Modeling immunity to malaria with an age-structured PDE Framework

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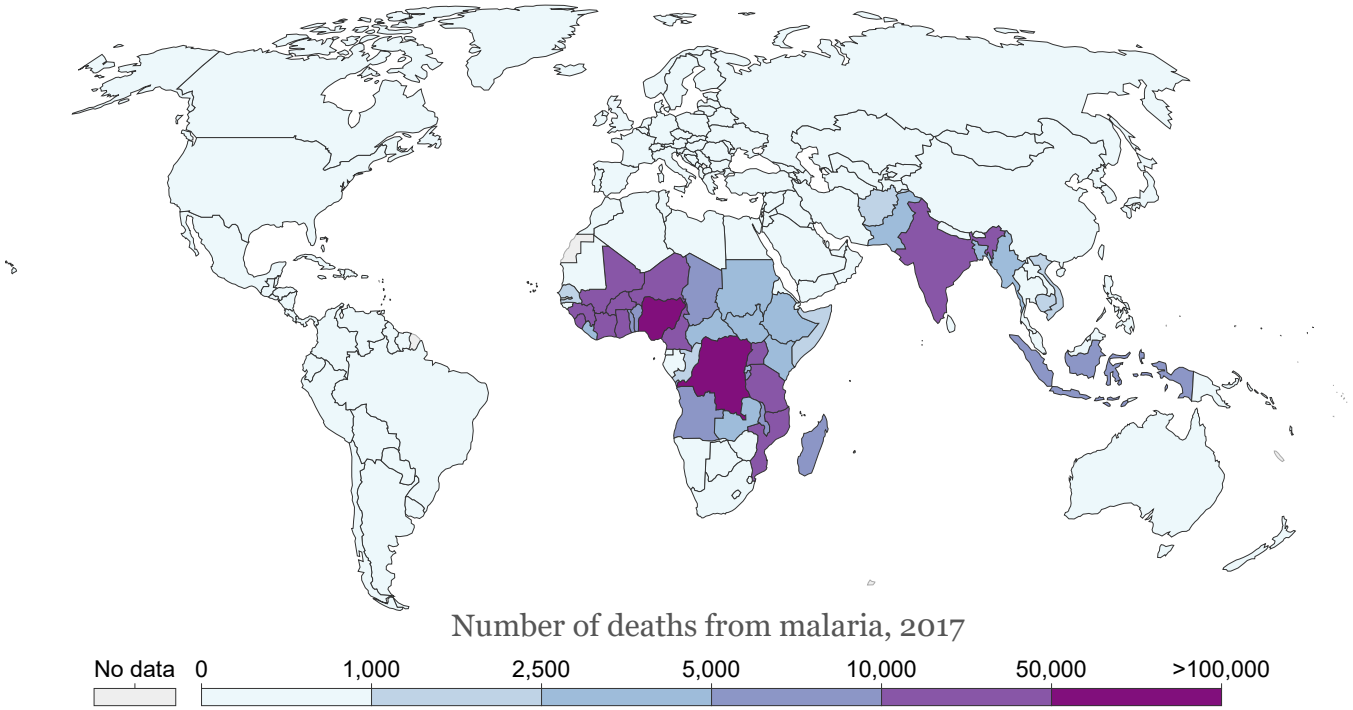
Outlines

Malaria

- Severe public health problems worldwide for a long time
  - about 229 million cases and 409K people died worldwide (2019)
  - poverty, economic development
  - children (age < 5) give 2/3 of fatalities, African region



Source: Our World in Data, Data: Institute for Health Metrics and Evaluation (IHME), 2018.

Malaria

- mosquito-borne disease

  vector: *Anopheles* mosquitoes (exclusively)

  parasites: *Plasmodium falciparum* (Africa, deadliest)

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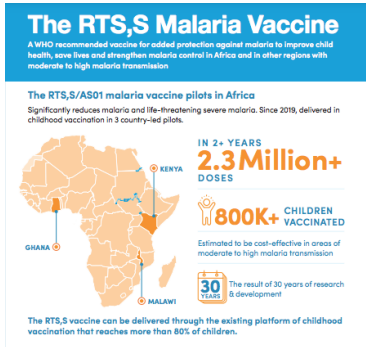
  insecticide-treated nets, indoor residual spraying

  antimalarial drug (drug resistance), Intermittent preventive therapy

  vaccine (RTS,S)



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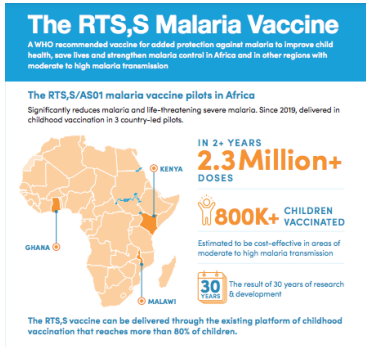


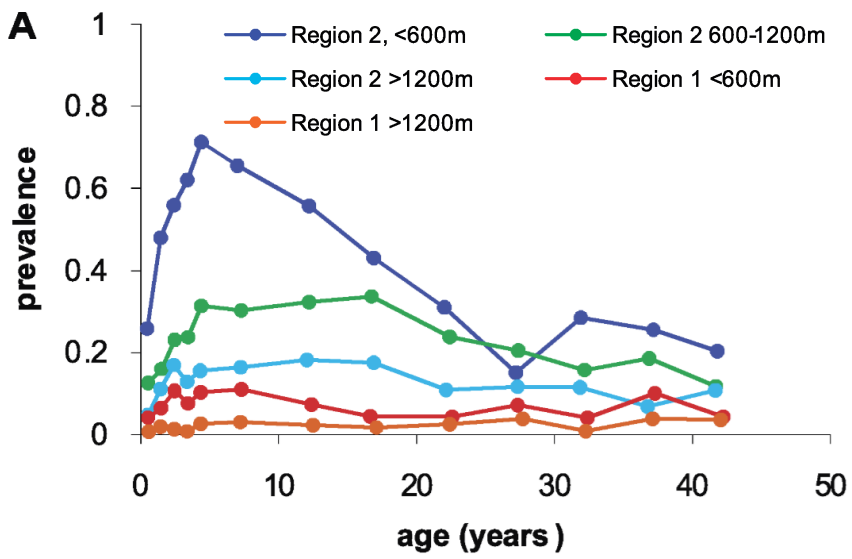
Better understand the disease dynamics – heterogeneity!

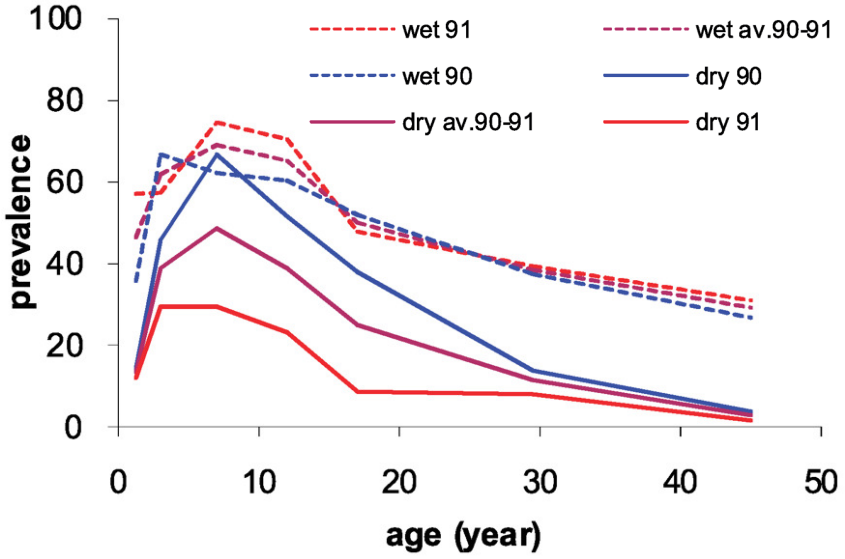
Source: MalariaWorld, USAID, WHO

Heterogeneity in malaria infection

Natural immunity to malaria can be acquired through repeated exposure.

- Age-related prevalence and immune profiles
- Vary with environment - different transmission level
  - Low transmission region: flat profile
  - High transmission region: peak in young children
- Seasonality (temperature, humidity), elevation





Filipe J et al, 2007, PLOS Computational Biology 3(12): e255, https://doi.org/10.1371/journal.pcbi.0030255

Heterogeneity in malaria infection

Develop model to capture the heterogeneity in

- Age-related prevalence and immune profiles
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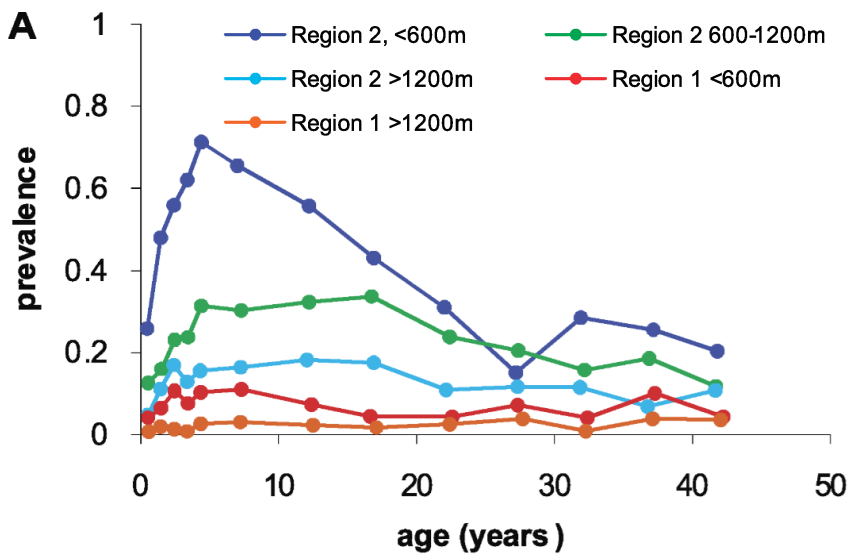

