

Staged progression epidemic models for the transmission of invasive nontyphoidal Salmonella (iNTS) with treatment

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Outlines

- 1 iNTS epidemic in sub-Saharan Africa
- 2 Staged progression models for iNTS
- 3 Numerical simulations

non-typhoidal *Salmonella* (NTS)

- foodborne disease - animal/food reservoir
- mild symptoms: diarrhea, fever, stomach cramps
→ self-limiting, recover in 4 ~ 7 days without treatment

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Food safety & recall



"Don't kiss or snuggle hedgehogs" - CDC



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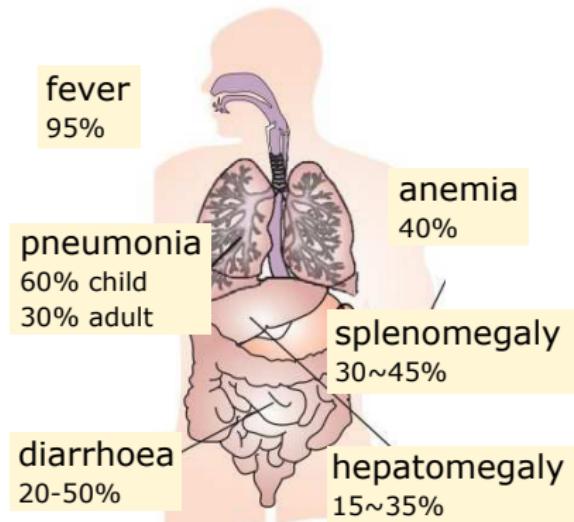
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- *Salmonella*: bacteria, > 2500 serotypes, ~ 100 cause human infection

i invasive strain (iNTS) in sub-Saharan Africa

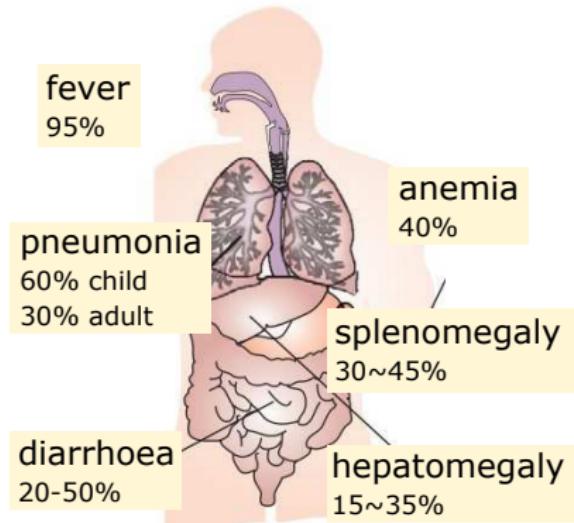
- blood-stream infections
- non-specific symptoms
→ close to pneumonia and malaria
→ hard to diagnose
- with proper diagnosis and antimicrobial drugs
high case fatality 22% - 47%



Clinical features for iNTS in Africa.

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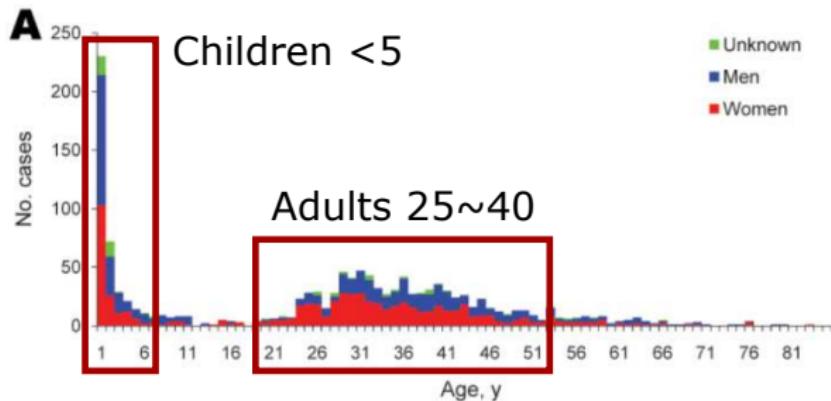
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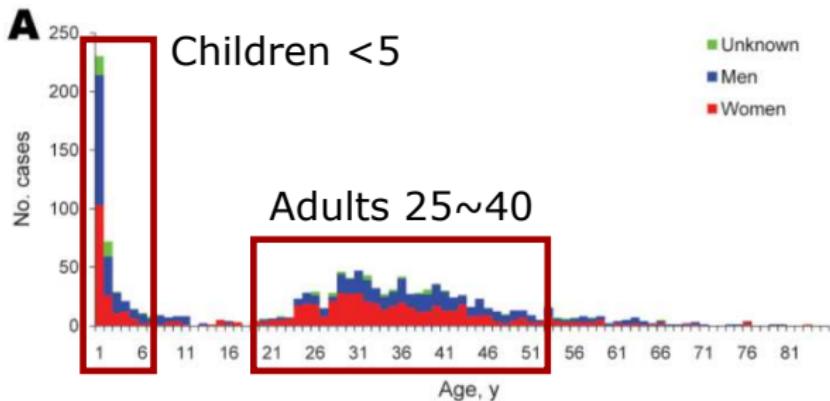
Clinical features for iNTS in Africa.

Why does the pathogen become so virulent?

Risk factors: immuno-compromised population



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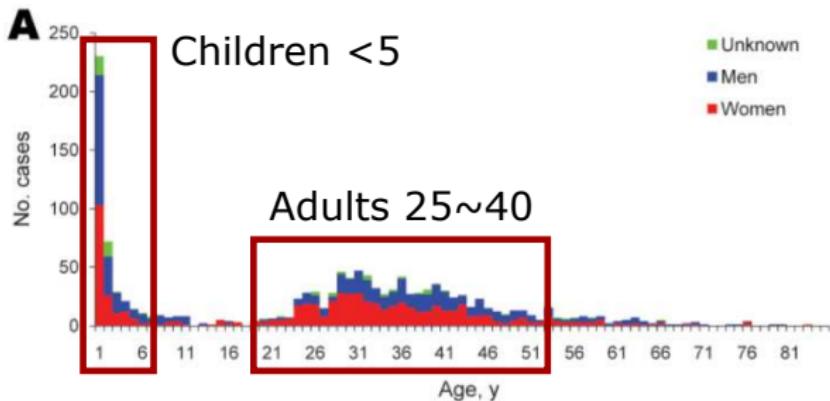
Children

- malnutrition 40%
- malaria 2%
- HIV infection (maternal) 2%
 - 175-388 cases/100K children

Adults (25 ~ 40 years old)

- advanced HIV infection 22%
- antiretroviral therapy (ART) 64%
 - 2000-7500 cases/100K HIV adults

