INFECTIOUS DISEASE MODELING & HIV

Ron Brookmeyer
Dept of Biostatistics
UCLA
SOME QUESTIONS MODELS TRY TO ANSWER

• What is current and future scope of epidemic?

• Under what conditions does an epidemic take off?

• What interventions will reduce transmission and by how much?
HISTORY (early 1900s)

- SIR RONALD ROSS
  Malaria

- LOWELL REED AND WADE HAMPTON FROST
  The Reed Frost Model
  Susceptible, infected, & immune
REPRODUCTIVE NUMBER \( R \)

Average number of new infections that one infectious person produces

At the beginning of an epidemic when nearly all are susceptible its called \( R_0 \)

 Depends on biological, behavioral, social and environmental factors
WHEN DOES AN EPIDEMIC OCCUR?

- $R_0 > 1$
- If $R_0 < 1$, there could still be (small) cluster of cases, but not generally self-sustaining epidemic
REPRODUCTIVE NUMBER $R$

Kate Winslet in the movie *Contagion*
WHAT DOES $R_0$ DEPEND ON\textsuperscript{1}?

TRANSMISSION PROBABILITY PER CONTACT

$\times$

CONTACT RATE

$\times$

DURATION OF INFECTIOUS PERIOD

\textsuperscript{1} basic case: random mixing, no heterogeneity
Figure 4-1. Natural history time lines for infection and disease.
GOAL: REDUCE $R_0 < 1$

- **GENITAL HERPES** $R_0 = 3$
  
  Decrease contact rate by factor of 4
  
  $R_0 = \frac{1}{4} \times 3 = 0.75$

  Vaginal foam
  
  Reduce transmission probability by 80%
  
  $R_0 = 0.2 \times 3 = 0.6$

- **TB** $R_0 = 5$
  
  Active case detection and treatment
  
  Reduce infectious period from 52 weeks to 6
  
  $R_0 = \frac{6}{52} \times 5 = 0.6$
$R$ versus $R_0$

- $R$ changes over the course of an epidemic (in part because the numbers susceptible decreases)

- $R = R_0 \times \text{Proportion susceptible in randomly mixing population}$

- Key to persistence: Continuing supply of susceptibles

- A goal of control measures is to try to reduce $R < 1$
What fraction should be vaccinated?
What fraction should be vaccinated?

• Suppose $R_0=5$ (small pox)

• Suppose $R_0=9$ (measles).

• Suppose the vaccine is not 100% efficacious
Figure 4–4. The fraction, \( f \), of a population needed to be vaccinated with a completely protective vaccine to eliminate transmission as a function of \( R_0 \), the basic reproductive number.
DETERMINISTIC S-I-R MODEL
random mixing

A: Closed population

\[ X \rightarrow \frac{cp}{N}Y \rightarrow Y \rightarrow rZ \]

\[\text{Susceptible} \rightarrow \text{Infection} \rightarrow \text{Infective} \rightarrow \text{Recovery} \rightarrow \text{Immune}\]

B: Open population

\[ X \rightarrow \text{Birth} \rightarrow \frac{cp}{N}Y \rightarrow Y \rightarrow rZ \]

\[\text{Susceptible} \rightarrow \text{Infection} \rightarrow \text{Recovery} \rightarrow \text{Immune}\]

\[ \text{Death} \rightarrow \text{Death} \rightarrow \text{Death} \]
Closed population

- Epidemic begins to decrease when prop susceptible < 1/R₀
- Not all susceptibles need to become infected before microbe dies out
- But ultimately epidemics end, one way or another, in closed populations

Halloran, 2001
KEY TO PERSISTENCE:
Continuing supply of susceptibles

BIRTH
IMMIGRATION
RECOVERY W/O IMMUNITY
WANING IMMUNITY
Closed population

Epidemic, low Ro

Epidemic, high Ro

Open population

Endemic, low Ro

Endemic, high Ro

Number of individuals

Time
HIV/AIDS COMPLEXITIES

TRANSMISSION PROBABILITY

CONTACT RATE

DURATION OF INFECTIOUSNESS
HIV TRANSMISSION PROBABILITY PER ACT

- Asymmetric transmission rates have different dynamics; lowers rate of spread\(^1\) (F→M, M→F)

- Sexual roles among MSM: dual/versatile roles increases spread\(^2\)

- Stage of disease
  - Infectivity varies by stage of disease (e.g. Viral load)

