Modelling HIV: How complicated do we want to make this?

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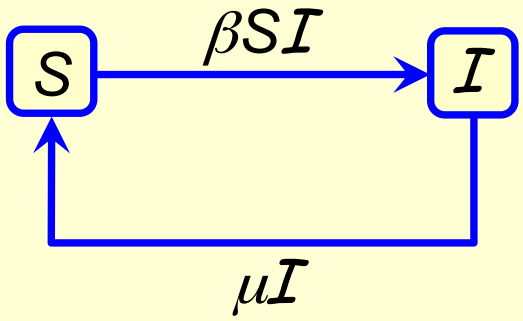
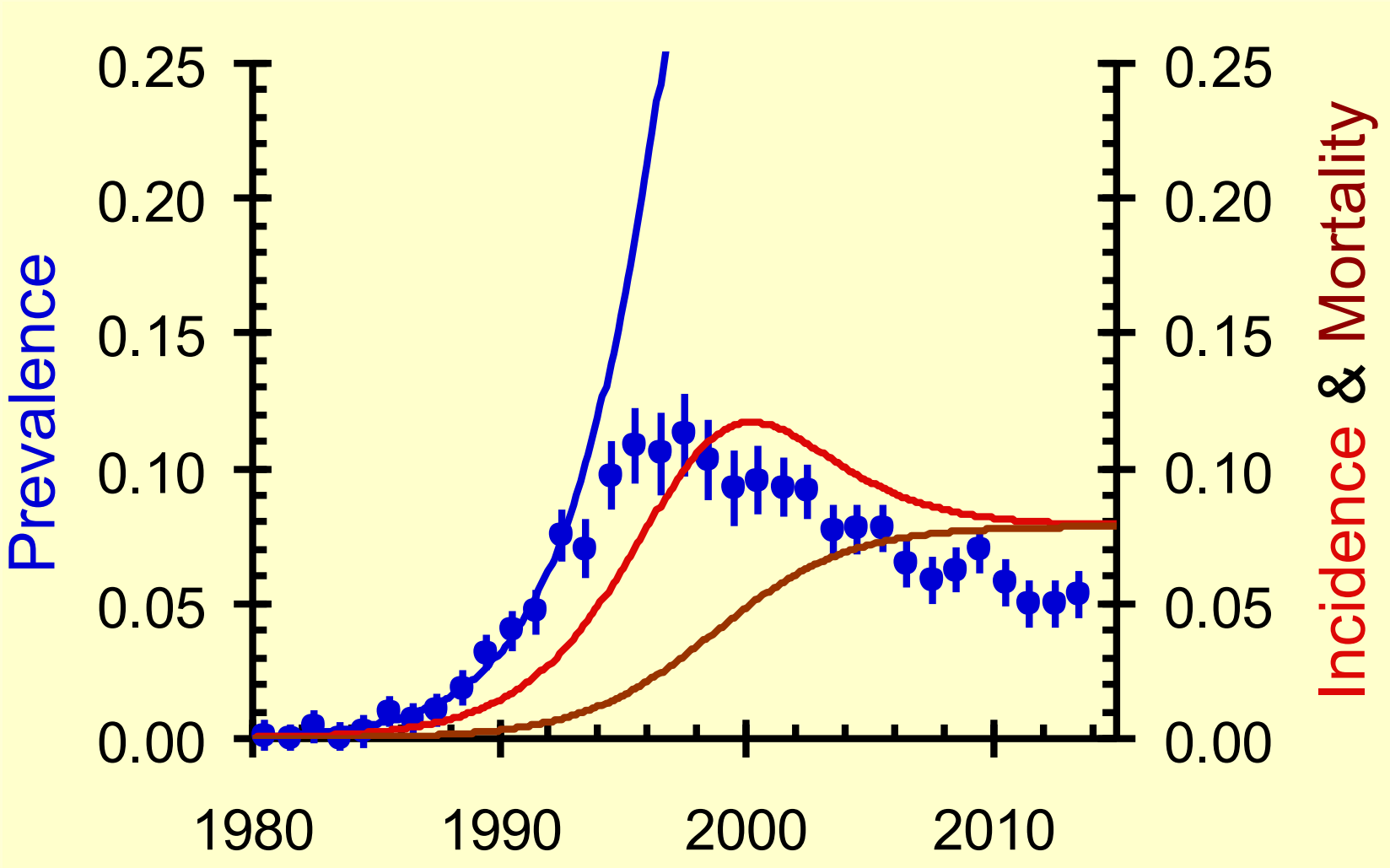
The basic SI model

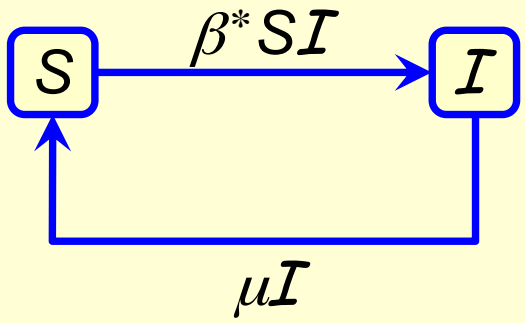


Working with proportions, susceptible people are infected at a *per capita* rate β *;* Infected people die at a *per capita* rate μ*.*



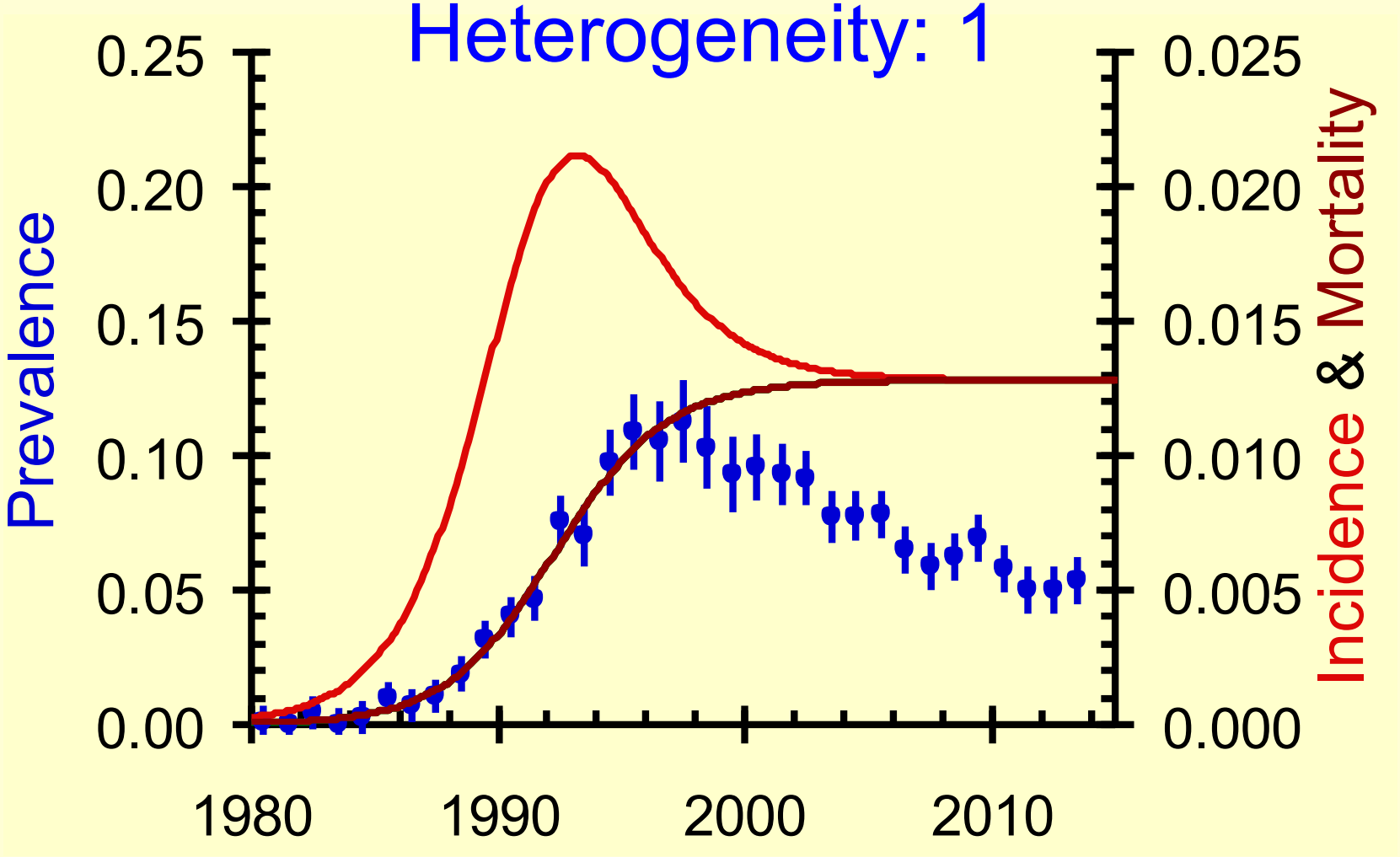
Exponential rise give $R_0 = \beta/\mu = 4.7$. Logistic increase to a steady state prevalence of $(R_0 - 1)/R_0 = 0.8$.

Heterogeneity in risk: 1



$$\beta^* = \beta\left(1 - \alpha P\right)$$

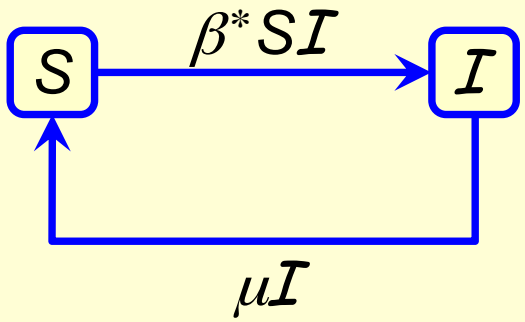
Imperial College: A proportion *1/α* of the population are at risk; (1 – *1/α*) are at no risk



We can now fit the peak prevalence (but not the decline). Model suggest that only 13% of people are at risk of HIV.

N.B. If the mortality is 10% per year, it is always 10% of the prevalence. The scales differ by a factor of 10 so the prevalence and mortality curves lie exactly on top of each other.

