Measuring HIV prevalence and incidence

- rationale

- contrast with risk factor studies

- prevalence
  representative probability samples
  surveys of "sentinel populations"
  back calculation

- incidence
  prospective cohorts
  serial prevalence surveys
  cross-sectional incidence surveys
Reasons to estimate prevalence and incidence

• resource planning

• targeting of interventions

• monitor spread

• provide estimates for mathematical modeling

• estimate proportion with sub-clinical disease
Contrast with risk factor studies

- risk factor studies commonly use convenience samples

- sample risk factor/disease associations assumed representative (no interaction of risk factors with being sampled)

- representativeness often plausible.

- estimating population proportions and totals is trickier.

- even expensive probability samples may not be adequately representative.
Representative probability samples

- enumerate sampling frame
- select subjects with known probability

San Francisco Men’s Health Study (SFMHS)

- probability sample of men 18-54 in 19 high-risk census tracts in SF
- estimated 1985 HIV seroprevalence among MSM: 49.4%
- very expensive sampling
- response rate only 59.1%
Sources of bias

- coverage bias
- assay errors
- under-reporting of risk behaviors
- nonresponse bias
Quantification of nonresponse bias

\[ f = \text{non-response rate} \]

\[ \pi_1 = \text{infection prevalence in responders} \]

\[ \pi_0 = \rho \pi_1 = \text{infection prevalence in non-responders} \]

\[ \rho = \text{relative risk for non-responders} \]

\[ \pi = (1 - f)\pi_1 + f \rho(\pi_1) \]

\[ \pi/\pi_1 = 1 + f(\rho - 1) \]

So \( \pi = \pi_1 \) if \( f = 0 \) or \( \rho = 1 \).
An estimate of nonresponse bias

- New Mexico STI clinic sample
- nonresponse bias estimated using blinded testing of samples for refusers
- anonymous samples categorized by race/ethnicity and sexual orientation

<table>
<thead>
<tr>
<th>group</th>
<th>HIV prevalence (%)</th>
<th>tested</th>
<th>refused</th>
<th>f</th>
<th>ρ</th>
<th>π/π₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>all</td>
<td></td>
<td>1.0</td>
<td>5.4</td>
<td>.18</td>
<td>5.3</td>
<td>1.8</td>
</tr>
<tr>
<td>MSM</td>
<td></td>
<td>5.6</td>
<td>41.0</td>
<td>.16</td>
<td>7.4</td>
<td>2.0</td>
</tr>
<tr>
<td>whites</td>
<td></td>
<td>1.5</td>
<td>4.0</td>
<td>.13</td>
<td>2.7</td>
<td>1.2</td>
</tr>
<tr>
<td>others</td>
<td></td>
<td>.7</td>
<td>6.1</td>
<td>.21</td>
<td>8.8</td>
<td>2.6</td>
</tr>
</tbody>
</table>

- overall nonresponse bias: -43%
Strategies for reducing nonresponse bias

- reduce nonresponse
  - community outreach
  - strict confidentiality or anonymity
  - stipends
  - multiple callbacks

- impute missing responses

- imputation assumes:
  - missingness is "ignorable"
  - model is correctly specified
  - enough data available for stable estimates
National Household Seroprevalence Survey (NHSS)

- aim: evaluate feasibility of estimating total U.S. HIV prevalence using probability sampling

- 1988 Washington, D.C. pilot abandoned after community leaders and public health officials refused cooperation

- in 1988 Pittsburgh pilot, close cooperation was established with community and public health officials

- Pittsburgh response rate: 263 / 308 (85%)

- success led to larger pretest in Dallas
Dallas pretest (1988-9) sample design

- target population: adults 18-54 living in households
- stratified on risk level by geographic area
- oversampling of high and medium risk strata
- post-survey quality assessment study (QAS) of initial non-responders
Dallas pretest results

<table>
<thead>
<tr>
<th>risk stratum</th>
<th>pop %</th>
<th>response rate n/N (%)</th>
<th>HIV+ N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>7.7</td>
<td>391/480 (81)</td>
<td>10 (2.6)</td>
</tr>
<tr>
<td>medium</td>
<td>21.7</td>
<td>546/676 (81)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>low</td>
<td>70.6</td>
<td>437/568 (77)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

pop % = # in stratum as percent of total population; response rate = # responding / # eligible.

