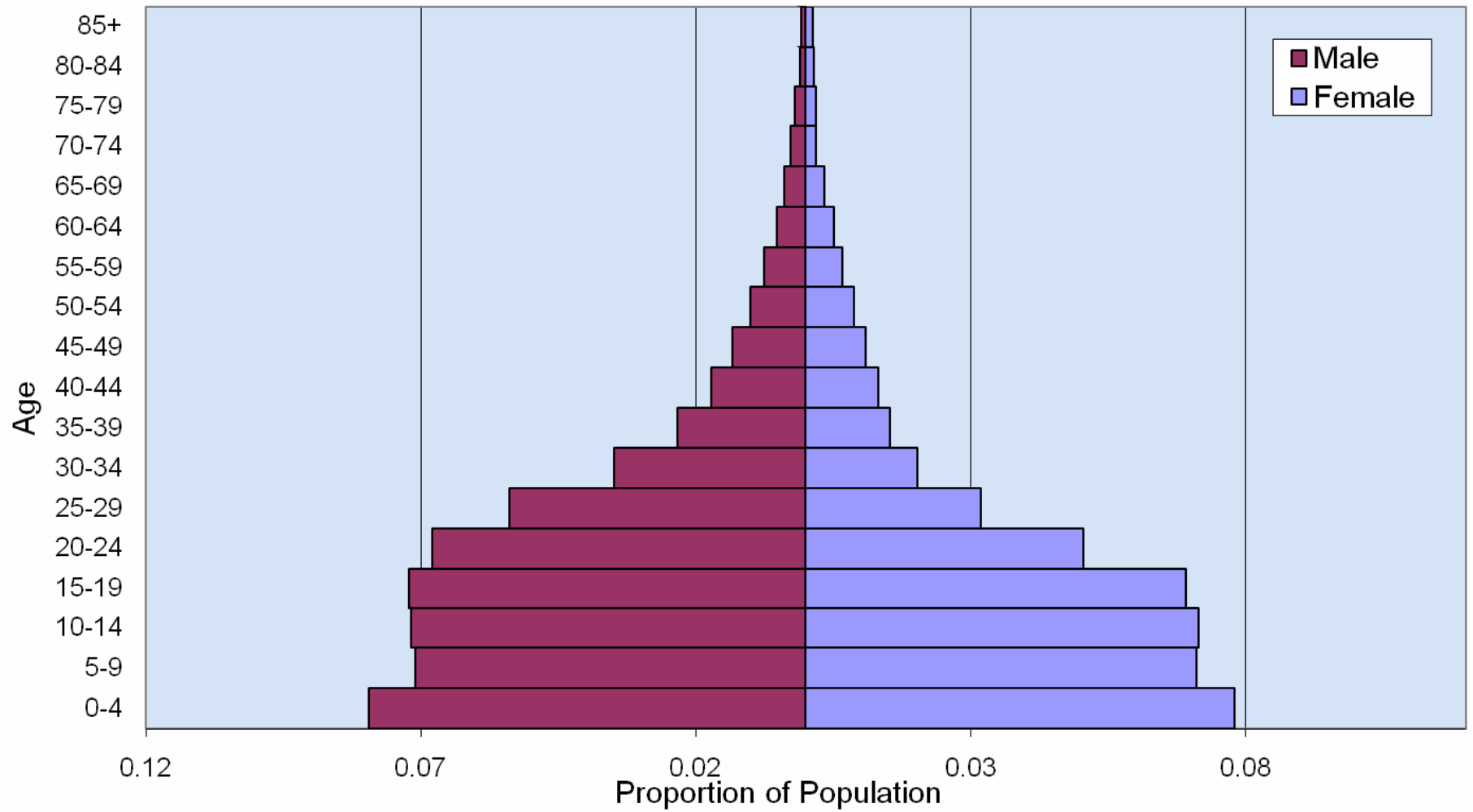
30 Years into Epidemic



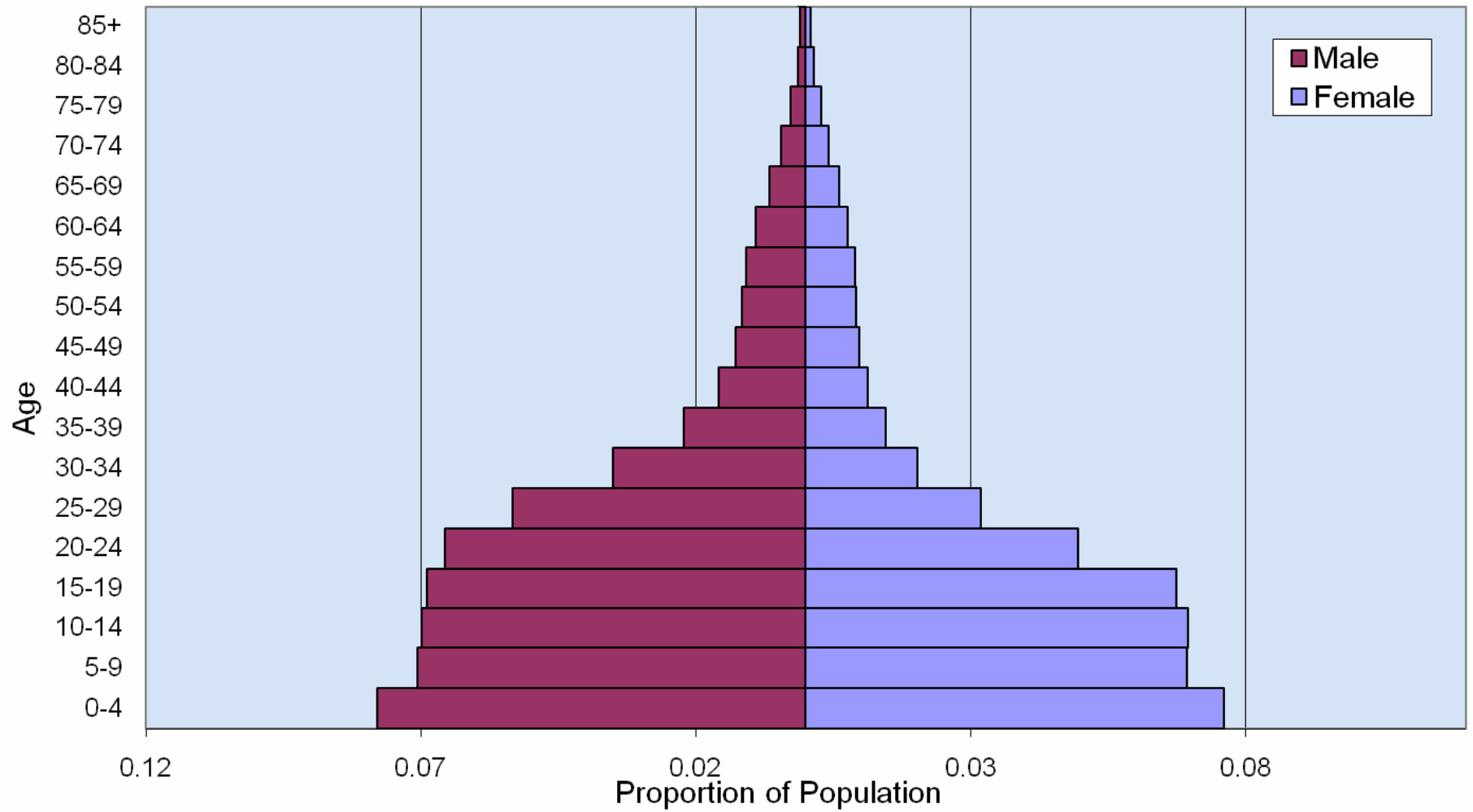
45 Years into Epidemic



60 Years into Epidemic



75 Years into Epidemic



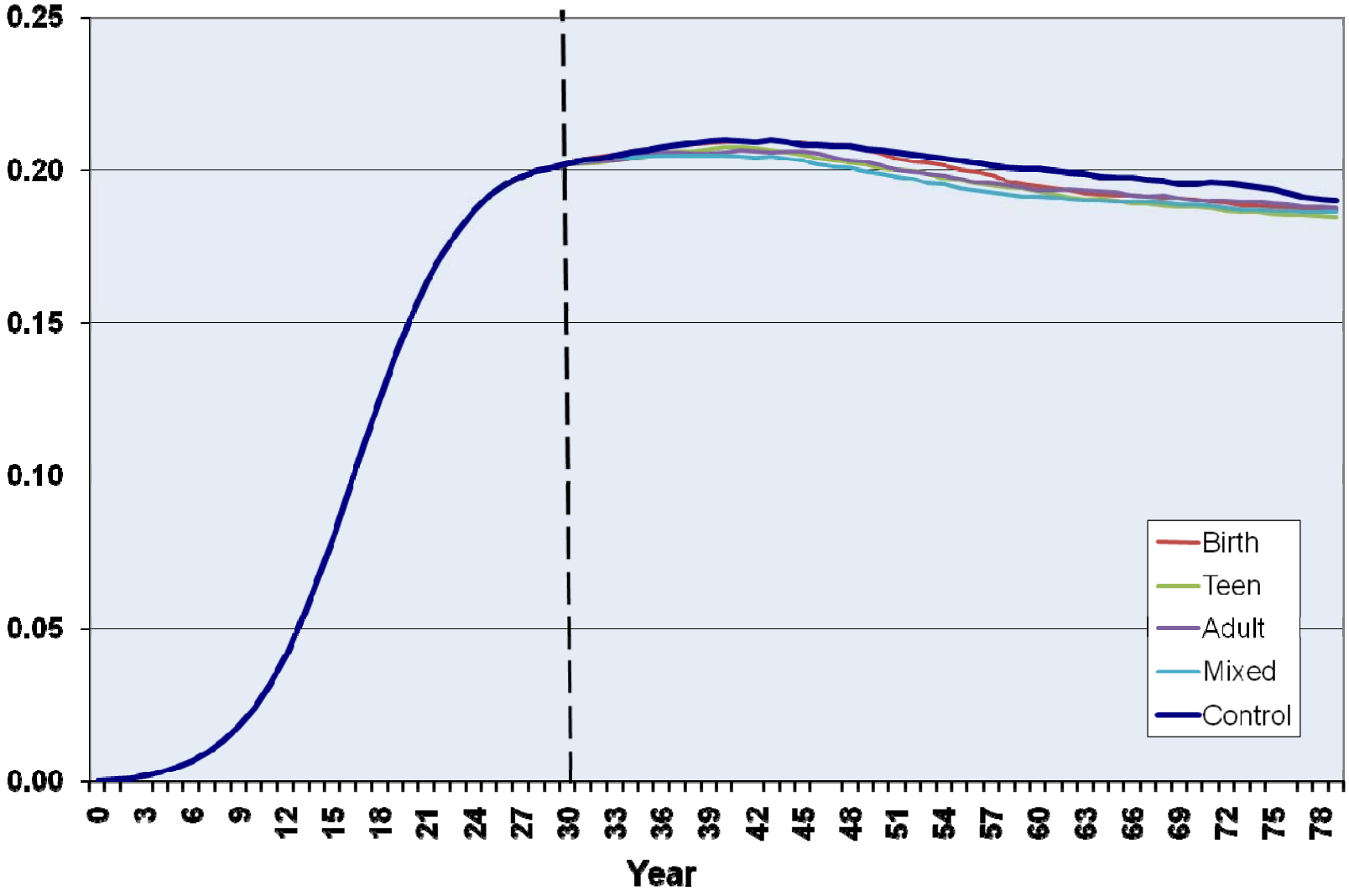
Intervention Scenarios

- Four Age Groups:
  - At Birth - ***Birth***
  - Age 10-13 - ***Teen***
  - Age 18-24 - ***Adult***
  - ***Mixed*** (Age 15-24 for 15 years, at birth thereafter)
- Four Intervention Levels, percent of uncircumcised males who are circumcised:
  - **10%**