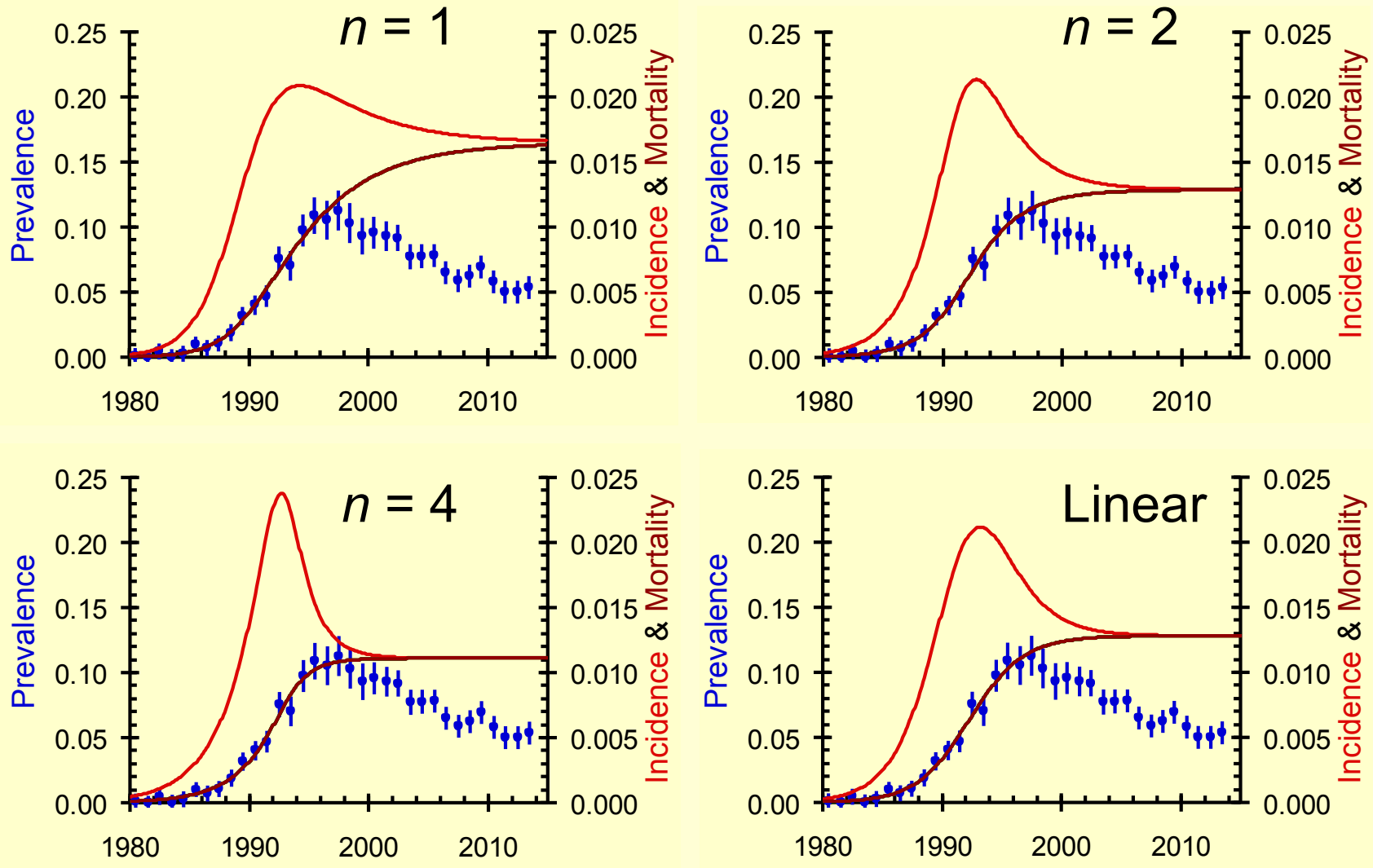
Heterogeneity in risk: 2



SACEMA: Risk of infection declines with prevalence.

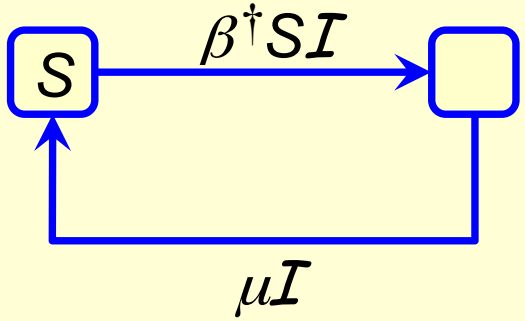
$$\beta^* = \beta \, \mathrm{e}^{-(\alpha P)^n}$$

n = 1: Exponential
n = 2: Gaussian
n = ∞: Step-function

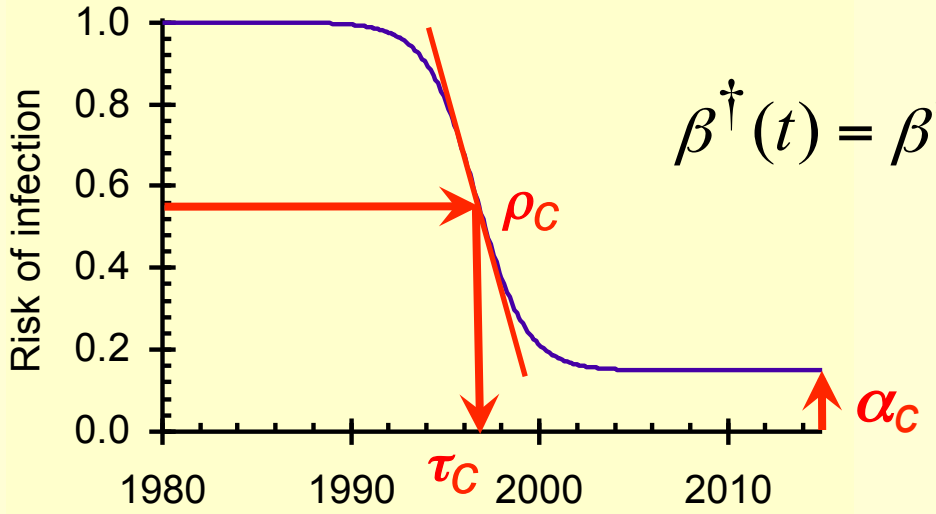


All fits are equally good but the implied incidence and the steady state prevalence are quite different. We will use $n = 2$.

