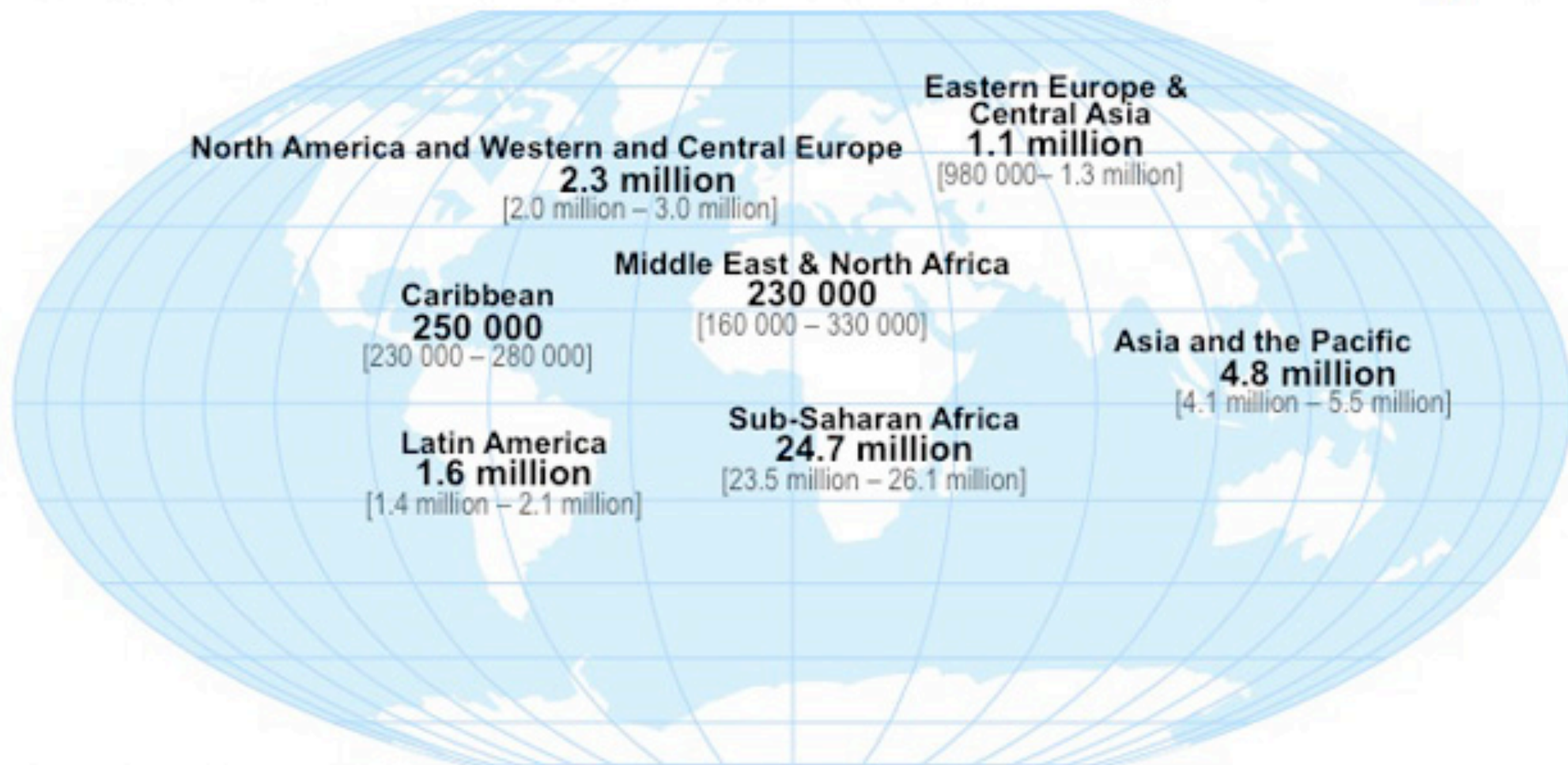


Adults and Children estimated to be living with HIV, 2013

Adults and children estimated to be living with HIV | 2013



Total: 35.0 million [33.2 million – 37.2 million]

Spending on HIV/AIDS

- Recent increase in the available money for HIV/AIDS
- The Gates foundation alone has over \$60 billion
- Present plans are to hold the money in reserve and spent it slowly over 20 years
- What if we spend it all at once?

How do we eradicate AIDS?

- Current tools:
 - Condoms
 - drugs
 - education
- Future tools:
 - vaccines
 - microbicides
 - etc.



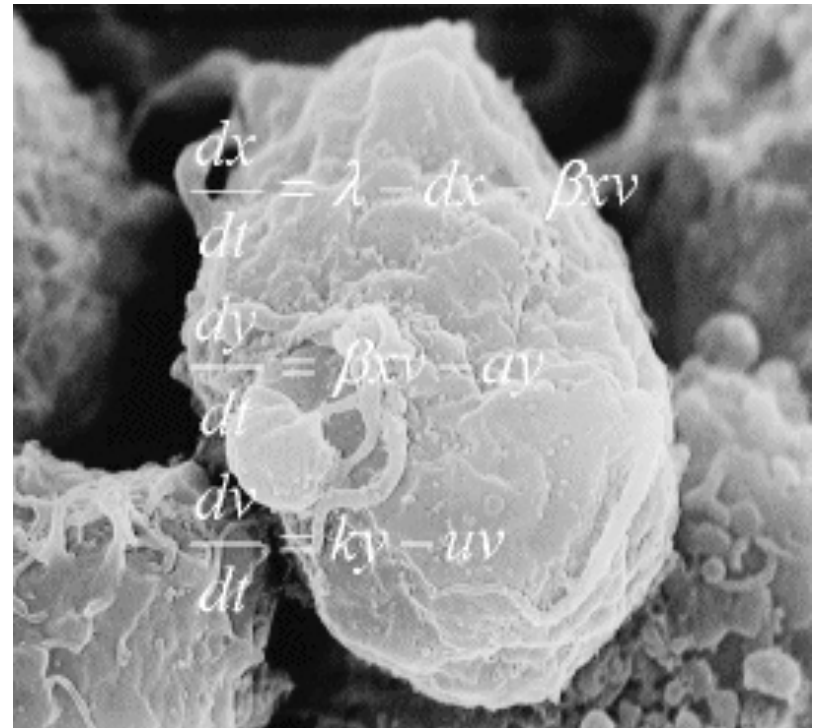
When have we done enough?

- When $R_0 < 1$
- R_0 is a threshold parameter that determines whether a disease will remain endemic or be eradicated
- (The value calculated by mathematical models is an eradication threshold, not necessarily the average number of secondary infections).



Some issues

- How do we measure R_0 ?
 - It's difficult
- If the R_0 for your country is less than 1, is that sufficient?
 - Clearly not
- If $R_0 < 1$ for all countries, is that sufficient?
 - Surprisingly, no.



Simplifying the problem

- But maybe we don't need R_0 exactly
- To model HIV is incredibly complicated
- However, a simple model might be sufficient...
- ...if it has the same eradication threshold as the more complicated model.