  - **25%**
  - **50%**
  - **75%**

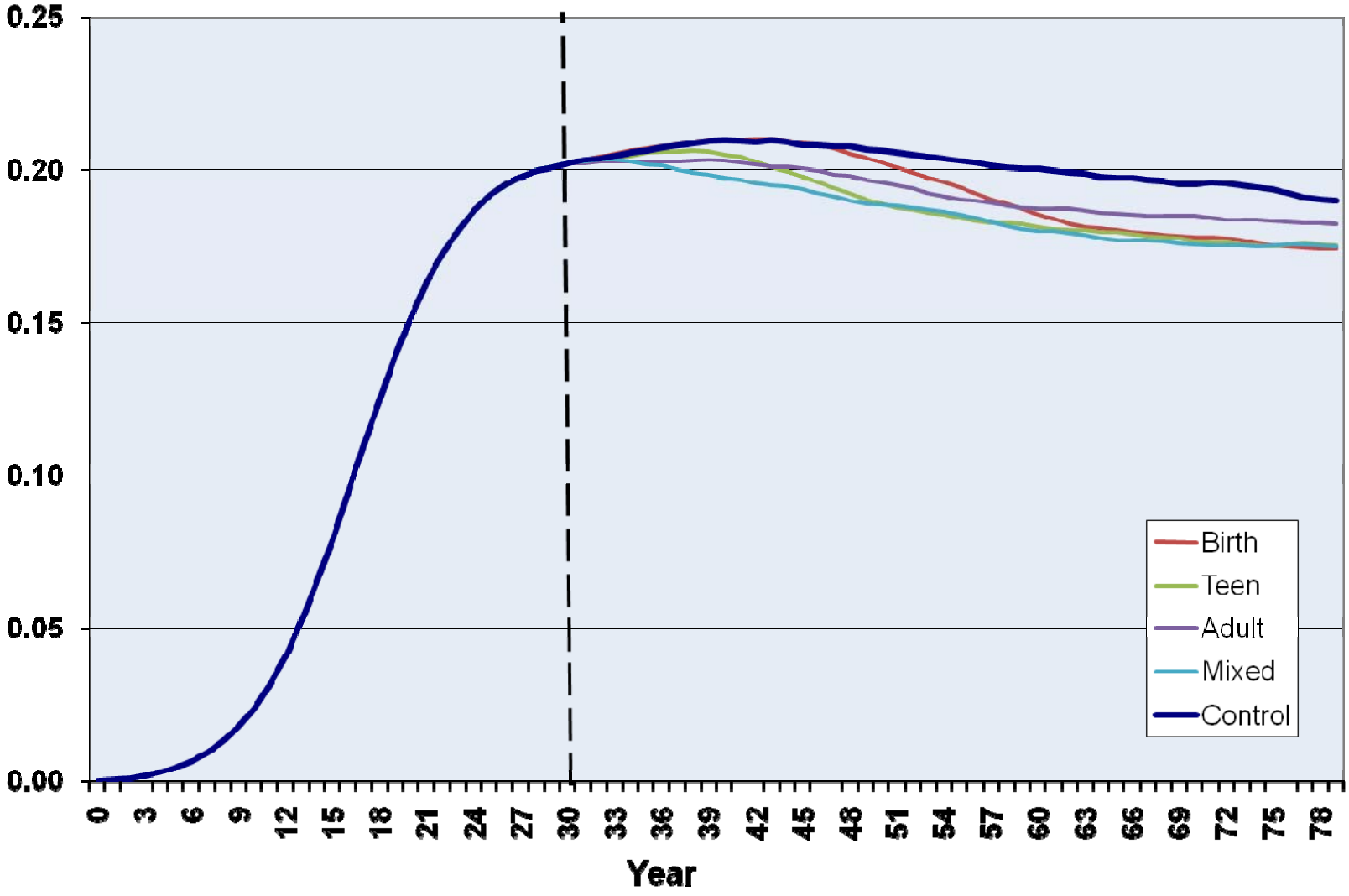
Simulation Procedure

- Simulate a stable population (no HIV) from initial population of 15 males and 15 females
  - 1,500 months for large enough population
- Create ‘Control’ epidemic by introducing 15 per 100,000 monthly random incidence
  - Simulate for 80 years
- Introduce intervention strategy at year 30 of each control epidemic and simulate for 100 years
- 16 interventions x 100 replications each for each intervention scenario

