Global Antibiotic Resistance Partnership

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Acknowledgements

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- Ramanan Laxminarayan, PI
- Modeling:
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  - David L Smith
    - Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
  - Eili Klein
    - Princeton University

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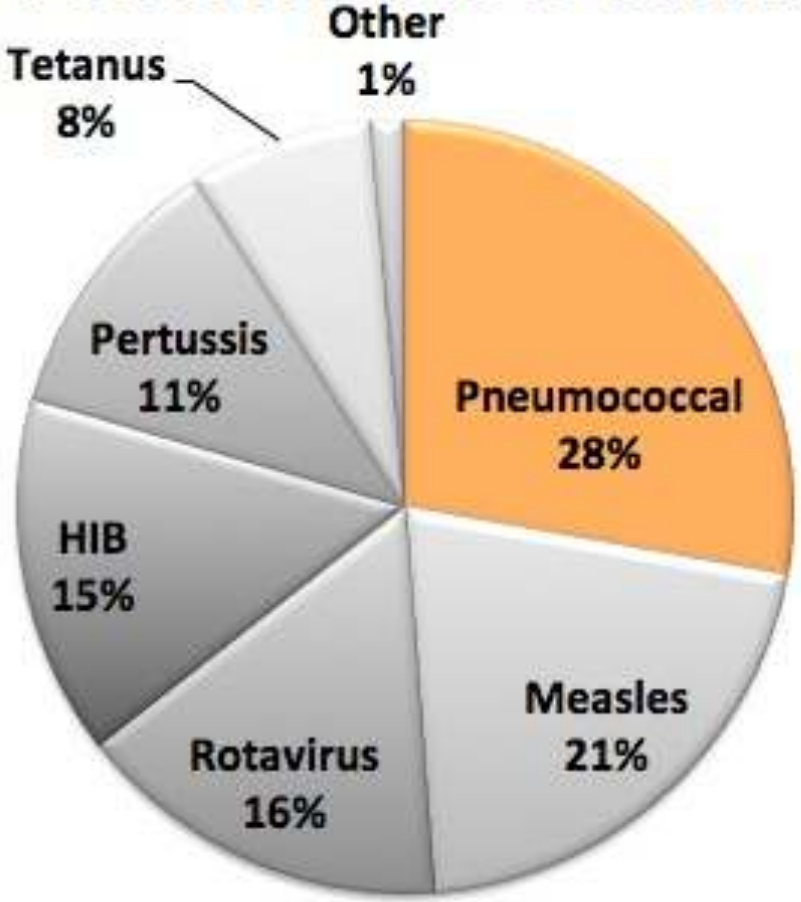
Outline

- **Introduction**
- Pneumococcal Modeling
- PneuMOD

Under-5 Vaccine Preventable Deaths



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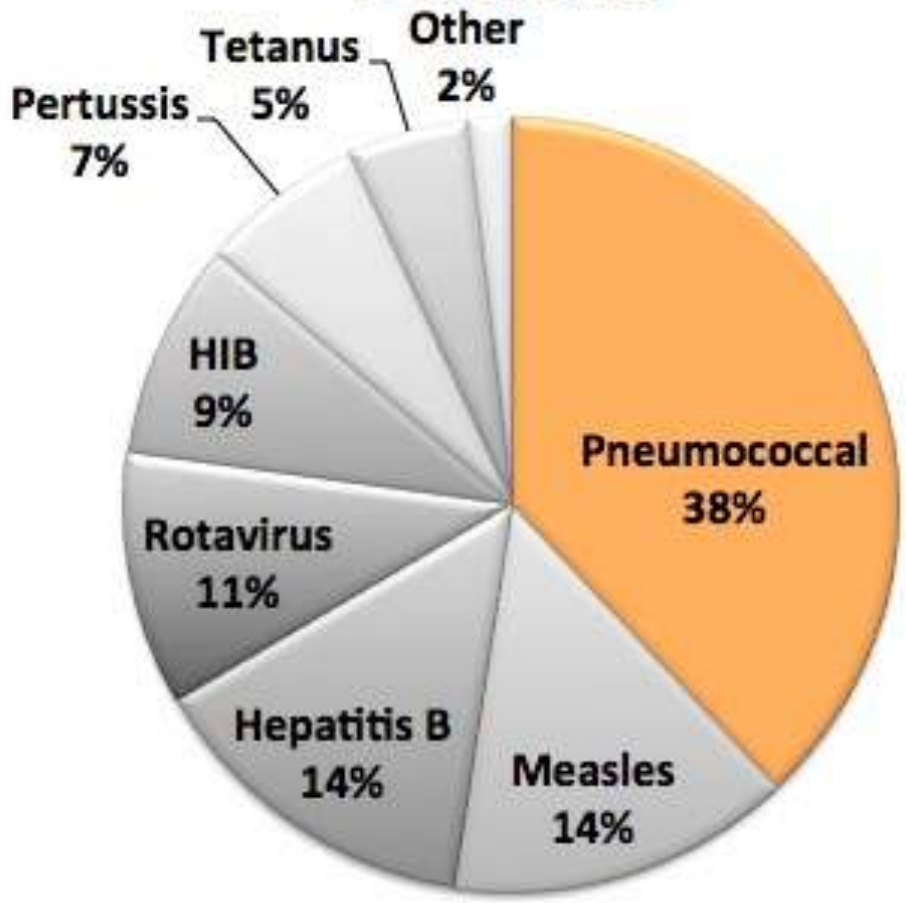
Source: World Health Organization, 2002