Infectives

- Let's look at infected people only
- People in a region (country, continent, etc) change their infection status when they're
 - infected
 - die (of the disease, or other causes)
 - relocate (immigration/emigration).



Infection model

- $\pi_i = \beta \times$ (total uninfected population in i th region)
- Thus, for p regions, in the i th region, we have

$$\frac{dI_i}{dt} = \pi_i I_i - d_i I_i + \sum_{j=1}^p m_{ij} I_j - \sum_{j=1}^p m_{ji} I_i$$

Diagram illustrating the components of the infection model equation:

- Infection rate** (points to $\pi_i I_i$)
- Death rate** (points to $-d_i I_i$)
- Immigration to the i th region from the j th** (points to $\sum_{j=1}^p m_{ij} I_j$)
- Emigration to the j th region from the i th** (points to $\sum_{j=1}^p m_{ji} I_i$)

Linear infection model

- This is a linear model

$$\frac{d\mathbf{I}}{dt} = K\mathbf{I}(t)$$

where

$$\mathbf{I} = (I_1, I_2, \dots, I_p)$$

I_i = # infectives in region *i* *π_i* = influx of infectives
d_i = death rate *m_{ij}* = migration rate

An eradication threshold

- This system is easy to analyse
- The only equilibrium is the disease-free equilibrium, $(0,0,\dots,0)$
- This equilibrium is stable if $s(\mathbf{K}) < 0$, where $s(\mathbf{K})$ is real part of the largest eigenvalue of \mathbf{K}
- It's unstable if $s(\mathbf{K}) > 0$
- Thus, we have an eradication threshold:

$$T_0 = e^{s(\mathbf{K})}.$$

Is the model too simplistic?

- The dynamics of HIV are not linear
- They depend, at a minimum, on the behaviour of susceptibles and their interaction with those infected
- Thus, this model does not capture the transient dynamics of infection and interaction.



Stability properties

- However, it does serve as a predictor for eradication
- If the disease-free equilibrium is unstable, then trajectories will increase without bound
- If the disease-free equilibrium is stable, it's globally stable
- In this case, the disease will be eradicated.



SI model

- Consider the two-dimensional SI model

$$\frac{dS}{dt} = \Lambda - \beta SI - \mu S$$

$$\frac{dI}{dt} = \beta SI - \mu I - \gamma I$$

- This model has equilibria

$$\left(\frac{\Lambda}{\mu}, 0 \right) \text{ and } \left(\frac{\mu + \gamma}{\beta}, \frac{\Lambda}{\mu} - \frac{\mu + \gamma}{\beta} \right) .$$

*S=susceptibles I=infectives Λ =birth rate
 β =infection rate μ =background death rate
 γ =disease death rate*

Jacobian

- The Jacobian is

$$J = \begin{bmatrix} -\beta I - \mu & \beta S \\ \beta I & \beta S - \mu - \gamma \end{bmatrix}$$

- Thus, the eigenvalues are

$$\lambda = -\mu, \frac{\beta \Lambda}{\mu} - \mu - \gamma.$$

Λ =birth rate μ =background death rate
 β =infection rate γ =disease death rate

Influx of infectives

- It follows that

$$R_{0,SI} = \frac{\beta\Lambda}{\mu(\mu + \gamma)}$$

- Since $S \leq \Lambda/\mu$, the influx of infectives is less than

$$\beta \times (\text{total population without infection})$$

- This is π_i in our linear model.

Λ = birth rate β =infection rate
 μ =background death rate
 γ =disease death rate



I-only model

- Thus, the model

$$\frac{dI}{dt} = \left(\frac{\beta\Lambda}{\mu} - \mu - \gamma \right) I$$

will always overestimate the epidemic

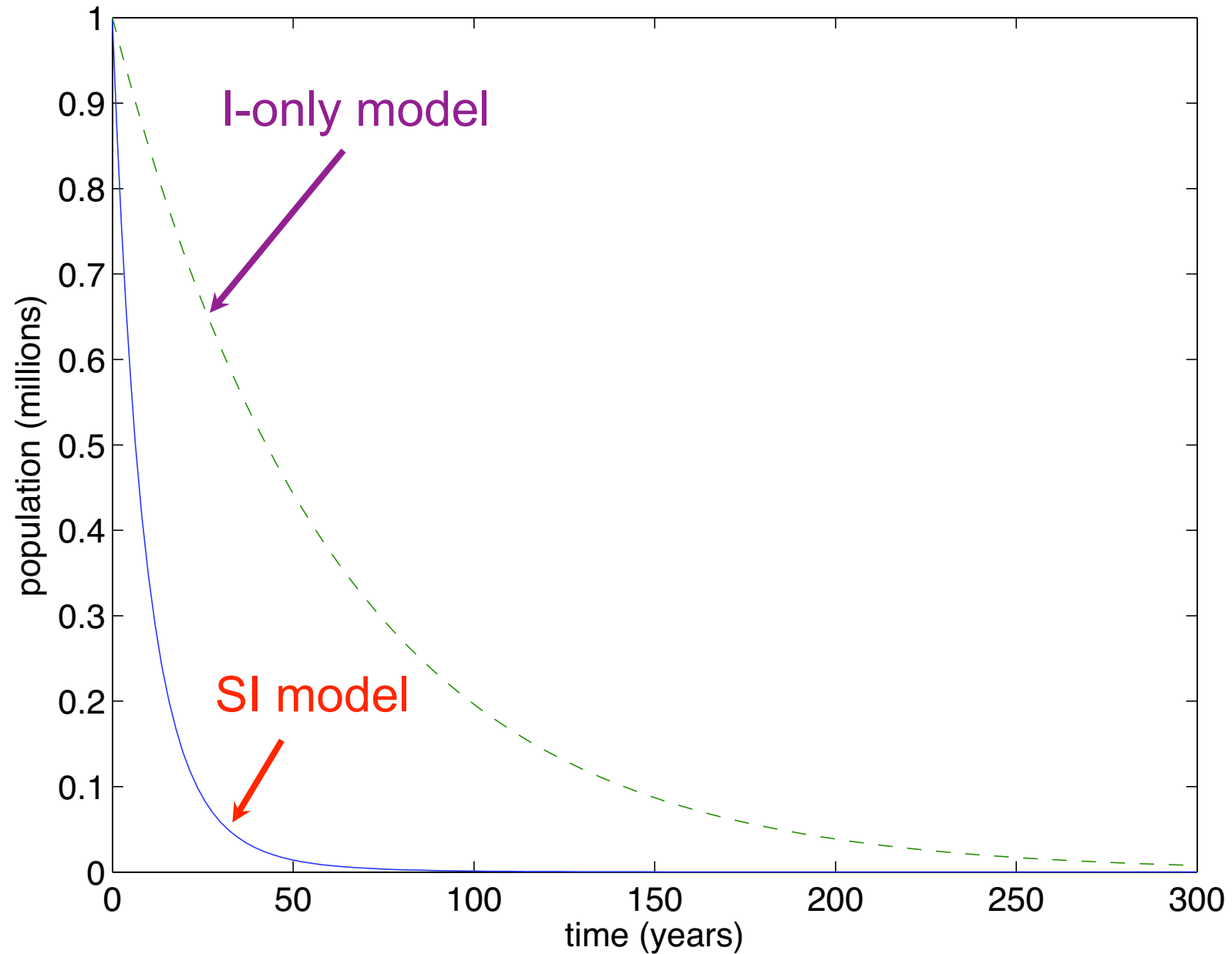
- This model also has eradication threshold