- Co-infection with other pathogens may increase infectivity; e.g. Herpes simplex; genital ulcers

references:
\(^1\) Cassels (2008)
\(^2\) Goodreau (2005)
TRANSMISSION PROBABILITY PER ACT

PREVENTION STRATEGIES:
Circumcision- 40% reduction

Topical microbicide gel (tenofovir)-39% reduction

ART for HIV pos “treat to prevent” -92% reduction

PREP for HIV neg- 44% reduction
(depends on adherence)
DURATION OF INFECTIOUSNESS

Anti-retroviral treatment

- decreases infectiousness (lower viral load)
- extending the duration of infectiousness (life expectancy)
CONTACT RATE

Oversimplification: random mixing with constant contact rate

(HIV) COMPLEXITIES

• Core groups; bridging groups

• Networks

• Migration

• Selective/assortive mixing
e.g., mixing by age; Serosorting
APPROACH: AGENT BASED MODEL

$N$ persons
Interconnected
Social/sexual networks
Stochastic simulation
Computer Intensive
Daily update
NETWORKS OF SEXUAL CONTACTS
COMBINATION HIV PREVENTION MSM IN SOUTH AFRICA

AGENT BASED MODELING
GOALS

• Potential effects of combination prevention? interactions?

• Help design prevention trials
COMBINATION HIV PREVENTION INTERVENTIONS

ART*
PREP*
UAI reduction
HIV testing

*eligible for ART: HIV test and <350CD4
*eligible for PREP: HIV test; >12 UAI in 6 months or main partner who’s infected
INPUTS

Peri-urban South Africa literature review sensitivity
Table 1. Main characteristics of agent based model for combination HIV prevention among MSM in peri-urban South Africa (additional information and specific parameter values are in the Supporting Information)

**Attributes assigned to each person at start**
- Frequency of sexual activity
- HIV status at start
- CD4 count at start if HIV +
- Knowledge of HIV status at start (yes, no)
- Sexual role preference (insertive, receptive, versatile)
- HIV testing frequency (3 levels: moderate, low, never)
- Some assigned a main partner
- Proportion of sexual contacts that are UAI (2 levels)
- Sexual networks of regular partners (allowance for sero-sorting)

**Daily updates**
- Daily sexual contacts depends on type of partnership
  - Likelihood of contact (in decreasing order): main, regular, casual, have other main partners
- HIV testing possible
- UAI rate adjusted if learns knowledge of HIV status
- CD4 levels updated for HIV positive
- Infection status updated

**Prevention Interventions**
- ART for eligible HIV positives
  - Eligible: HIV test within 6 months and CD4<350
  - Considered varying levels of coverage
- PREP for eligible HIV negatives
  - Eligible: in last 6 months had both HIV test and >12 UAI or in sero-discordant main partnership.
  - Considered varying levels of PREP acceptance with two levels of adherence (low and high)
- Reduction in UAI frequency (considered varying levels)
- Increase in HIV testing: convert 50% of the never testers to low frequency testers
# INFECTIONS AVERTED OVER 5 YEARS

Agent based model results

<table>
<thead>
<tr>
<th>Prevention package component</th>
<th>percent infections prevented due to addition of component</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART (50% coverage of newly eligible) [incremental]</td>
<td>3.4</td>
</tr>
<tr>
<td>PREP (50% acceptance)</td>
<td>11.7</td>
</tr>
<tr>
<td>UAI reduction of 15%</td>
<td>21.0</td>
</tr>
<tr>
<td>HIV testing increase</td>
<td>4.9</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>33.9</strong></td>
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</table>
HOW CAN MODELING HELP IN DESIGNING PREVENTION TRIALS?

• EFFECT SIZE

• VARIABILITY
162 data points each refers to a different combination of HIV prevention; with replicates there were 2157 runs of the agent based model.
RECAP

• EPIDEMIC MODELS HAVE A LONG HISTORY

• $R_0$ GOAL: REDUCE $R<1$

• KEY TO PERSISTENCE: CONTINUING SUPPLY OF SUSCEPTIBLES

• COMPLEXITIES:
  HETEROGENEITIES, NETWORKS, ASYMMETRICAL TRANSMISSION PROBABILITY, SELECTIVE MIXING (SEROSORTING)

• AGENT BASED MODELS
  MASSIVE COMPUTER SIMULATIONS

• EVALUATING COMBINATION PREVENTION; DESIGN
REFERENCES


Halloran ME, chapter 27 in *Modern Epidemiology*, Greenland and Rothman


Goodreau S, Sexual Role and Transmission among MSM in Peru, *JID*, 2005