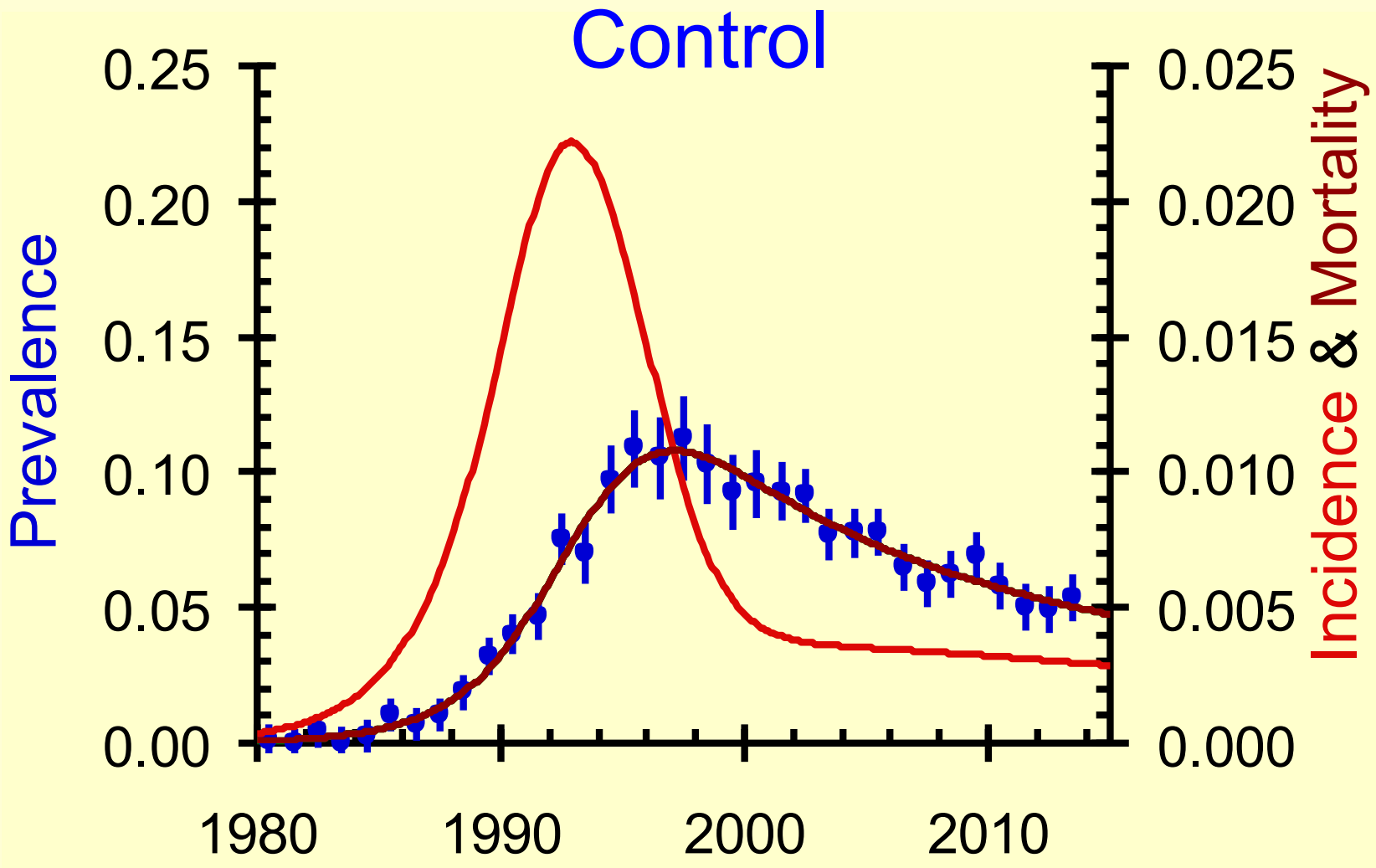
Control



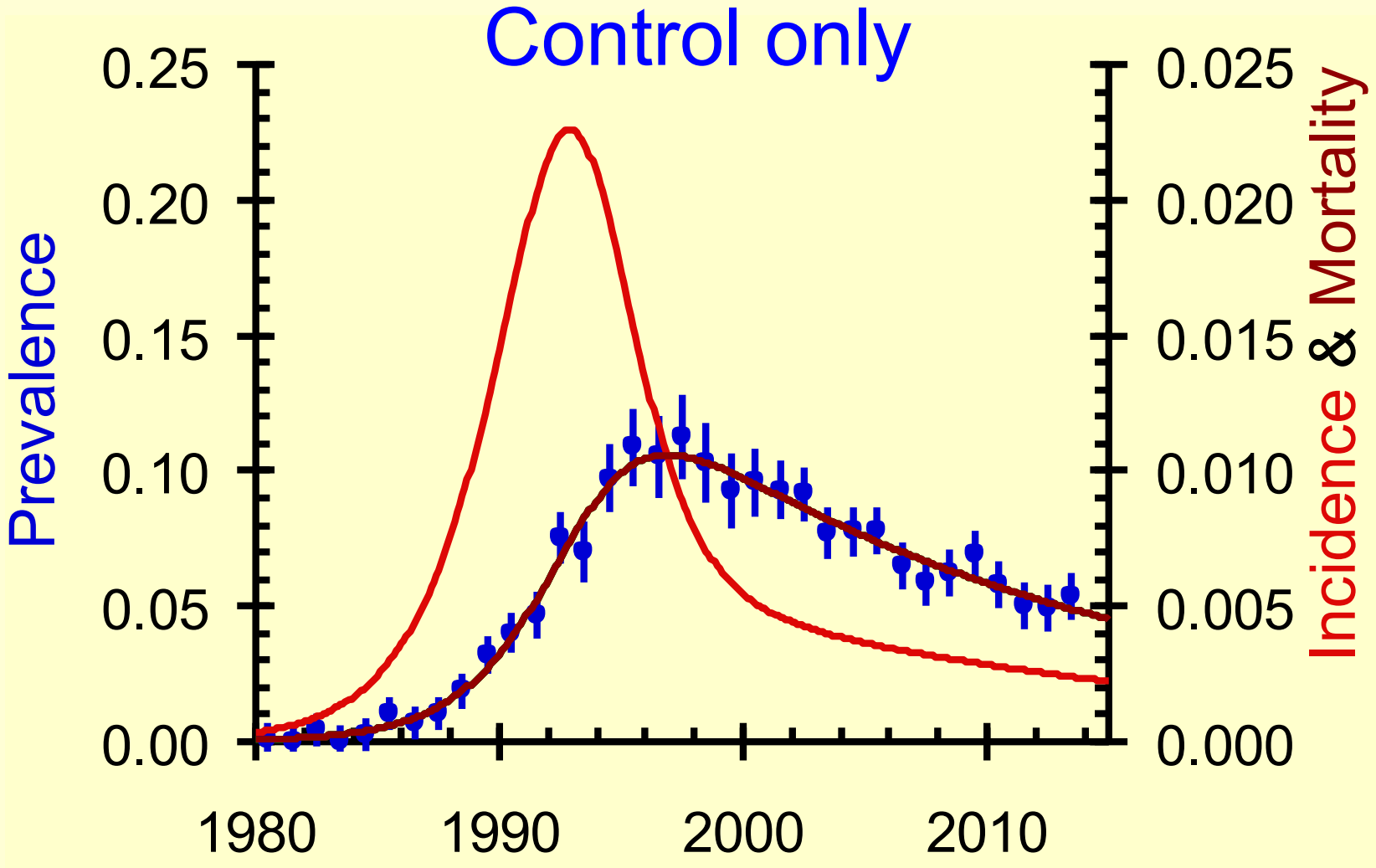
Let risk decline logistically with time



$$\beta^{\dagger}(t) = \beta^{*}(t)\left[(1-\alpha_c)\frac{e^{\rho_c(t-\tau_c)}}{1+e^{\rho_c(t-\tau_c)}} + \alpha_c\right]$$

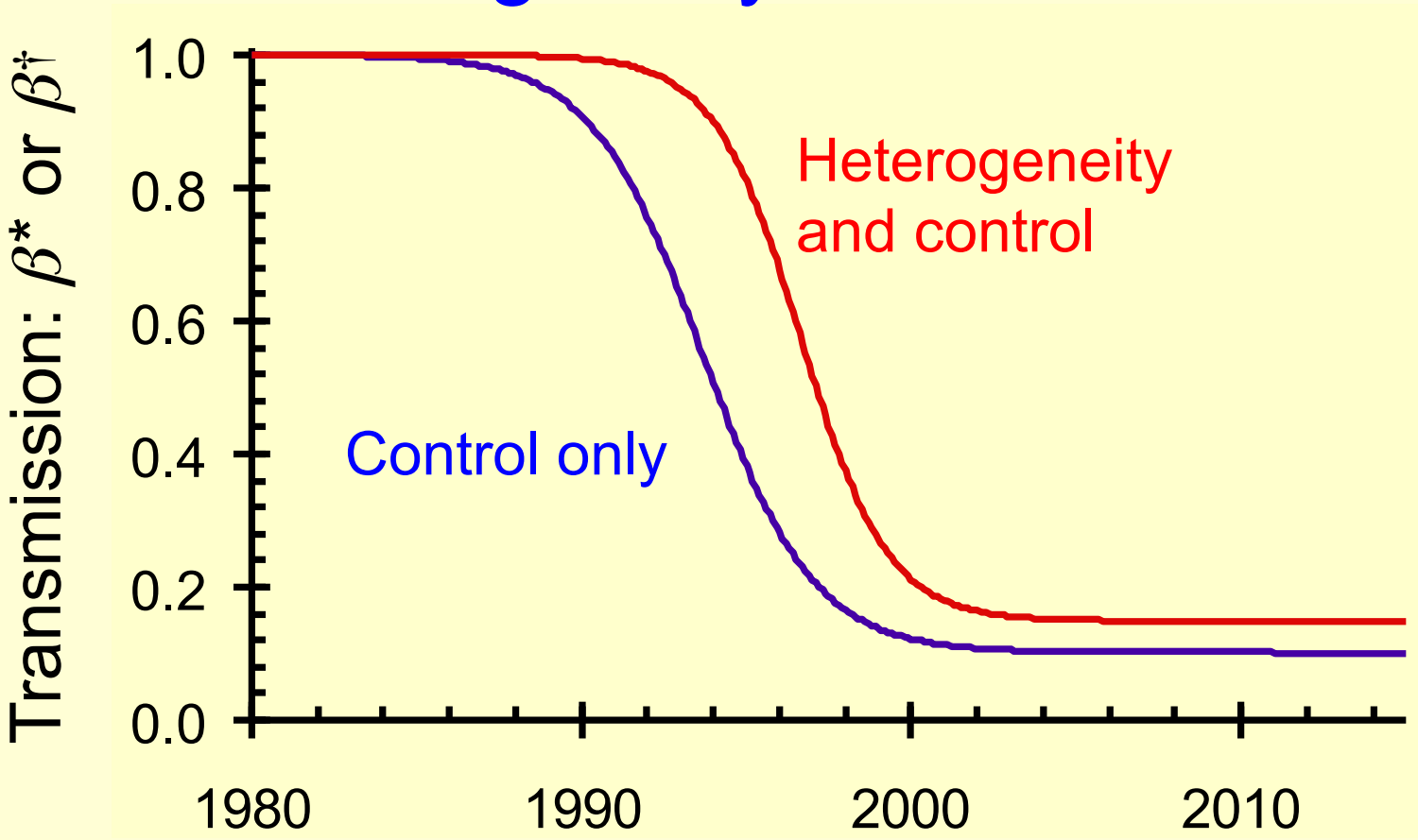


We now get a good fit to all the data. Transmission fell by 85% between 1992 and 2002



But we get an equally good fit if we drop the heterogeneity and increase the ‘control’. Transmission fell by 90% between 1987 and 2003.

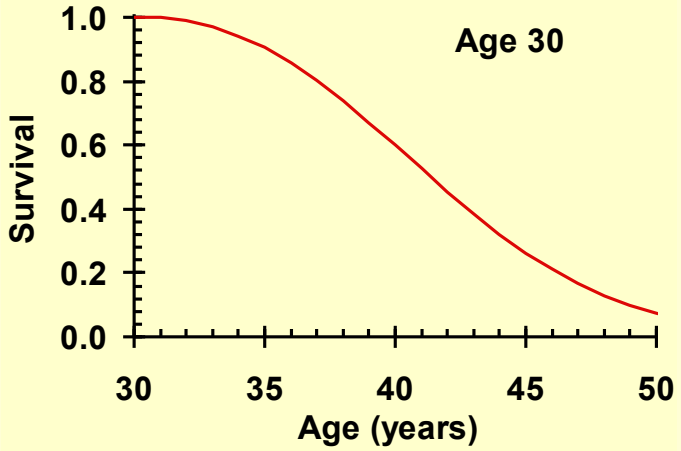
Heterogeneity v. control



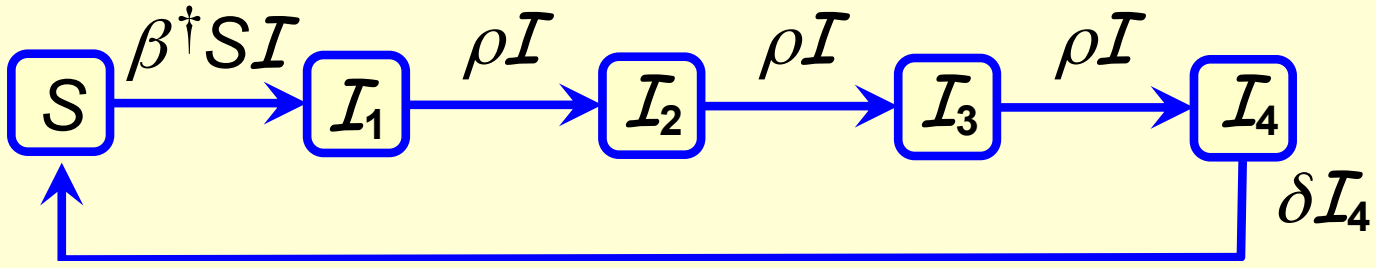
Without heterogeneity control has to start 3 years earlier and has to fall further 90% v. 85%.