Risk factors: immuno-compromised population



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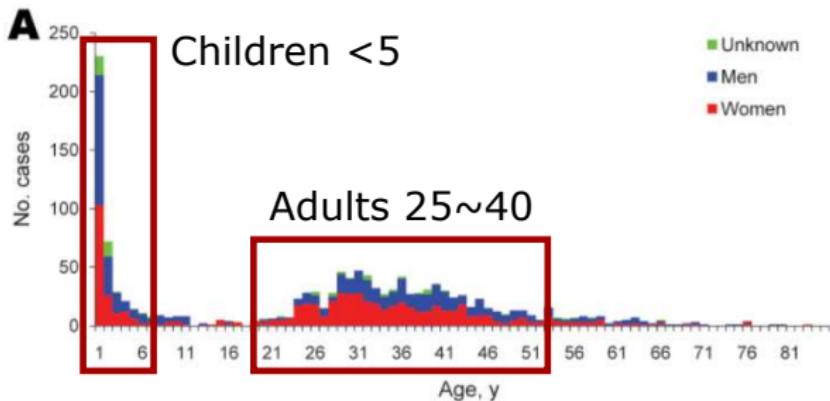
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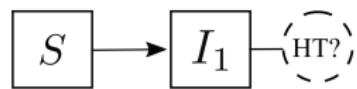
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human reservoir for the invasive NTS → human-to-human transmission

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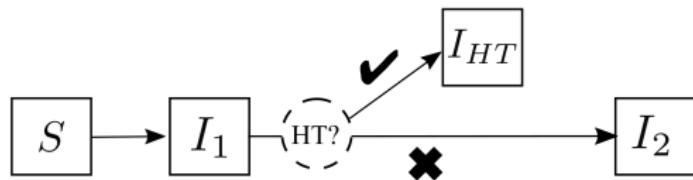
Staged progression model with treatment



S Susceptible

I₁ Infected - mild symptom

Staged progression model with treatment



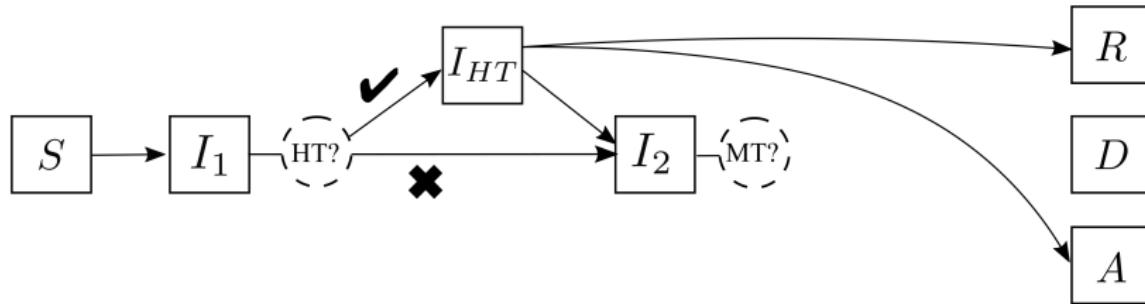
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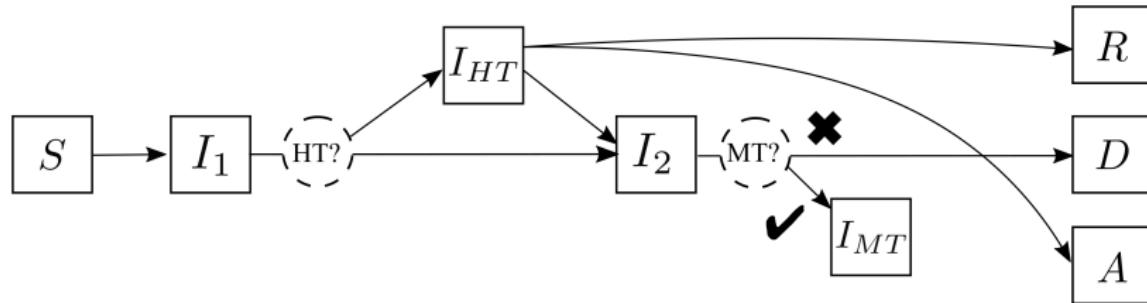
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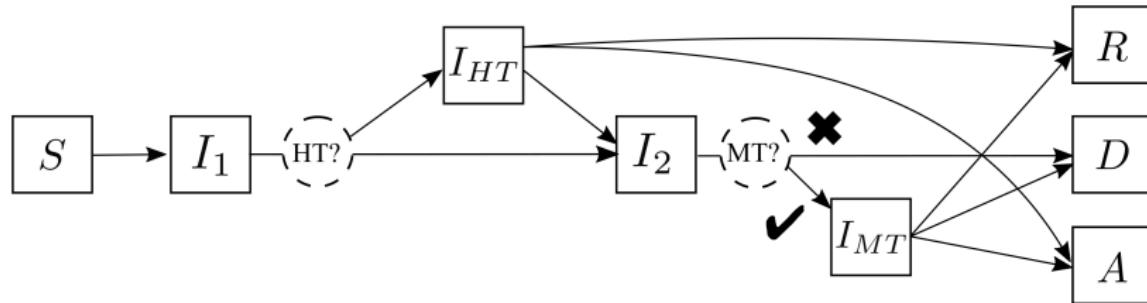
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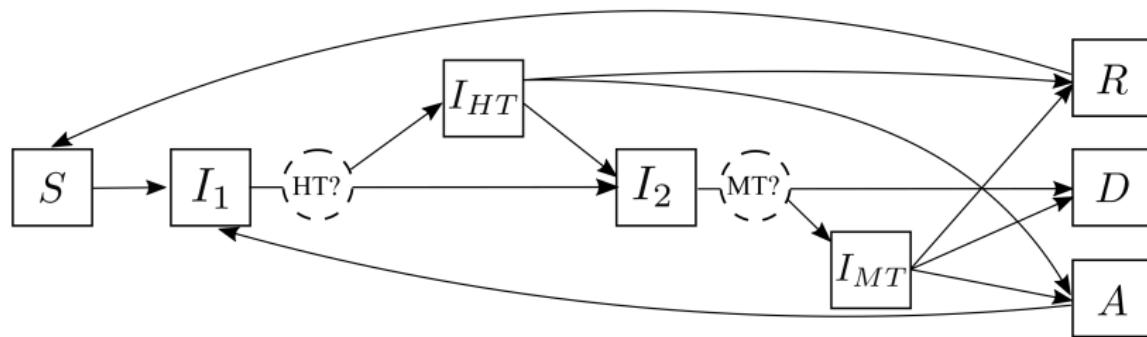
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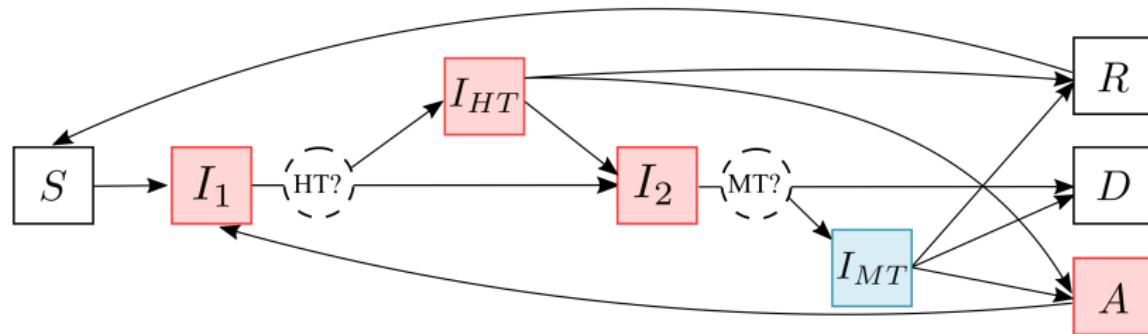
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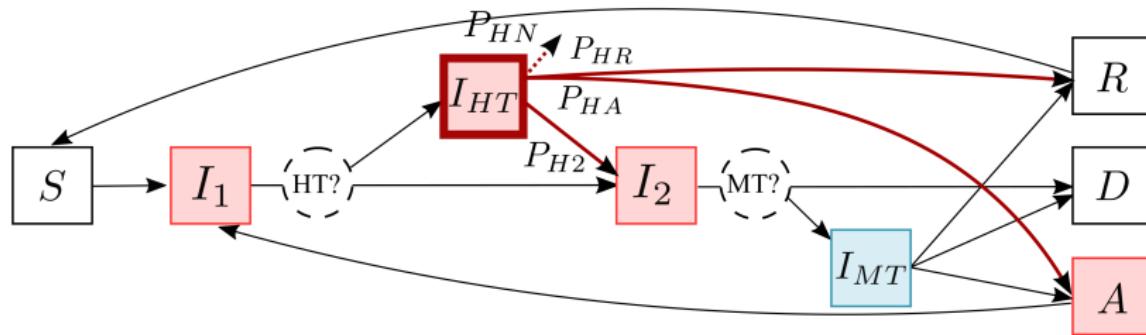
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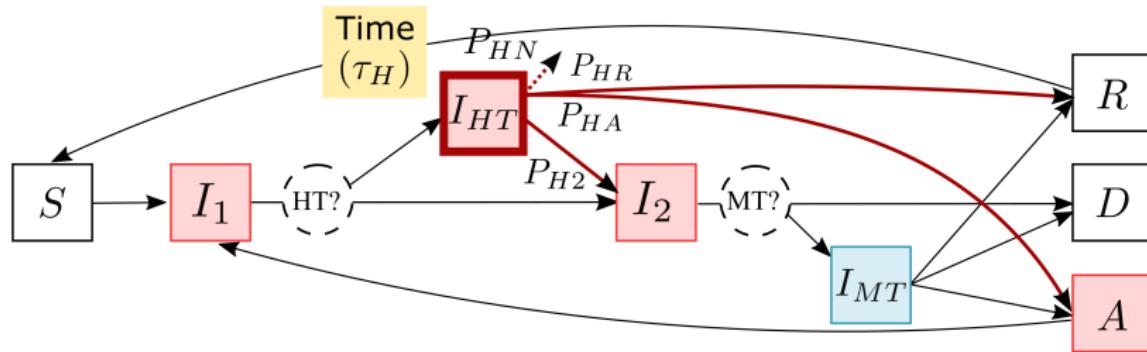
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Define progression rates using branching process