Total Vaccine Preventable Deaths



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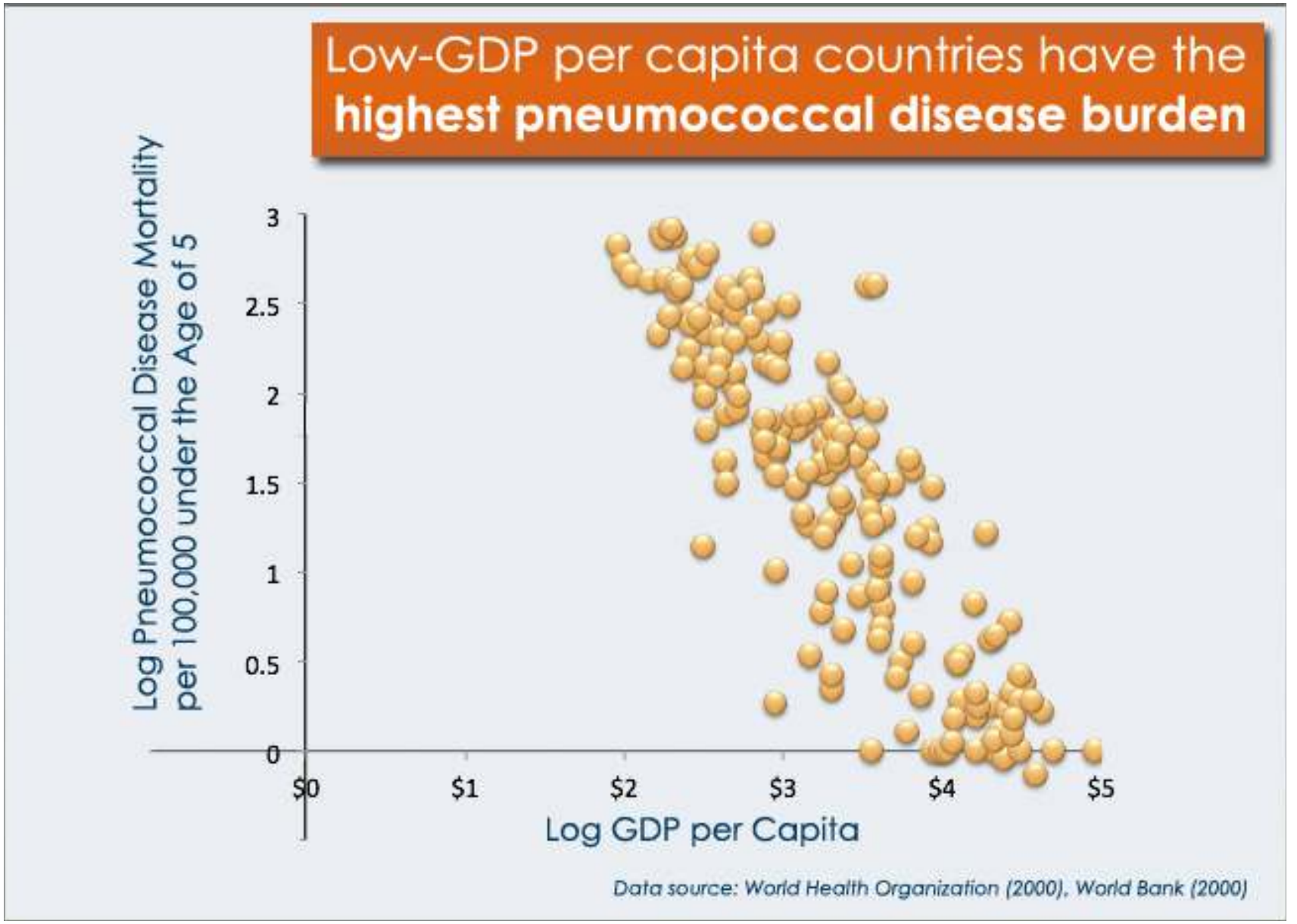
Source: World Health Organization, 2002



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Interventions to prevent & control pneumococcal disease

Prevention

Treatment

Protection

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Policy Questions

- How can we best (most cost-effectively) reduce pneumococcal disease burden through a combination of tools (vaccination, treatment)?
- Can increased treatment access reduce the burden of disease in the long term when drug resistance is likely?
- What is the value of treatment access improvements in countries with pneumo vaccination?
- What population level strategies (like multiple first line treatments or subsidized high quality antibiotics) can most address the challenge of resistance?

Outline

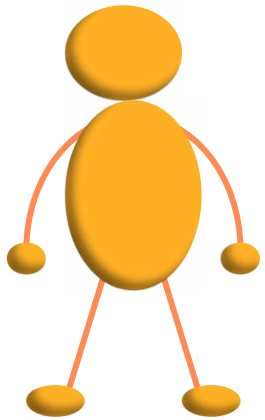
- Introduction
- **Pneumococcal Models**
- PneuMOD

Why model pneumococci?

- How many lives could be saved?
- At what cost?
  - Purchase cost of interventions
  - Opportunity cost
- How certain are the answers?
- How could uncertainty be reduced?

What is a model?

How does a model of pneumococci work?



From Individuals

To Populations

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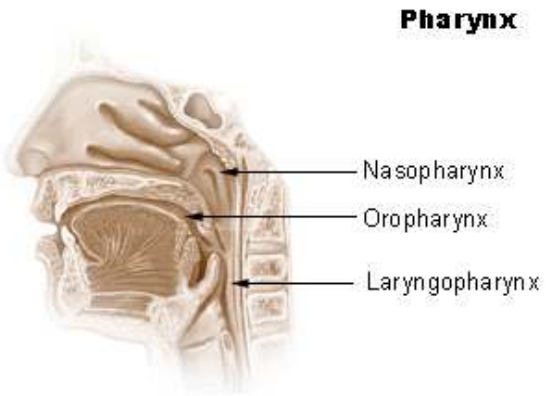
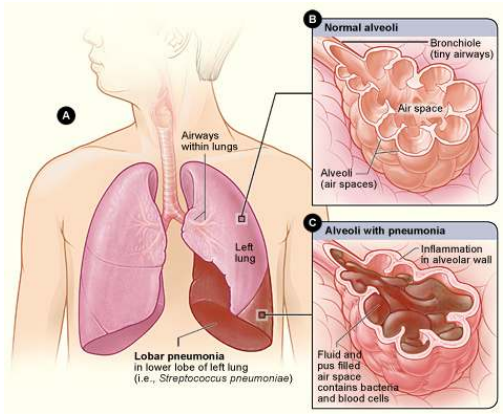
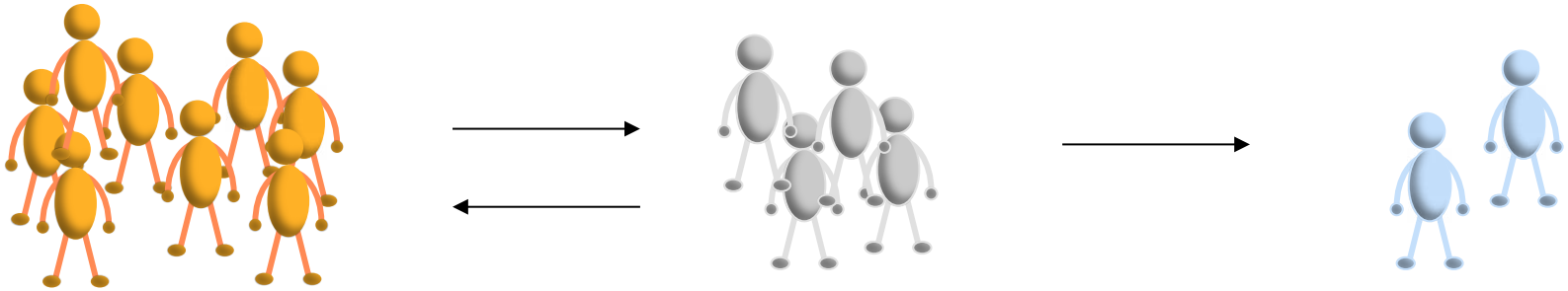
Colonization / Infection