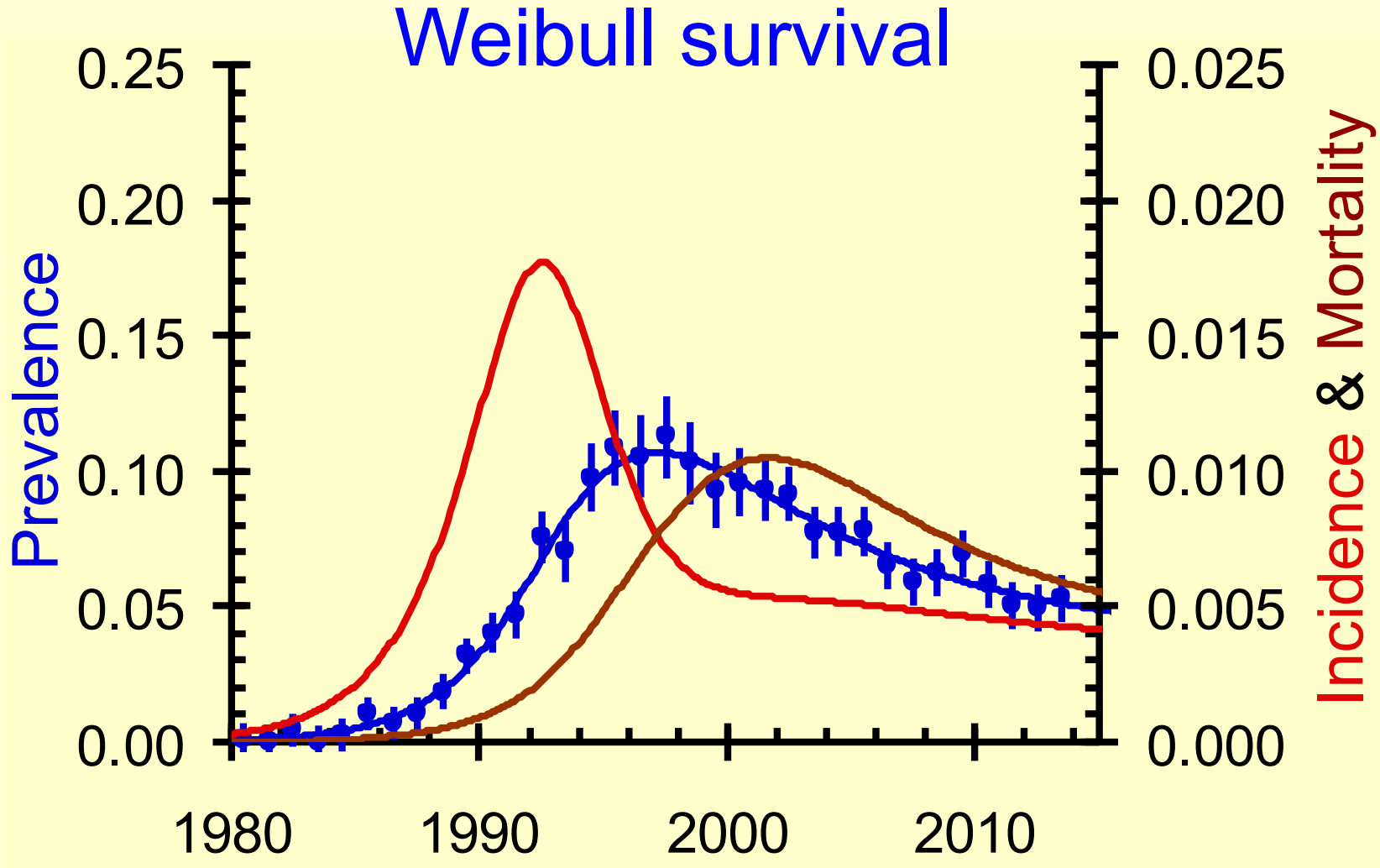
Weibull survival

Survival on HIV follows a Weibull survival curve with a median survival of 10 years and a shape parameter of 2.25.



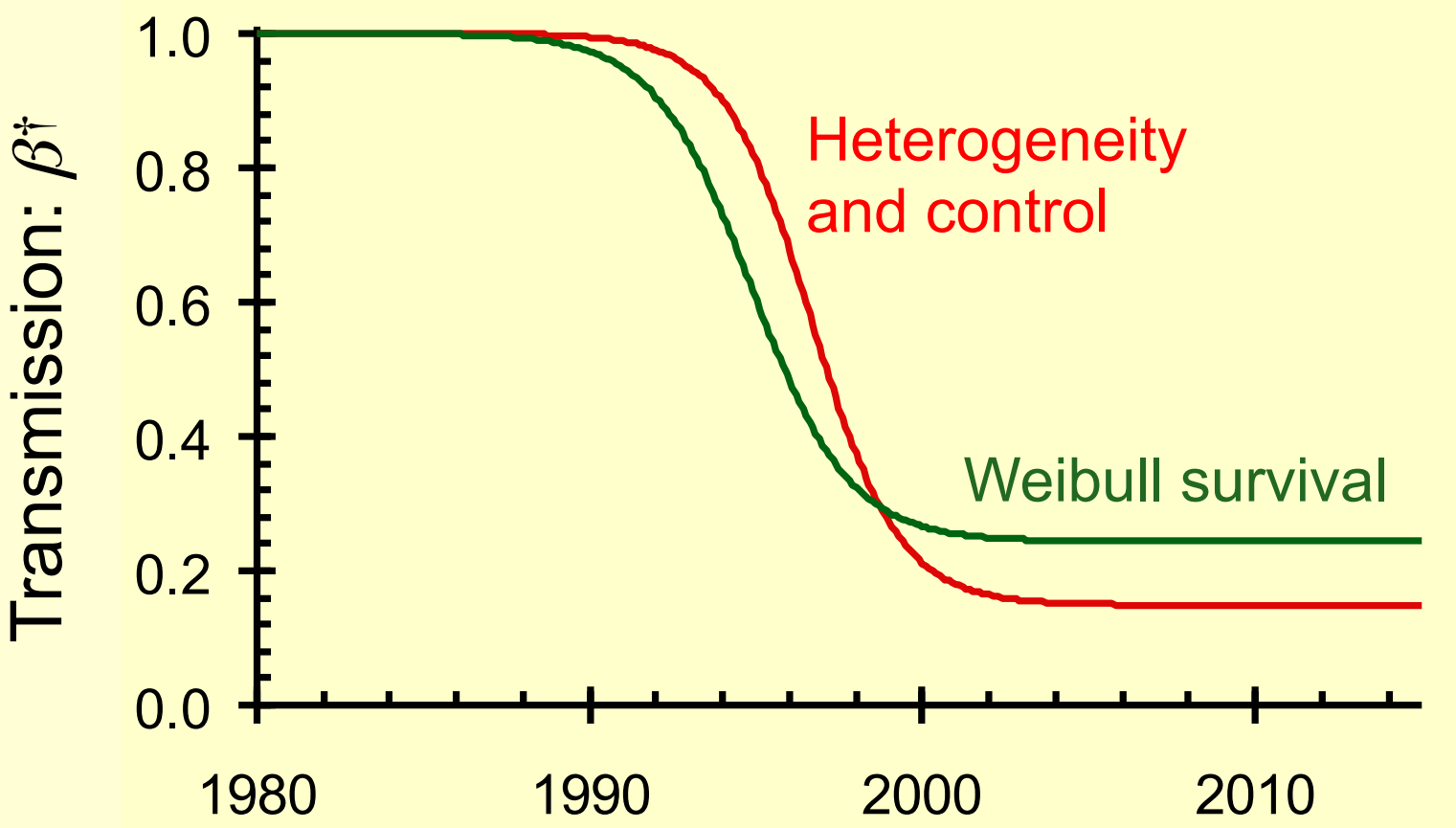
Close to a survival for a Γ-function with a shape parameter of 4. We use four successive compartments for those with HIV.





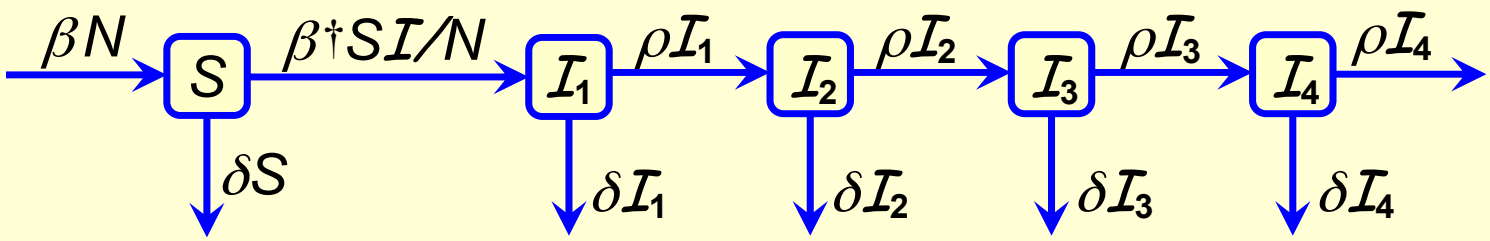
Mortality now rises about 8 years after the rise in incidence and about 3 years after the rise in prevalence. Weibull survival introduces an important delay.

Weibull survival and control

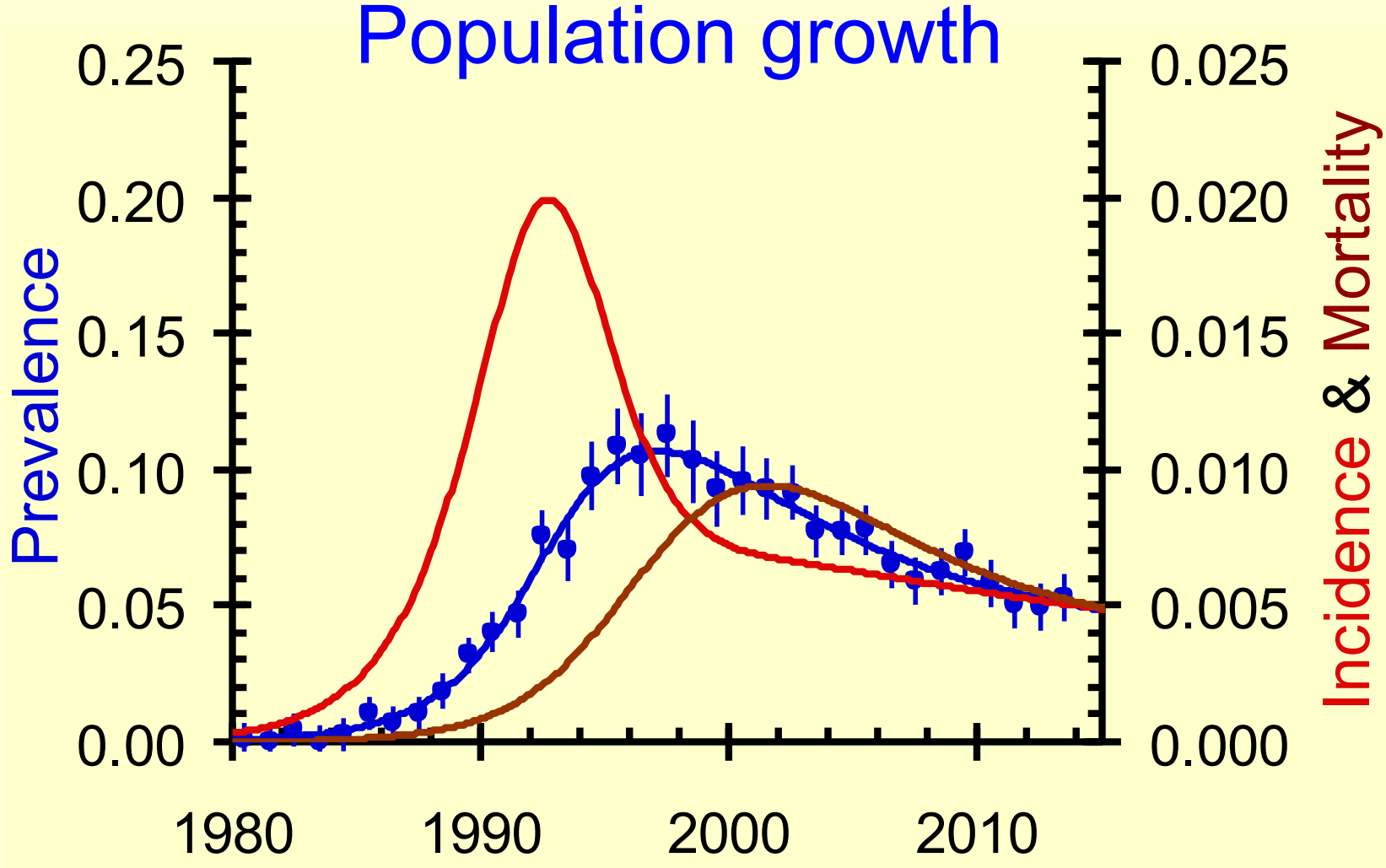


Allowing for the Weibull survival, control has to start one year later and has to fall less (76% v. 85%).