$$R_{0,I} = \frac{\beta\Lambda}{\mu(\mu + \gamma)}$$

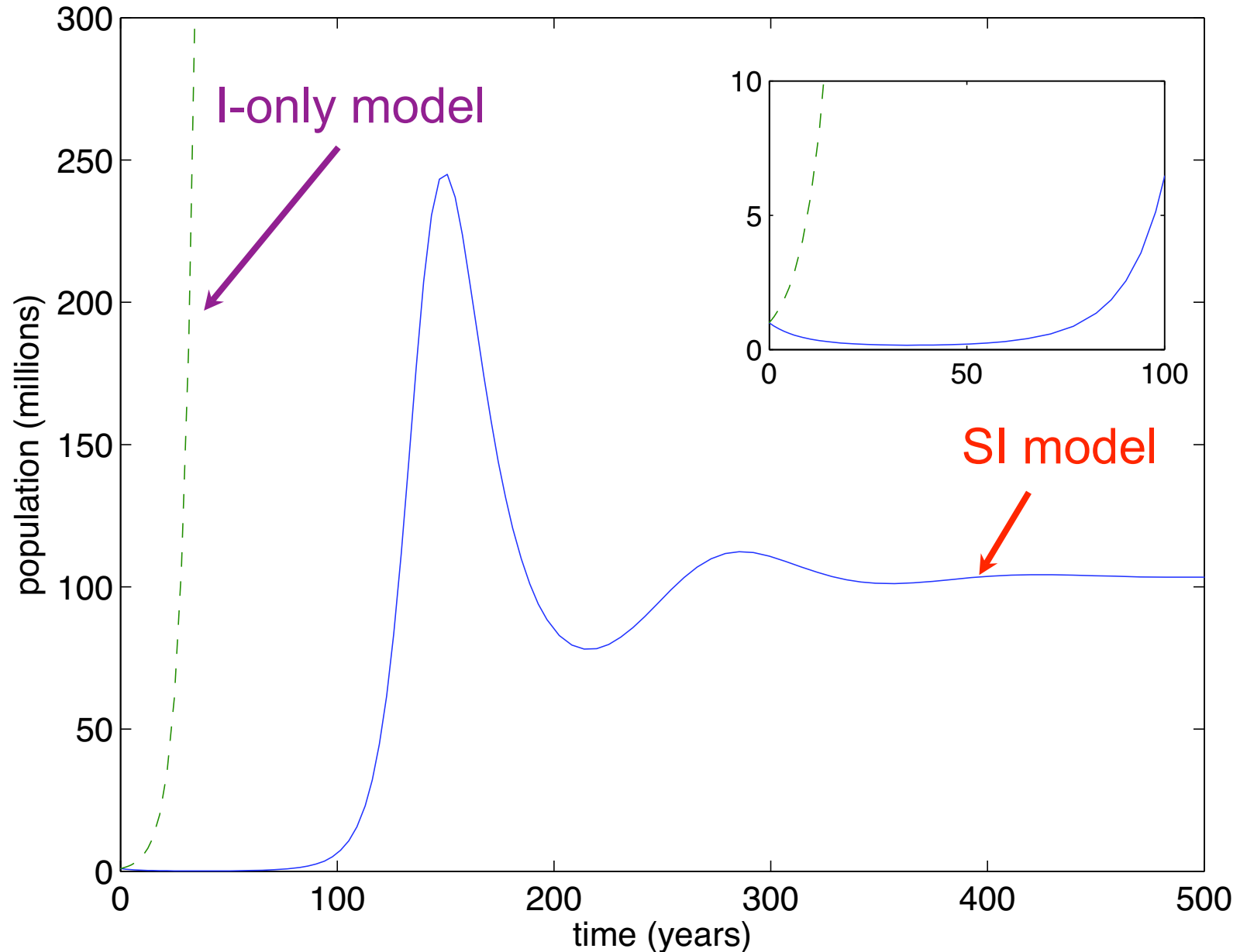
- It follows that there will be eradication in the linear model if and only if there is eradication in the SI model.

Λ =birth rate μ =background death rate
 β =infection rate γ =disease death rate

Eradication ($R_0=0.8575$)



Persistence ($R_0=2.45$)



A patch model with p regions

- For $i=1, \dots, p$,

$$\frac{dS_i}{dt} = \Lambda_i - \beta_i S_i I_i - \mu_i S_i + \sum_{j=1}^p n_{ij} S_j - \sum_{j=1}^p n_{ji} S_i$$

$$\frac{dI_i}{dt} = \beta_i S_i I_i - (\mu_I + \gamma_i) I_i + \sum_{j=1}^p m_{ij} I_j - \sum_{j=1}^p m_{ji} I_i$$