Branching probabilities: $P_{HN} + P_{HR} + P_{HA} + P_{H2} = 1$

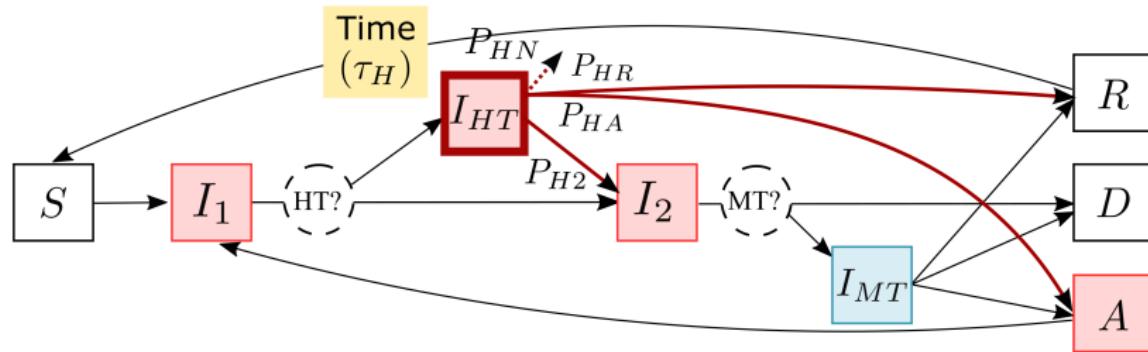
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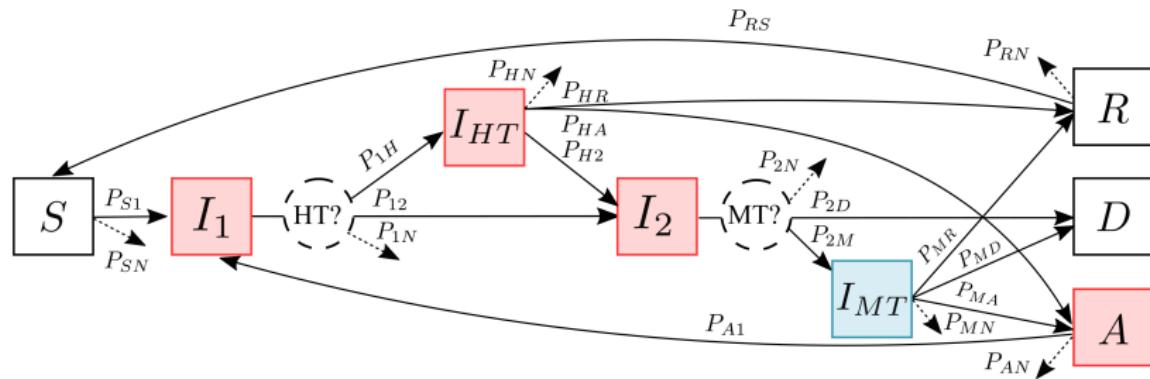