Population growth

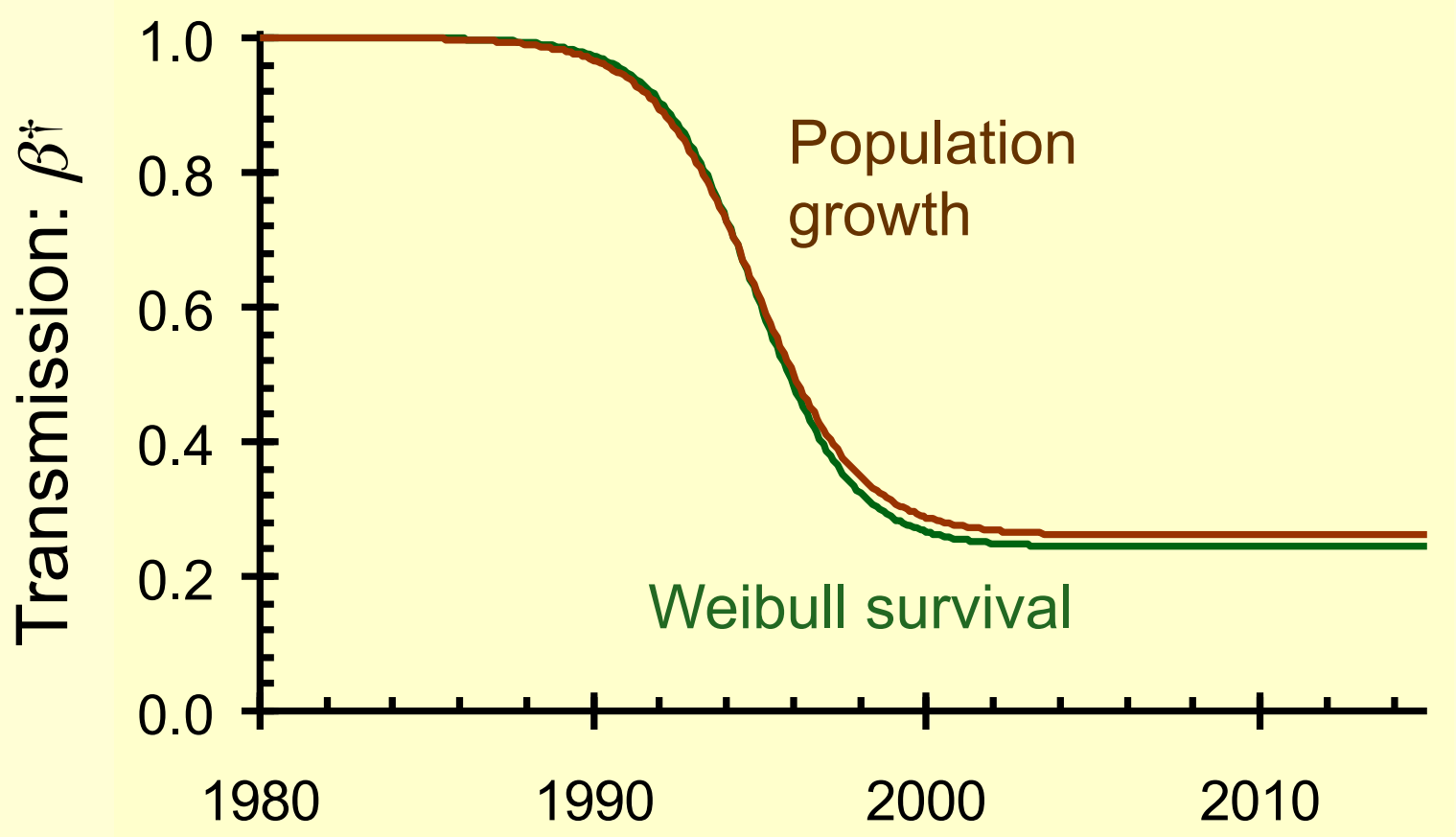


Separate the birth rate from the death rate and allow people to die from natural causes in each stage.
(Birth rate = 3.6% p.a.; death rate = 1.2% p.a.)



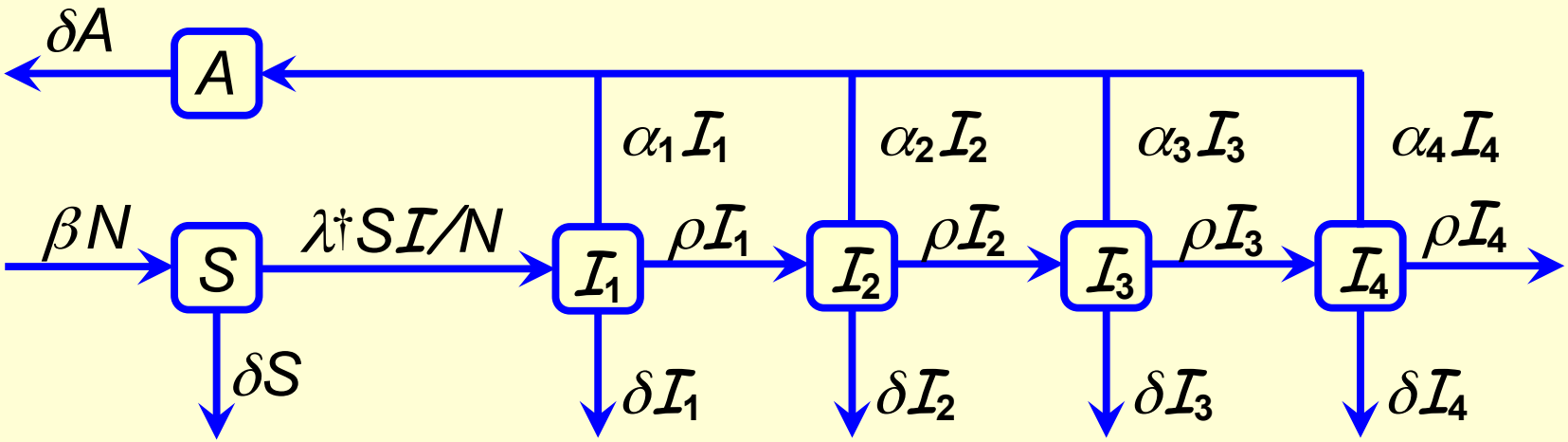
Allowing the population to grow (2.4% p.a.) increases incidence and reduces mortality but only slightly.

Weibull survival and control



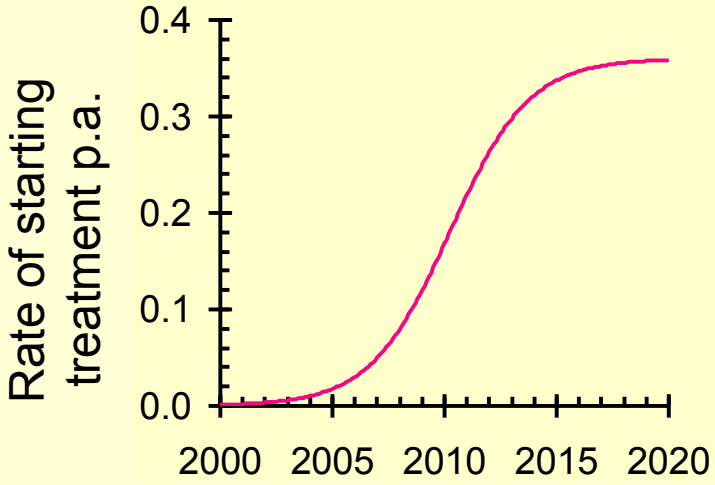
Allowing for the population growth has little effect on the level of control needed to fit the data.