- We can bound

$$S_i(t) \leq L^*, \text{ for } i = 1, \dots, p$$

where

$$L^* = \frac{\Lambda_1 + \dots + \Lambda_p}{\min\{\mu_1, \dots, \mu_p\}}.$$

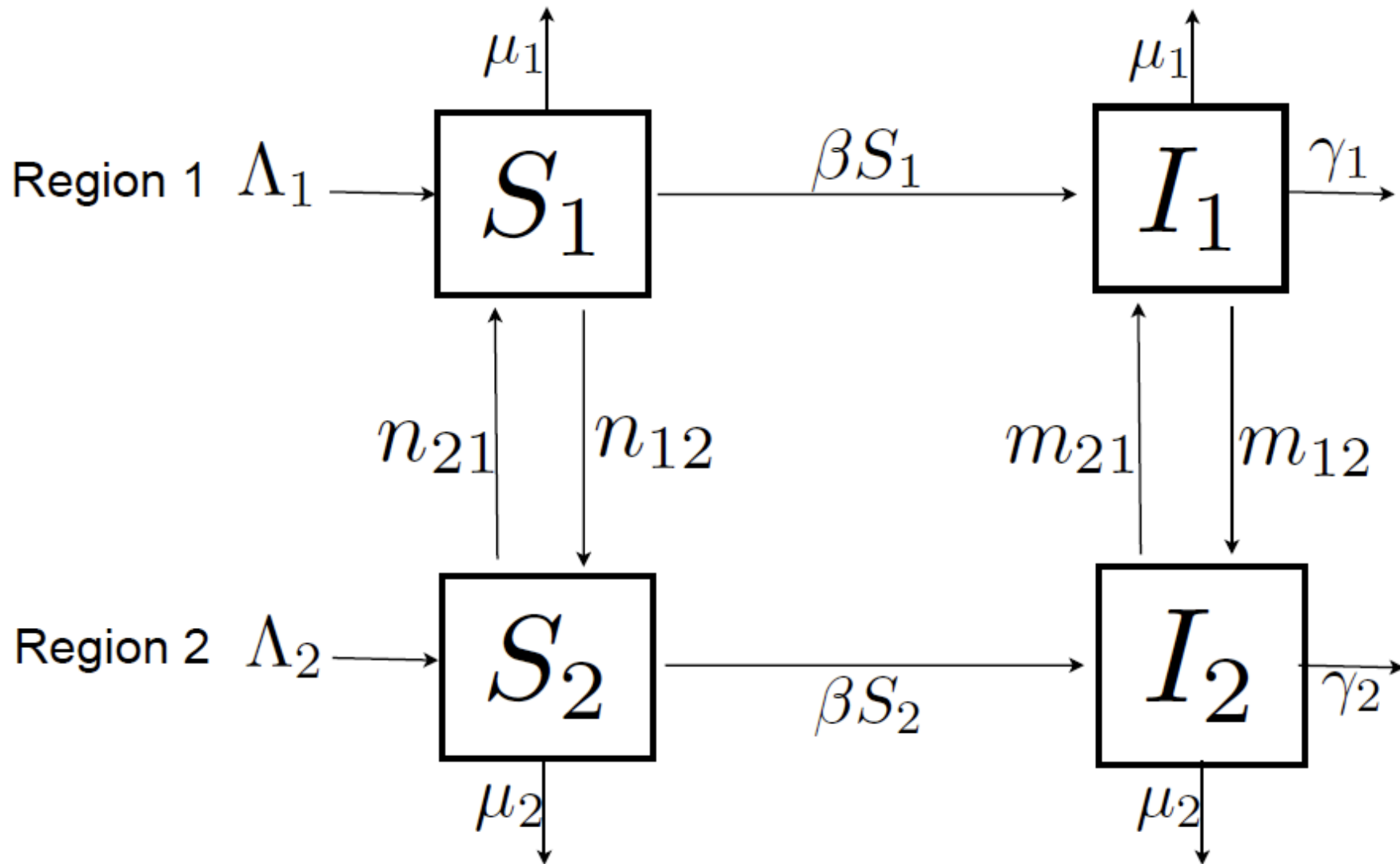
Λ =birth rate μ =background death rate β =infection rate γ =disease death rate
 n_{ik} =migration rate (susceptibles) m_{ik} =migration rate (infectives)

The linear model is an overestimate

- The linear model has the same eradication threshold as the more accurate SI model
- The linear model always overestimates the epidemic
- For eradication purposes, the linear model should determine whether our control methods will be sufficient.



A two-region example: the flow chart



Λ =birth rate μ =background death rate β =infection rate γ =disease death rate n_{ik} =migration rate (susceptibles) m_{ik} =migration rate (infectives)

Case 1: Two isolated regions

$$\frac{dS_i}{dt} = \Lambda_i - \beta S_i I_i - \mu_i S_i$$

$$\frac{dI_i}{dt} = \beta S_i I_i - (\mu_i + \gamma_i) I_i$$

which has the eradication condition

$$R_{0,i}^{(0)} = \frac{\beta \Lambda_i}{\mu_i (\mu_i + \gamma_i)} \text{ for } i = 1, 2$$

- This is the same as the previous SI model.

Λ =birth rate μ =background death rate
 β =infection rate γ =disease death rate

Case 2: Only susceptibles travel

$$\frac{dS_1}{dt} = \Lambda_1 - \beta S_1 I_1 - \mu_1 S_1 + n_{12} S_2 - n_{21} S_1$$

$$\frac{dS_2}{dt} = \Lambda_2 - \beta S_2 I_2 - \mu_2 S_2 + n_{21} S_1 - n_{12} S_2$$

$$\frac{dI_1}{dt} = \beta S_1 I_1 - (\mu_1 + \gamma_1) I_1$$

$$\frac{dI_2}{dt} = \beta S_2 I_2 - (\mu_2 + \gamma_2) I_2$$

- The basic reproductive ratio is

$$\bar{R}_0 = \max \left\{ \frac{\beta S_1^*}{\mu_1 + \gamma_1}, \frac{\beta S_2^*}{\mu_2 + \gamma_2} \right\}.$$

Λ =birth rate μ =background death rate β =infection rate γ =disease death rate
 n_{ik} =migration rate (susceptibles) m_{ik} =immigration rate (infectives)

When only susceptibles travel...

- Denote $\bar{R}_{0,1} = \frac{\beta S_1^*}{\mu_1 + \gamma_1}$ and $\bar{R}_{0,2} = \frac{\beta S_2^*}{\mu_2 + \gamma_2}$

- When only susceptibles travel,

$$\bar{R}_{0,1} = R_{0,1}^{(0)} \cdot \frac{\mu_2 + n_{12} + \frac{\Lambda_2}{\Lambda_1} n_{12}}{\mu_2 + n_{12} + \frac{\mu_2}{\mu_1} n_{21}} \quad \text{and} \quad \bar{R}_{0,2} = R_{0,2}^{(0)} \cdot \frac{\mu_1 + n_{21} + \frac{\Lambda_1}{\Lambda_2} n_{21}}{\mu_1 + n_{21} + \frac{\mu_1}{\mu_2} n_{12}}$$

- If $R_{0,1}^{(0)} < 1$ and $R_{0,2}^{(0)} < 1$, there are conditions on n_{12} and n_{21} such that $\bar{R}_{0,1} > 1$ and $\bar{R}_{0,2} < 1$
- If $R_{0,1}^{(0)} < 1$ and $R_{0,2}^{(0)} > 1$, there are conditions on n_{12} and n_{21} such that $\bar{R}_{0,1} > 1$ and $\bar{R}_{0,2} > 1$.

Λ =birth rate μ =background death rate β =infection rate
 γ =disease death rate n_{ik} =migration rate (susceptibles)

Travel could sustain the epidemic

- The disease-free equilibrium is unstable, even though both R_0 's are less than one
- Even if HIV could be eradicated within every region, the epidemic could still be sustained if there is sufficient travel of susceptibles (not infectives)
- Thus, travel restrictions are likely useless.