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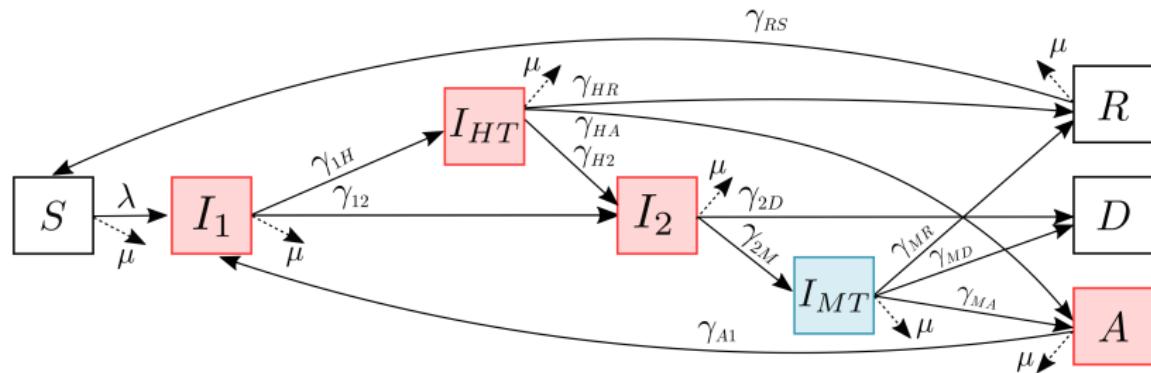


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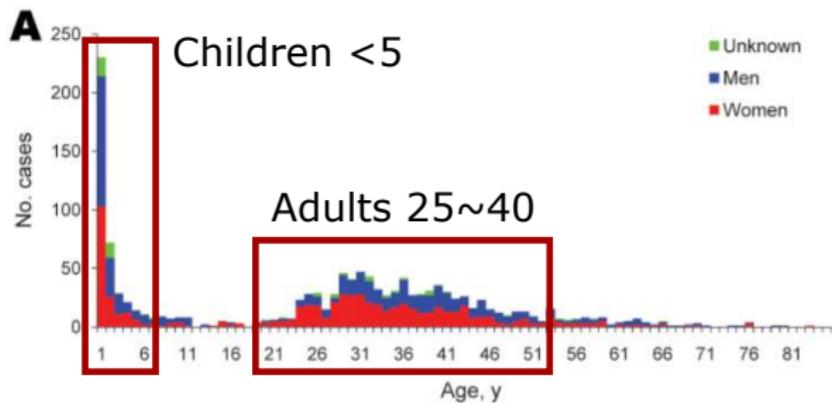


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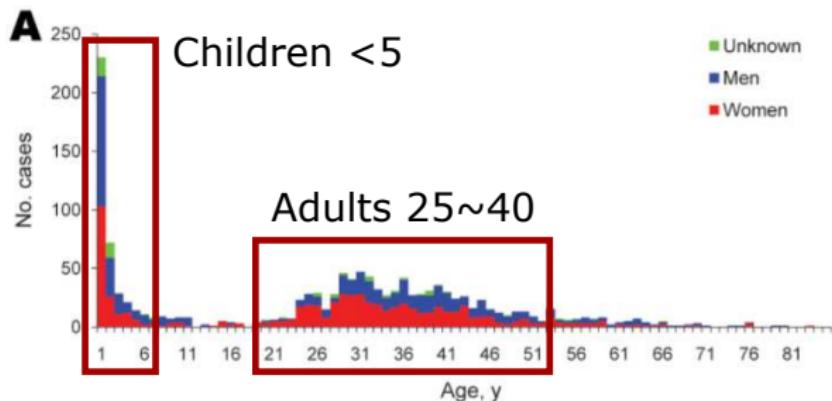
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Incorporating different risk groups



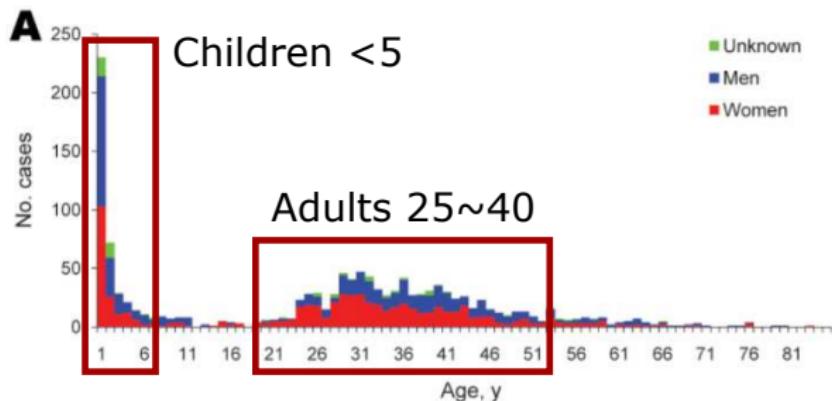
- Children < 5 years old
- Adults 25 ~ 40 years old (HIV-infection status)

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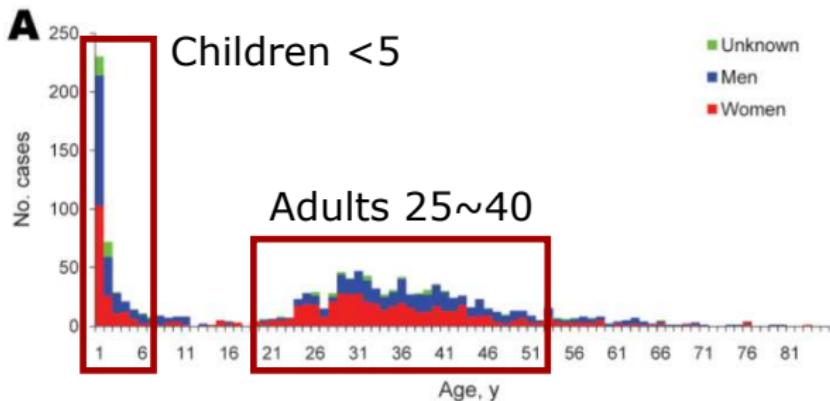
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- ⇒ 4 population groups, 8 infection stages

Staged progression model (group $\kappa = 1, \dots, 4$)

$$\begin{aligned}\dot{S}^\kappa &= \mu^\kappa (S_0^\kappa - S^\kappa) - \lambda^\kappa S^\kappa + \gamma_{RS}^\kappa R^\kappa, \\ \dot{I}_1^\kappa &= \lambda^\kappa S^\kappa + \gamma_{A1}^\kappa A^\kappa - (\gamma_{1H}^\kappa + \gamma_{12}^\kappa) I_1^\kappa - \mu^\kappa I_1^\kappa, \\ \dot{I}_{HT}^\kappa &= \gamma_{1H}^\kappa I_1^\kappa - (\gamma_{HR}^\kappa + \gamma_{HA}^\kappa + \gamma_{H2}^\kappa) I_{HT}^\kappa - \mu^\kappa I_{HT}^\kappa, \\ \dot{I}_2^\kappa &= \gamma_{H2}^\kappa I_{HT}^\kappa + \gamma_{12}^\kappa I_1^\kappa - (\gamma_{2D}^\kappa + \gamma_{2M}^\kappa) I_2^\kappa - \mu^\kappa I_2^\kappa, \\ \dot{I}_{MT}^\kappa &= \gamma_{2M}^\kappa I_2^\kappa - (\gamma_{MR}^\kappa + \gamma_{MD}^\kappa + \gamma_{MA}^\kappa) I_{MT}^\kappa - \mu^\kappa I_{MT}^\kappa, \\ \dot{A}^\kappa &= \gamma_{HA}^\kappa I_{HT}^\kappa + \gamma_{MA}^\kappa I_{MT}^\kappa - \gamma_{A1}^\kappa A^\kappa - \mu^\kappa A^\kappa, \\ \dot{R}^\kappa &= \gamma_{HR}^\kappa I_{HT}^\kappa + \gamma_{MR}^\kappa I_{MT}^\kappa - \gamma_{RS}^\kappa R^\kappa - \mu^\kappa R^\kappa, \\ \dot{D}^\kappa &= \gamma_{2D}^\kappa I_2^\kappa + \gamma_{MD}^\kappa I_{MT}^\kappa,\end{aligned}$$