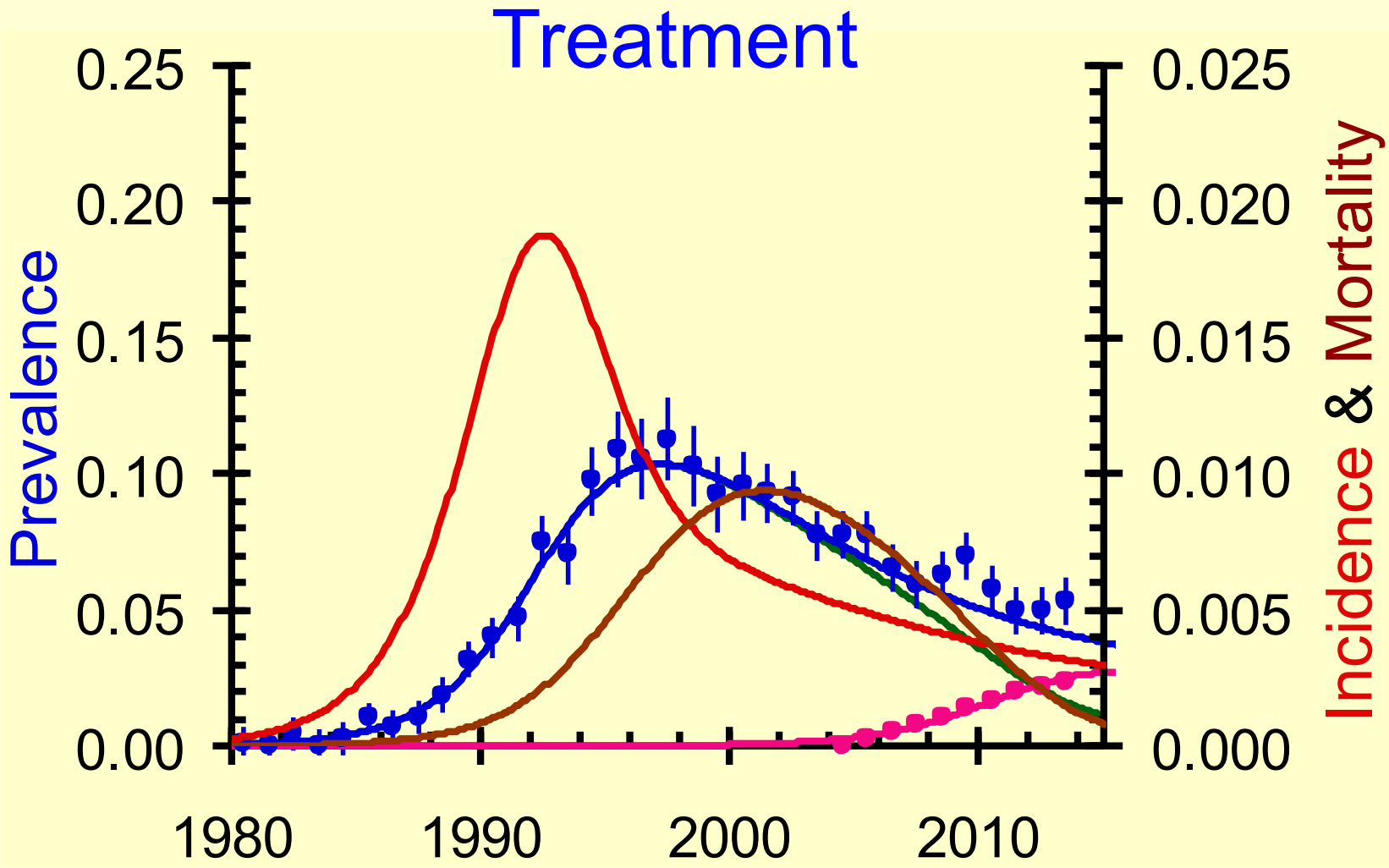
Including treatment



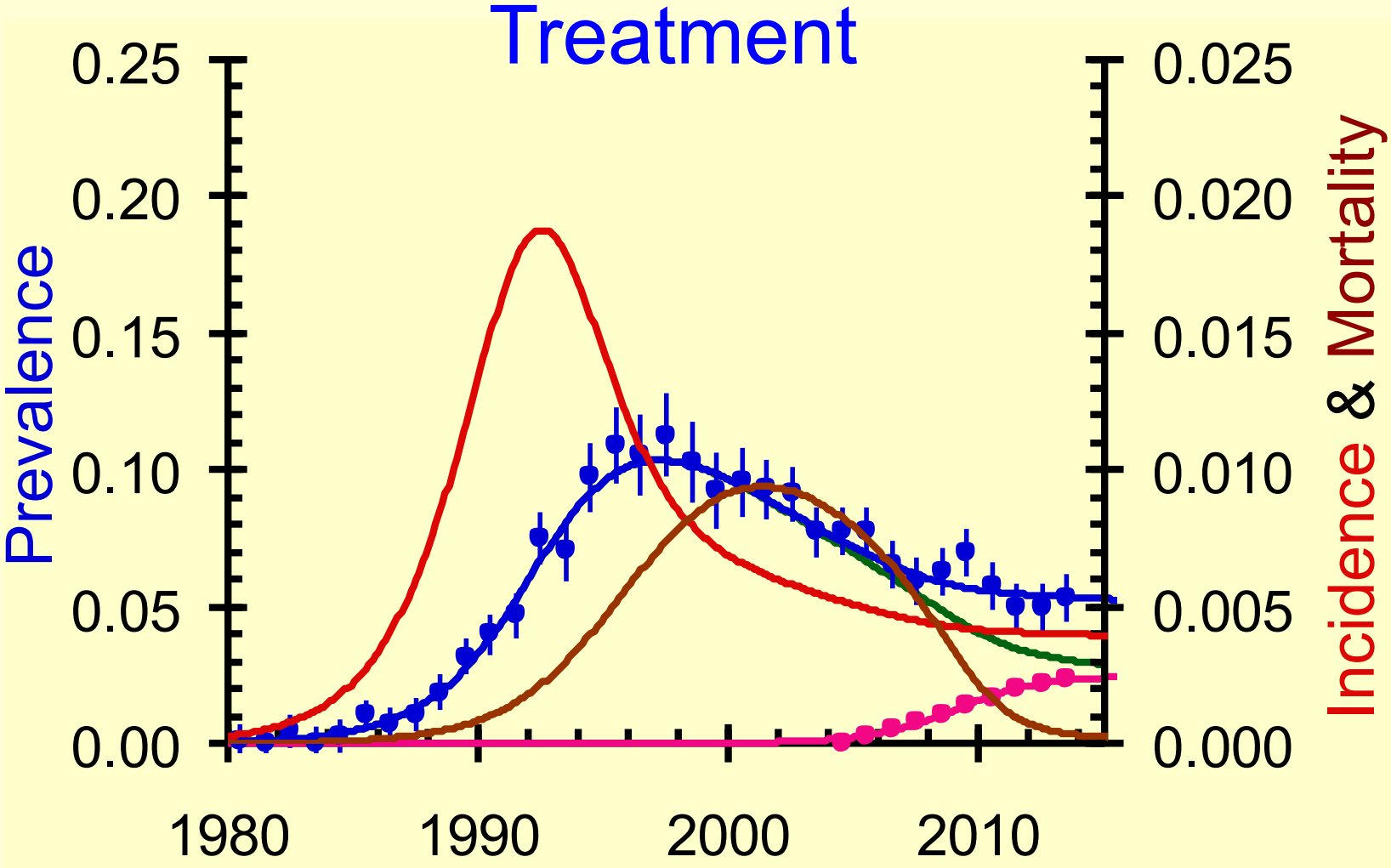
People may start treatment and go onto ART (A) from any of the infected classes. Let the rate of starting treatment increase logistically with time.