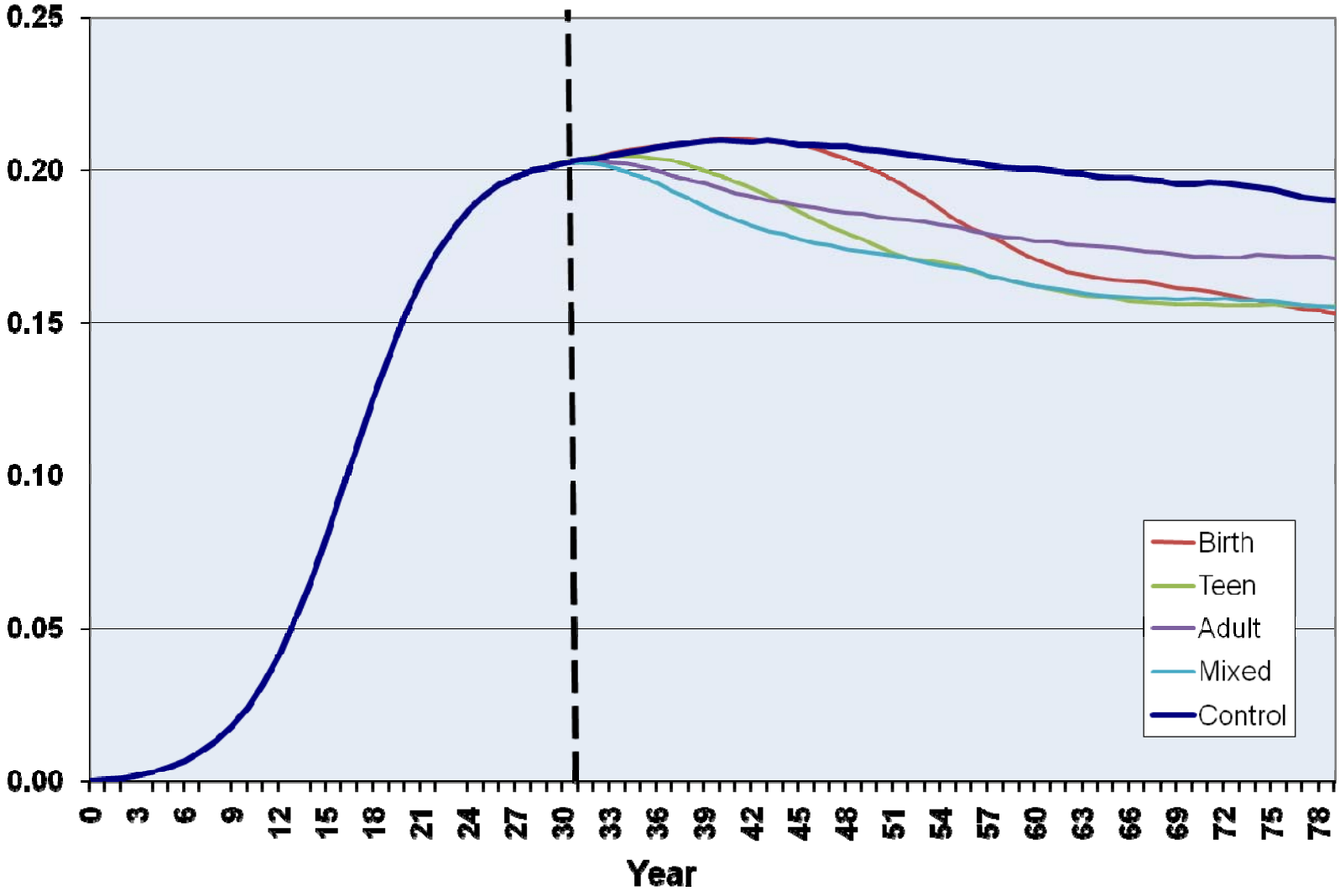
Male HIV Prevalence: Level 10



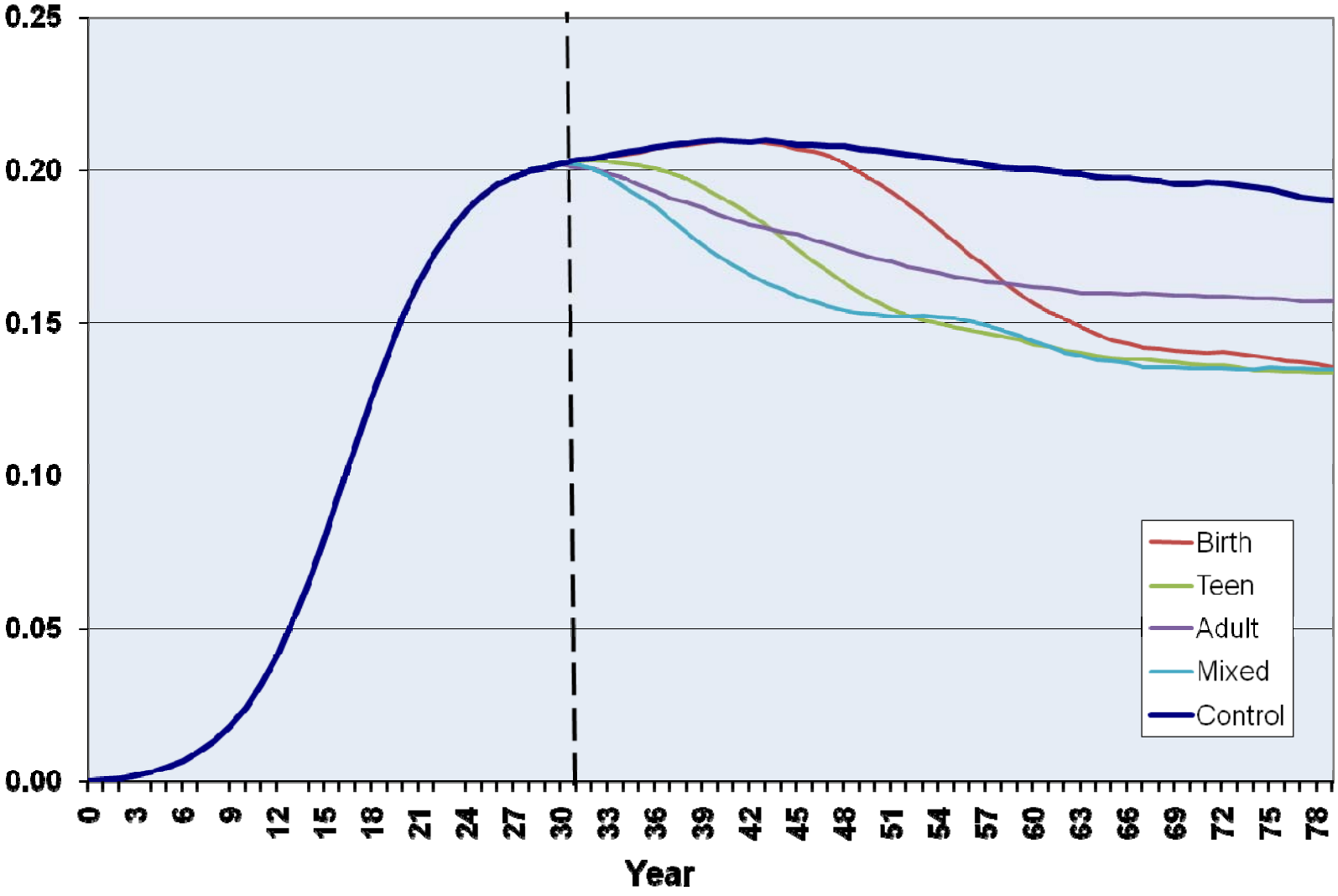
Male HIV Prevalence: Level 25



Male HIV Prevalence: Level 50



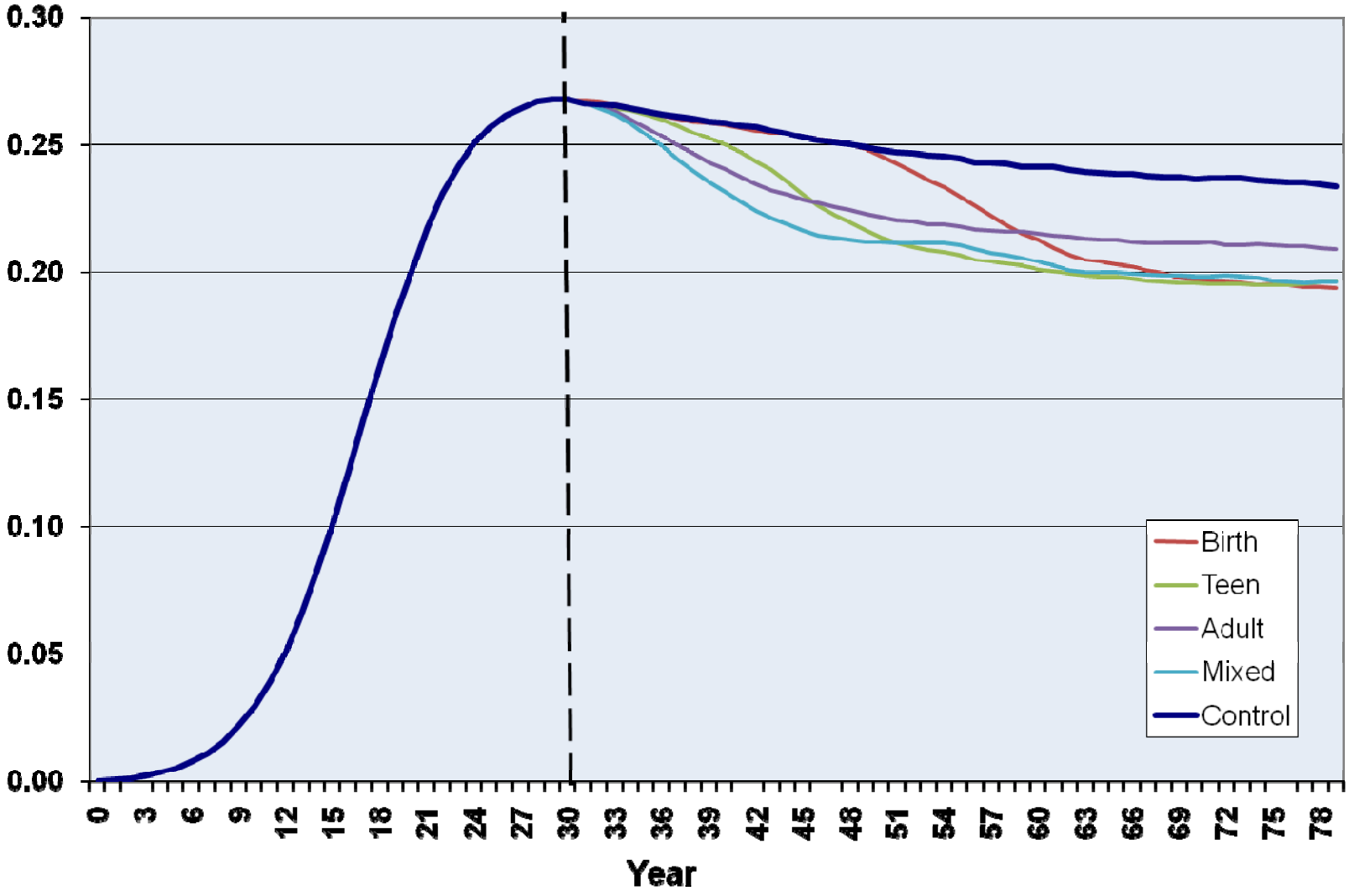
Male HIV Prevalence: Level 75



Effect of MC on Females ?