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Force of Infection: $\lambda^\kappa = c^\kappa \beta^\kappa \frac{\sum_{\ell=1}^4 I_1^\ell + I_{HT}^\ell + I_2^\ell + A^\ell}{N}$

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Migration: $\mu^\kappa = \text{natural mortality rate} + \text{aging in/out}$

Basic reproduction number (One infected case → ? secondary cases)

Using the next generation matrix approach...

\mathcal{R}_0 is a weighted average:

$$\mathcal{R}_0 := \sum_{\kappa=1}^4 \frac{S_0^\kappa}{N_0} \mathcal{R}_0^\kappa$$

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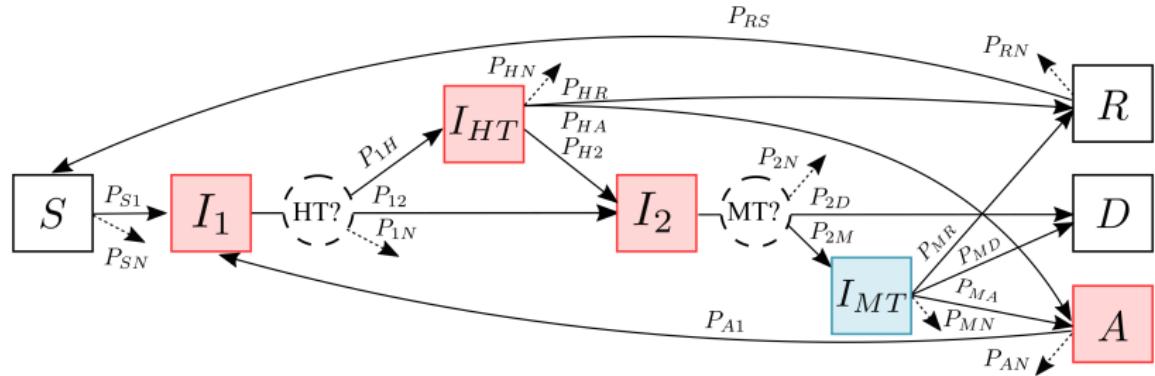
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 group size
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 ↗ \mathcal{R}_0 for each group

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Interpretation \mathcal{R}_0^κ for subpopulation

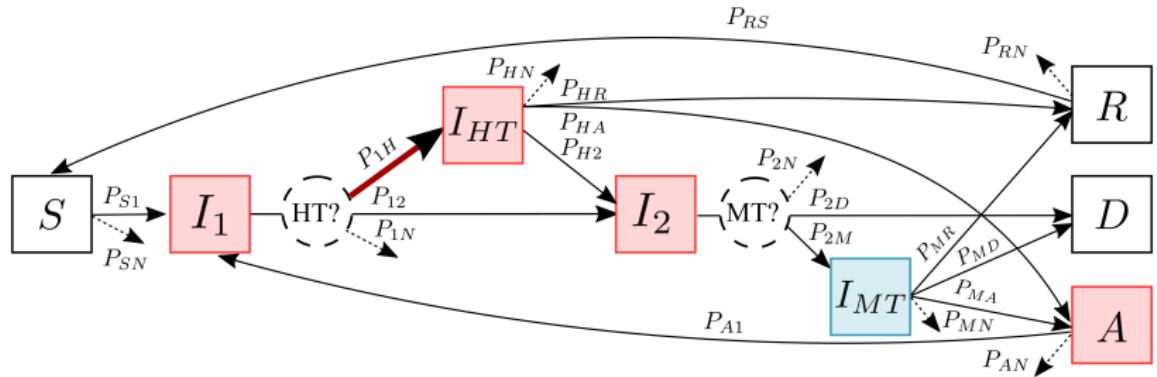
Given one infectious person (group κ), he/she spends...
 τ_1^κ time in stage I_1^κ