HIV is a world issue

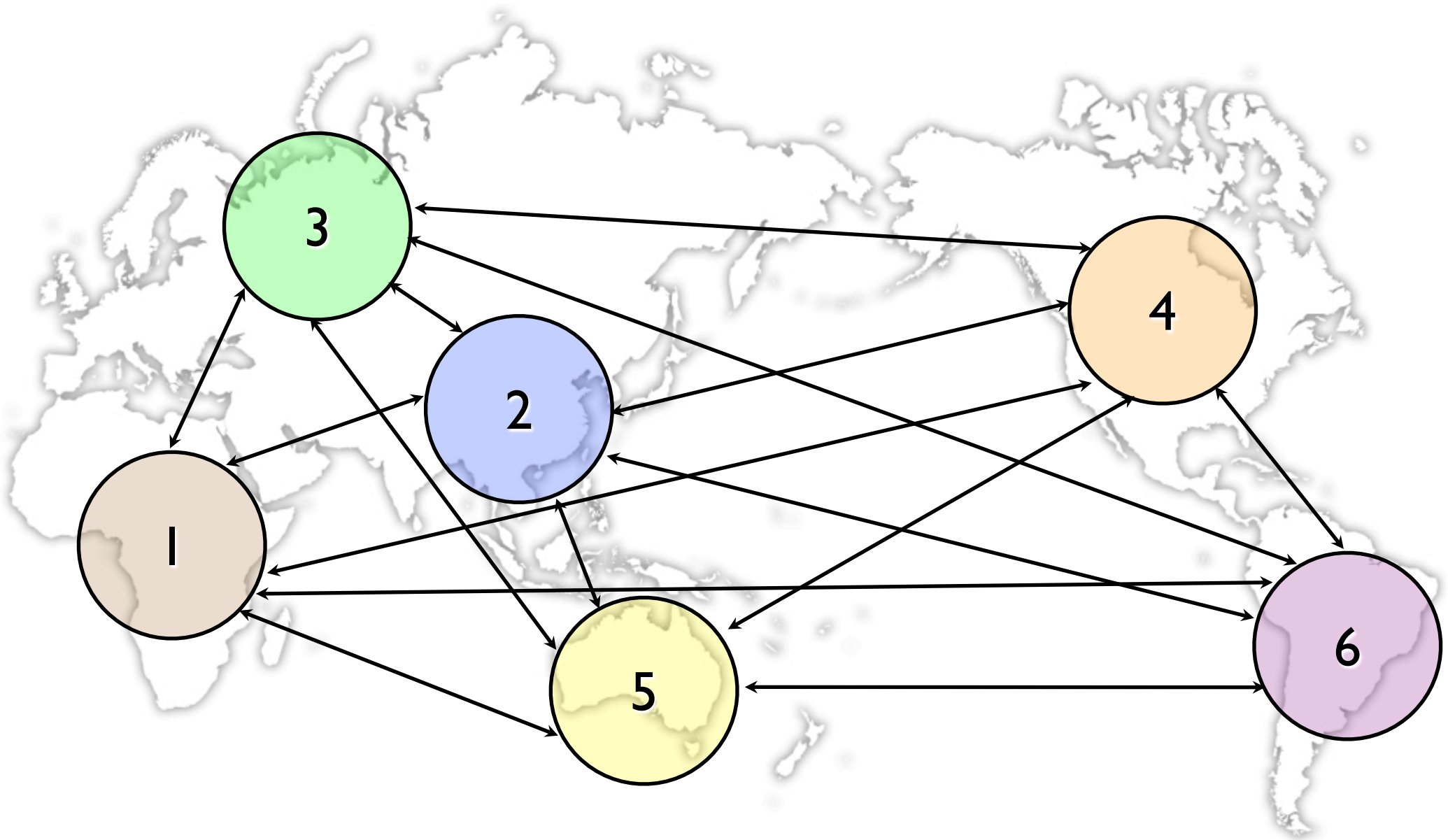
- Thus, eradication isn't possible if there is any region sustaining the epidemic
- eg, if the disease is eradicated in Europe, we would not have eradication unless it was also eradicated from Africa...
- ...and there was insufficient travel of susceptibles between regions
- This explains why HIV must be considered as a world problem, not just a problem for individual countries, or continents, to tackle independently.

A continent-level example

We divide the world into six regions:

1. Africa
2. Asia
3. Europe
4. North America
5. Oceania
6. South America.





The continent-level model

$$\begin{aligned}\frac{dI_1}{dt} &= \pi_1 I_1 - d_1 I_1 + m_{12} I_2 + m_{13} I_3 + m_{14} I_4 + m_{15} I_5 + m_{16} I_6 \\ &\quad - m_{21} I_1 - m_{31} I_1 - m_{41} I_1 - m_{51} I_1 - m_{61} I_1\end{aligned}$$

$$\begin{aligned}\frac{dI_2}{dt} &= \pi_2 I_2 - d_2 I_2 + m_{21} I_1 + m_{23} I_3 + m_{24} I_4 + m_{25} I_5 + m_{26} I_6 \\ &\quad - m_{12} I_2 - m_{32} I_2 - m_{42} I_2 - m_{52} I_2 - m_{62} I_2\end{aligned}$$

$$\begin{aligned}\frac{dI_3}{dt} &= \pi_3 I_3 - d_3 I_3 + m_{31} I_1 + m_{32} I_2 + m_{34} I_4 + m_{35} I_5 + m_{36} I_6 \\ &\quad - m_{13} I_3 - m_{23} I_3 - m_{43} I_3 - m_{53} I_3 - m_{63} I_3\end{aligned}$$

$$\begin{aligned}\frac{dI_4}{dt} &= \pi_4 I_4 - d_4 I_4 + m_{41} I_1 + m_{42} I_2 + m_{43} I_3 + m_{45} I_5 + m_{46} I_6 \\ &\quad - m_{14} I_4 - m_{24} I_4 - m_{34} I_4 - m_{54} I_4 - m_{64} I_4\end{aligned}$$

$$\begin{aligned}\frac{dI_5}{dt} &= \pi_5 I_5 - d_5 I_5 + m_{41} I_1 + m_{42} I_2 + m_{43} I_3 + m_{45} I_5 + m_{46} I_6 \\ &\quad - m_{14} I_4 - m_{24} I_4 - m_{34} I_4 - m_{54} I_4 - m_{64} I_4\end{aligned}$$

$$\begin{aligned}\frac{dI_6}{dt} &= \pi_6 I_6 - d_6 I_6 + m_{61} I_1 + m_{62} I_2 + m_{63} I_3 + m_{64} I_4 + m_{65} I_5 \\ &\quad - m_{16} I_6 - m_{26} I_6 - m_{36} I_6 - m_{46} I_6 - m_{56} I_6.\end{aligned}$$

π_i =influx of infectives
 d_i =death rate
 m_{ik} =migration rate

Birth and death rates by continent

	Population	Births/Popn	Birth Rate	Deaths/Popn	Death Rate
AF	954879489	33203380	0.0348	12625314	0.0132
AS	4043347897	76536061	0.0189	27947177	0.0069
EU	729546003	7321919	0.0100	8437988	0.0116
NA	527814776	8712554	0.0165	3798366	0.0072
OC	33970173	545421	0.0161	244250	0.0072
SA	383907961	6773241	0.0177	2354551	0.0061

- Data from the CIA world factbook (2008).

Immigration data

Des/Ori	AF	AS	EU	NA	OC	SA
AF		15973	16987	4263	0	0
AS	286806		298431	13062	1621	32500
EU	5312095	3566013		1167954	252860	1337972
NA	1176374	9690228	8573379		353095	4466748
OC	221003	1380652	2470078	136804		76873
SA	16595	218415	1087422	197314	3324	

- Data from the Global Migrant Origin Database (2007)
- Gives number of foreign born individuals by country of origin and destination.

Economic intervention

- One possibility: reduce the infection rate
- eg through funding education/condom campaigns
- All other factors remain constant.