Uncolonized

Colonized

Infected

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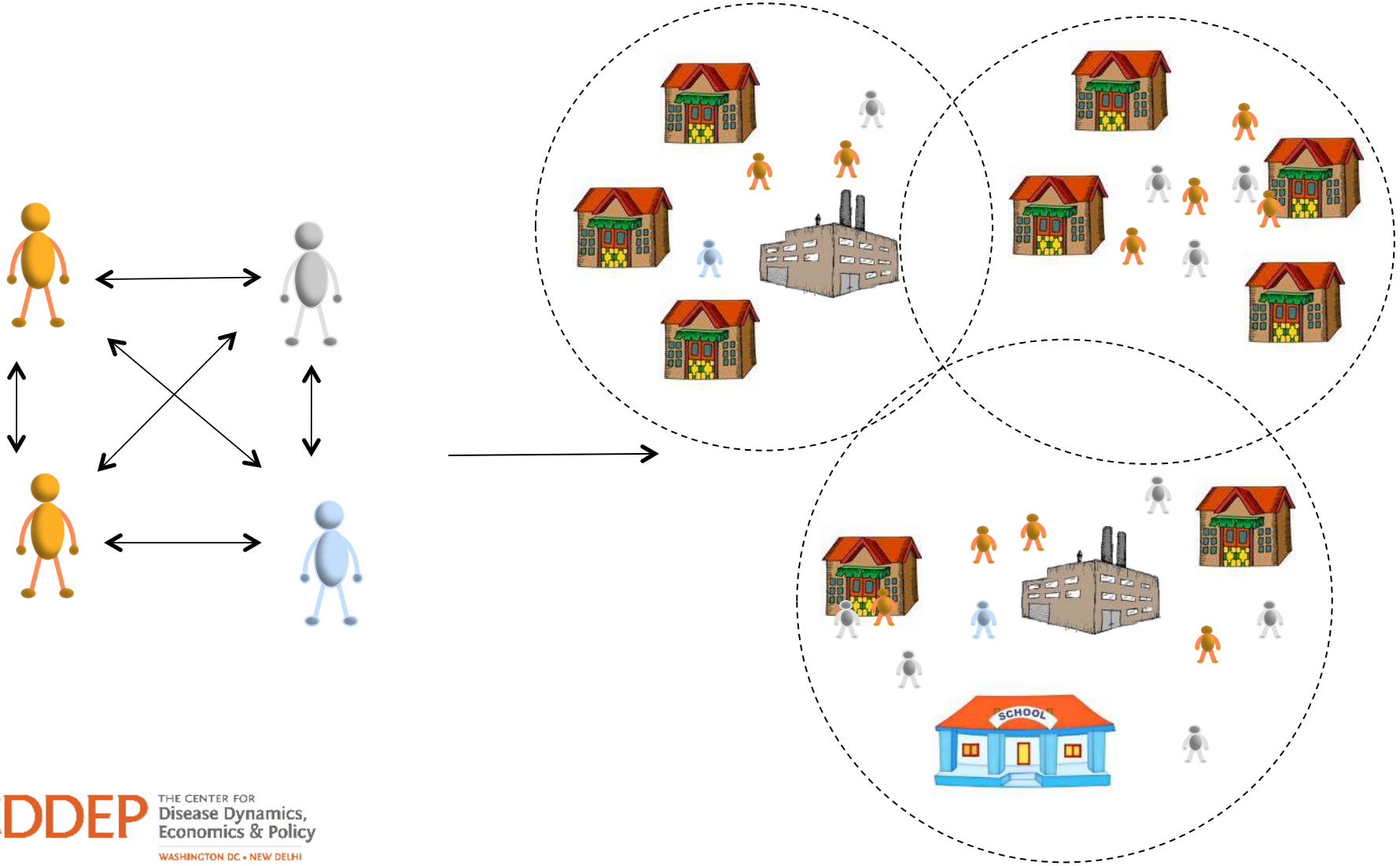
Transmission

Shedding/ Mixing / Exposure



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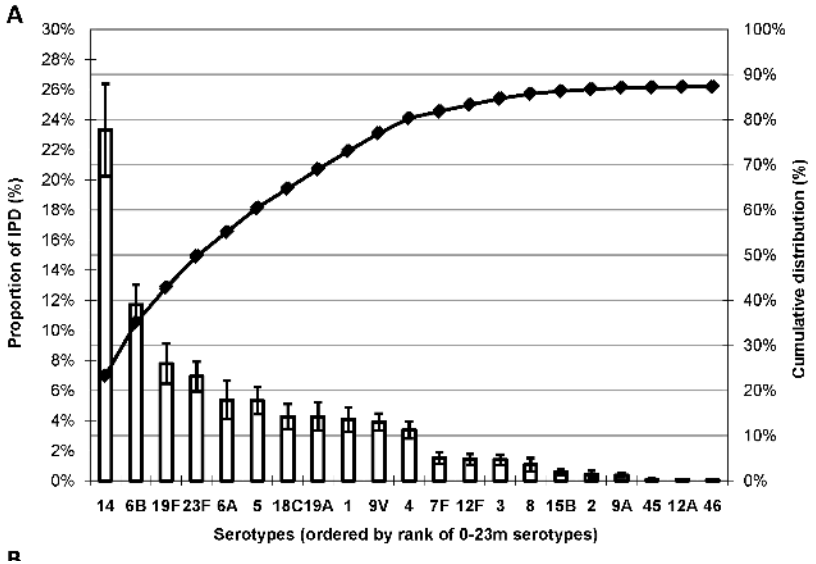
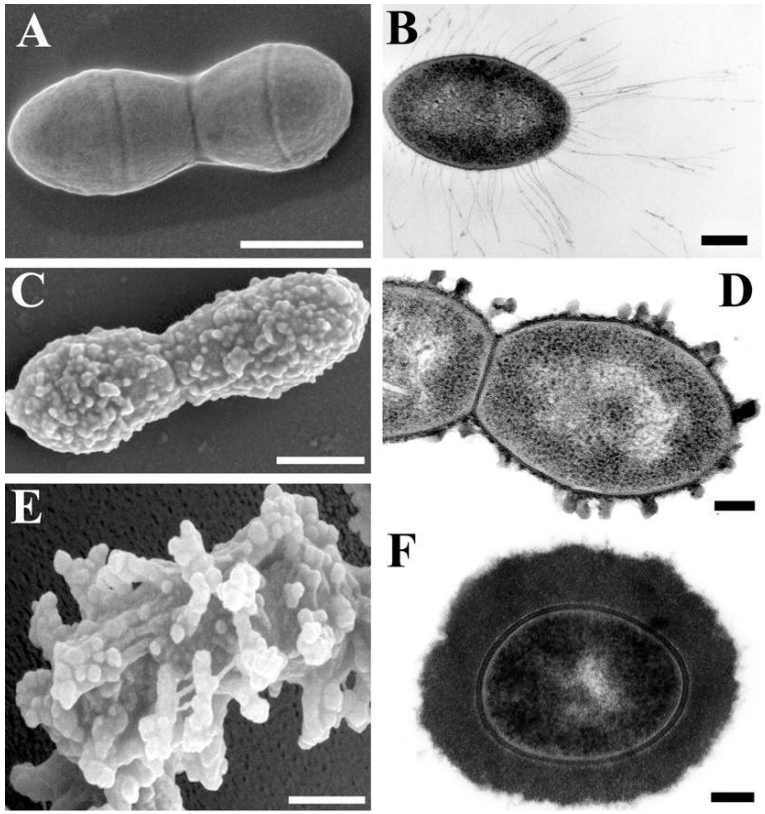
Serotypes