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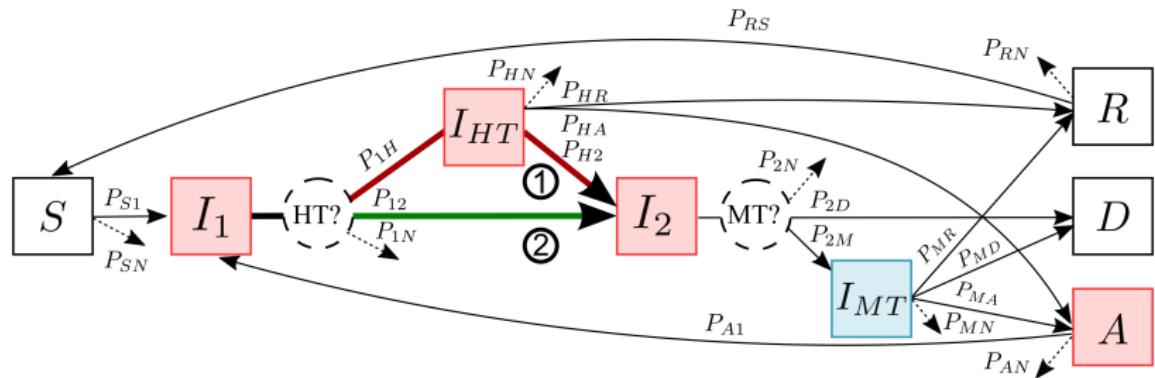
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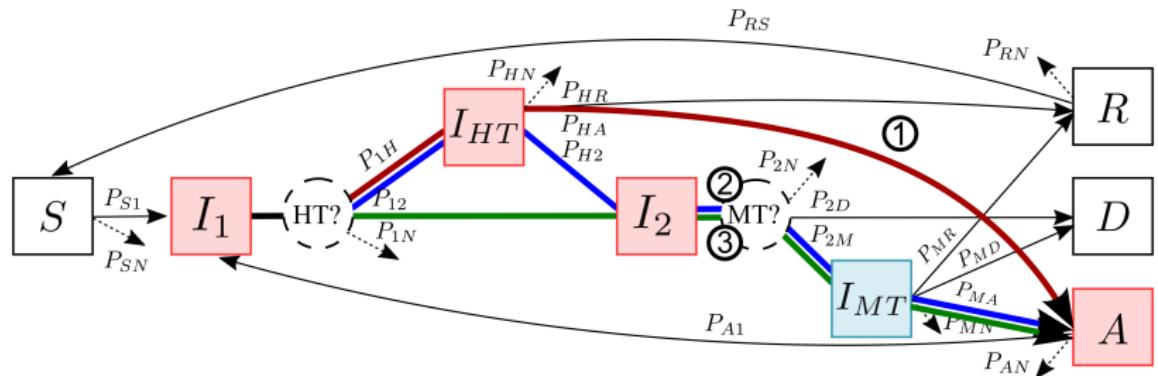
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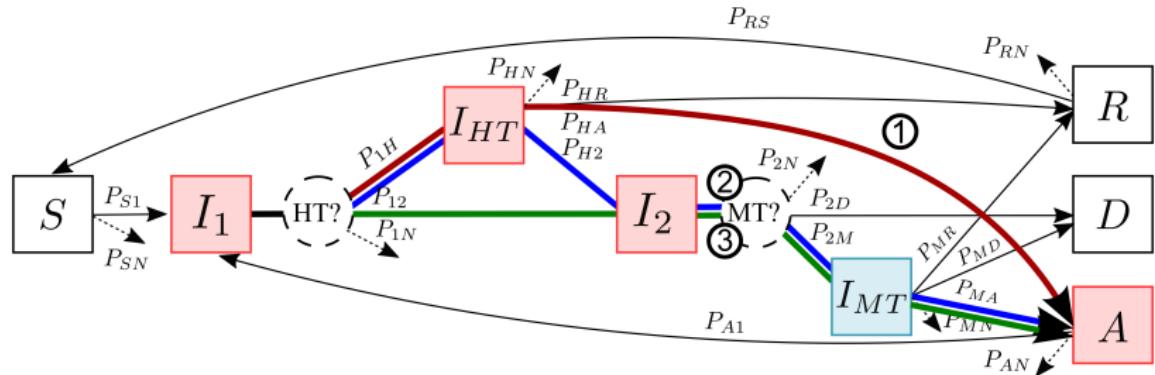
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$$\begin{aligned} \mathcal{R}_0^\kappa &= c^\kappa \beta^\kappa \frac{\tau_1^\kappa + P_{1H}^\kappa \tau_H^\kappa + (P_{12}^\kappa + P_{1H}^\kappa P_{H2}^\kappa) \tau_2^\kappa + [(P_{1H}^\kappa P_{HA}^\kappa + P_{1H}^\kappa P_{H2}^\kappa P_{2M}^\kappa P_{MA}^\kappa + P_{12}^\kappa P_{2M}^\kappa P_{MA}^\kappa) \tau_A^\kappa]}{1 - P_{A1}^\kappa (P_{1H}^\kappa P_{HA}^\kappa + P_{1H}^\kappa P_{H2}^\kappa P_{2M}^\kappa P_{MA}^\kappa + P_{12}^\kappa P_{2M}^\kappa P_{MA}^\kappa)} \\ &= c^\kappa \beta^\kappa \frac{\tau_1^\kappa + \text{Prob}(I_1^\kappa \rightarrow I_{HT}) \tau_H^\kappa + \text{Prob}(I_1^\kappa \rightarrow I_2^\kappa) \tau_2^\kappa + \text{Prob}(I_1^\kappa \rightarrow A^\kappa) \tau_A^\kappa}{1 - \text{Prob}(I_1^\kappa \rightarrow A^\kappa) P_{A1}^\kappa} \end{aligned}$$

Interpretation \mathcal{R}_0^κ for subpopulation

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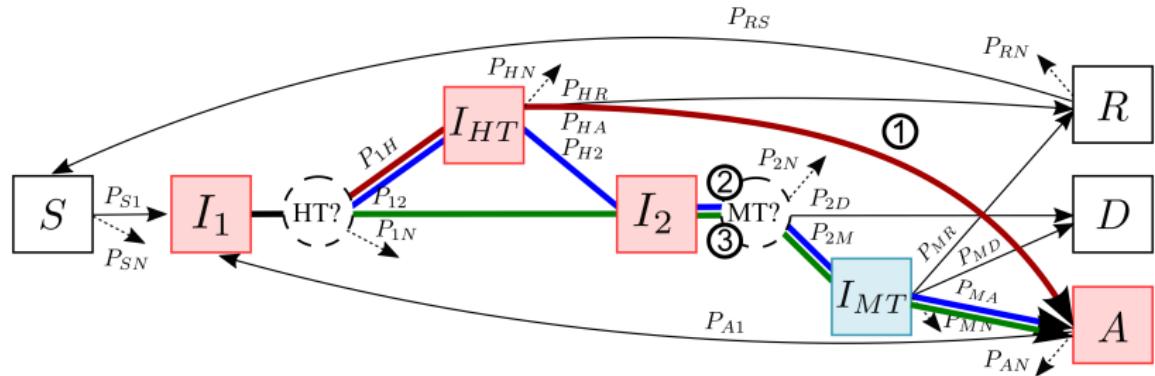


numerator = infectious time in one cycle = $(\mathcal{R}_0^\kappa)^{\text{cycle}}$

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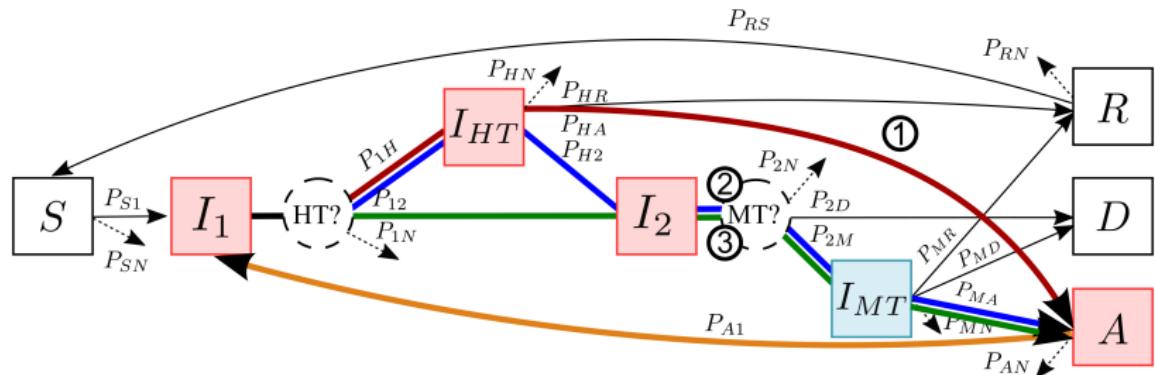