- Does MC based intervention affect HIV prevalence and incidence in women the same way and with similar magnitude?

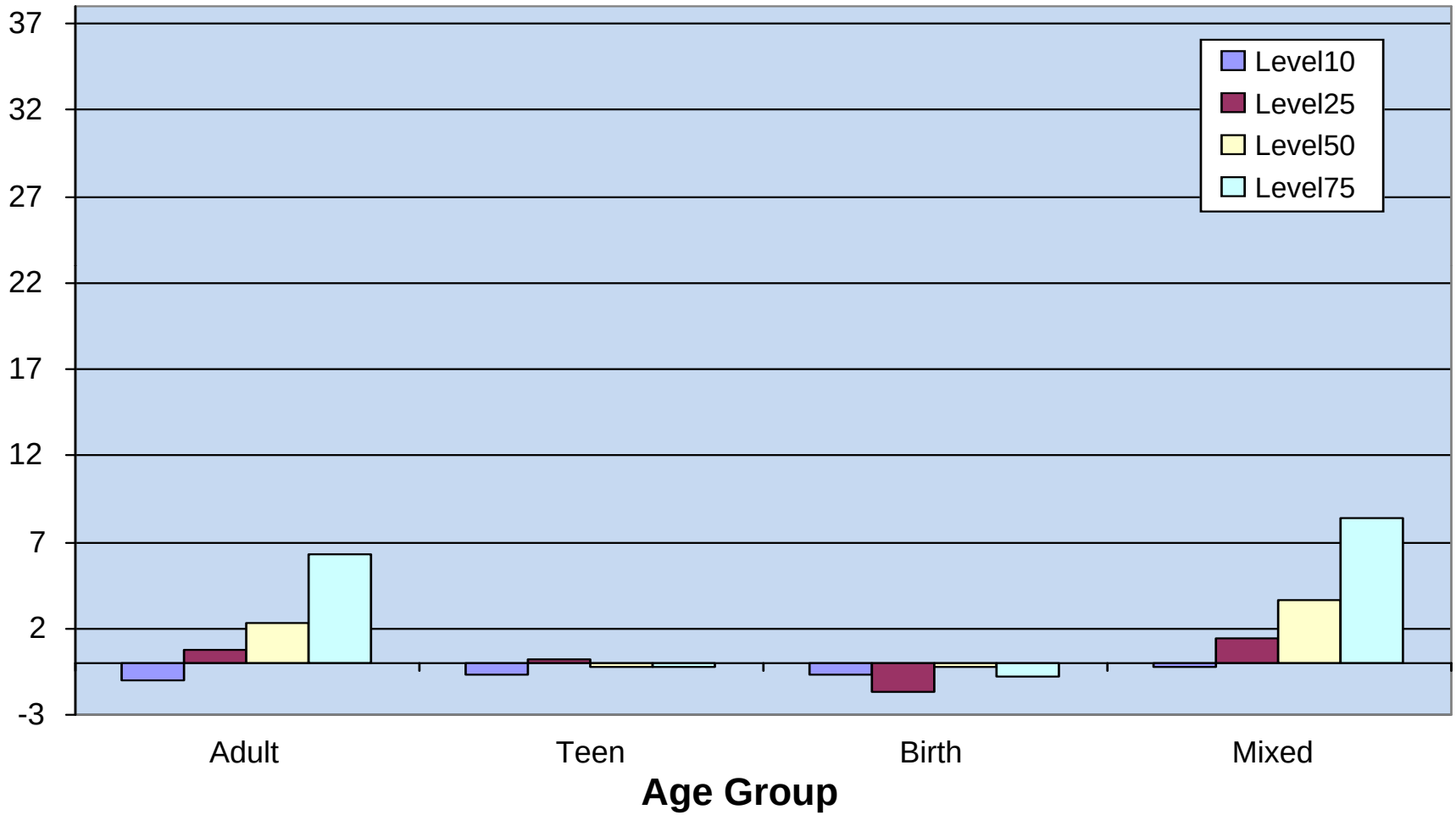
Female HIV Prevalence: Level 50



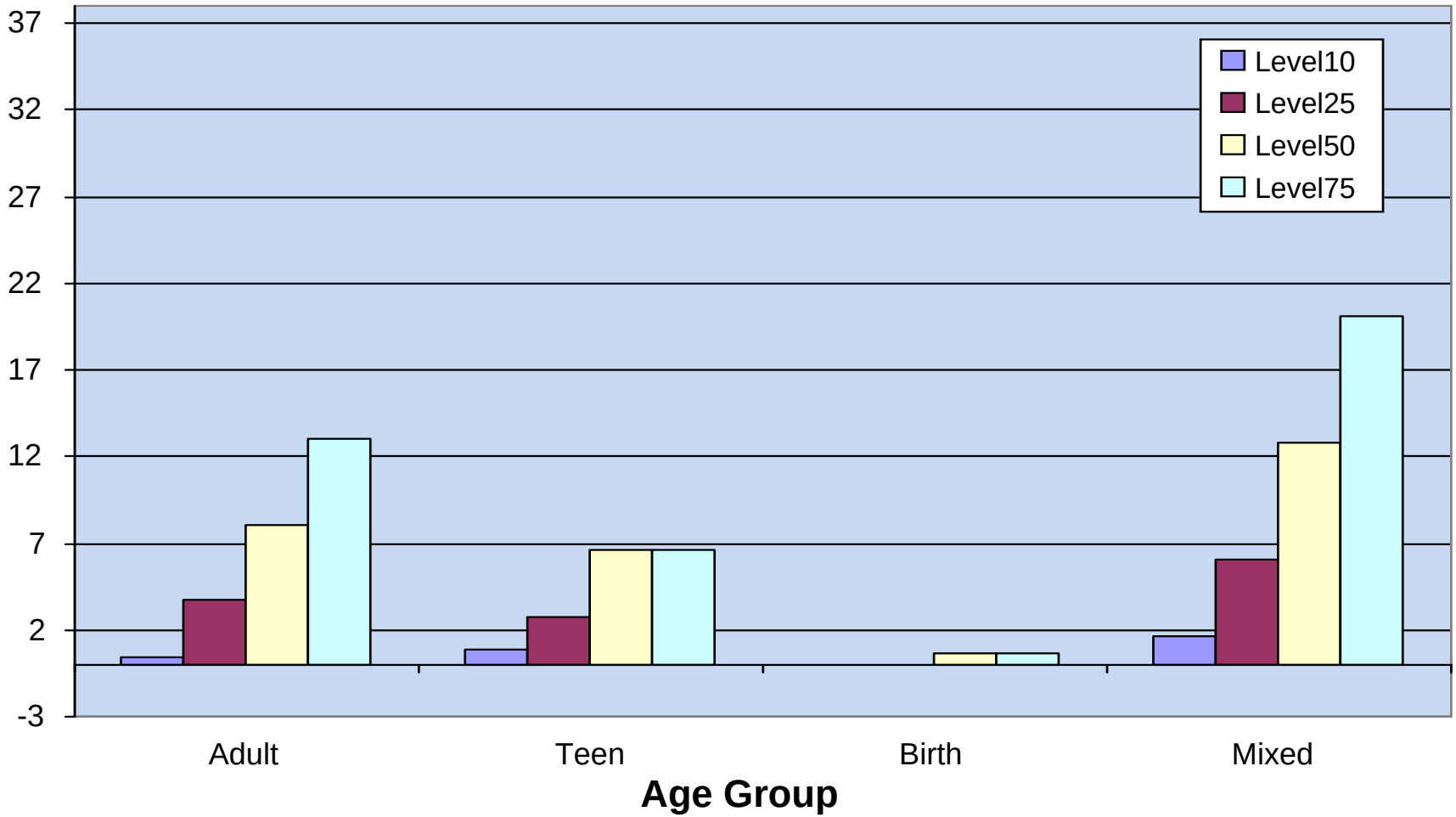
Effect of MC by Age

- Does the magnitude of the effect from MC depend on the age at which males are circumcised?
- Does the age at which males are circumcised change the time horizon of the MC effect?