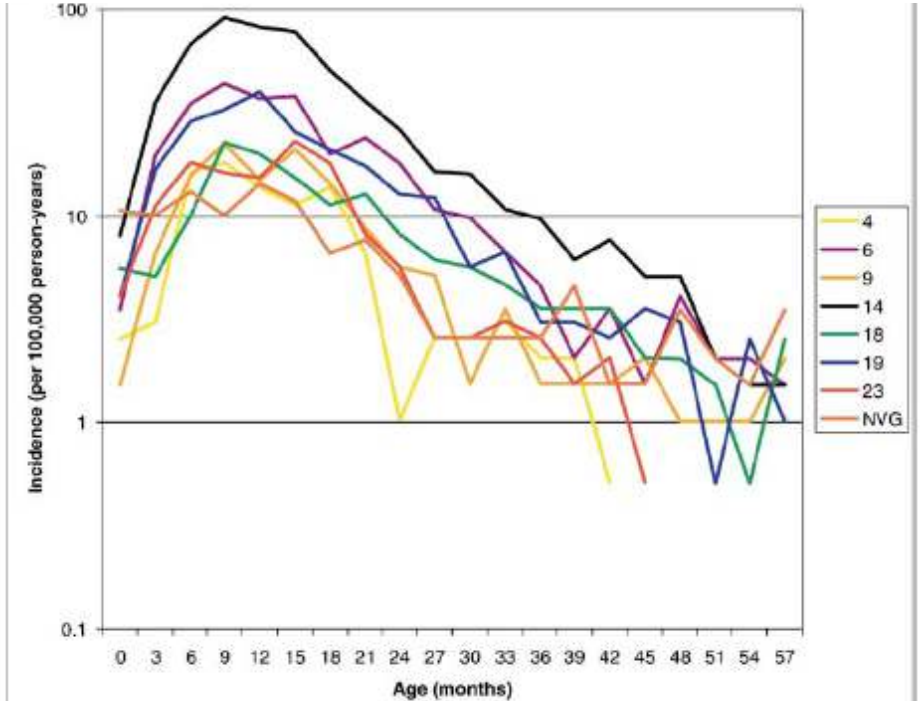




Infection and Immunity, August 2005, p. 4653-4667, Vol. 73, No. 8
0019-9567/05/$08.00+0 doi:10.1128/IAI.73.8.4653-4667.2005

Illustration of Pneumococcal Polysaccharide Capsule during Adherence and Invasion of Epithelial Cells

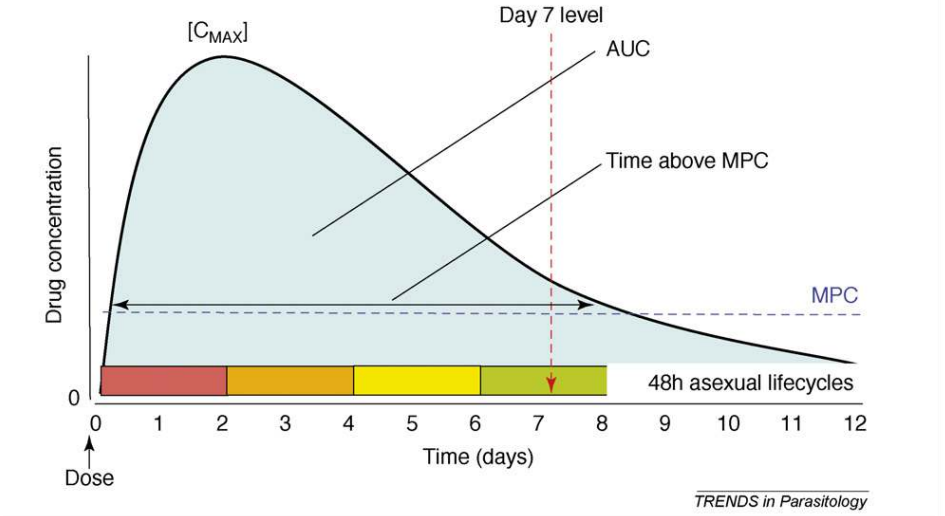
Immunity

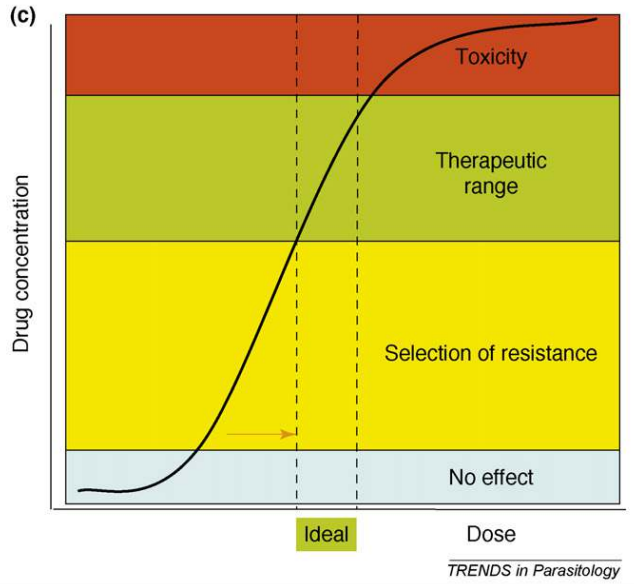


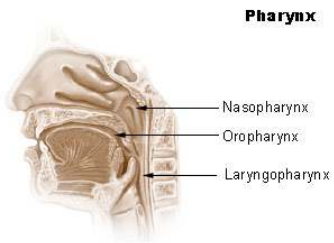
Age-Specific Incidence of Invasive Pneumococcal Disease in the United States by Serogroup

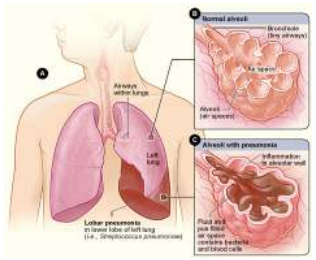
Lipsitch, M. et al. PLoS Med **2**, e15 (2005).