$$\alpha_i(t) = a_i \frac{e^{a_i(t-t_i)}}{1+e^{a_i(t-t_i)}}$$

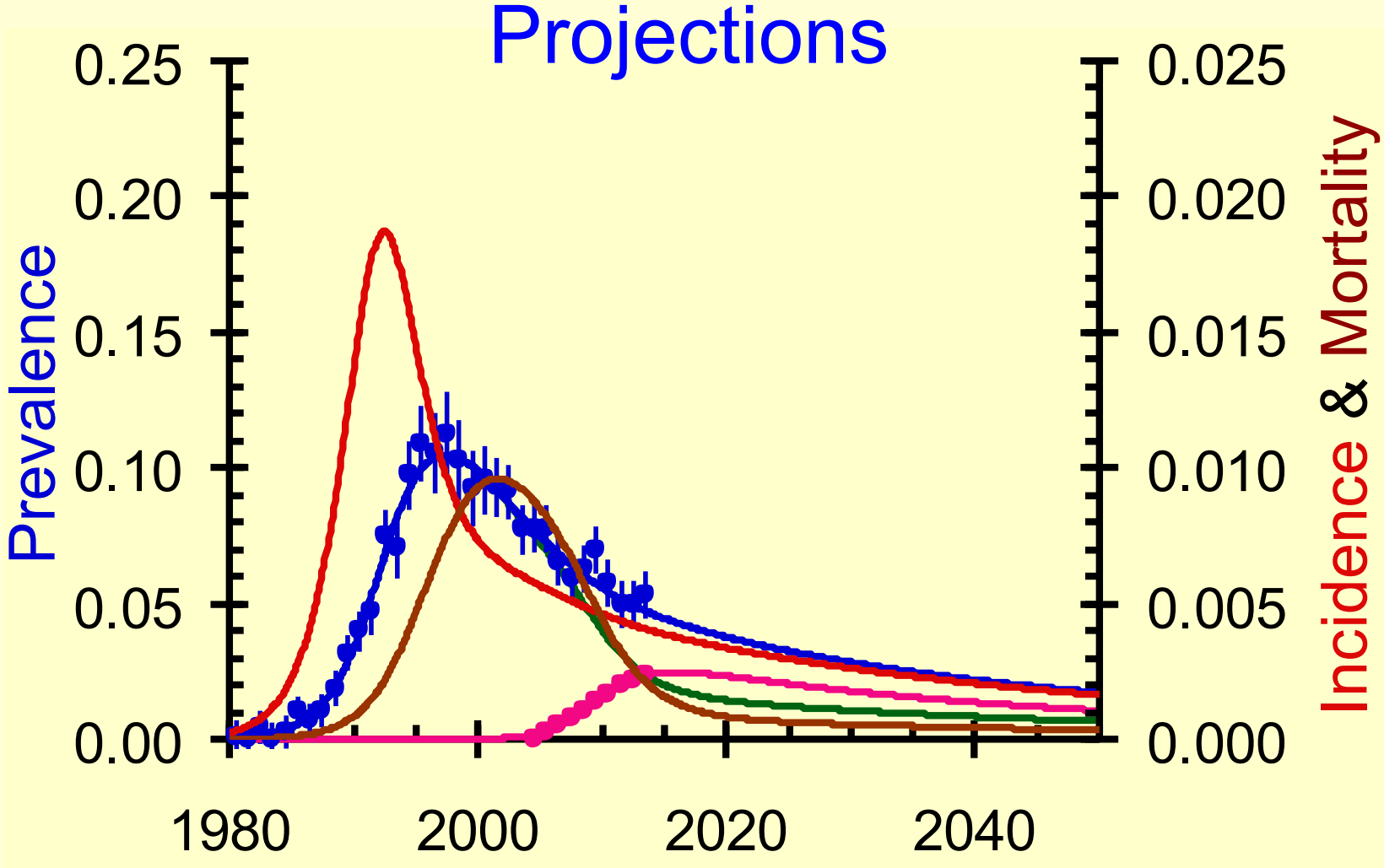




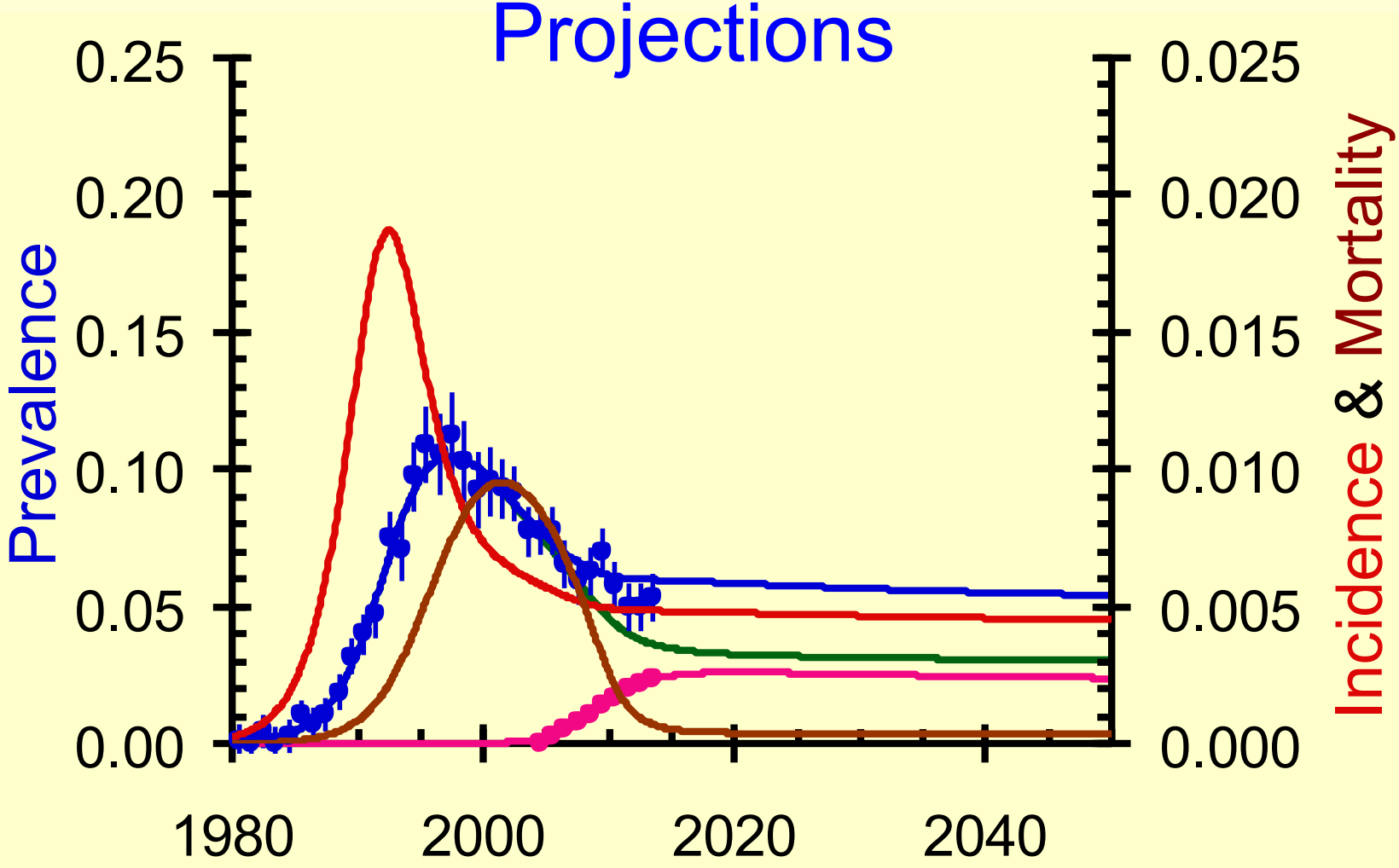
Assuming the same treatment rate in all classes. Treatment (pink) changes the proportion of people not on ART (green), has some effect on incidence (red), and a bigger effect on mortality (brown). People would have to be tested every two years (on average).



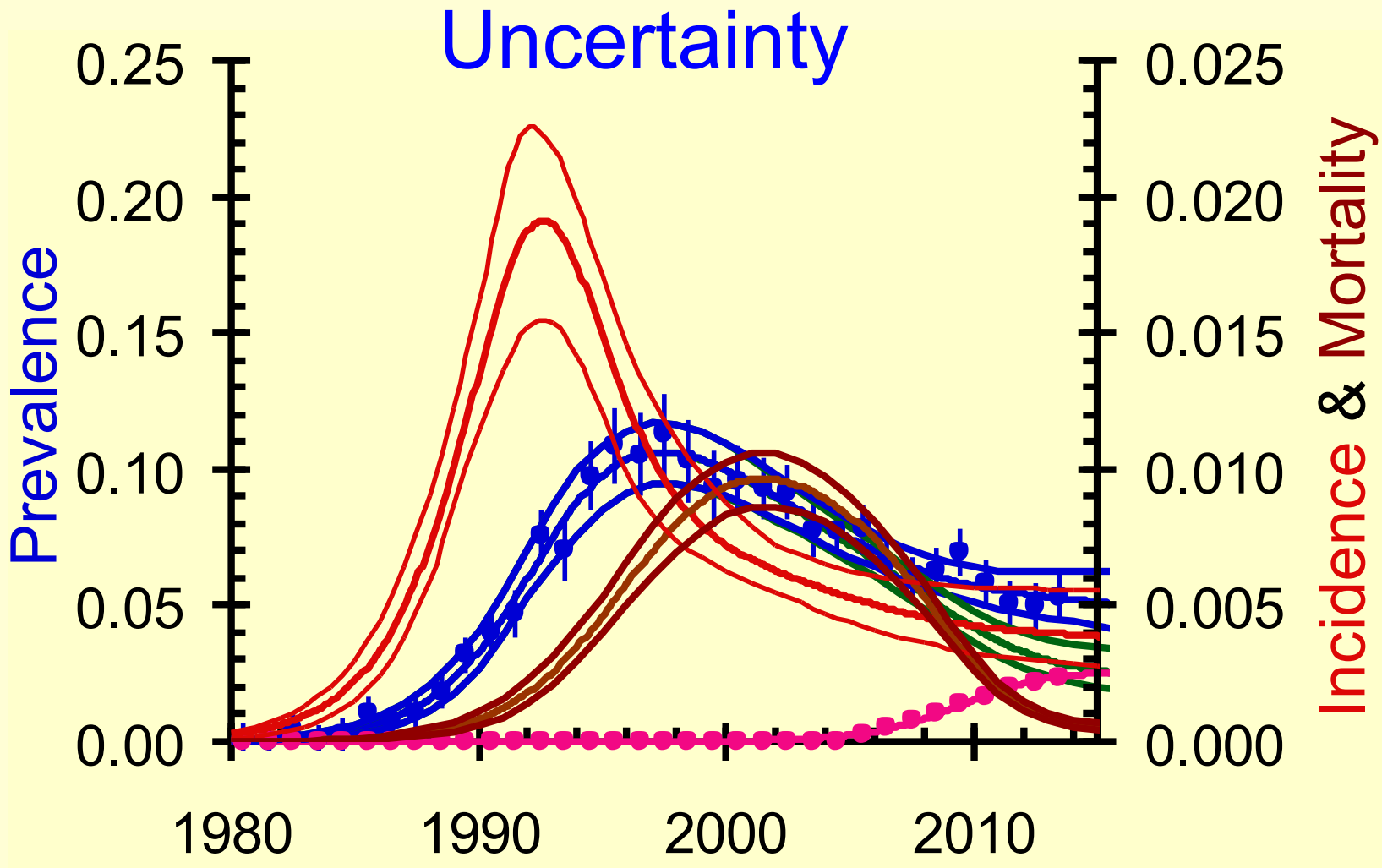
Assuming that only those in Stage 4 are treated. This has a bigger impact on mortality but a smaller impact on transmission. People would have to be tested every 5 weeks (on average).



Assuming the same treatment rate in all classes will drive the epidemic down slowly

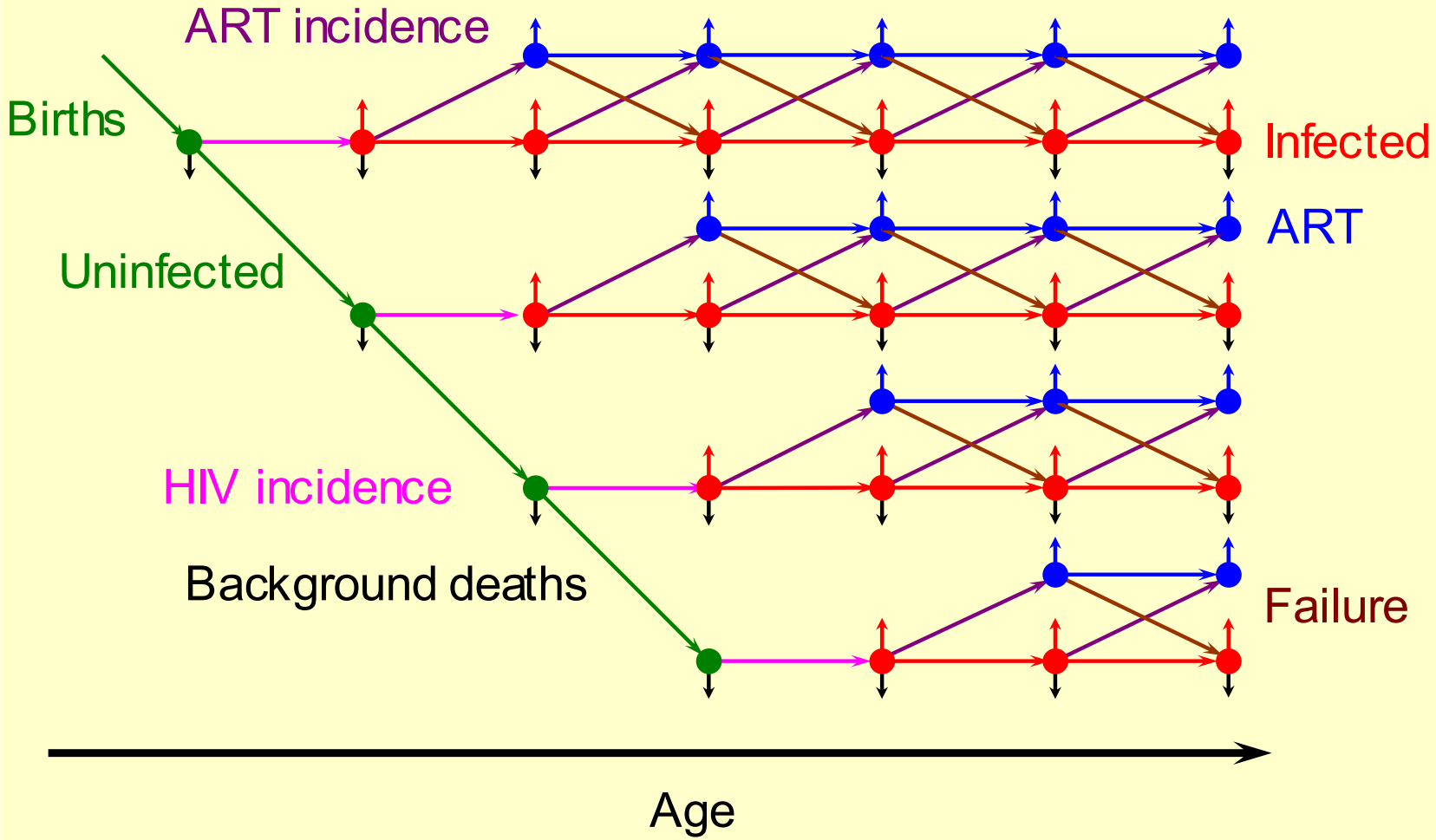


Keeping the same number of people on ART but only treating those in Stage 4 will have a bigger impact on mortality in the short term but will not bring the epidemic under control in the long term.