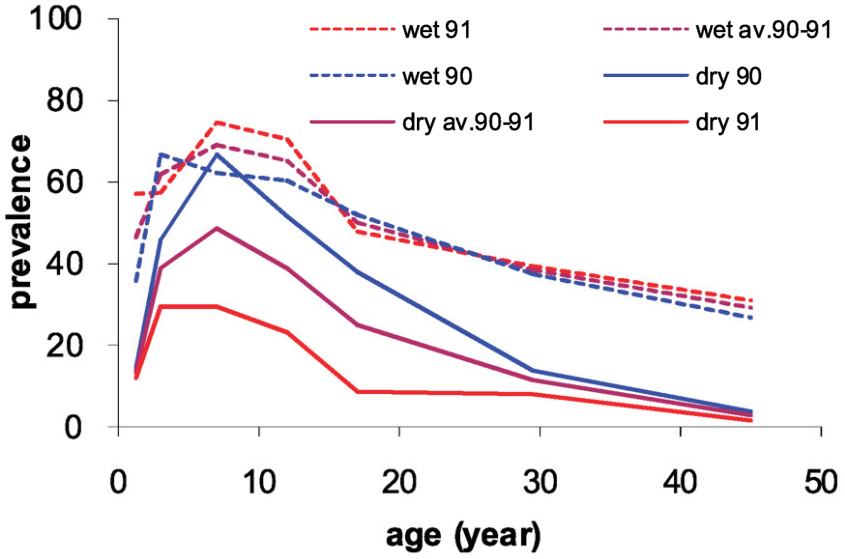

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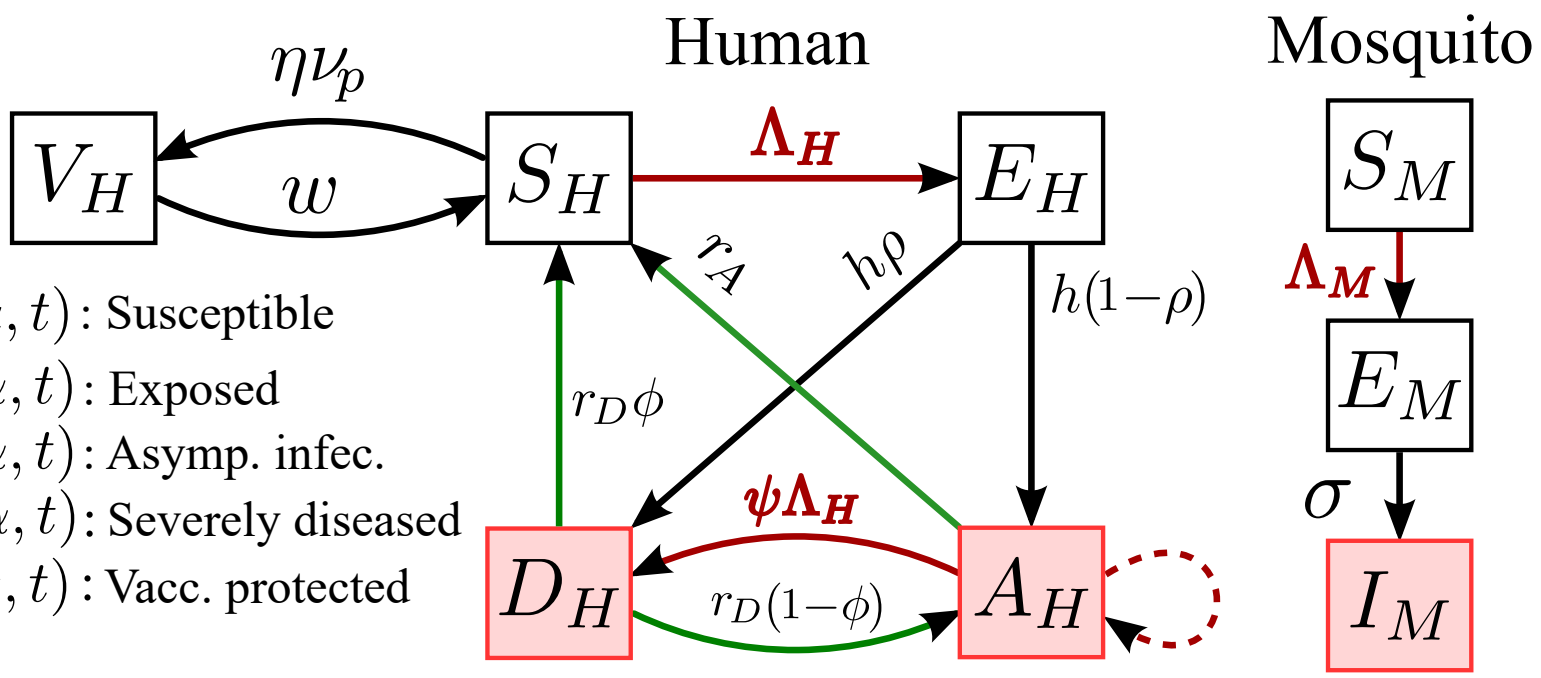
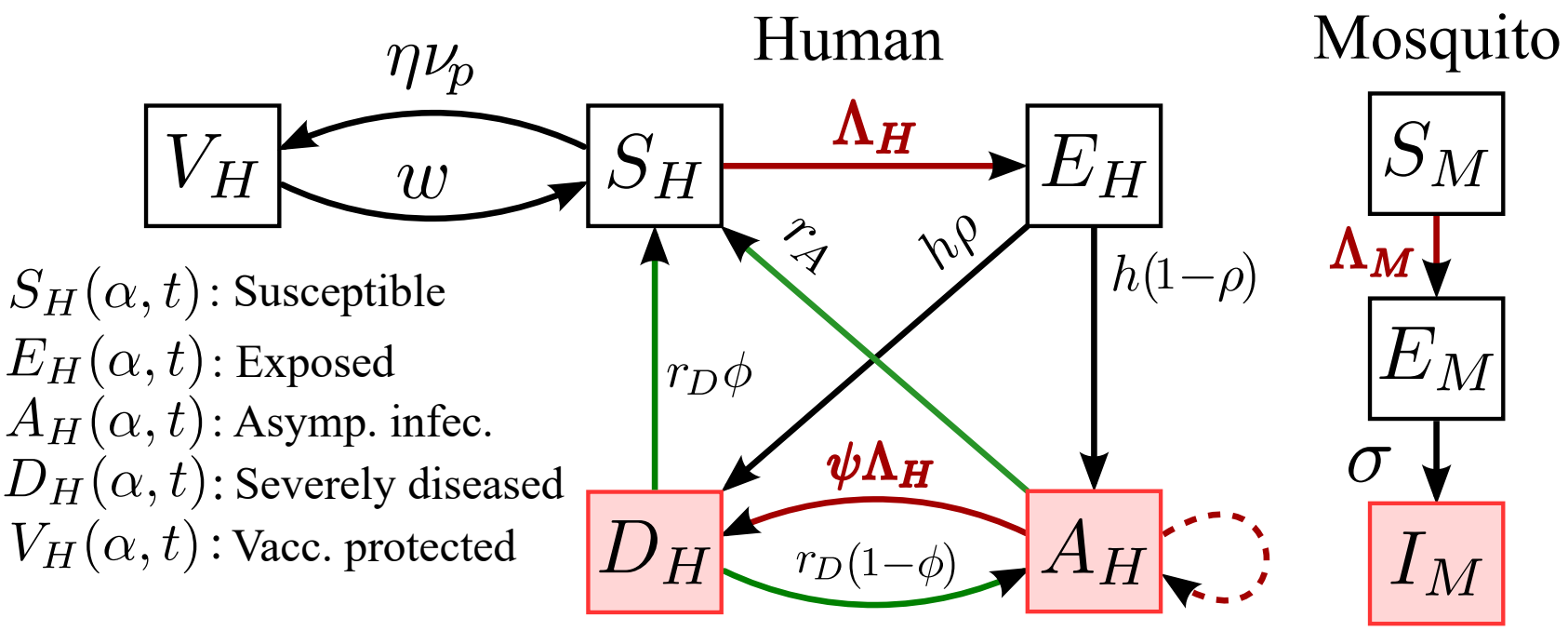
Outlines

Human-mosquito transmission model



$S_H(\alpha,t)$: Susceptible
$E_H(\alpha,t)$: Exposed
$A_H(\alpha,t)$: Asymp. infec.
$D_H(\alpha,t)$: Severely diseased
$V_H(\alpha,t)$: Vacc. protected

Human-mosquito transmission model



$$\Lambda_H(t) = b_H\big(N_M(t), N_H(t)\big)\,\beta_M\,\frac{I_M^\star(t)}{N_M(t)}$$

$$\Lambda_M(t) = b_M\big(N_M(t), N_H(t)\big)\frac{1}{N_H(t)}\int_0^\infty \Big(\beta_D D_H(\alpha,t) + \beta_A A_H(\alpha,t)\Big)\,d\alpha$$

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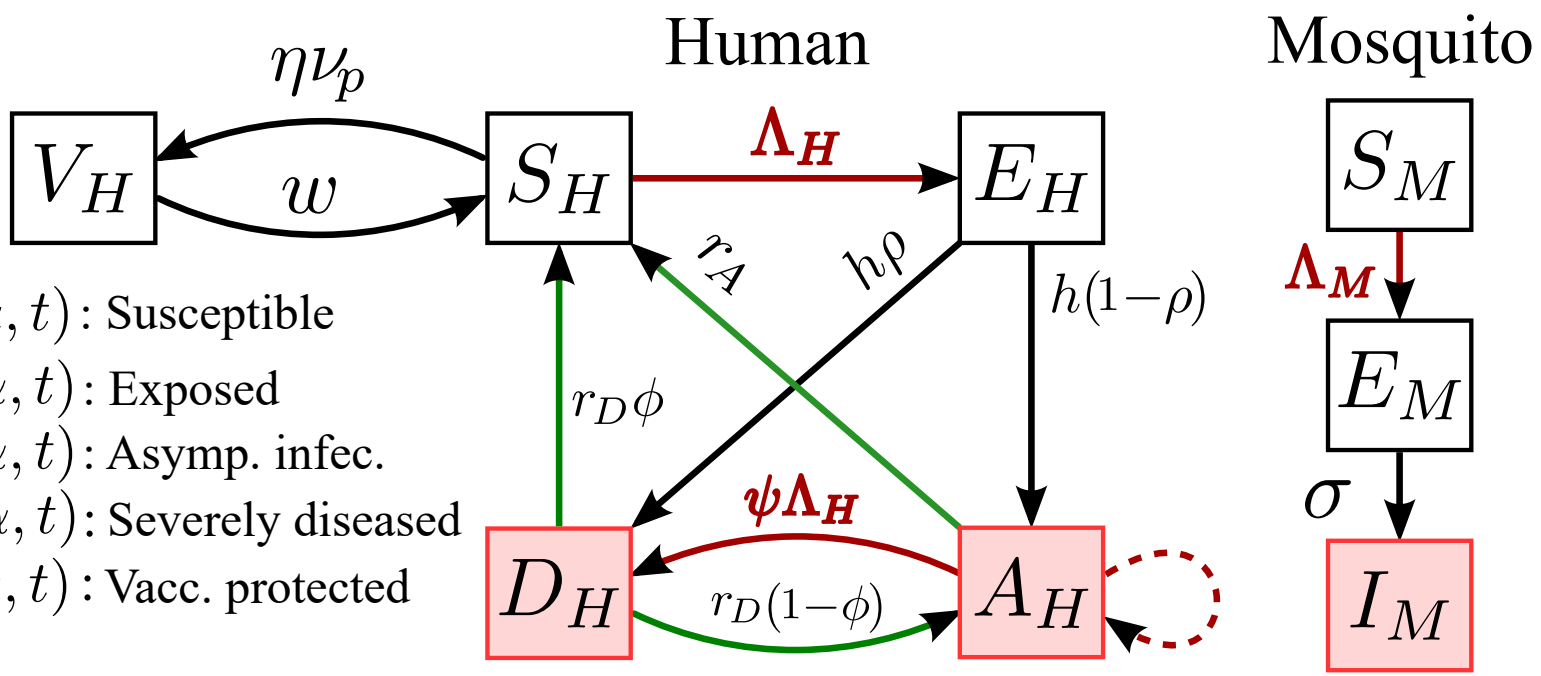