Drug Treatment & Resistance









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Biology, Ecology, Epidemiology, Economics…

- Colonization
  - Duration
- Transmission
  - Shedding
  - Contact
  - Establishment
- Microbial Competition
  - Exclusion
  - Dominance
- Infection
- Immunity
  - Inhibit Colonization
  - Prevent Disease
  - Strain Specificity
- Interventions
  - Drugs
  - Vaccines

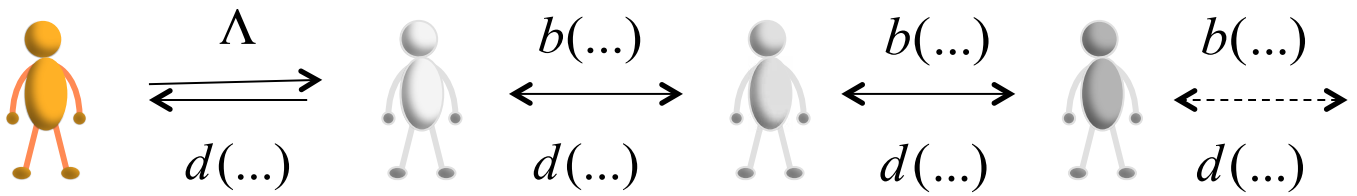
Outline

- Introduction
- Pneumococcal Models
- **PneuMOD**

Markov-Chain Carriage Model

Colonized

Population growth

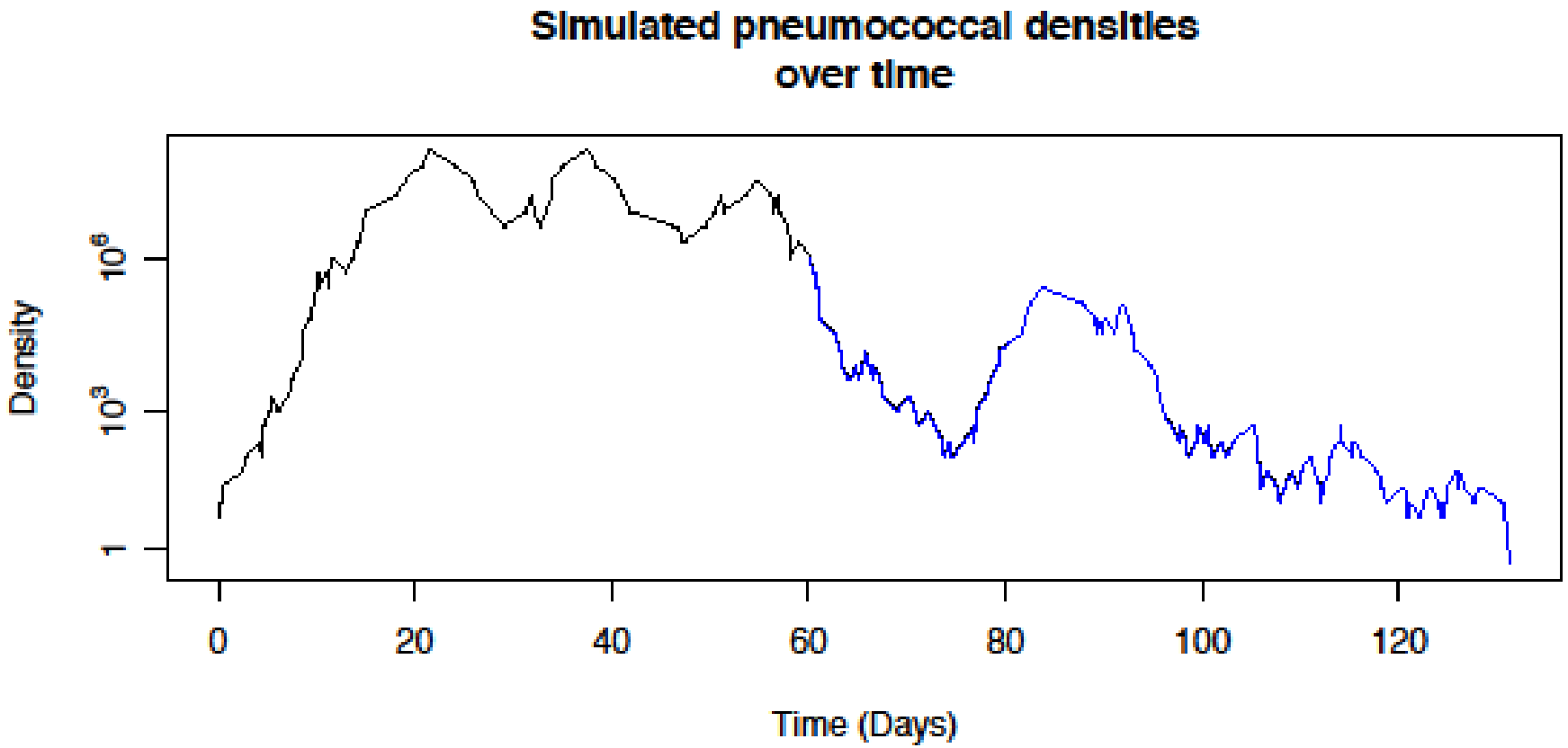


Population decay

Uncolonized

Shedding Increases

Markov-Chain Carriage Model



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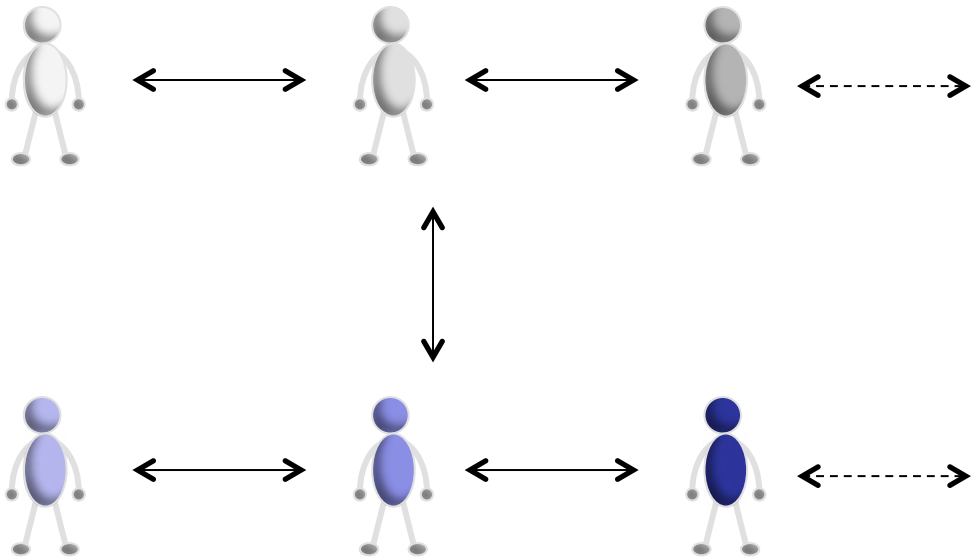
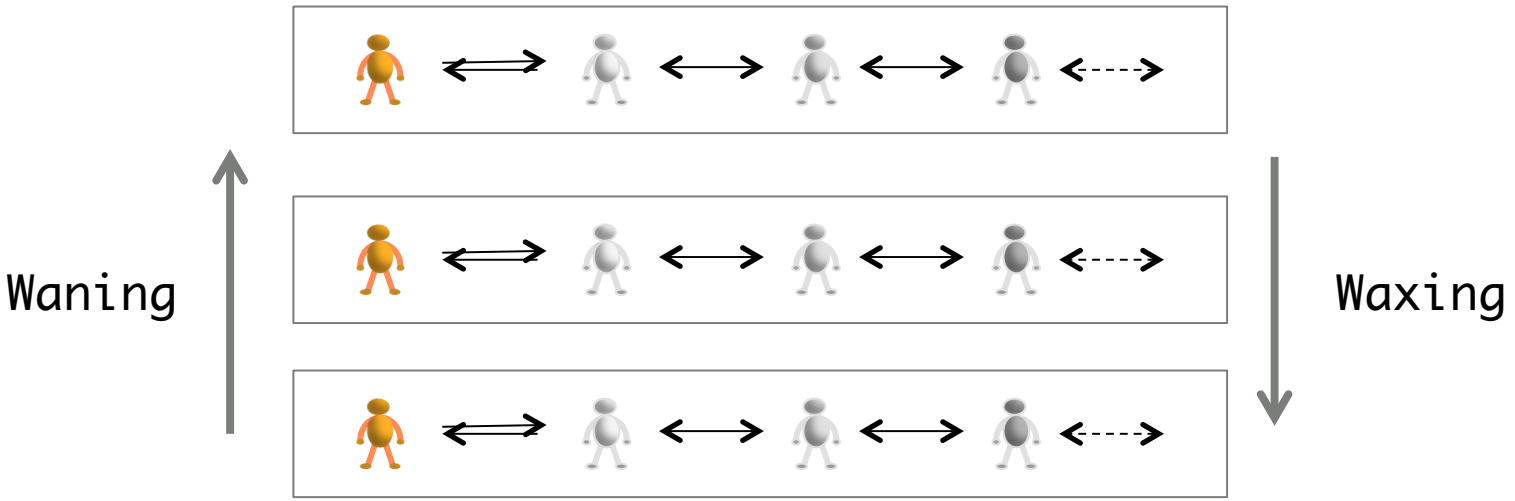
Infection