With a simple compartmental model we can estimate confidence limits on the the parameters and the fitted curves. (This is an MCMC estimate.)

Demography: The model



As people age they can remain uninfectious, be infected, progress with HIV, start treatment, remain on treatment, or fail treatment. They can die of other causes, AIDS, or die on ART.

The computational problem

Without demography

9 states (Susceptible 1; Infected 4; ART 4)

16 possible state transitions (20 with treatment failure)

500 time steps (50 years at intervals of 0.1 year)

10^4 calculations of state transitions

With demography

Each state can have 1,000 ages (100 years at intervals of 0.1 year)

10^7 calculations of state transitions

In both cases about 6 variable parameters

Many more fixed parameters with demography

The computational problem

Without demography

Solver in Excel converges after about 20 iterations taking about 5 seconds.

MCMC estimates of uncertainty require about 1,000 iterations taking about 5 minutes.

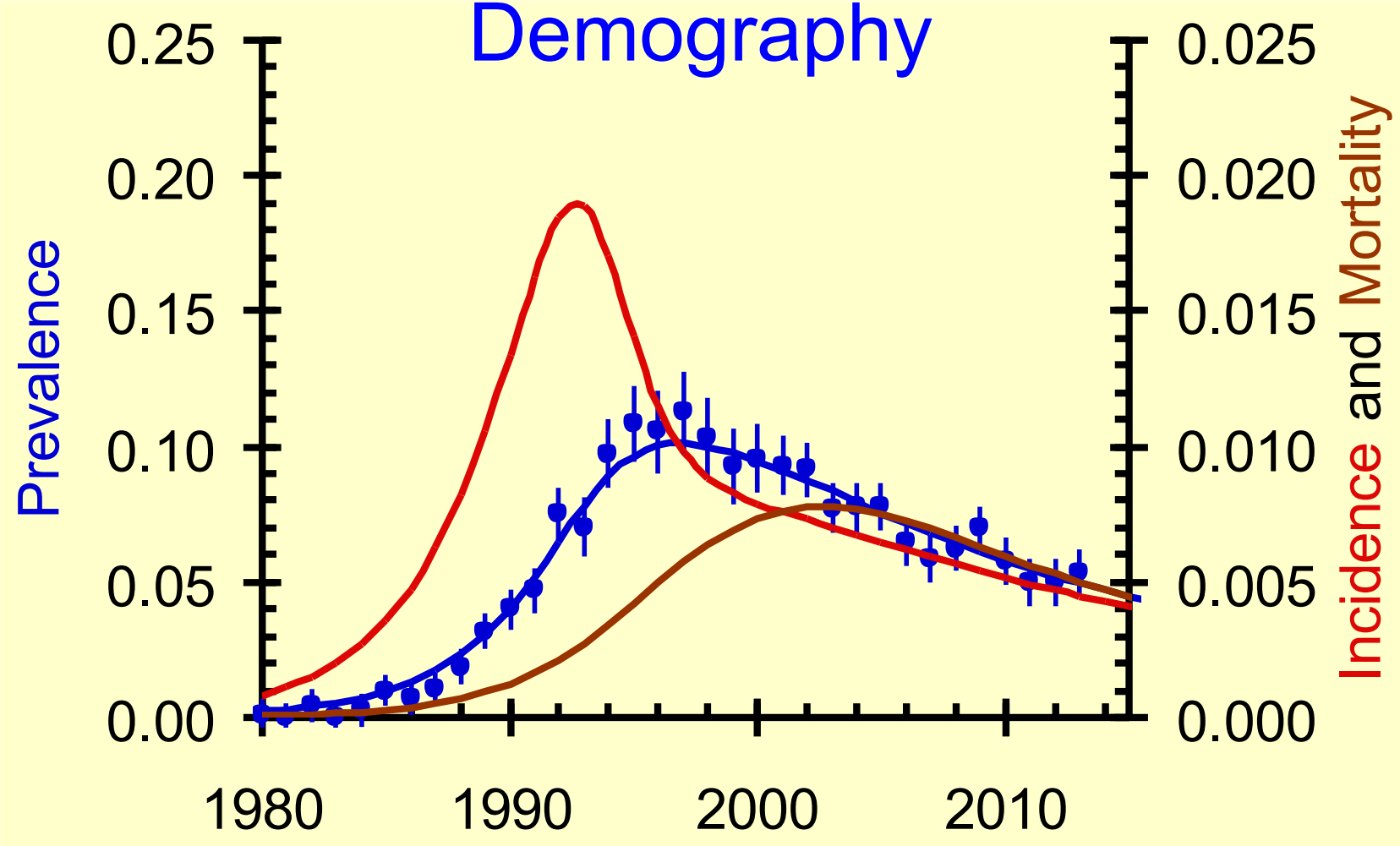
With demography

This is going to take about $5x10^4$ seconds = 14 hours to optimizing the fit and about $5x10^4$ minutes = 35 days to estimate the uncertainty.

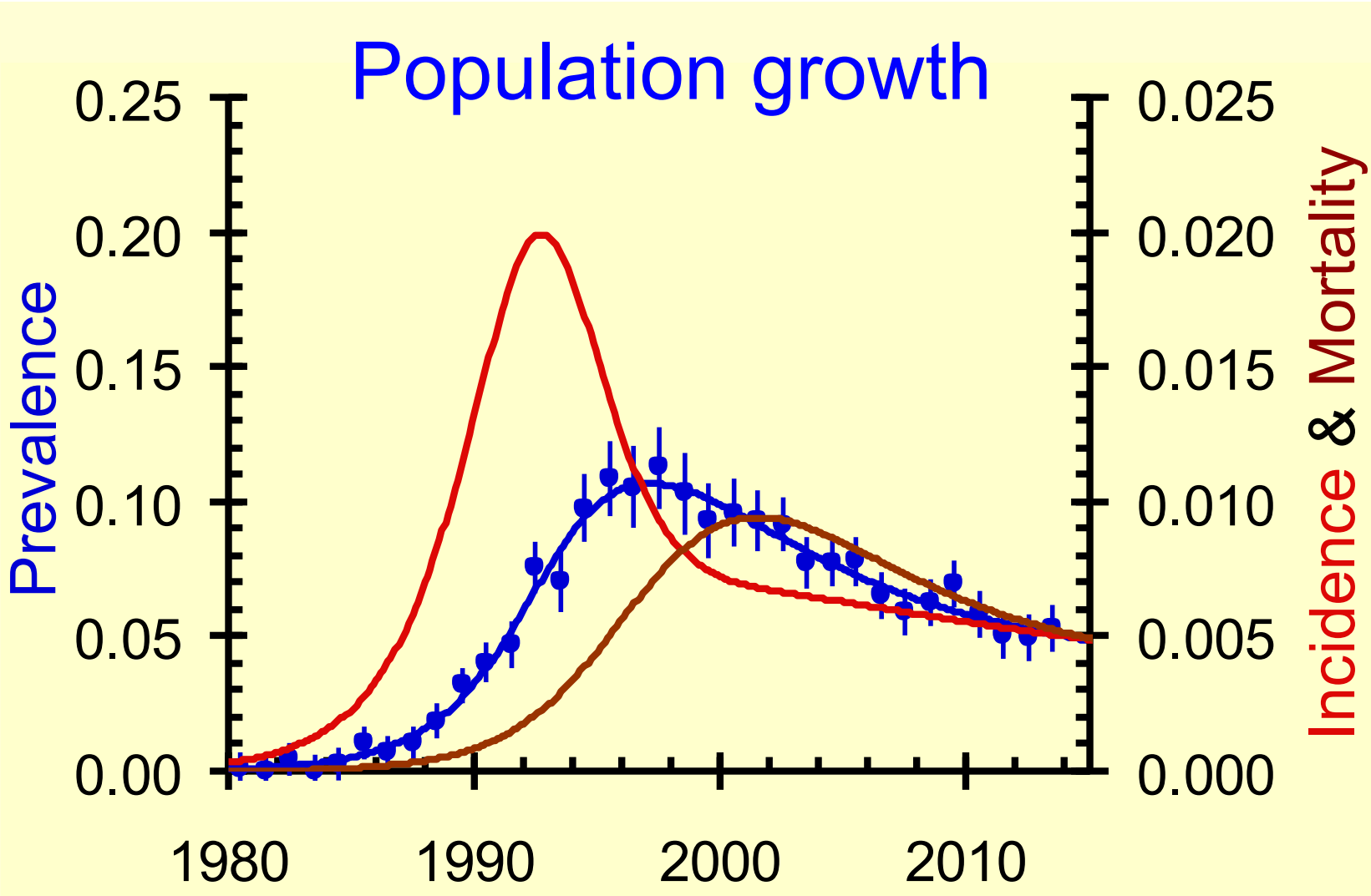
Is it worth it?

Demography: Fixed parameters

1. Assume that the current age-distribution is a stable age-distribution.
2. From the overall population growth rate calculate the age-specific mortality for HIV-negative people.
3. Check that this gives the current stable age-distribution and population growth rate.
4. Use the age mortality as a function of age for those not on ART. This declines linearly with age and the survival distribution is Weibull with a shape parameter of 2.25 at all ages.
5. Estimate the (relative) age-specific incidence of infection.
6. Run and fit the demographic equivalent of the model (without ART).
7. Note that this is still a one-sex model so we are averaging over a loop of transmission male→female→ male ignoring age-matching of partners and other aspects of the network.



The demography only changes the fits and predictions by a small amount. Incidence declines more quickly, mortality is a little lower (next slide). But both within the uncertainty limits.



Repeat of Slide 14.

As complicated as this (but no more….)

States

Susceptible; infected (x4); ART (x4)

Transitions

Births, deaths, incidence, progression, treatment, failure

Variable parameters

Initial value, transmission, heterogeneity, control (x3), treatment (x12)*.

Fixed parameters

Population growth rate, survival on ART, failure rate.

* Timing, rate of roll out and asymptotic rate x 4 stages. Collapse values where appropriate.

Outputs

Prevalence

In each of 4 states off treatment and on treatment with implications for rates of opportunistic infections.

Incidence

Overall incidence of HIV

Starting ART

Rate at which people start ART with implications for testing rates.

Mortality

Death rates off ART.

Interventions

The model indicates the extent to which transmission appears to have fallen pre-ART. Time trends in the levels of different interventions should be used to see if they can reasonably explain the pre-ART decline.

Possible interventions include: fewer partners, less age-discordancy, condoms, PreP, PEP, VMMC.