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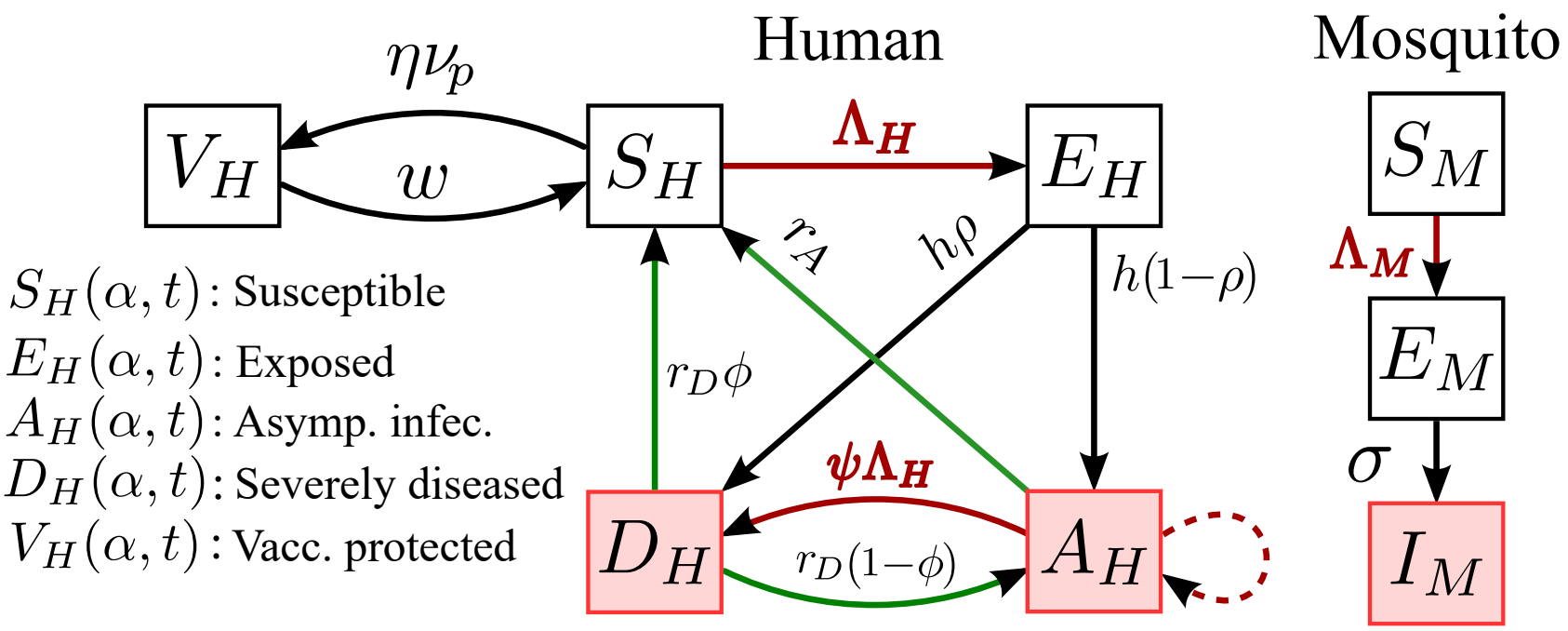
$I_M^\star(t)$: quasi-static equilibrium $\quad I_M^\star(t) = N_M \cdot \dfrac{\sigma}{\sigma+\mu_M} \cdot \dfrac{\Lambda_M(t)}{\Lambda_M(t)+\mu_M}$

Tracking the population immunity



- What to track?
- anti-disease immunity: clinical symptoms, e.g. $E_H \to D_H$?
- anti-parasite immunity: parasite clearance, e.g. recovery rates r_A, r_D

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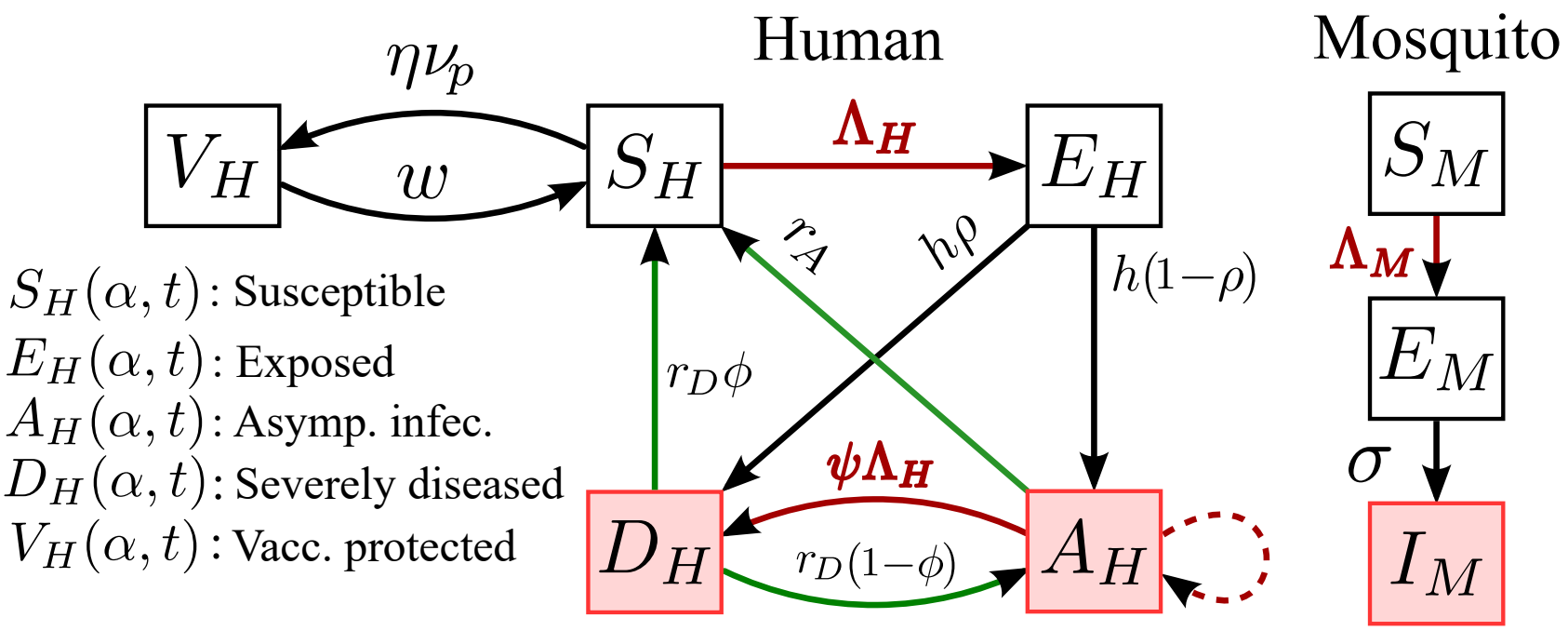

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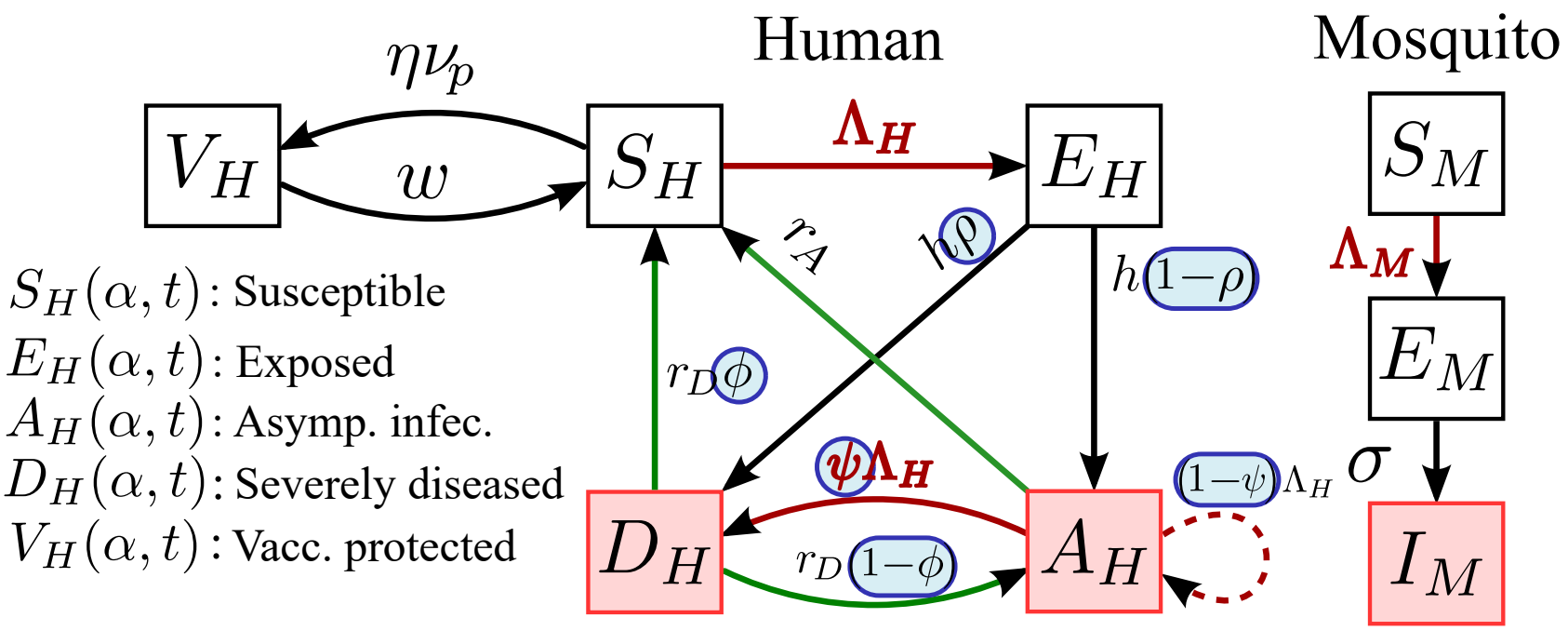

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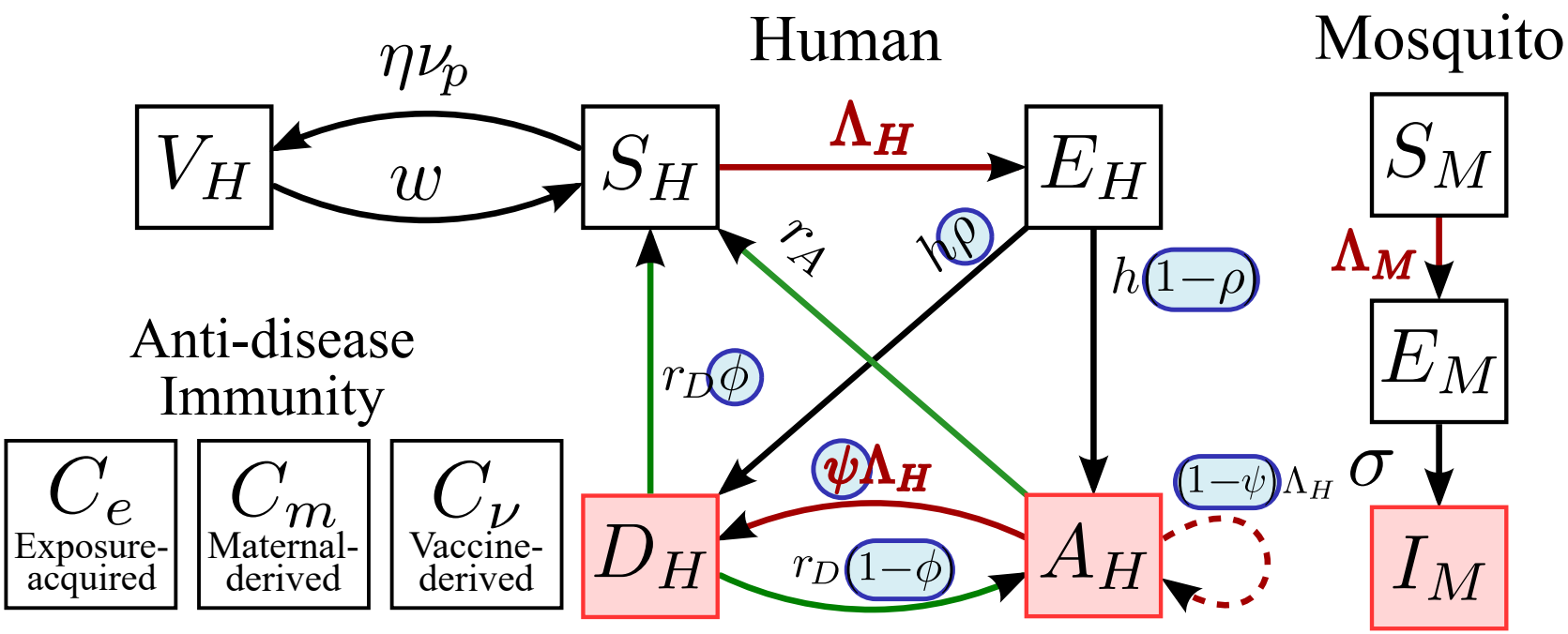
- anti-disease immunity: clinical symptoms, e.g. $E_H \to D_H$?