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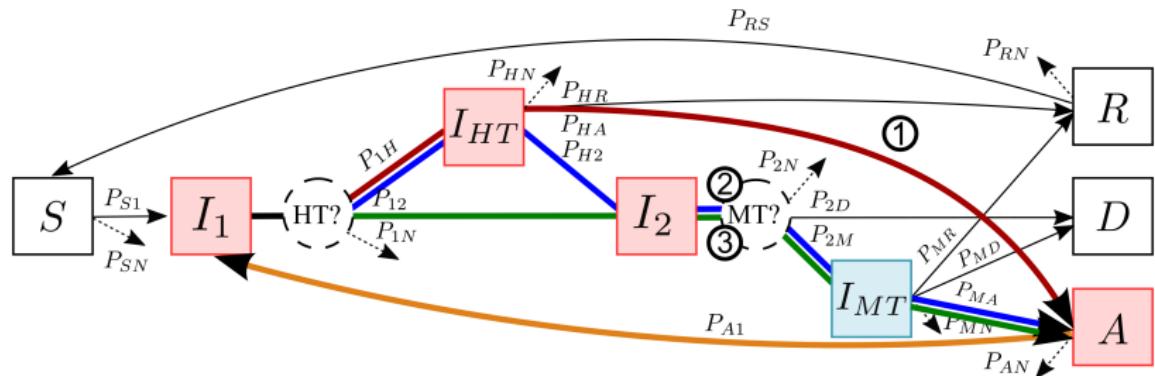


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Interpretation \mathcal{R}_0^κ for subpopulation

Given one infectious person (group κ), he/she spends...
 Total infectious time = sum of an infinite loop



numerator = infectious time in one cycle = $(\mathcal{R}_0^\kappa)^{\text{cycle}}$

$$\mathcal{R}_0^\kappa = c^\kappa \beta^\kappa \frac{\tau_1^\kappa + \text{Prob}(I_1^\kappa \rightarrow I_{HT}^\kappa) \tau_H^\kappa + \text{Prob}(I_1^\kappa \rightarrow I_2^\kappa) \tau_2^\kappa + \text{Prob}(I_1^\kappa \rightarrow A^\kappa) \tau_A^\kappa}{1 - \text{Prob}(I_1^\kappa \rightarrow A^\kappa) P_{A1}} \quad \text{Probability of next cycle} = \mathcal{P}_\gamma^\kappa$$

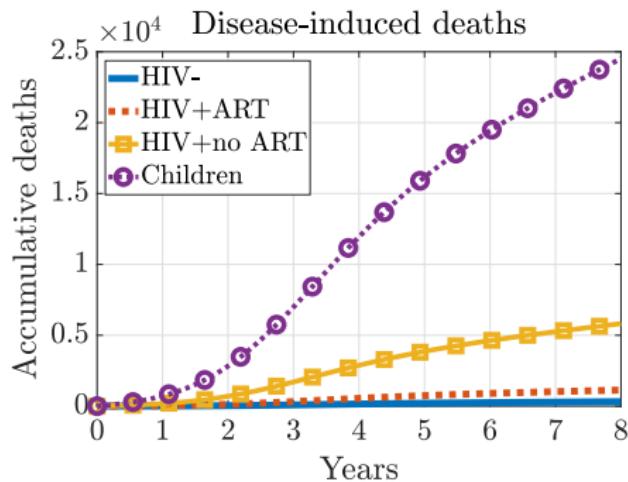
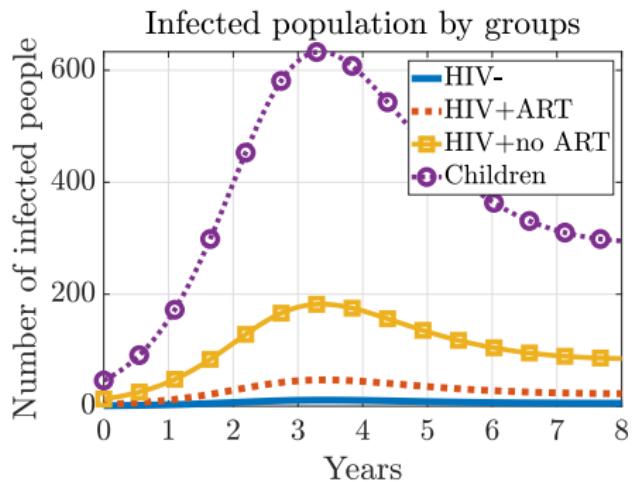
Summation of geometric series:

$$\underbrace{(\mathcal{R}_0^\kappa)^{\text{cycle}}}_{\text{1st cycle}} + \underbrace{\mathcal{P}_\gamma^\kappa (\mathcal{R}_0^\kappa)^{\text{cycle}}}_{\text{2nd cycle}} + \cdots + \underbrace{(\mathcal{P}_\gamma^\kappa)^{n-1} (\mathcal{R}_0^\kappa)^{\text{cycle}}}_{\text{n-th cycle}} + \cdots = \frac{(\mathcal{R}_0^\kappa)^{\text{cycle}}}{1 - \mathcal{P}_\gamma^\kappa}$$

Outlines

- 1 iNTS epidemic in sub-Saharan Africa
- 2 Staged progression models for iNTS
- 3 Numerical simulations

Baseline simulation (Siaya County, Kenya)



The child group has the worst disease outcome: most infected cases (left) and deaths counts (right) among all the population cohorts.

Driving force of the epidemic?

$\mathcal{R}_0 = 1.08$	\mathcal{R}_0^κ	I_1	I_{HT}	I_2	A
HIV- adults	0.03	5×10^{-3}	3×10^{-3}	0.02	-
HIV+ART adults	0.77	0.10	0.06	0.37	0.24
HIV+ no ART adults	8.47	0.41	0.25	1.50	6.31
Children	1.35	0.25	0.37	0.74	-