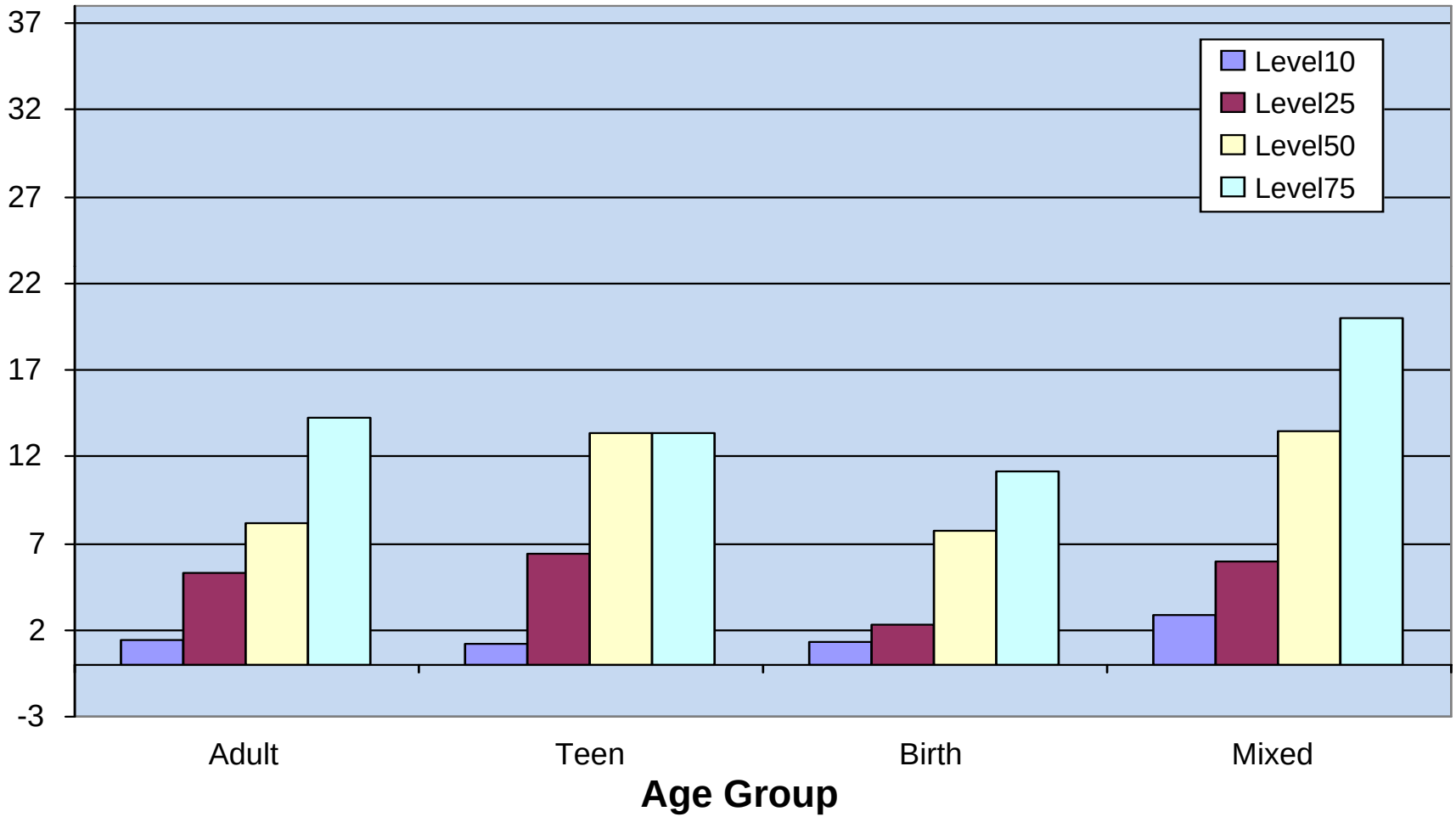
Incidence Averted: Years 0-4 of Epidemic



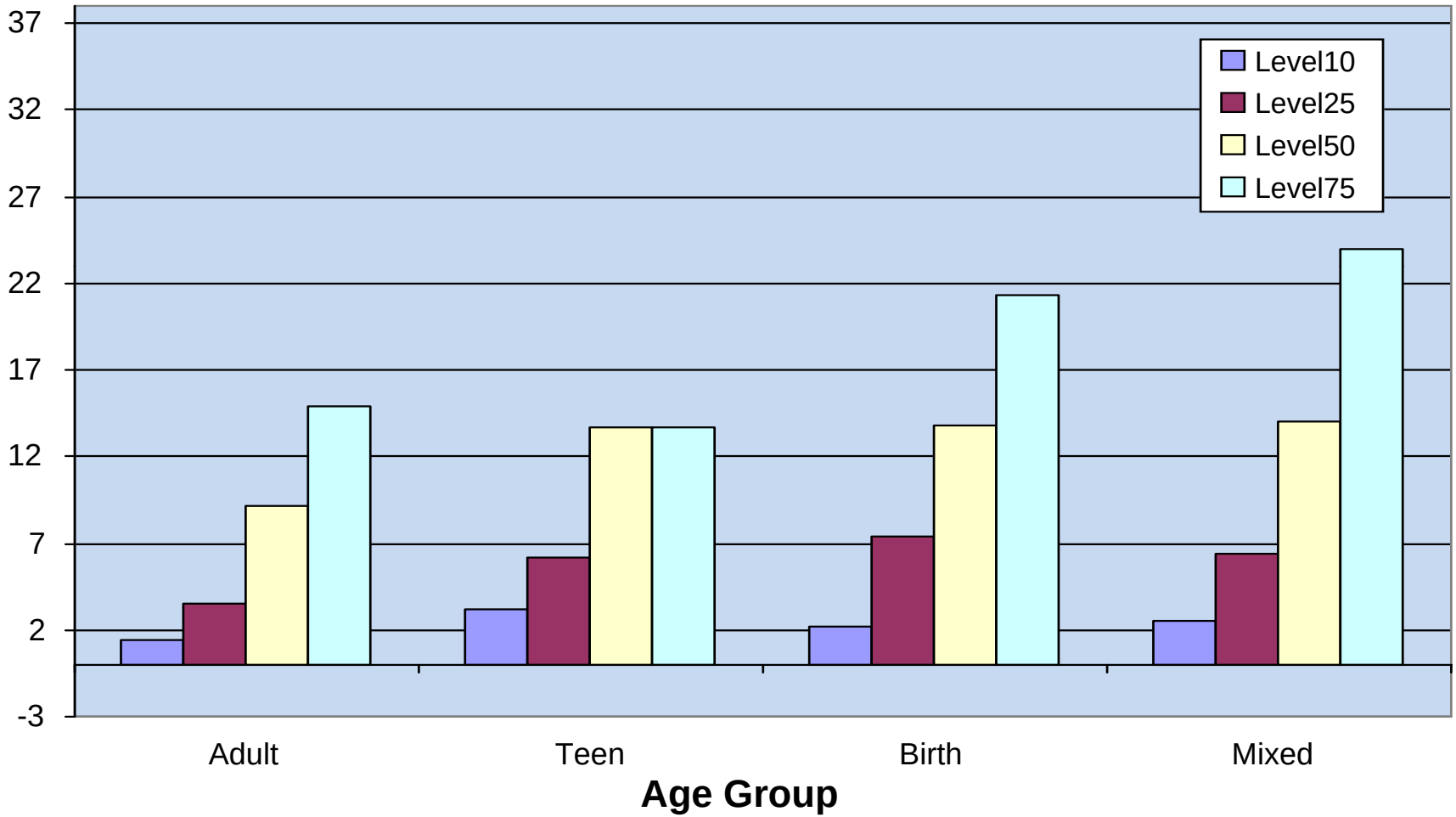
Incidence Averted: Years 5-14 of Epidemic