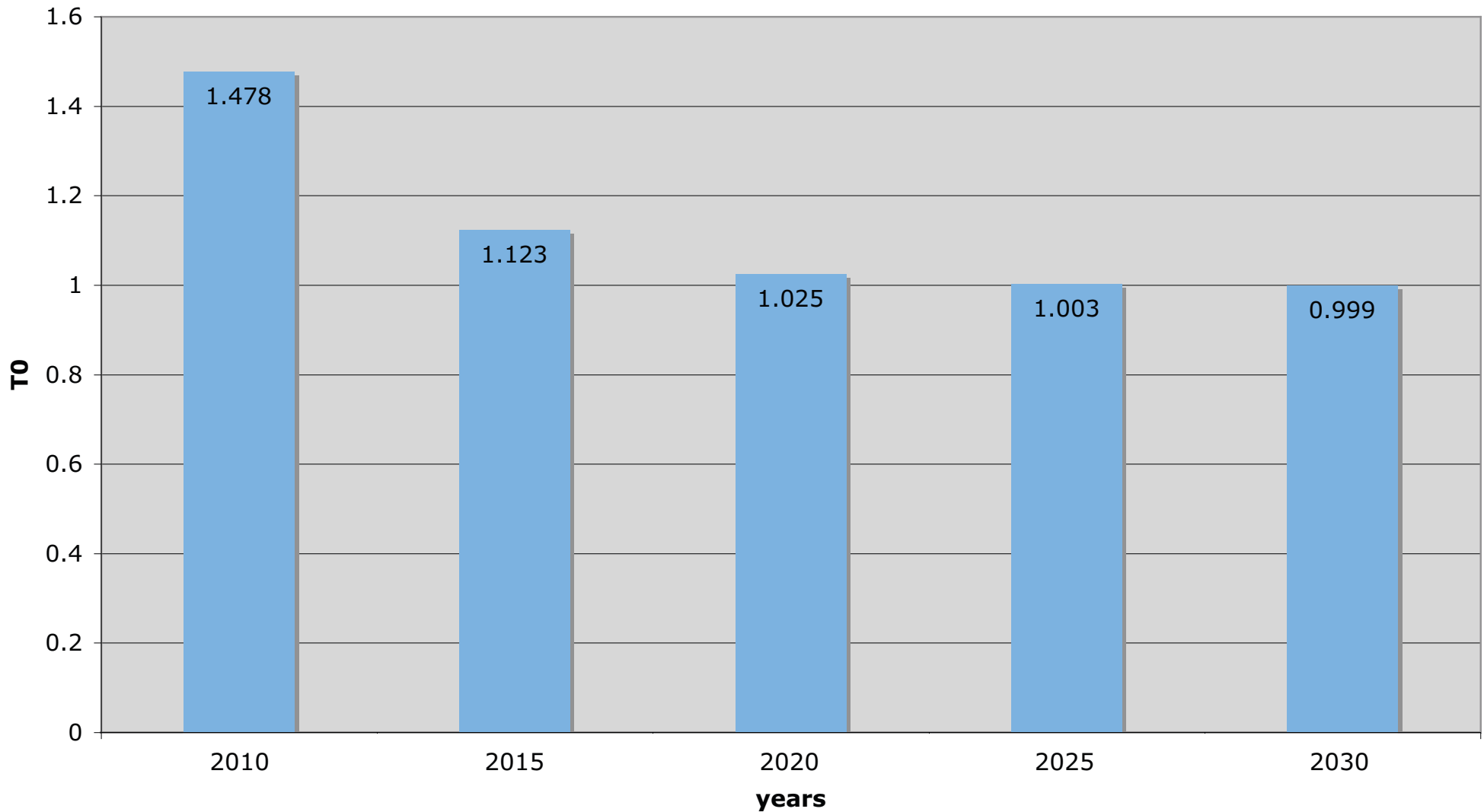
Reducing the infection rate by 3/5

- $\beta=0.0002$ people⁻¹years⁻¹, $\Lambda=p_i c/\mu_i$, where p_i is the continent's birth rate, c is 20 uninfected sex partners per year and $1/\gamma=10$ years
- If we reduce the infection rate by 3/5, then

$$T_0 = e^{-7.59 \times 10^{-5}} < 1$$

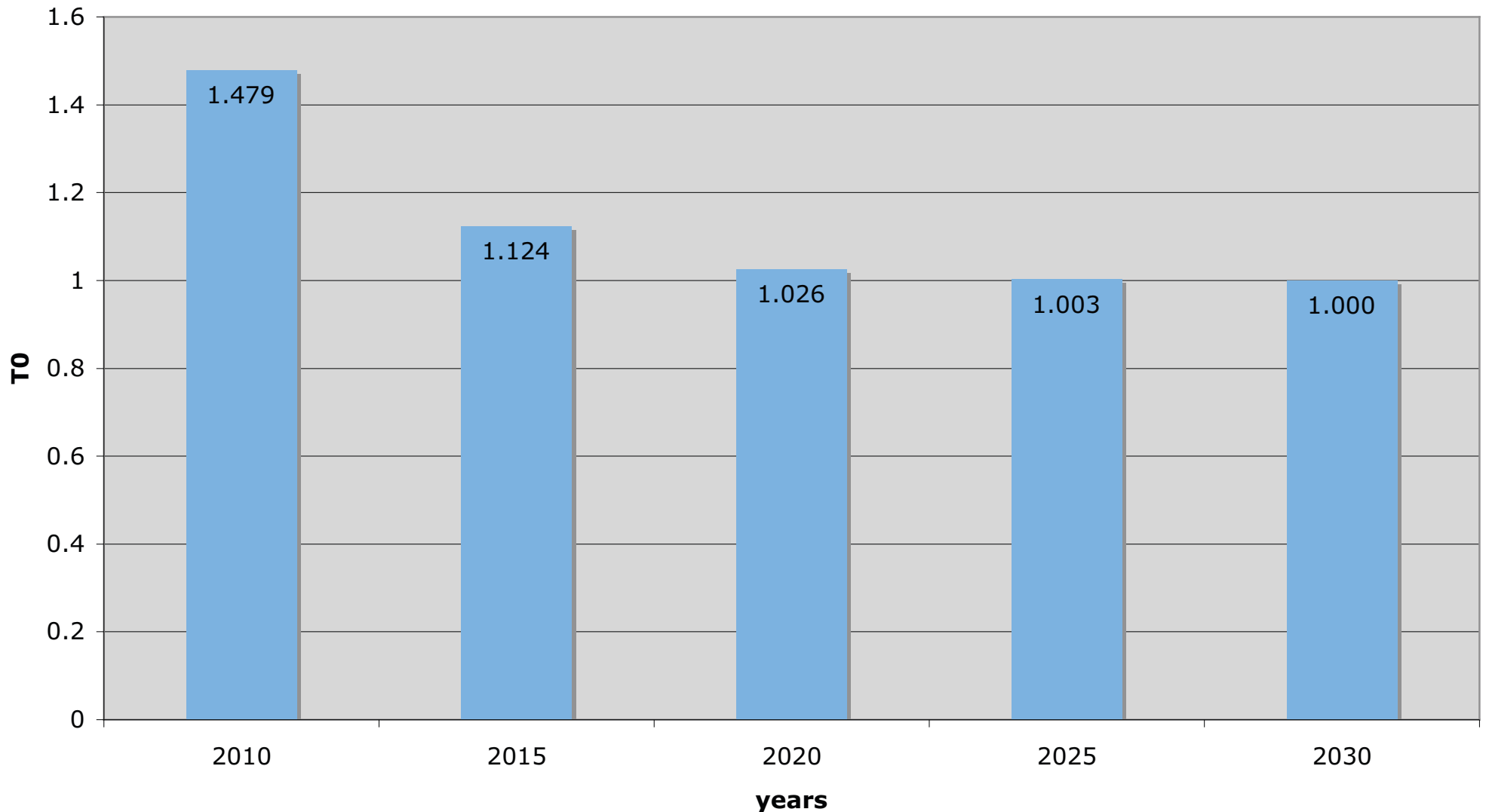
- This trips the eradication threshold
- However, this assumes no change in population growth
- Over a 20 year timeframe, we might need to take population growth into account.