- overall response rate among screened households: 80%
- 4% of sampled households refused screening
- weighted prevalence estimate: 0.40%
Quality assessment survey

• QAS was allowed to recontact 175 of 345 initial nonresponders

• half were offered a moderate stipend to answer the questionnaire, and the other half a larger stipend to do that and provide a blood sample

• 64 provided questionnaire only, 23 provided both
Imputation adjustment

- no imputation for women

- zero imputed prevalence for men without risk factors

- probability of infection was imputed, given risk behavior category, for 36 men with questionnaire but no blood sample

- imputation based on logistic model (n = 86 men, including 12 HIV+, with at least one risk behavior)

- risk behavior category imputed for 91 "ultimate non-responders"

- this imputation used a 2nd logistic model (n = 754 men with questionnaires)

- then probability of infection imputed, given imputed risk behavior category
## Imputation results

<table>
<thead>
<tr>
<th>risk behavior</th>
<th>HIV prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS</td>
<td>#MP</td>
</tr>
<tr>
<td>yes</td>
<td>10+</td>
</tr>
<tr>
<td>yes</td>
<td>5-9</td>
</tr>
<tr>
<td>yes</td>
<td>5-9</td>
</tr>
<tr>
<td>yes</td>
<td>1-4</td>
</tr>
<tr>
<td>no</td>
<td>10+</td>
</tr>
<tr>
<td>no</td>
<td>1-4</td>
</tr>
<tr>
<td>no</td>
<td>1-4</td>
</tr>
<tr>
<td>no</td>
<td>0</td>
</tr>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>

| overall | 0.5 | 0.2 | 1.5 |

RAS - receptive anal sex

#MP - number male partners

IR - initial responders

QASR - QAS responders

UNR - ultimate non-responders
Dallas seroprevalence estimates

- weighted prevalence rate: 0.40%
- fully adjusted prevalence rate: 0.42%
- estimated HIV prevalence:
  4,047 (2,200 - 7,500)
Reasons to doubt adjustment

- nonresponders may have had higher risk behavior than predicted by the model

- logistic model for HIV positivity was estimated with only 86 observations and 12 events

- infection rates lower among QAS responders providing blood than among initial responders

- \( \rho \) (estimated relative risk for ultimate non-responders) only 3.1, substantially lower than in New Mexico study (5.3)

- back calculation "plausible range" for Dallas: 7,500-14,600

- 1 in 58 AIDS cases had been reported from Dallas, but 58 x 4047 = 234,700 infections is much lower than all other national estimates
Sensitivity analysis

• in the large low-risk stratum (71% of population), no observed infections consistent with low but positive seroprevalence

• $\rho$ for Dallas pretest seems too low

• varying low-risk stratum seroprevalence and $\rho$ gives larger estimates of prevalence

<table>
<thead>
<tr>
<th>$\pi_{lr}$ (%)</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>3780</td>
<td>4547</td>
<td>6848</td>
<td>10685</td>
</tr>
<tr>
<td>0.1</td>
<td>4457</td>
<td>5362</td>
<td>8076</td>
<td>12600</td>
</tr>
<tr>
<td>0.2</td>
<td>5125</td>
<td>6166</td>
<td>9287</td>
<td>14489</td>
</tr>
</tbody>
</table>
NHSS summary

- imputation adjustment requires strong assumptions
- survey may provide a lower bound on true prevalence
- nonresponse bias may vary over time
- probably not cost effective; national survey was not carried out
CDC surveys of "sentinel" populations

- mostly blinded anonymous testing of routinely collected blood samples
- some demographic and risk behavior available
- data collection, sample testing, and analysis are standardized
- nonresponse bias is avoided, but "deferral" bias is a possibility
**Sentinel survey populations**