  ρ: *Prob* $(E_H \to D_H)$ exposure $\to$ severe disease

  ψ: *Prob* $(A_H \to D_H)$ "superinfection" $\to$ severe disease

  ϕ: *Prob* $(D_H \to S_H)$ severe disease $\to$ fully recover

Tracking the population immunity



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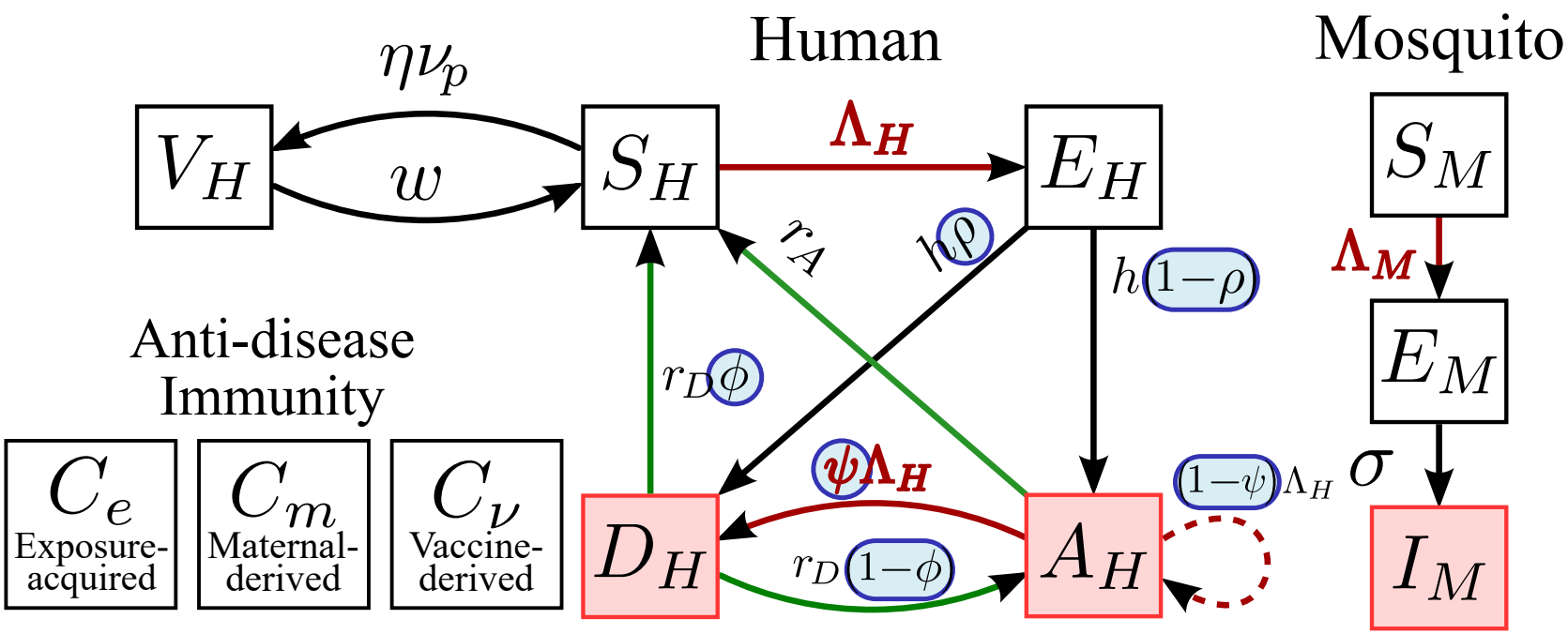
- three different sources

Tracking the population immunity



- What to track?
- anti-disease immunity: clinical symptoms, e.g. $E_H \to D_H$?
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  C_ν - immunity boosting vaccine (blood-stage vaccine)

  V_H - infection protection vaccine (RTS,S)

Tracking the population immunity - different sources

$C_e(\alpha, t)$: exposure-acquired immunity for people age $= \alpha$

immunity acquision (exposure)

$$\frac{\partial C_e}{\partial t} + \frac{\partial C_e}{\partial \alpha} = \boxed{f(\Lambda_H)\,(c_S S_H + c_E E_H + c_A A_H + c_D D_H)}$$

waning

loss from death

$$-\boxed{\frac{C_e}{d_e}} - \boxed{\mu_H(\alpha) C_e - \mu_D(\alpha) \frac{D_H}{P_H} C_e}$$

(natural) (disease)

$$C_e(0, t) = 0$$

$$f(\Lambda_H) = \frac{\Lambda_H}{\gamma \Lambda_H + 1}, \quad \gamma \geq 0$$

Saturation function

$$P_H(\alpha, t) = S_H + E_H + A_H + D_H + V_H$$

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Tracking the population immunity - different sources

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Saturation function

$$P_H(\alpha, t) = S_H + E_H + A_H + D_H + V_H$$

$C_m(\alpha, t)$: maternal-derived immunity for people age $= \alpha$

$$\frac{\partial C_m}{\partial t} + \frac{\partial C_m}{\partial \alpha} = -\overbrace{\boxed{\frac{C_m}{d_m}}}^{\text{waning}} - \overbrace{\boxed{\mu_H(\alpha) C_m - \mu_D(\alpha)\frac{D_H}{P_H} C_m}}^{\text{loss from death}}$$

(natural) (disease)

$$C_m(0, t) = m_0 \int_0^\infty \overbrace{\boxed{g_H(\alpha)}}^{\text{birth}} \left(c_1 C_e(\alpha, t) + c_3 C_\nu(\alpha, t)\right) d\alpha$$

Tracking the population immunity - different sources

$C_\nu(\alpha, t)$: vaccine-derived immunity for people age $= \alpha$

$$\frac{\partial C_\nu}{\partial t} + \frac{\partial C_\nu}{\partial \alpha} = \underbrace{\boxed{c_\nu \nu_b(\alpha, t) S_H}}_{\text{(vaccine)}}^{\text{boosting}} - \boxed{\frac{C_\nu}{d_\nu}}^{\text{waning}} - \boxed{\mu_H(\alpha) C_\nu - \mu_D(\alpha) \frac{D_H}{P_H} C_\nu}^{\text{loss from death}}$$

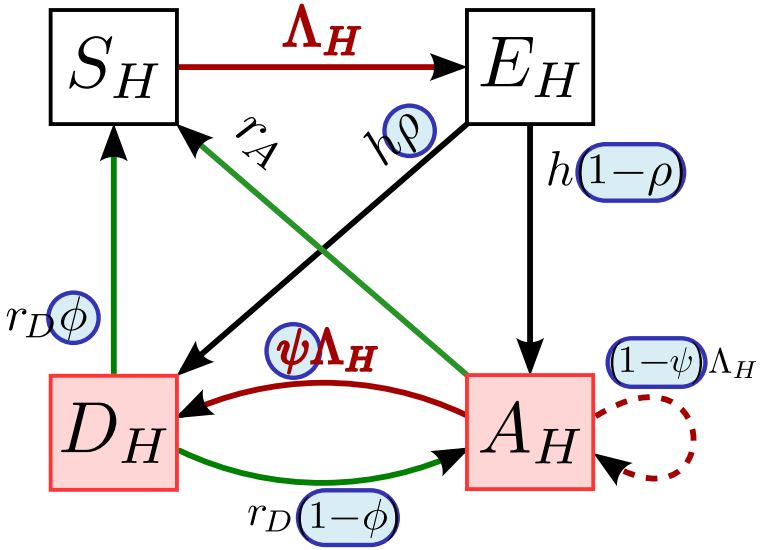
(natural) (disease)

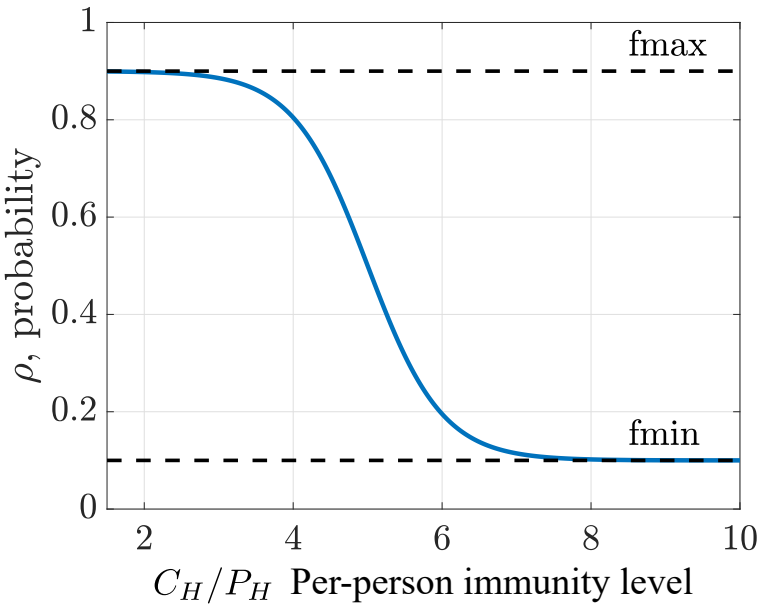
$$C_\nu(0, t) = \boxed{c_\nu \nu_b(0, t) S_H(0, t)}$$

- $C_H = c_1 C_e + c_2 C_m + c_3 C_\nu$

Connecting immunity to transmission

- Immunity dynamics create feedback on infection dynamics: linking functions
- $\rho(C_H/P_H)$, $\psi(C_H/P_H)$, $\phi(C_H/P_H)$





$$\partial_t S_H + \partial_\alpha S_H = \phi(\widetilde{C}_H) r_D D_H + r_A A_H - \Lambda_H(t) S_H - \eta(\alpha)\, \nu_p(\alpha,t) S_H + w V_H - \mu_H(\alpha) S_H,$$

$$\partial_t E_H + \partial_\alpha E_H = \Lambda_H(t) S_H - h E_H - \mu_H(\alpha) E_H,$$

$$\partial_t A_H + \partial_\alpha A_H = (1-\rho(\widetilde{C}_H)) h E_H - \psi(\widetilde{C}_H)\Lambda_H(t) A_H + (1-\phi(\widetilde{C}_H)) r_D D_H - r_A A_H - \mu_H(\alpha) A_H,$$

$$\partial_t D_H + \partial_\alpha D_H = \rho(\widetilde{C}_H) h E_H + \psi(\widetilde{C}_H)\Lambda_H(t) A_H - r_D D_H - (\mu_H(\alpha) + \mu_D(\alpha)) D_H,$$

$$\partial_t V_H + \partial_\alpha V_H = \eta(\alpha)\, \nu_p(\alpha,t) S_H - w V_H - \mu_H(\alpha) V_H,$$