Increasing Risk

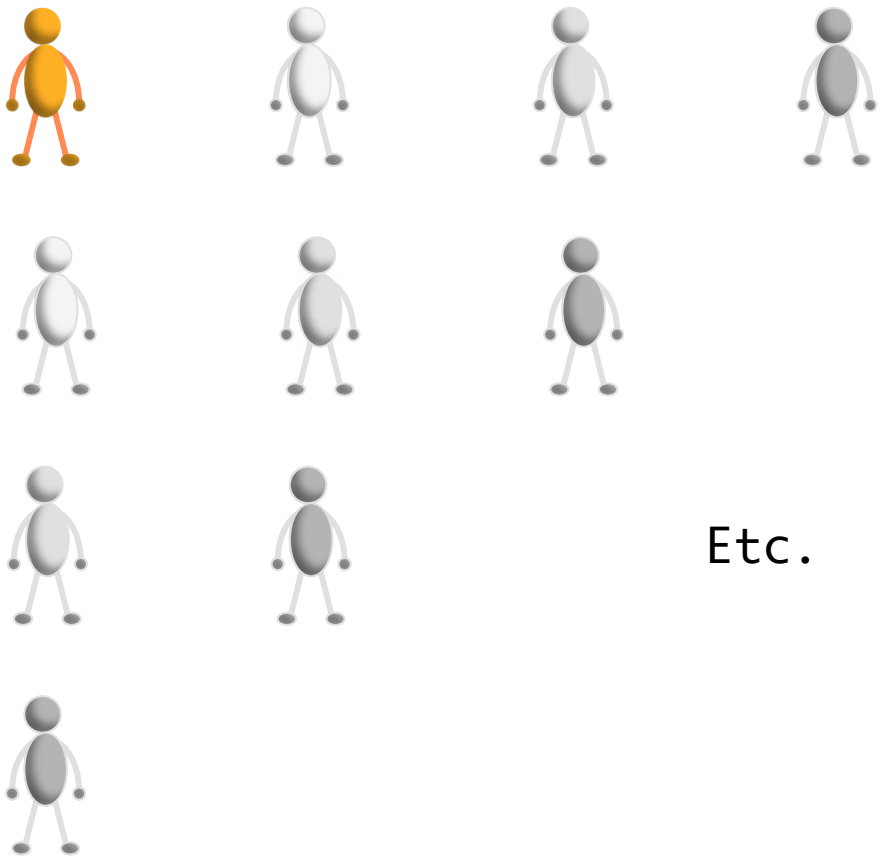
Immune Stages



- ↓ Duration of Carriage
- ↓ Prob. Colonization after Exposure
- ↓ Shedding
- ↓ Risk of Infection
- ↓ Severity of Disease

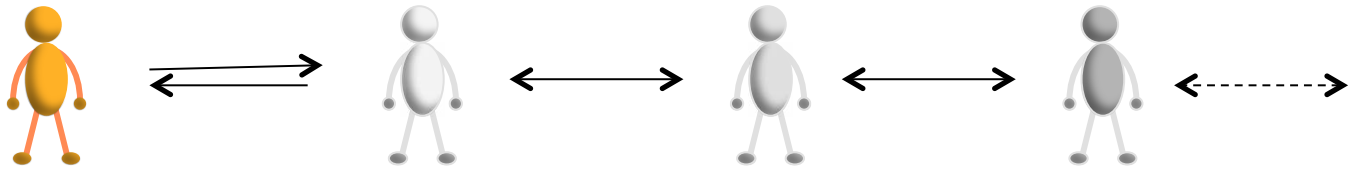
Competition (Serotypes & Strains)

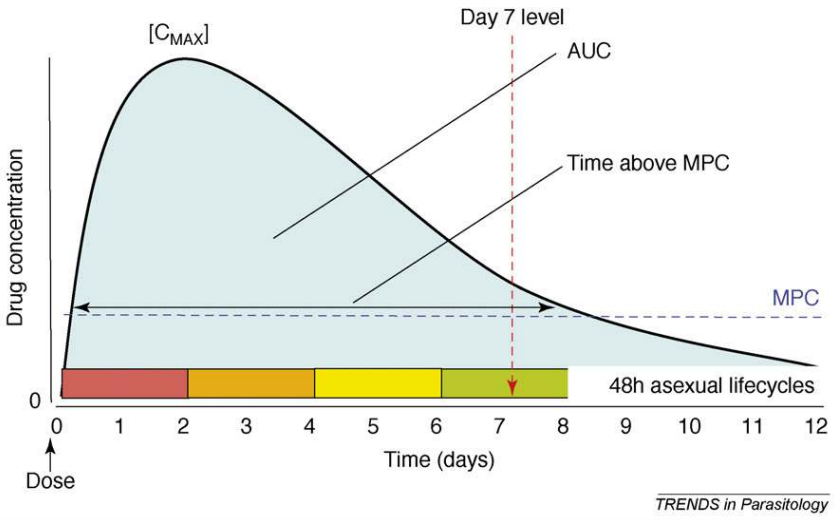
Meets Strong "Neutrality" Conditions

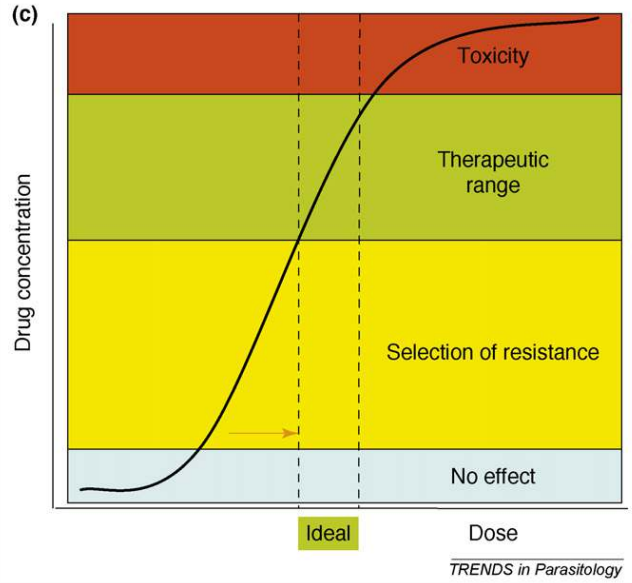


Etc.