Reduction in transmission



Assuming population demographics remain unchanged.

Reduction in transmission



Assuming 3% population growth per year results in the inability to eradicate the disease.

A prevention example only

- This example assumes no change in the AIDS death rate
- eg condoms, vaccines, microbicides
- Antiretroviral drugs will have a more complicated effect, due to longer lifespans for infectives (so the infection rate will need to be lowered even further).



Costs of interventions

- Interventions includes changes in education, condoms and drugs
- The costs applied different interventions vary from region to region
- Eg HAART costs more in high-income regions than low-income regions
- Can we trip the eradication threshold using available money?

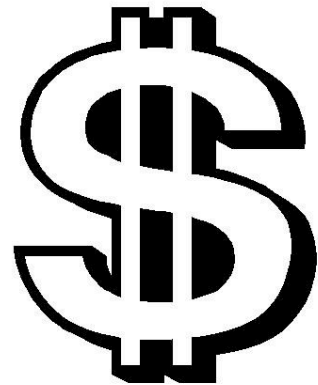


Costs of HIV/AIDS intervention methods

Intervention	Cost (US\$)
HIV testing in low-income countries	\$200-\$4000 per test
Combination antiretroviral therapy in high-income countries	\$10,000-\$15,000 per patient annually
Combination antiretroviral therapy in low-income countries	\$350-\$4,000 per patient annually
Costs of monitoring viral load and cell count	\$25-\$100 per test
Health education	\$500-\$3000 per patient
Patient out-of-pocket expenses for medical care in low-income areas	\$60-\$250
Adult male circumcision	\$40-\$100
Male condom	\$0.02 per condom.

The cost formula

- Let n be the proportion of men who receive condoms
- m be the fraction of infected individuals who receive treatment
- r be the timescale
- The cost formula is



$$C(n, m, r) = 3 \times 10^9 \times \frac{1.03^r - 1}{0.03} \times 100 \times 0.02 \times n + 6 \times 10^6 \\ + 3.3 \times 10^6 \times \frac{1.03^r - 1}{0.03} \times 2500 \times m .$$

The makeup of costs

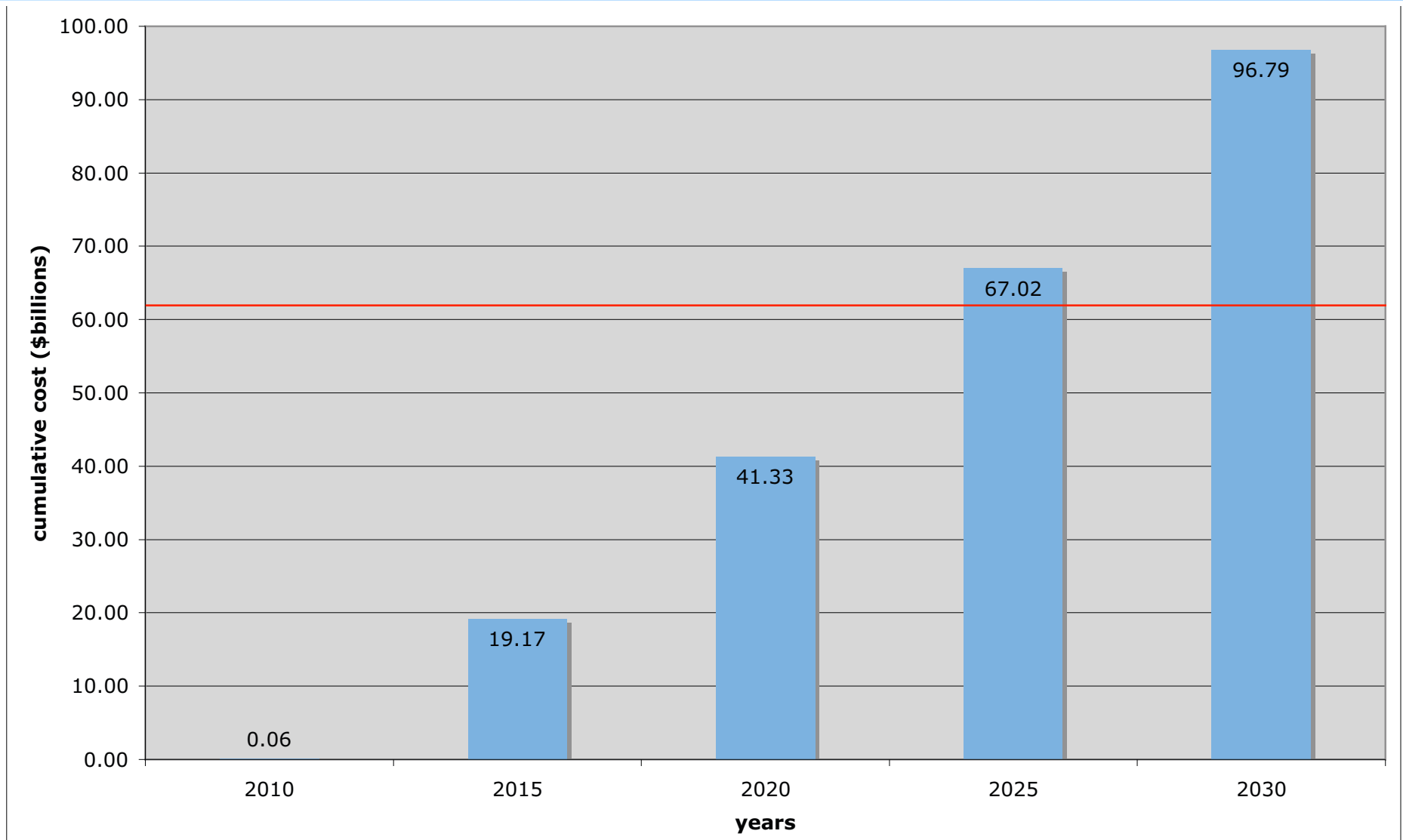
$$C(n, m, r) = 3 \times 10^9 \times \frac{1.03^r - 1}{0.03} \times 100 \times 0.02 \times n + 6 \times 10^6 \\ + 3.3 \times 10^6 \times \frac{1.03^r - 1}{0.03} \times 2500 \times m$$

- First term: 3 billion men, 3% population growth, 100 condoms a year at \$0.02 per condom
- Second term: (fixed) cost of education and distribution
- Third term: one tenth of infected individuals require treatment, 3% population growth, average cost of \$2500 per year.