$$\frac{dS_M}{dt} = -\Lambda_M(t) S_M + g_M - \mu_M S_M$$

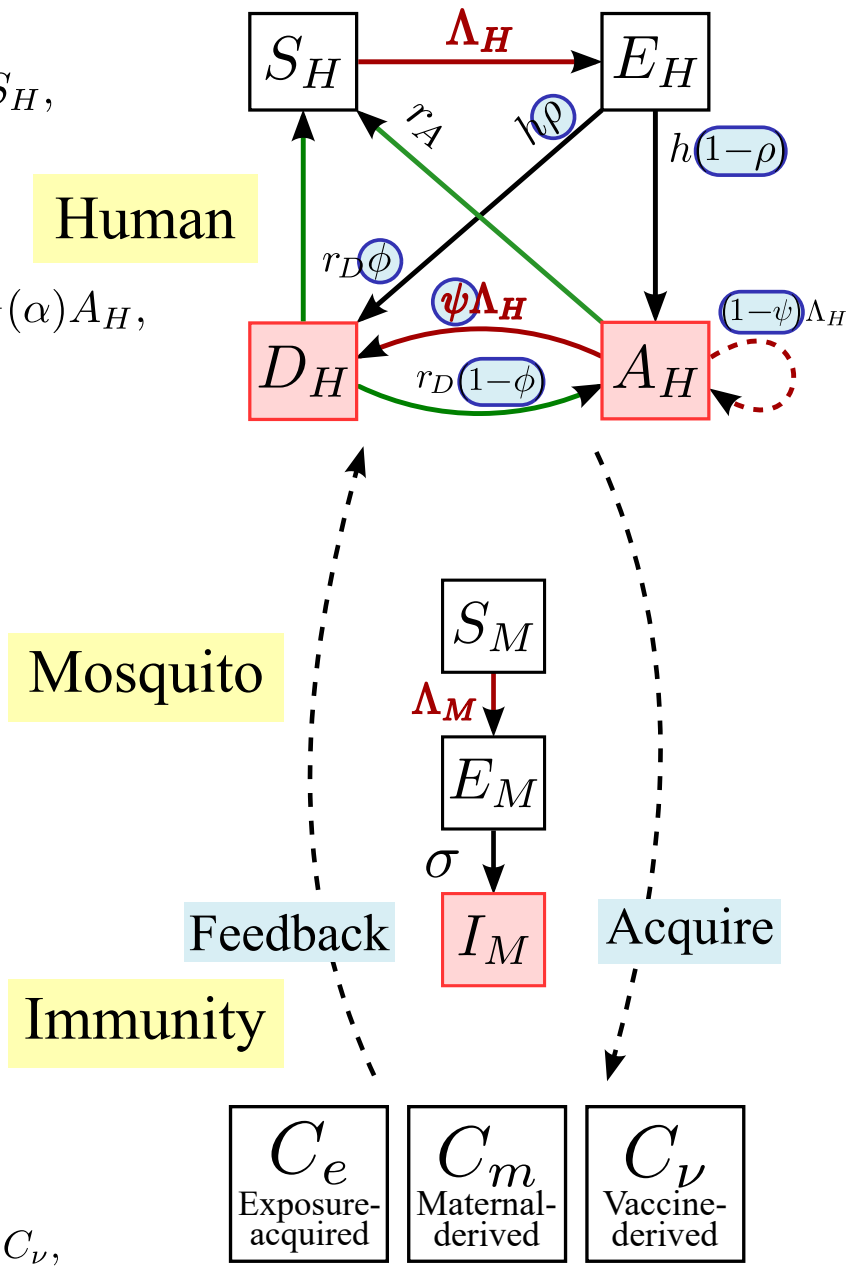
$$\frac{dE_M}{dt} = \Lambda_M(t) S_M - \sigma E_M - \mu_M E_M$$

$$\frac{dI_M}{dt} = \sigma E_M - \mu_M I_M$$

$$\partial_t C_e + \partial_\alpha C_e = f(\Lambda_H)\left(c_S S_H + c_E E_H + c_A A_H + c_D D_H\right) - \left(\frac{1}{d_e} + \mu_H(\alpha) + \mu_D(\alpha)\frac{D_H}{P_H}\right) C_e,$$

$$\partial_t C_m + \partial_\alpha C_m = -\left(\frac{1}{d_m} + \mu_H(\alpha) + \mu_D(\alpha)\frac{D_H}{P_H}\right) C_m,$$

$$\partial_t C_\nu + \partial_\alpha C_\nu = c_\nu\, \nu_b(\alpha,t) S_H - \left(\frac{1}{d_\nu} + \mu_H(\alpha) + \mu_D(\alpha)\frac{D_H}{P_H}\right) C_\nu,$$



Outlines

Basic reproduction number $\mathcal{R}_0$

- $\mathcal{R}_0 =$ the number of cases one case generates within its infectious period, in a totally susceptible population
- threshold condition for the disease transmission: $\mathcal{R}_0 > 1$

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By analyzing the threshold condition for the stability of DFE ...

$$\mathcal{R}_0^\star = C^\star \int_0^\infty e^{-M(\alpha)} \left(\beta_D \, \mathcal{D}(\alpha, 0) + \beta_A \, \mathcal{A}(\alpha, 0)\right) d\alpha$$

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$$C^\star = \frac{\mu_H^* \, b_m^2 \, b_h^2 \, N_M \, N_H \, \beta_M \, \sigma}{(b_m \, N_M + b_h \, N_H)^2 (\sigma + \mu_M) \mu_M}, \quad M(\alpha) := \int_0^\alpha \mu_H(a) da$$

$$\mathcal{E}(\alpha, 0) = \int_0^\alpha e^{-h(\alpha - a)} \theta(a) \, da,$$

$$\mathcal{D}(\alpha, 0) = \int_0^\alpha e^{-r_D(\alpha - a)} \rho \, h \, \mathcal{E}(a, 0) \, da,$$

$$\mathcal{A}(\alpha, 0) = \int_0^\alpha e^{-r_A(\alpha - a)} \Big(h(1-\rho) \, \mathcal{E}(a, 0) + r_D(1-\phi) \, \mathcal{D}(a, 0) \Big) \, da.$$

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Interpretation?

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$\mathcal{R}_0$ interpretation

$$\mathcal{R}_0^\star = \left(b_M \, \beta_M \, \frac{\sigma}{\sigma + \mu_M} \frac{1}{\mu_M} \right) \left(b_H \int_0^\infty \mu_H^* e^{-M(\alpha)} \left(\beta_D \, \mathcal{D}(\alpha, 0) + \beta_A \, \mathcal{A}(\alpha, 0) \right) d\alpha \right)$$
$$=: \mathcal{R}_{MH} \times \mathcal{R}_{HM}$$

- $\mathcal{R}_{MH}$: Mosquito $\to$ human transmission route
- $\mathcal{R}_{HM}$: Human $\to$ mosquito transmission route

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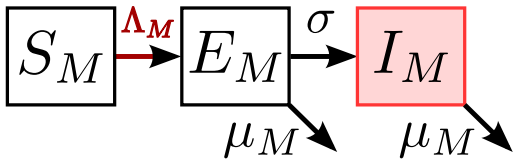

Expected infect. period (days)

Prob. of survive to infectious stage

bites per day

Prob. of transmission per bite

Human $\rightarrow$ mosquito transmission route

- $\mathcal{R}_{HM} = b_H \int_0^\infty \mu_H^* e^{-M(\alpha)} \left(\beta_D \, \mathcal{D}(\alpha, 0) + \beta_A \, \mathcal{A}(\alpha, 0)\right) d\alpha$
- $\mathcal{E}(\alpha, 0) = \int_0^\alpha e^{-h(\alpha - a)} \theta(a) \, da,$
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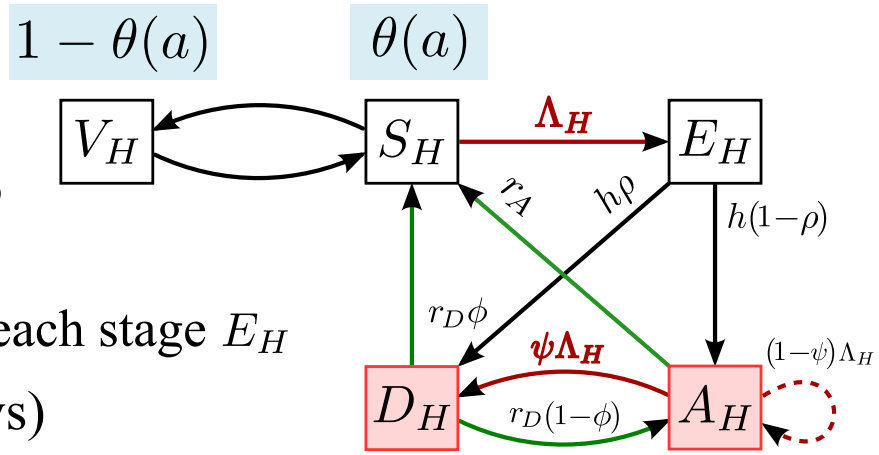
$$h\,\mathcal{E}(\alpha,0) = \int_0^\alpha \underbrace{he^{-h(\alpha-a)}}_{\text{Prob.(leave } E_H \text{ after } \alpha-a \text{ days)}} \underbrace{\theta(a)}_{\text{Prob. age - } a \text{ reach stage } E_H}\, da,$$



Human $\rightarrow$ mosquito transmission route

- $\mathcal{R}_{HM} = b_H \int_0^\infty \mu_H^* e^{-M(\alpha)} \left(\beta_D \mathcal{D}(\alpha,0) + \beta_A \mathcal{A}(\alpha,0)\right) d\alpha$
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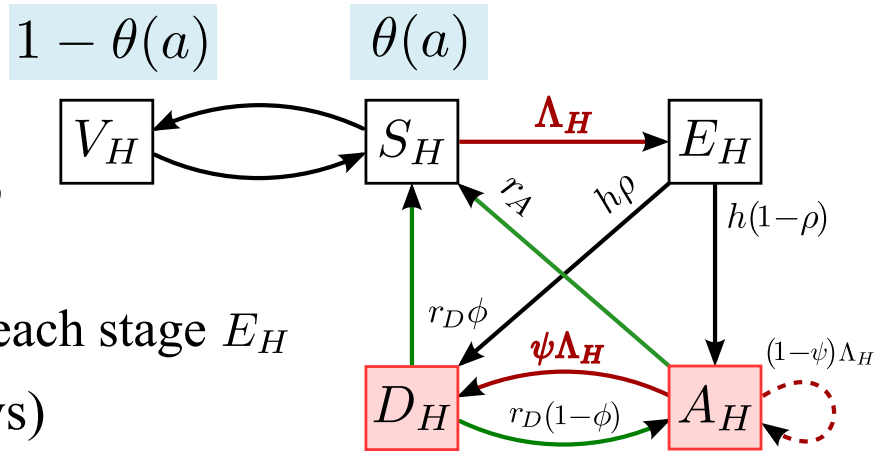

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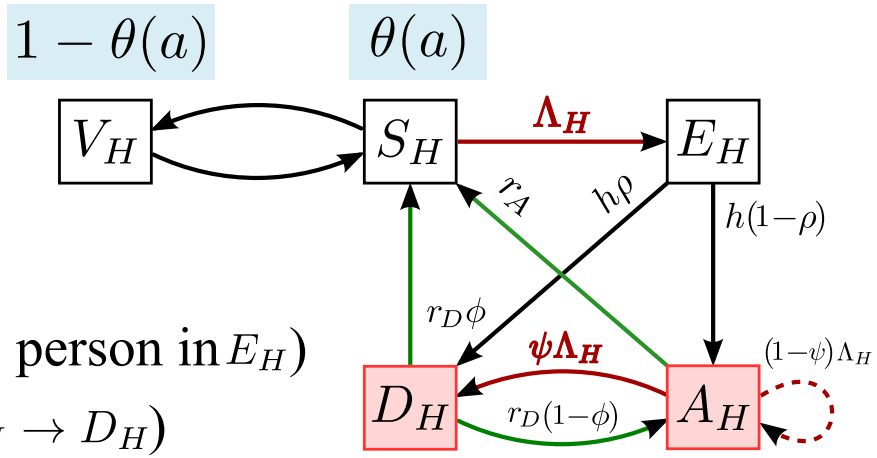
Prob.$(E_H \to D_H)$