Drug Treatment / Compliance







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Ordinary Differential Equations….
…Individual-Based Simulation

With maternal immunity

$$\dot{u}_0 = d_{1,0}\left(x_{1,0} + y_{1,0}\right) - \Lambda u_0 + \mu\left(1 - u_0\right) \overbrace{-mu_0}$$

if $k > 1$ in m.i. case m.i. if $k = 1$

$$\dot{u}_k = d_{1,k}\left(x_{1,k} + y_{1,k}\right) - \omega_k \Lambda u_k - \overbrace{\gamma_k u_k} + \gamma_{k+1} u_{k+1} - \mu_N u_k \overbrace{+mu_0}$$

$$s.t. \quad k \geq 1$$

$$\dot{x}_{i,k} = d_{i+1,k} x_{i+1,k} + b_{i-1,k} x_{i-1,k} - \left(d_{i,k} + b_{i,k}\right) x_{i,k} + \left(\alpha_{i,k} y_{i,k} - \sigma_{i,k} x_{i,k}\right) - \theta_{x,i,k} x_{i,k} + \theta_{x,i,k-1} x_{i,k-1}$$
$$+ c_{i,k} \omega_k \Lambda\left(1 - p_{i,k}\right)\left(u_k + \sum_{w \leq i-2} x_{w,k}\right) + c_{i-1,k} \omega_k \Lambda\left(1 - p_{i-1,k}\right) x_{i-1,k}$$
$$- \omega_k \Lambda \sum_{w \geq i-1} c_{w,k} x_{i,k} - \mu_N x_{i,k} \underbrace{+ \; mx_k}_{-}$$

m.i. $k = 0$ (-) ; $k > 0$ (+)

$$\dot{y}_{i,k} = d_{i+1,k} y_{i+1,k} + b_{i-1,k} y_{i-1,k} - \left(d_{i,k} + b_{i,k}\right) y_{i,k} + \left(\sigma_{i,k} x_{i,k} - \alpha_{i,k} y_{i,k}\right) - \theta_{y,i,k} y_{i,k} + \theta_{y,i,k-1} y_{i,k-1}$$
$$+ c_{i,k} \omega_k \Lambda\left(p_{i,k}\left[u_k + \sum_{w \leq i-1} x_{w,k}\right] + \sum_{w \leq i-1} y_{w,k}\right) + c_{i-1,k} \omega_k \Lambda\left(p_{i-1,k} x_{i-1,k} + y_{i-1,k}\right)$$
$$- \omega_k \Lambda \sum_{w \geq i-1} c_{w,k} y_{i,k} - \left(\mu_N + \mu_I\right) y_{i,k} \underbrace{+ \; mx_k}_{-}$$

m.i. $k = 0$ (-) ; $k > 0$ (+)

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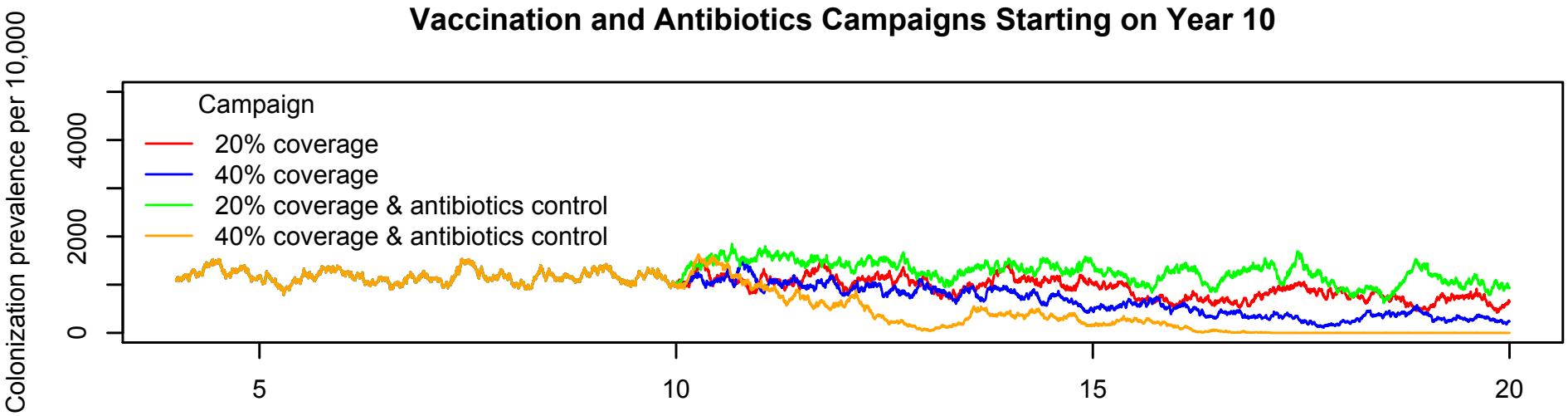
Simulated Vaccination



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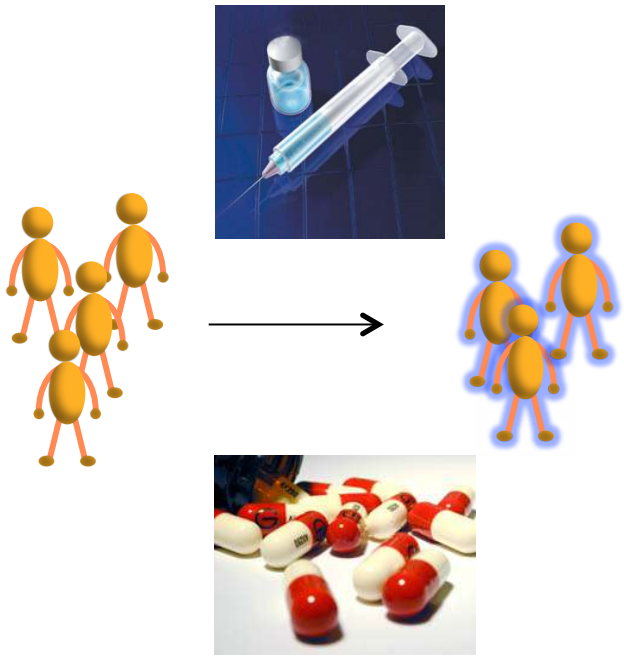
The model produces important policy relevant results