Incidence Averted: Years 15-29 of Epidemic

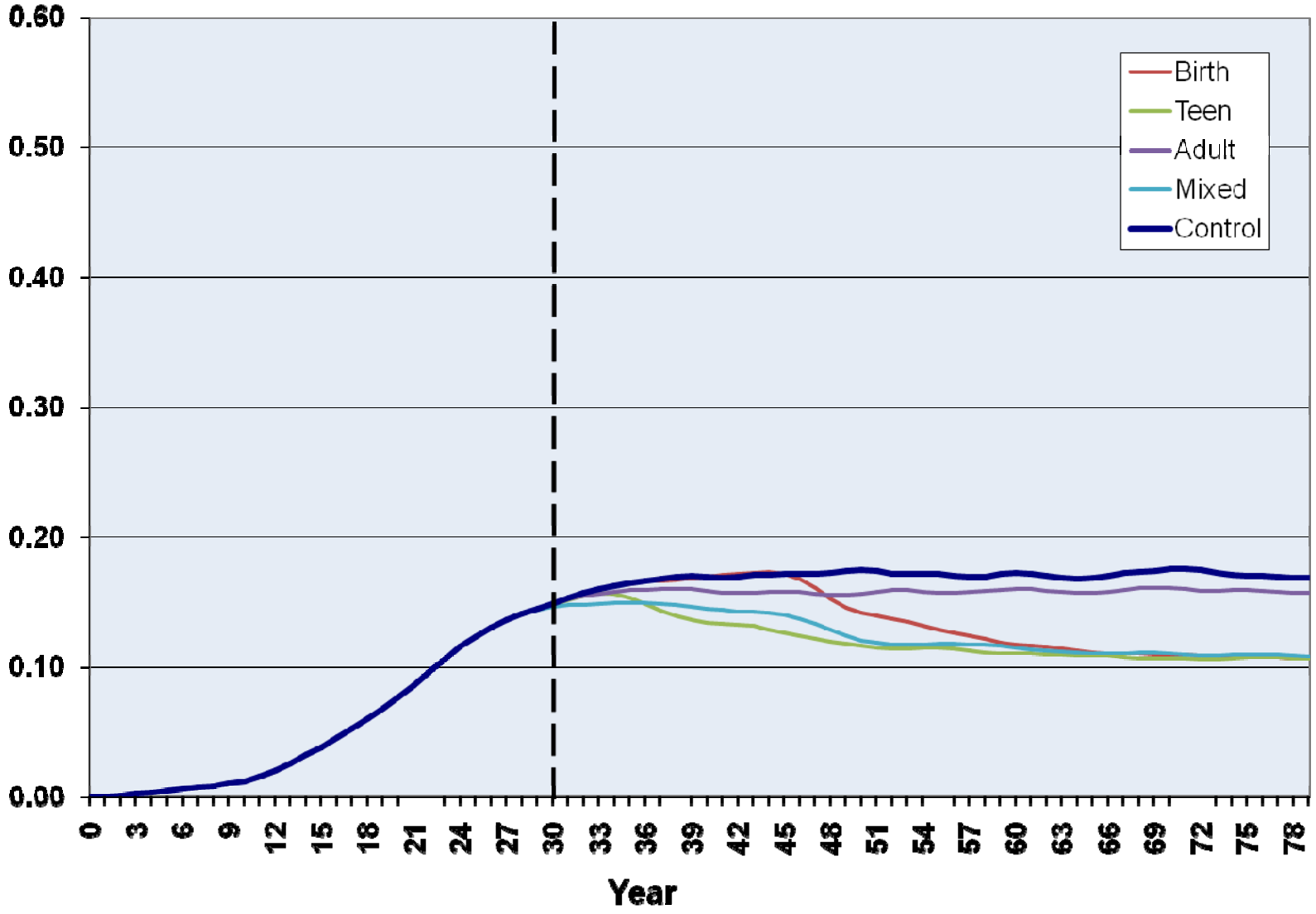


Incidence Averted: Years 30-49 of Epidemic

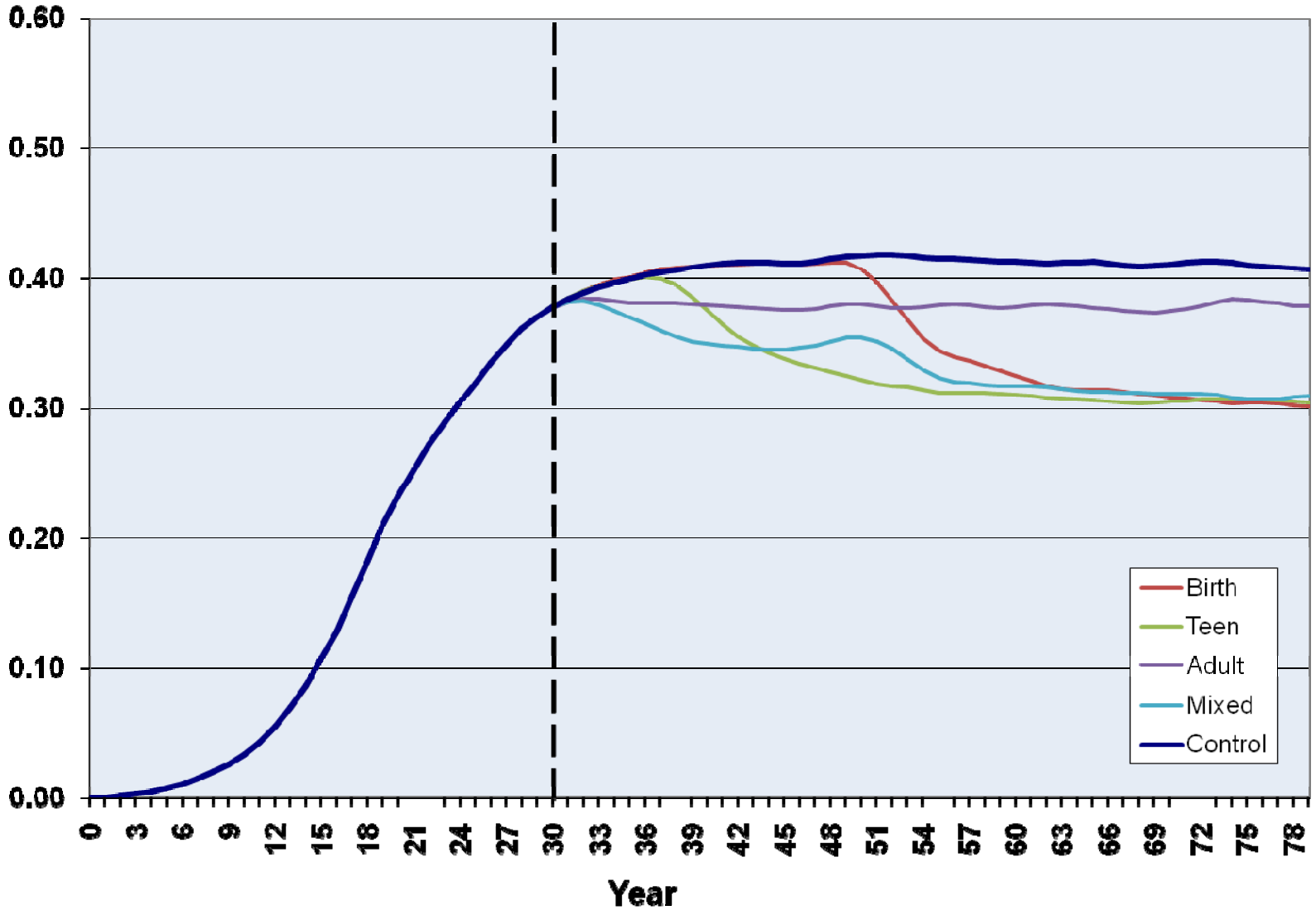


Trends in Age-Specific Prevalence

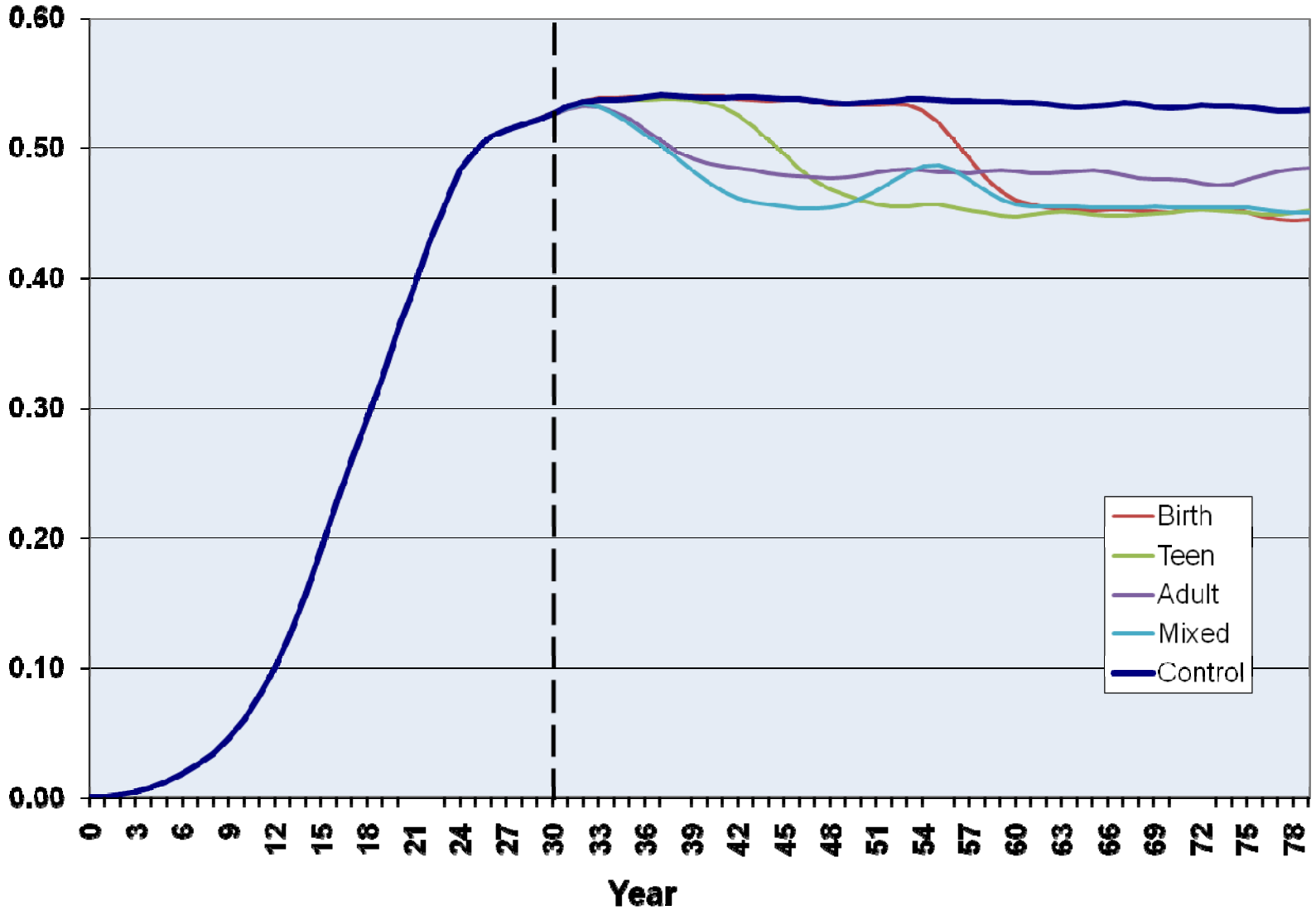
Male Prevalence Ages 15-19 (Level 50)