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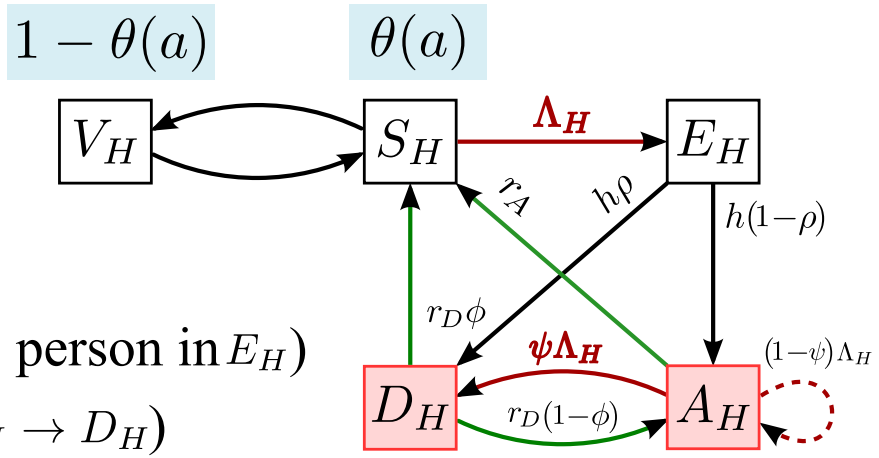
Prob.$(E_H \rightarrow D_H)$



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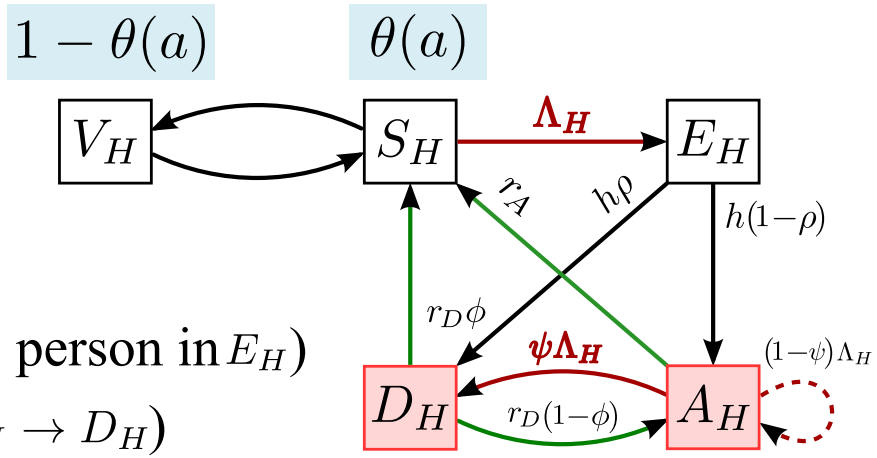

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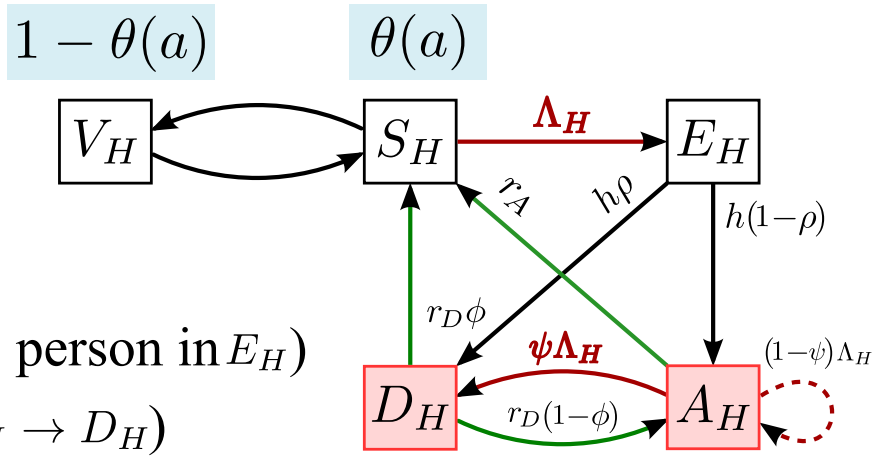
- $E_H \to D_H$ route only at DFE

$$\mathcal{D}(\alpha,0) = \underbrace{\frac{1}{r_D}}_{\text{average time in stage } D_H} \times \underbrace{\int_0^\alpha \underbrace{r_D e^{-r_D(\alpha-a)}}_{\text{Prob.(leave } D_H \text{ after } \alpha-a \text{ days)}} \underbrace{\rho}_{\text{Prob.}(E_H \to D_H)} \underbrace{h\,\mathcal{E}(a,0)}_{\text{Prob.(age-}a\text{ person in } E_H)} da}_{\text{Prob. age - } \alpha \text{ in stage } D_H}$$



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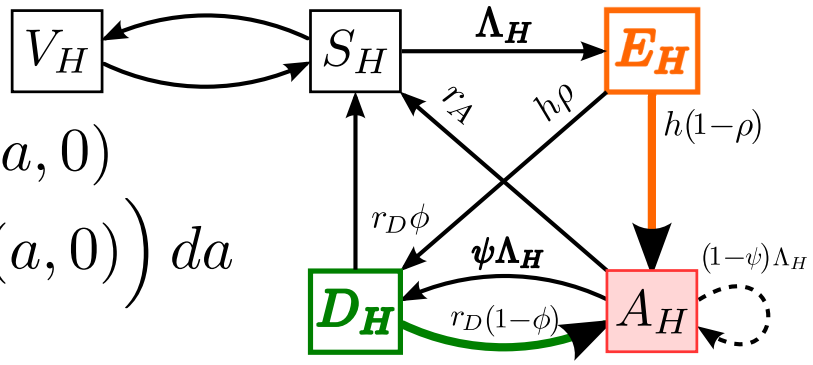
$$\underbrace{\boxed{\text{average time in stage } A_H}}_{} \times \boxed{\text{Prob. age - }\alpha\text{ in stage } A_H}$$

$$\mathcal{A}(\alpha,0) = \frac{1}{r_A}\int_0^\alpha r_A e^{-r_A(\alpha-a)} \Big(\overbrace{(1-\rho)\, h\,\mathcal{E}(a,0)}^{E_H \to A_H} + \underbrace{(1-\phi)\, r_D\,\mathcal{D}(a,0)}_{D_H \to A_H} \Big)\, da$$



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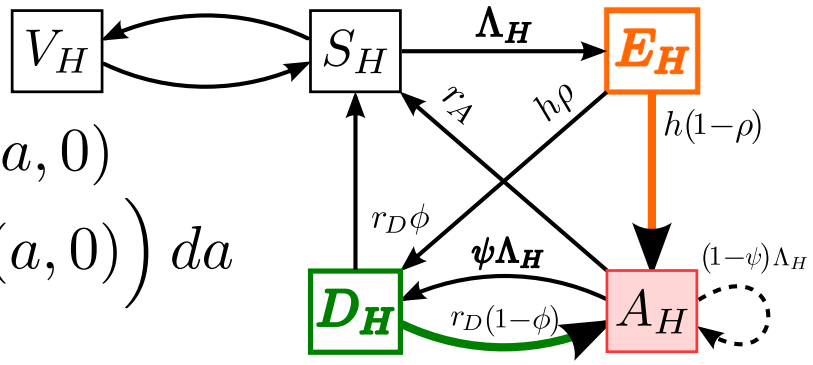

$\mathcal{R}_0$ interpretation

- $\mathcal{R}_{HM} = b_H \int_0^\infty \mu_H^* e^{-M(\alpha)} \left(\beta_D \mathcal{D}(\alpha, 0) + \beta_A \mathcal{A}(\alpha, 0)\right) d\alpha$

$\mathcal{R}_0$ interpretation

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- $\mathcal{R}_{HM,\alpha} = b_H \beta_D \mathcal{D}(\alpha, 0) + b_H \beta_A \mathcal{A}(\alpha, 0)$

  $=$ new cases produced by infectious age-α people

$\mathcal{R}_0$ interpretation

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- $\mathcal{R}_{HM} = \int_0^\infty \mathcal{R}_{HM,\alpha} P_H(\alpha) \, d\alpha,$

  where $P_H(\alpha) = \mu_H^* e^{-M(\alpha)}$, age distribution of population at DFE

$\mathcal{R}_0$ interpretation

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The overall basic reproduction number

$$\mathcal{R}_0 = \sqrt{\mathcal{R}_0^\star} = \sqrt{\mathcal{R}_{MH} \times \mathcal{R}_{HM}}$$

Outlines

Numerical discretization

Numerical scheme to mimic biological properties...

- positivity preserving
- conservation law of population (people don't disappear magically)

Not too severe time-step constraint

$$\frac{\partial S_H}{\partial t} + \frac{\partial S_H}{\partial \alpha} = -\Lambda_H(t) S_H + \phi r_D D_H + r_A A_H - \mu_H(\alpha) S_H \quad \text{*no vaccine}$$

- uniform grid (α_k, t_n), $\Delta\alpha = \Delta t$

- LHS $= \dfrac{\partial S_H}{\partial t} + \dfrac{\partial S_H}{\partial \alpha} \quad \rightarrow \quad \dfrac{S_H^{k+1,n+1} - S_H^{k,n}}{\Delta t}$
- RHS: "explicit" - "implicit" approach

$$-\Lambda_H(t)\underline{S_H} + \phi r_D D_H + r_A A_H - \mu_H(\alpha)\underline{S_H}$$

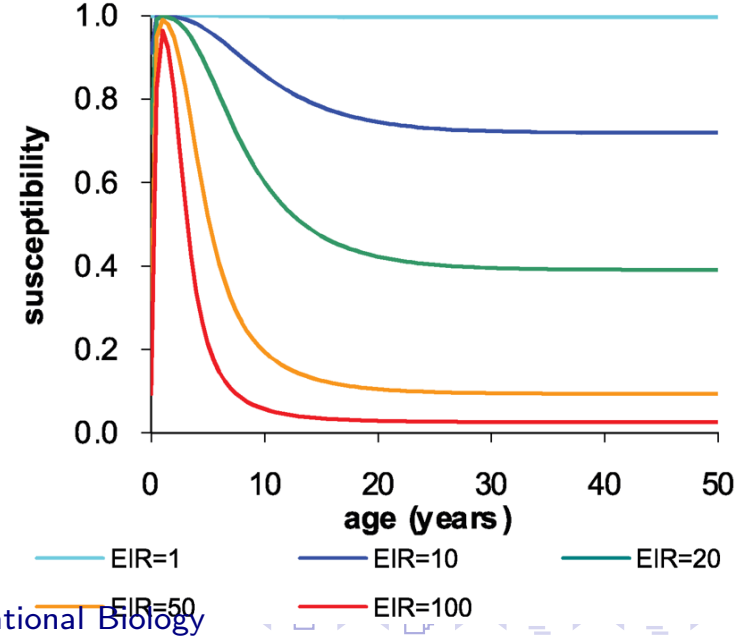
Martcheva, M., 2015. An introduction to mathematical epidemiology (Vol. 61). New York: Springer.