<table>
<thead>
<tr>
<th>survey site</th>
<th>seroprevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median</td>
</tr>
<tr>
<td>STI clinics</td>
<td></td>
</tr>
<tr>
<td>homosexual men</td>
<td>3.2</td>
</tr>
<tr>
<td>men w/o other risk</td>
<td>1.1</td>
</tr>
<tr>
<td>women w/o other risk</td>
<td>0.7</td>
</tr>
<tr>
<td>drug treatment centers</td>
<td>3.9</td>
</tr>
<tr>
<td>women’s health clinics</td>
<td>0.2</td>
</tr>
<tr>
<td>neonatal screening</td>
<td>0.07</td>
</tr>
<tr>
<td>hospital inpatients</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Also:  
- Native Americans  
- Job Corps entrants  
- university students  
- prisoners  
- homeless persons  
- applicants for military service  
- blood donors  
- outpatients
Usefulness of sentinel surveys

- monitoring trends in prevalence
- targeting
- ante-natal and STI clinic surveys primary measure in sub-Saharan Africa

Possible weaknesses

- sites not randomly selected
- unknown selection or deferral biases
- some trends and comparisons valid provided biases are constant
- in Africa, biases are probably small compared to severity of epidemic
"Components" estimate of US prevalence

- population is exhaustively stratified (on risk group, age, sex, and/or area)

- $N_i$, the size of stratum $i$, as well as $p_i$, its infection prevalence are estimated

- then estimated national prevalence is

$$\hat{n} = \sum_i \hat{N}_i \hat{p}_i$$

- 1986 CDC estimate of US prevalence: 1-1.5 million
Possible weaknesses

- size of risk groups is difficult to estimate
- representativeness (prevalence not homogeneous within risk groups)
- selection bias
- prevalence estimates highly variable
Estimating incidence of infection:

- harder to estimate than prevalence
- new infections in prospective cohorts
- sequential cross-sectional prevalence surveys in birth cohort
- newer methods for detecting new infections in cross-sectional surveys
Prospective cohorts

- incidence estimated using person-time methods, nonparametric methods for interval- and right-censored data

Possible weaknesses

- frailty selection
- differential loss to follow-up
- "cohort" effects
- representativeness of cohort
Sequential cross-sectional surveys of a birth cohort

- incidence is estimated by increases in prevalence
- estimate based on military applicants: 40,000 new HIV infections per year

Possible weaknesses

- sampling variability
- immigration, emigration, deaths
- bias is assumed constant
- representativeness
- sentinel surveys unsuitable
Direct measures of incidence in cross-sectional surveys

- detect markers of early infection

- p24 antigen is detectable for 2-3 weeks before seroconversion

- requires high incidence (>= 5%) and very large survey

- antibody test "detuned" to give negative results for 15 to 21 weeks after seroconversion on fully sensitive assay

- positives on fully sensitive test are retested with less sensitive assay

- new infections are negative on less sensitive assay

- (most) established infections positive on both
Prevalence and incidence

- prevalence of "detuners" (those with discrepant test results) estimated using a cross-sectional sample; samples positive on both tests removed from denominator

- duration of early period with discrepant test results estimated from serial measurements on seroconverting plasma donors

- duration of interval "doubly censored" and hard to estimate

- information combined to estimate incidence rates:

  - incidence = prevalence / duration
Performance of sensitive / less sensitive assay

- good specificity with established HIV infection

<table>
<thead>
<tr>
<th>group</th>
<th>false positive rate (%)</th>
<th>OD = .75</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-AIDS</td>
<td>0.4</td>
<td>0.0-1.9</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>2.4</td>
<td>1.4-10.1</td>
<td></td>
</tr>
</tbody>
</table>

- precision is not great

<table>
<thead>
<tr>
<th>true HIV incidence (%)</th>
<th>95% CI width (%)</th>
<th>required sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3-3.0</td>
<td>3000</td>
</tr>
<tr>
<td>5</td>
<td>2.5-10.0</td>
<td>1400</td>
</tr>
</tbody>
</table>
Usefulness

- estimation of population incidence rates
- identification of incident cases for studies of early infection, contact tracing
- strategy generalizable to other infections?

Possible weaknesses

- representativeness of samples
- not very efficient
SFDPH Update

- Probability sample of MSM using RDD
  - 30% of sampled households include MSM
  - 70% response rate among eligibles
  - mail-in urine samples for HIV testing
  - positives retested to detect recent infections

- "venue-based" quasi-probability sampling
  - useful for hard-to-reach populations (IDUs, sex workers, MSM)
  - venues enumerated and selected with known probability
  - participant selection probability estimated using questionnaire

- sentinel surveys using detuned assay