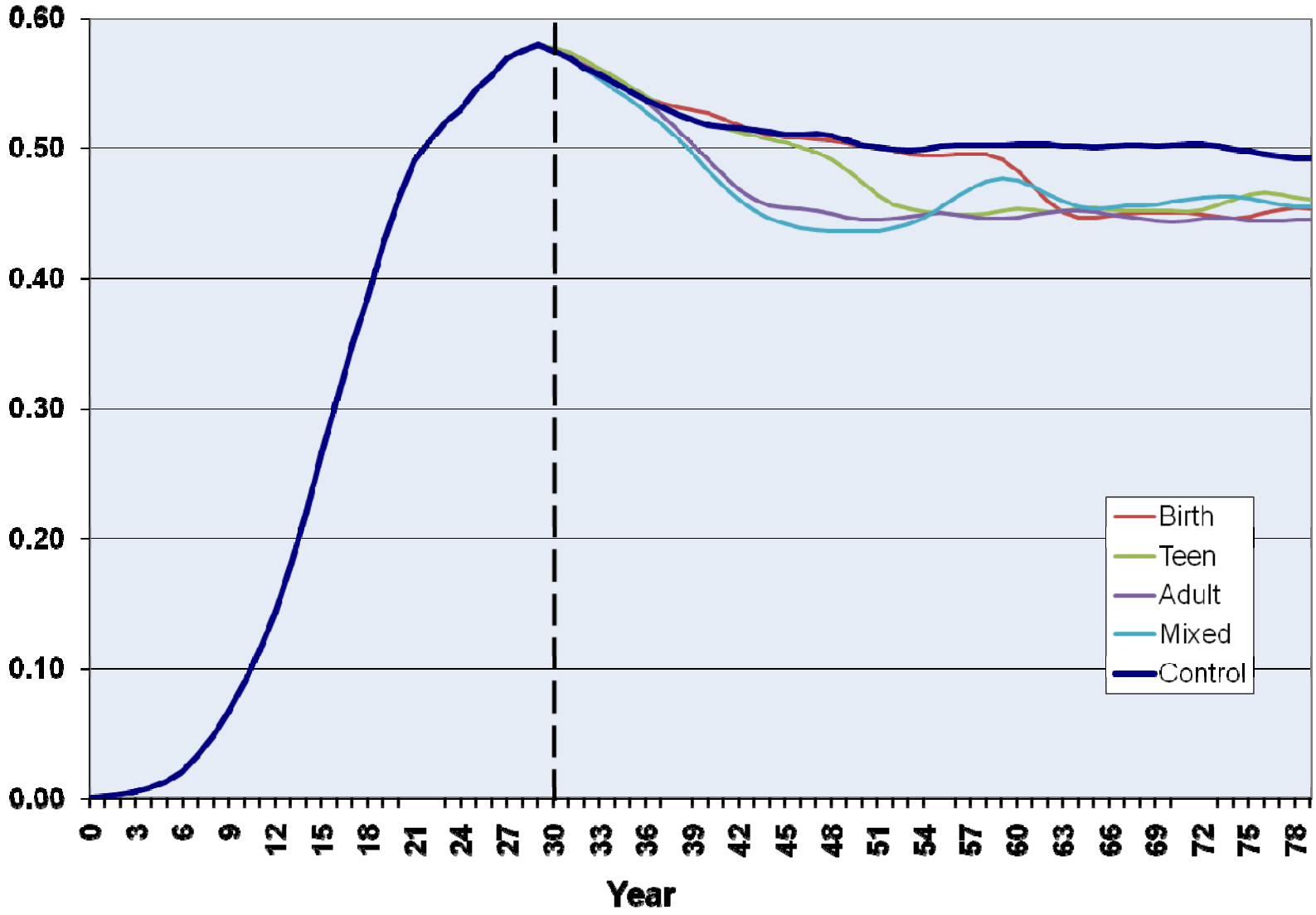
Male Prevalence Ages 20-24 (Level 50)



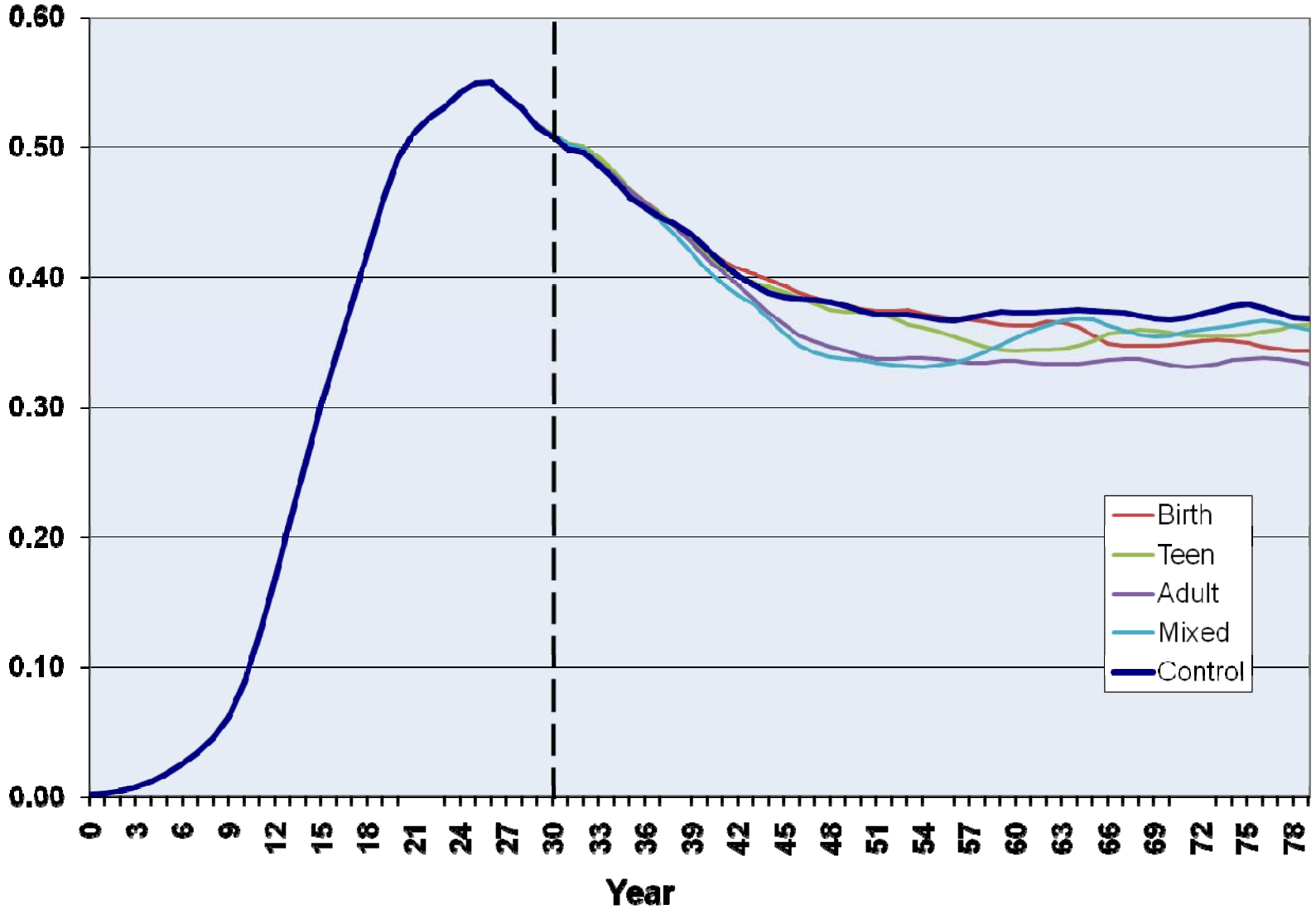
Male Prevalence Ages 25-29 (Level 50)