Model calibration

- Assumptions
  - no disease-induced mortality
  - constant demographic structure
- Immunity linking parameters
  - susceptibility to developing clinical disease: ρ(age, aEIR)
  - aEIR: annual entomological inoculation rate

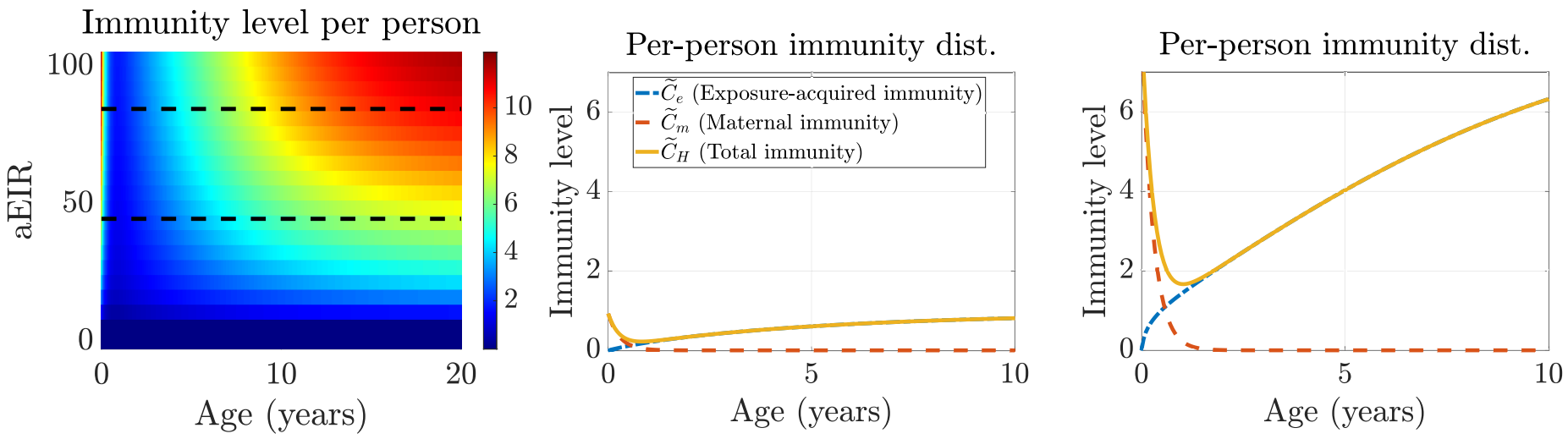
- $\mathcal{R}_0 \approx 6.9$

  $aEIR \approx 85$ at endemic



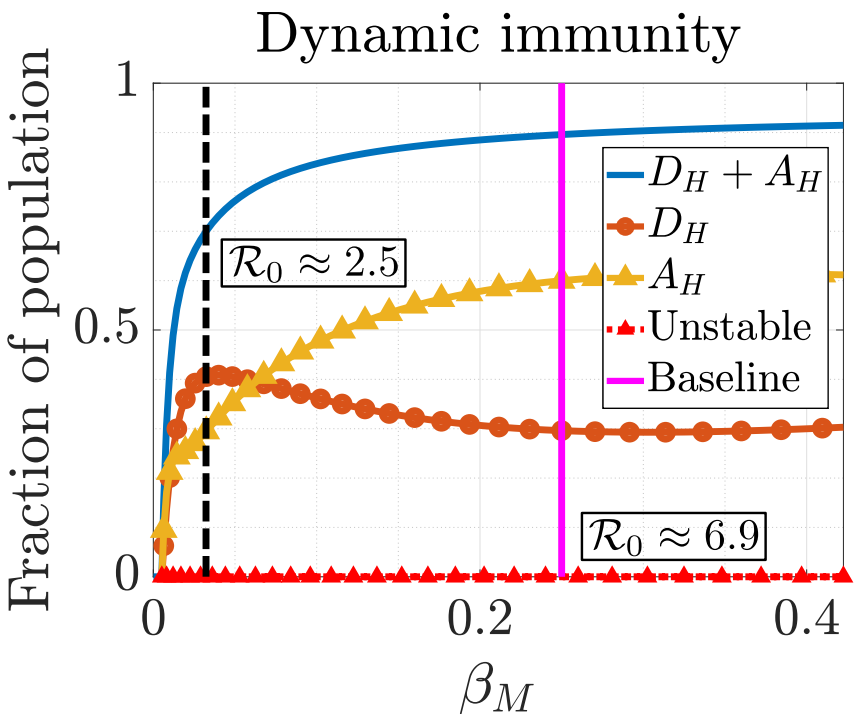
Rogers, D. et al, 2002, Nature; Filipe J et al, 2007, PLOS Computational Biology

Immunity profile (age, aEIR)



- low aEIR region (center): flat immunity
- high aEIR region (right): fast decay of maternal immunity after birth and increases as getting older due to repeated exposure

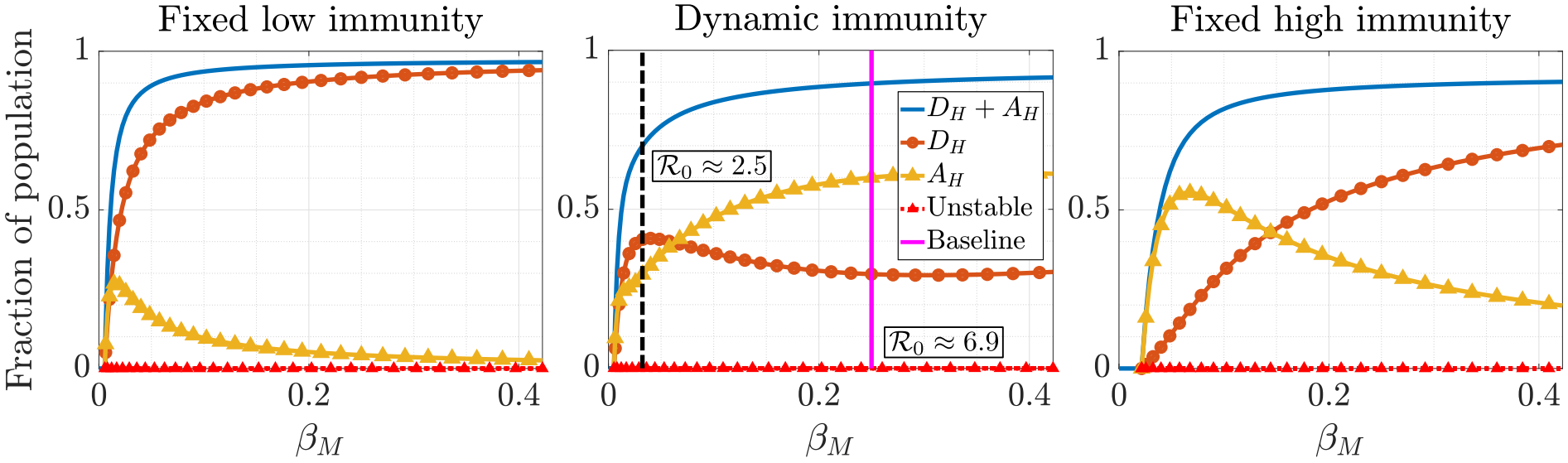
Impact of immunity feedback



When having dynamic immunity feedback

- As β_M (exposure level) increases, A_H keeps increasing, D_H peaks
- stronger exposure, larger feedback onto progression parameters ρ, ψ, more likely to become A_H than D_H

Impact of immunity feedback

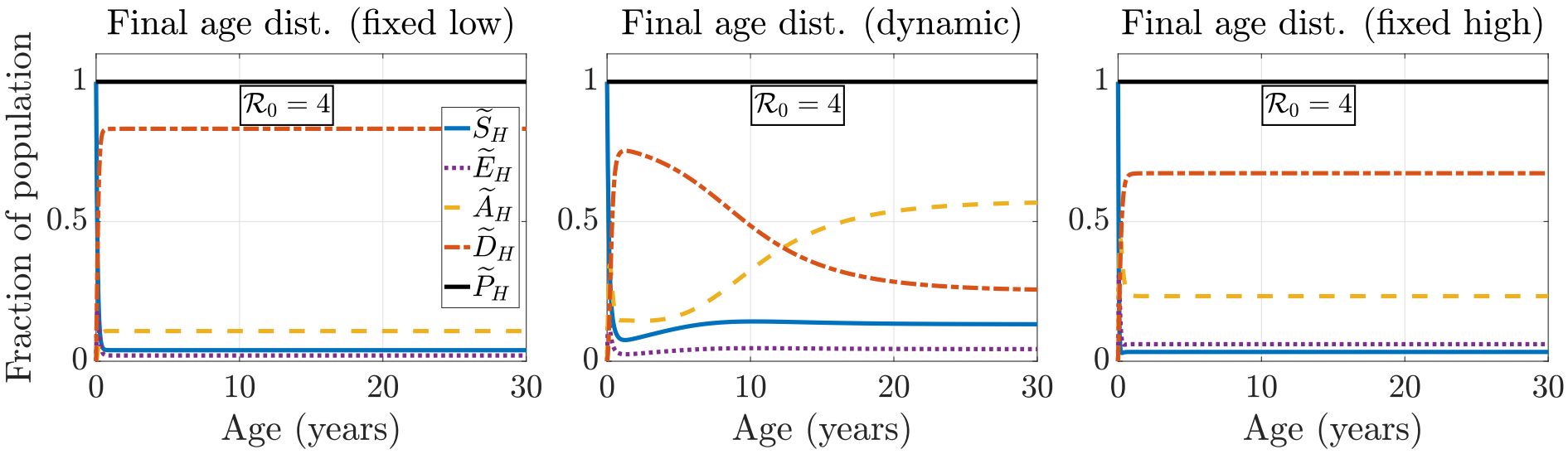


When fixing the population immunity at constant level (low or high)

- as β_M (exposure level) increases, monotone increase in D_H
- worse disease outcome

Immunity feedback onto age-distributions

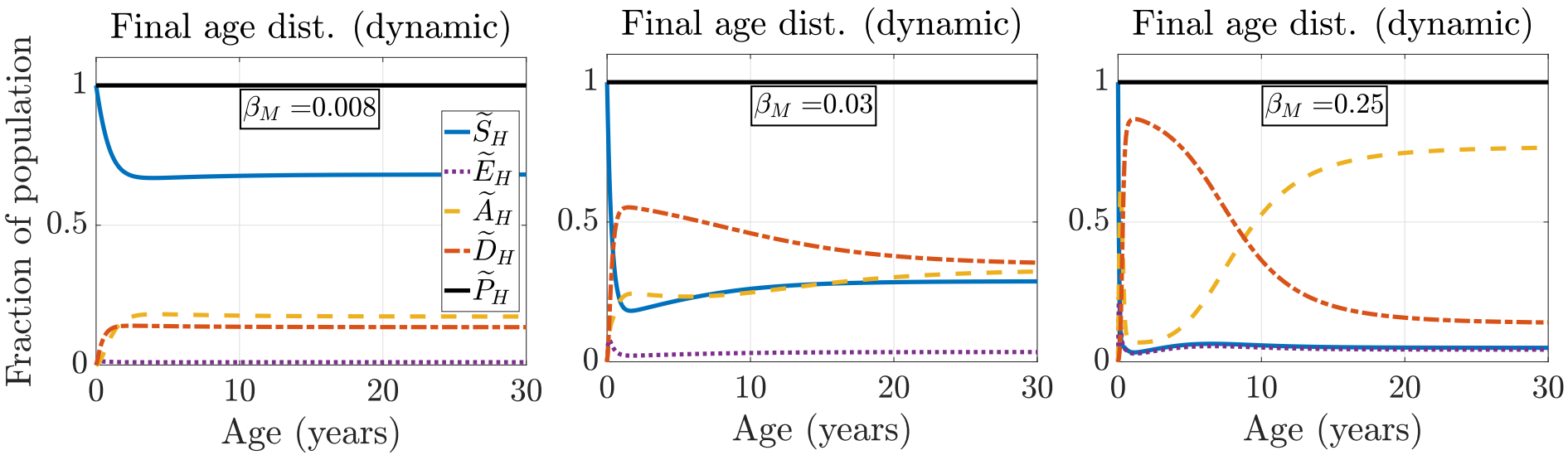
Y-axis - fraction of population: $\widetilde{S}_H(\alpha) = S_H(\alpha)/P_H(\alpha)$ at EE