The 20 year timeframe

- Provide condoms to 3/5 of all men and treat nobody
 - Cost: \$96 billion
- No condoms, treat everybody
 - Cost: \$221 billion
- Provide condoms to 1/5 of all men, treat 50% of those who need it
 - Cost \$143 billion
- Thus, interventions spread over 20 years are unaffordable.

Cumulative cost will blow up



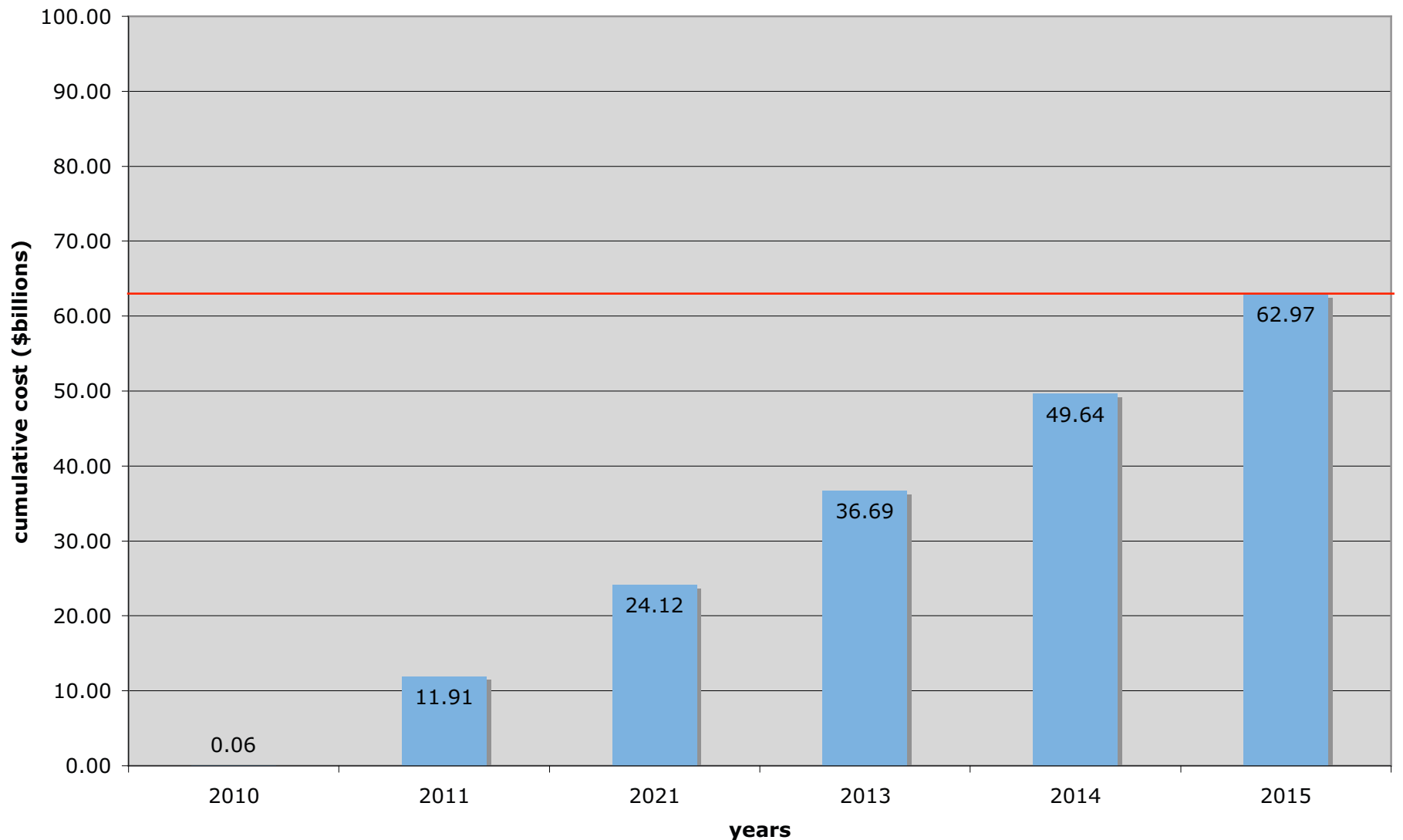
The cumulative cost of reducing the infection rate to $\frac{2}{5}$ of its current rate over 20 year (and treating nobody)

The 5 year timeframe

- Provide condoms to 3/5 of all men, treat everybody
- Cost: \$63 billion
- This is within our existing \$60 billion budget (with interest).



Cumulative cost



The cumulative cost of reducing the infection rate to $\frac{2}{5}$ of its current rate over the next 5 years and treating everybody who requires it.

Putting it all together

- Reducing infection by 3/5:

	5 year timeframe	20 year timeframe
Pop growth negligible	$T_0 < 1$ Affordable	$T_0 < 1$ Not affordable
Pop growth important	$T_0 < 1$ Affordable	$T_0 > 1$ Not affordable

- Treat everyone: ethically important
- May switch $T_0 < 1$ (or it may not)
- But still not affordable over 20 years.

Millennium Development Goals

- Currently, about \$9 billion a year is spent on AIDS
- UNAIDS has estimated we need to be spending about \$22 billion per year in order to reach the Millennium Development Goals of reversing global AIDS within five years
- Over five years, the difference would be

(\$22 billion - \$9 billion) x 5 years = \$65 billion

- This (independently) matches our estimates.

Implications

- Using this model, a combination of factors can be evaluated
- The model can be used to predict eradication and evaluate the usefulness of control methods
- However, it can't estimate the transient dynamics or interactions
- Also, we used a continent-level example, but it could be expanded for a country-level data
- The strategy we have used could be adopted by countries with different epidemic patterns.

Limitations

- Our model does not quantify the prevalence of the disease or the time course of infection
- Our parameter estimates also have limitations; eg disease-specific death rate is negligible, compared to the background death rate
- We assume travellers/immigrants receive no intervention help, such as education or treatment
- Our immigration/emigration data did not include tourism, especially sex tourism
- Our treatment costs do not explicitly take into account many of the specific costs associated with treatment (eg healthcare worker training).

Conclusion

- Eradication is possible, but only if HIV is considered as a world problem
- Our model determines eradication thresholds, not the transient dynamics
- Using this model, the effect of control methods can be evaluated
- This model can provide us with an easy-to-grasp way of understanding what needs to be done...
 - harnessing all existing intervention techniques in significant strength –
 - ...and when to do it: right now.