Calibrate model parameters

Run/solve model implementing interventions

Output:

- **Mortality**
- **Infection**
- **Colonization**
- **….**



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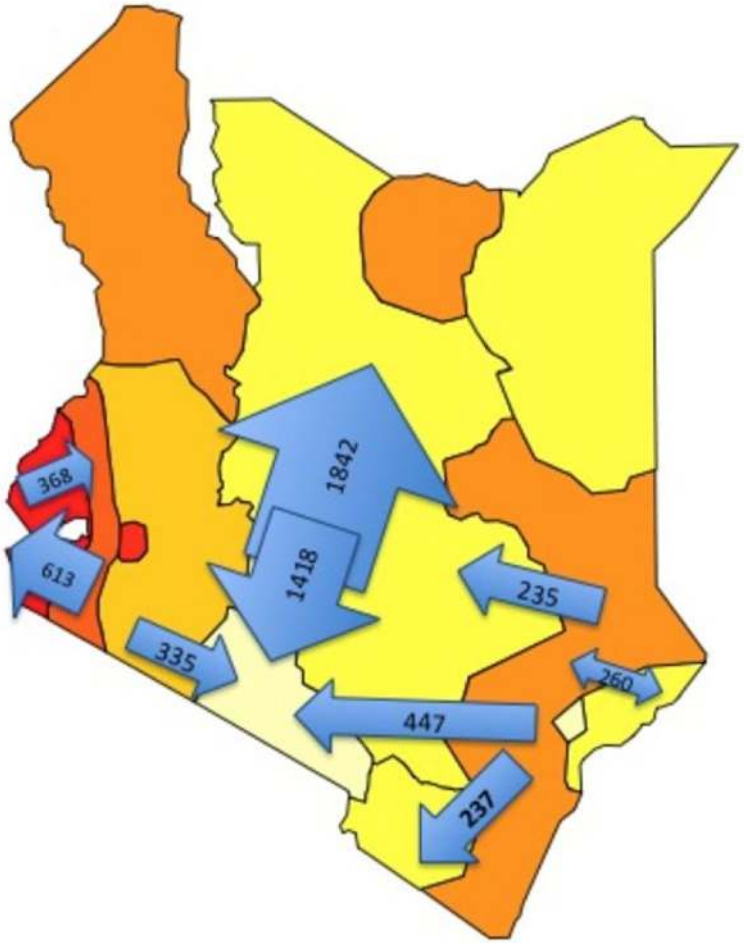
Simulated for Kenya



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Need better data for…

- Duration of carriage
- Complexity of colonies
- Risk of infection
- Competitive dominance
- Immunity
  - Colonization
  - Infection
  - Cross-immunity
  - Age
- Local strains
- Health seeking
- Treatment compliance
- Non-sterile tissue PK/PD
- Underlying populations
- Human mobility

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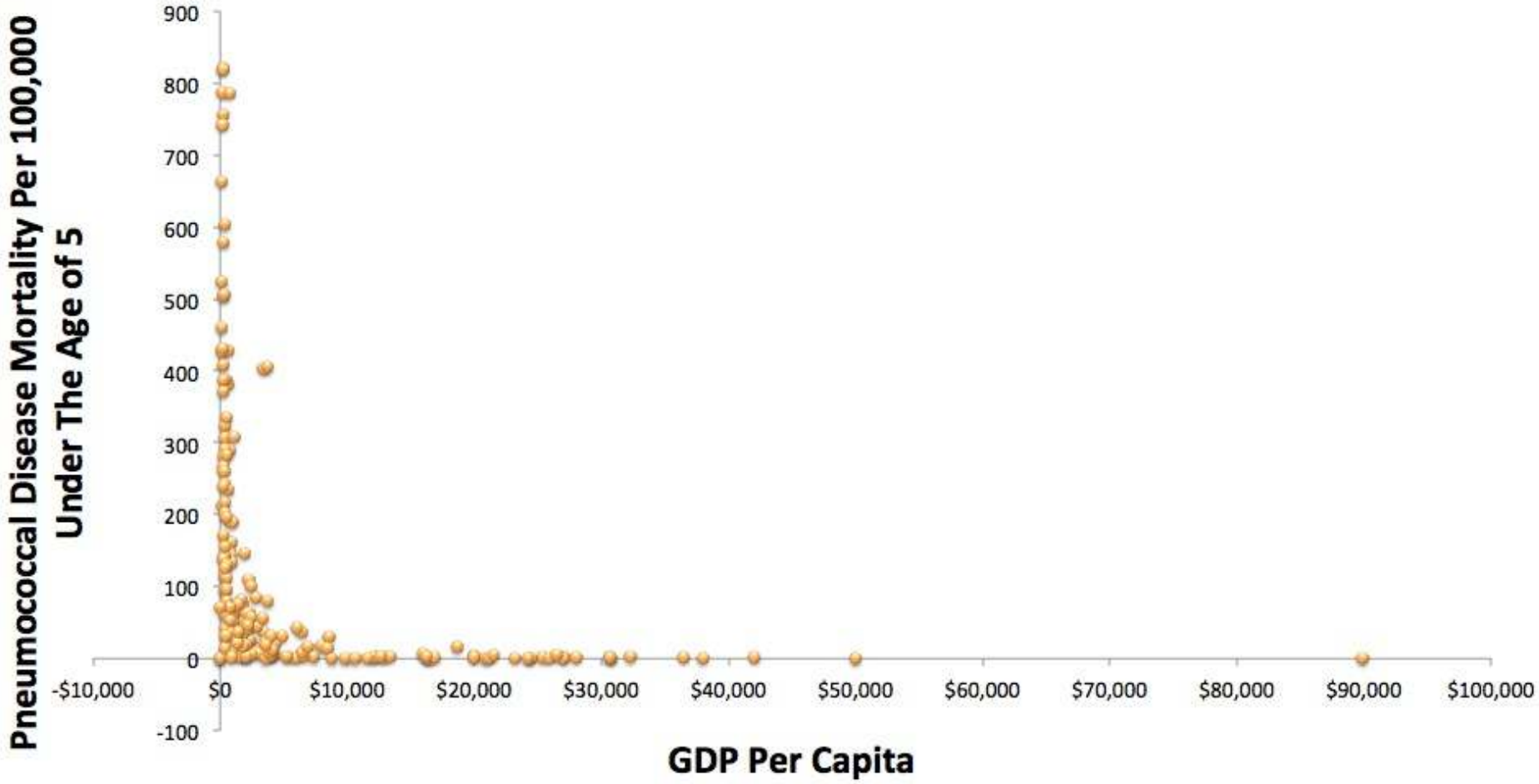
afri pop

Pneumo Carr

Pneumococcal Disease Under-5 Country Burdens



Source: World Bank, 2000; World Health Organization, 2000

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