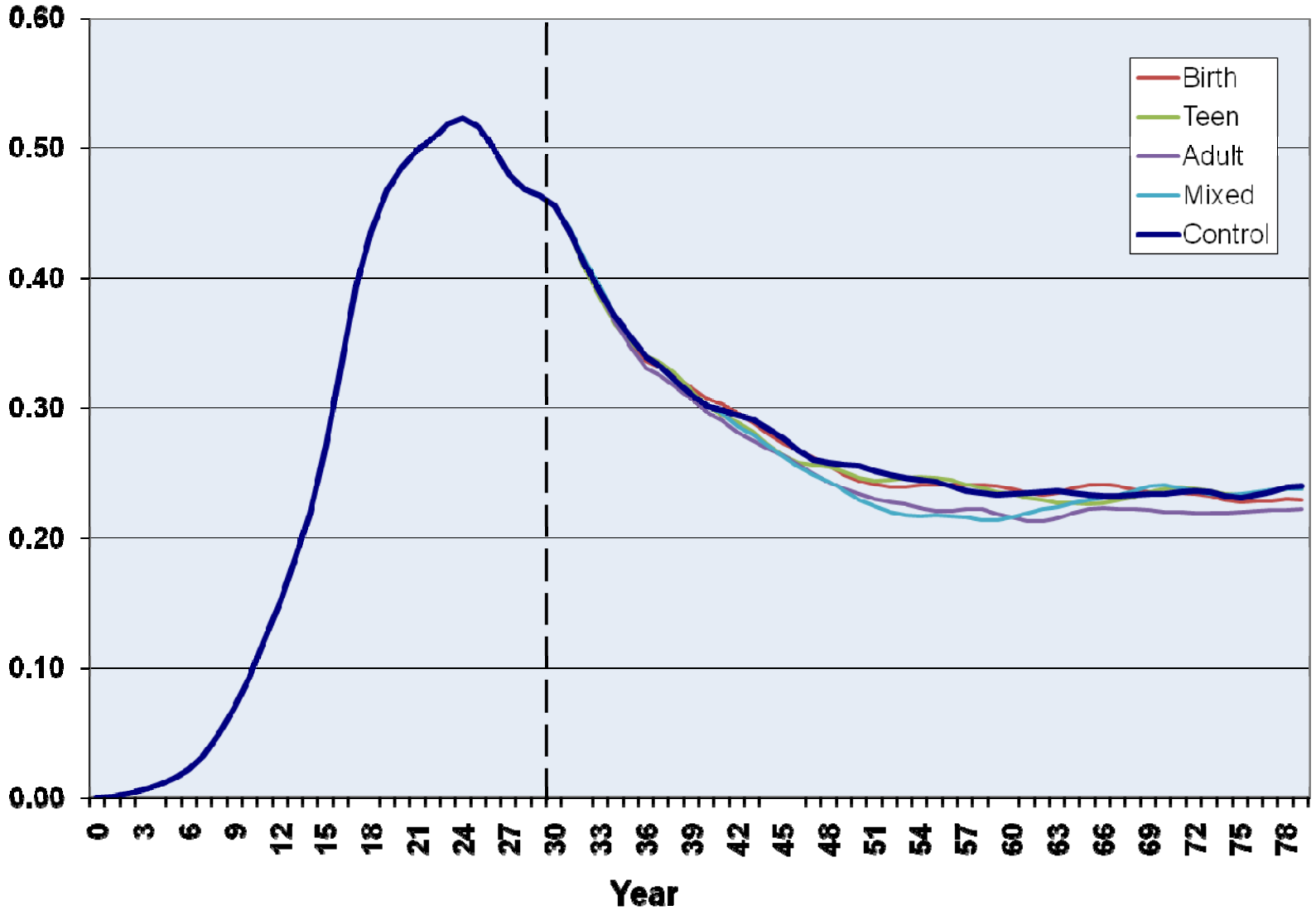
Male Prevalence Ages 30-34 (Level 50)



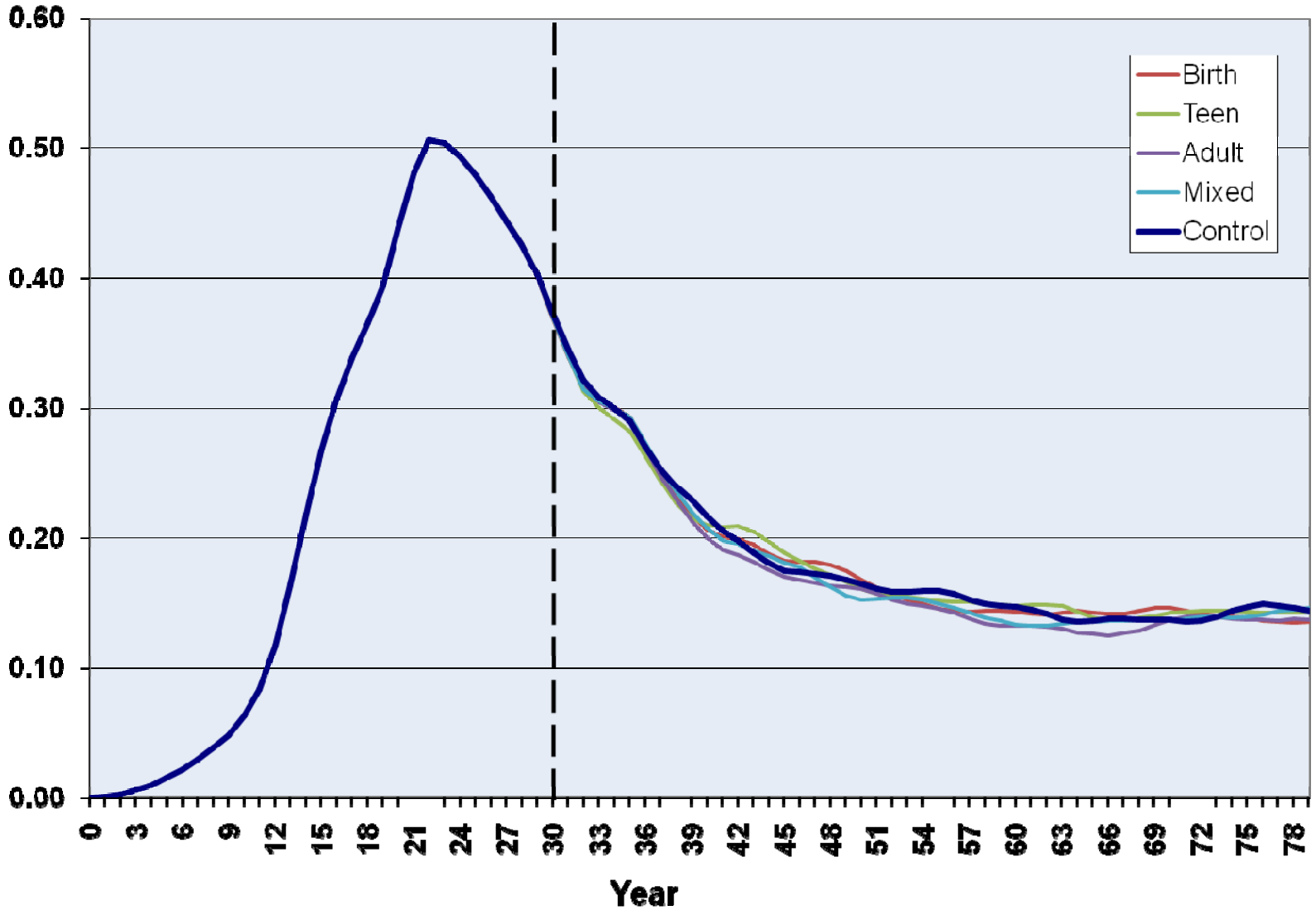
Male Prevalence Ages 35-39 (Level 50)



Male Prevalence Ages 40-44 (Level 50)



Male Prevalence Ages 45-49 (Level 50)



Conclusions

- MC intervention programs can have a substantial impact on an HIV epidemic, although alone such an intervention is not likely to end an epidemic
- MC interventions should have a similar positive effect on females as they do on males
- MC intervention programs need to reach a substantial percentage of the uncircumcised male population to produce a substantial effect
  - 'Dose response' does not appear linear

Conclusions

- A mixed age intervention appears most effective:
  - Provides intervention before most begin having sexual intercourse
  - Has nearly immediate impact
- Real intervention strategies should be take these general observations into account and do more modeling to fine-tune the approach taking into account the balance between costs and effectiveness

Limitations & Future Directions

- Does not account for uncertainty in level or type of protection provided by MC
- Specific intervention outcomes depend on the demography of and assumptions about the modeled population
- Stochastic nature of this problem makes it difficult to tease out slight differences between intervention scenarios, requires:
  - A large number of model runs
  - Lots of tedious analysis

Acknowledgements

- **Jeffrey Eaton**
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