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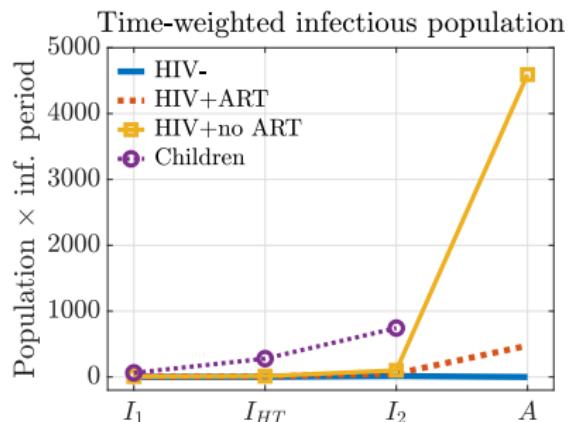
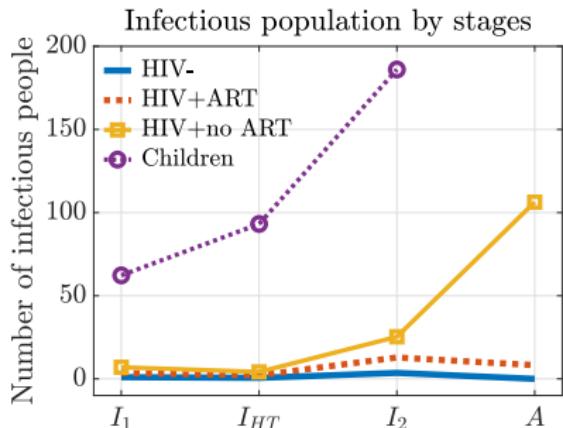
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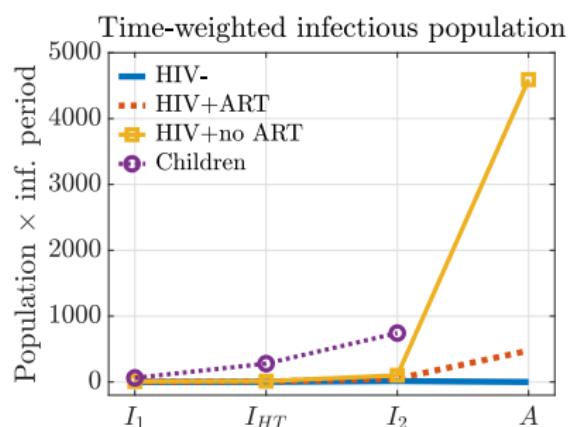
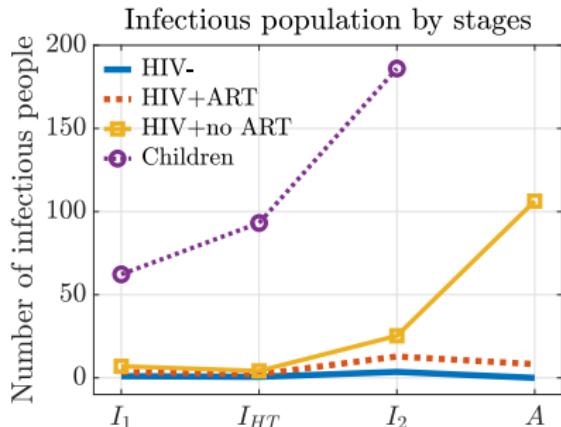
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The HIV+ without ART adults are the driving force of the epidemic.

Potential mitigation strategies

Sensitivity analysis

- vary the parameter of interest (POI)
→ impact on the quantity of interest (QOI)

Sensitivity index: \mathcal{S}_p^q



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		Normalized sensitivity indices					
POI \ QOI	\mathcal{R}_0	Asymp. no-ART adults (peak)	Peaking time	Total infect. at peak	Total infect. at endemic	Accum. deaths	
σ_{MN}	0.53	5.84	-5.94	10.86	7.12	7.67	
σ_{ART}	-0.56	-7.59	5.01	-9.98	-6.70	-7.25	
σ_{HIV}	0.39	5.21	-3.54	7.18	4.88	5.20	
σ_{MA}	0.07	0.82	-1.24	1.52	1.00	1.07	
σ_{MAT}	0.04	0.43	-0.42	0.81	0.53	0.57	

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Coverage of ART		5.21	-3.54	7.18	4.88	5.20
for HIV+ adults ↗		0.82	-1.24	1.52	1.00	1.07
σ_{MAT}	0.04	0.43	-0.42	0.81	0.53	0.57

Potential mitigation strategies

Sensitivity analysis

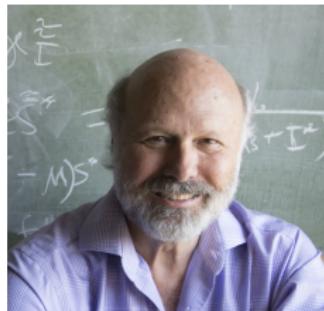
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σ_{MN}	0.53	5.84	-5.94	10.86	7.12	7.67
Preval. of malnutrition among children ↘		-7.59	5.01	-9.98	-6.70	-7.25
		5.21	-3.54	7.18	4.88	5.20
σ_{MA}	0.07	0.82	-1.24	1.52	1.00	1.07
σ_{MAT}	0.04	0.43	-0.42	0.81	0.53	0.57

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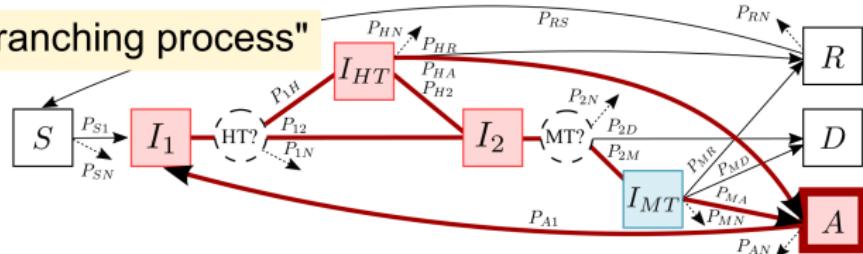
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Univ. of New Mexico

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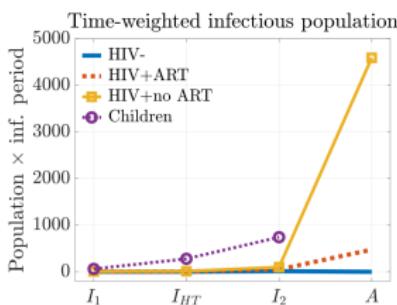
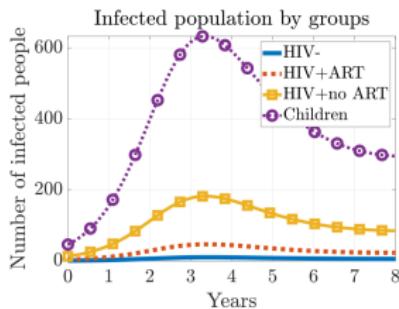
- NSF/MPS/DMS award
- NIH/NIGMS Models of Infectious Disease Agent Study (MIDAS)
- NIH/NIAID R01 award, NIH/FIC D43 awards

Staged progression model for iNTS

"branching process"



$$\mathcal{R}_0^\kappa = c^\kappa \beta^\kappa \frac{\tau_1^\kappa + \text{Prob}(I_1^\kappa \rightarrow I_{HT}^\kappa) \tau_H^\kappa + \text{Prob}(I_1^\kappa \rightarrow I_2^\kappa) \tau_2^\kappa + \text{Prob}(I_1^\kappa \rightarrow A^\kappa) \tau_A^\kappa}{1 - \text{Prob}(I_1^\kappa \rightarrow A^\kappa) P_{A1}^\kappa}$$



- Children (<5yo):
- highest disease burden
 - reduce malnutrition
- HIV+no ART adults (25~40)
- asymptomatic carrier
 - driving force of epidemic
 - improve ART coverage

Slides & preprint available at zhuolinqu.github.io