- fast transition near age zero due to maternal protection
- dynamic immunity creates heterogeneity in the age-distributions
- for fixed immunity, almost homogeneous age-distributions

Immunity feedback onto age-distributions

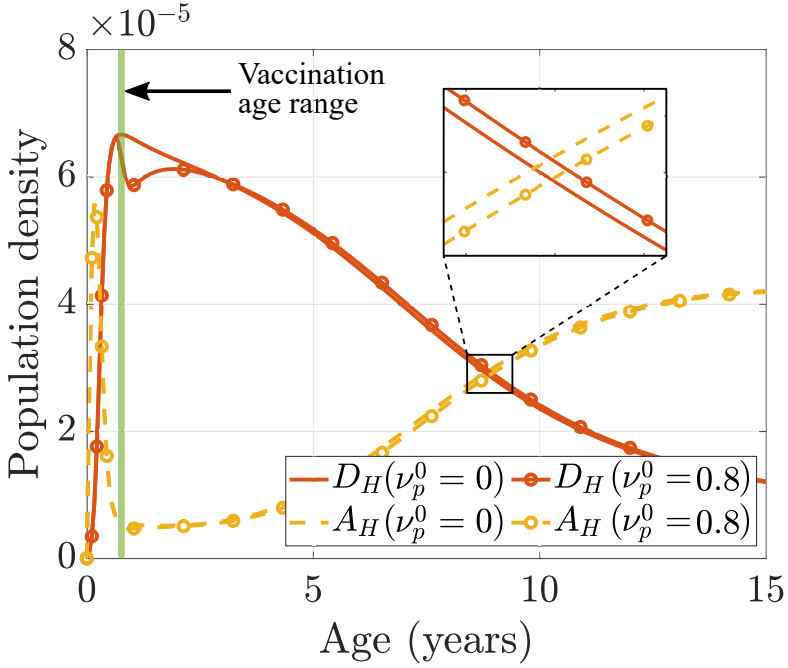
Dynamic immunity with different exposure level

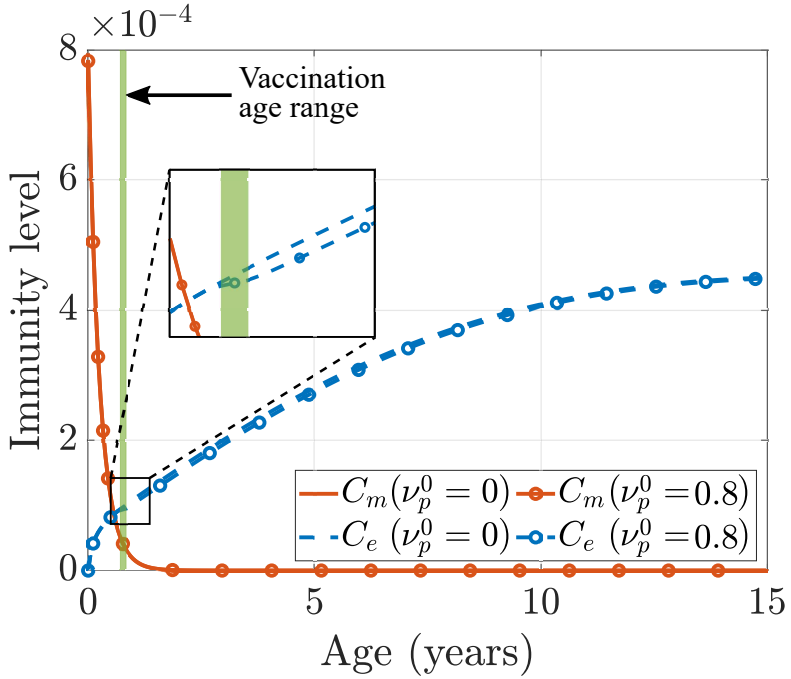


- amount of heterogeneity depends on the exposure level
- low transmission (left): limited boosting in immunity for age < 3
- high transmission (right): more heterogeneity for children < 15

Preliminary simulation of RTS,S vaccination

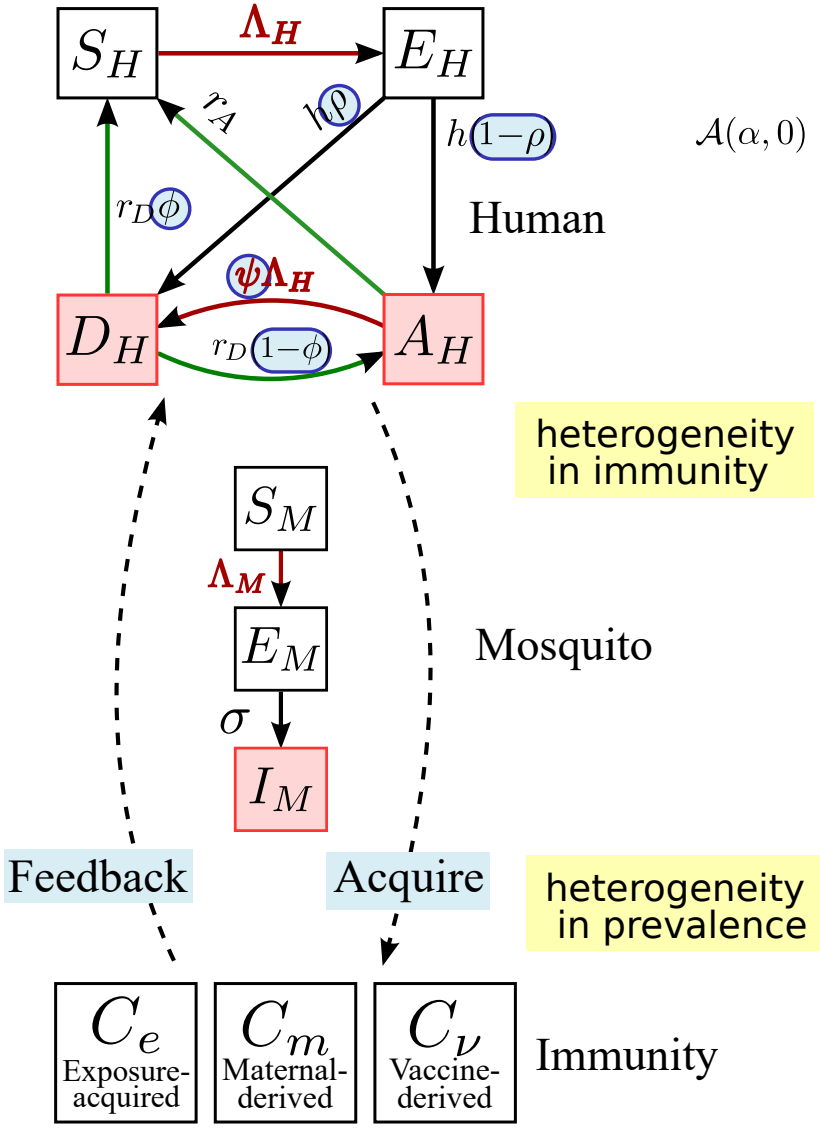
- children complete three doses series around 9 months old
- ν_p^0: daily per-capita vaccination rate





- drop in the D_H, but slightly higher D_H curve when > 3 years old
- reduced exposure delays the development of exposure-acquired immunity

Modeling immunity to malaria with an age-structured PDE Framework



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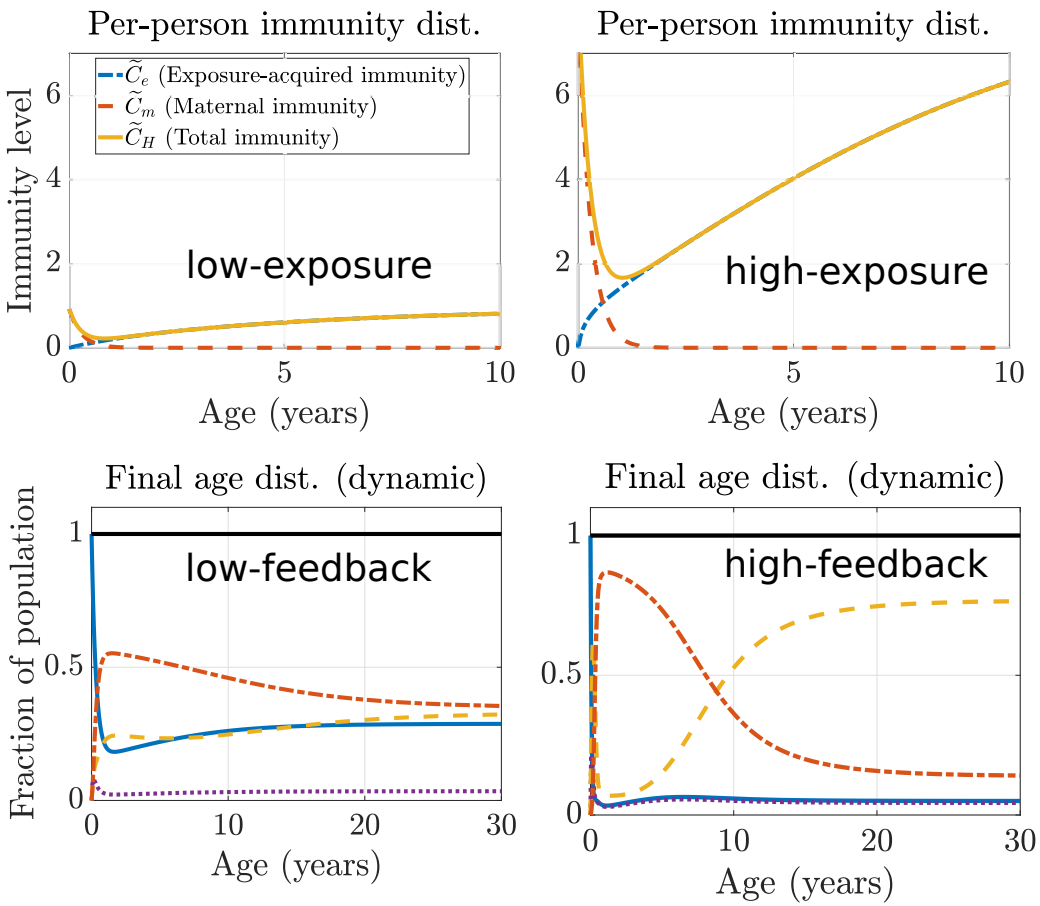

Future work

- model assumptions
  - diseased-induced mortality
  - growing population in sub-Saharan Africa
- vaccination
  - more realistic description of RTS,S vaccine
  - boosting dose, optimal strategy
  - blood-stage vaccine (boosting C_ν rather than protection V_H)
- seasonality
- spatial heterogeneity, human movement

Acknowledgment

- AMS / Mathematics Research Communities - 2021
  "Dynamics of Infectious Diseases: Ecological Models Across Multiple Scales"

Qu Z, Patterson D, Childs L., Edholm C, Ponce J, Prosper O, Zhao L
Modeling Immunity to Malaria with an Age-Structured PDE Framework, arXiv

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Thank you!