Sources of repeat *Chlamydia trachomatis* infections:

The importance of different sex partners revealed by a behavioral and molecular epidemiologic approach

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Public health importance of chlamydia

- Chlamydia is common.

Figure 1. Chlamydia—Rates: Total and by sex: United States, 1989–2008

1,210,523 cases

NOTE: As of January 2000, all 50 states and the District of Columbia had regulations requiring the reporting of chlamydia cases.

Public health importance of chlamydia

❖ Chlamydia is common.

Figure 11. Chlamydia—Trends in positivity among 15- to 24-year-old women tested in family planning clinics by HHS region, 2004–2008


Public health importance of chlamydia

❖ Chlamydia has adverse health outcomes.

Genital chlamydia infections in women

- Tubal scarring
- Infection of infants
- Increased susceptibility to HIV
- PID
- Pneumonia
- Conjunctivitis
- Infertility
- Chronic pelvic pain
- Ectopic pregnancy
Public health importance of chlamydia

- Chlamydia disproportionately affects young women.

![Figure 5. Chlamydia—Age- and sex-specific rates: United States, 2008](image)


Repeat chlamydia infections are also common

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>POPULATION</th>
<th>REPEAT CHLAMYDIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whittington (2001)</td>
<td>Young women seeking health care in 5 US cities (n=1,194)</td>
<td>7% at 4 months</td>
</tr>
<tr>
<td>Golden (2005)</td>
<td>Men and women in treatment RCT in WA (n=2,751)</td>
<td>13% at 19 weeks (control arm)</td>
</tr>
<tr>
<td>Fortenberry (1999)</td>
<td>Adolescent females seeking care in IN (n=490)</td>
<td>18% within 6 months</td>
</tr>
<tr>
<td>Blythe (1992)</td>
<td>Adolescent females receiving GYN care in IN (n=1,308)</td>
<td>38% within mean 9.7 months</td>
</tr>
<tr>
<td>LaMontagne (2005)</td>
<td>Women age 16-24 in UK (n=592)</td>
<td>24% per year</td>
</tr>
<tr>
<td>Hills (1994)</td>
<td>Retrospective analysis of case report data in WI</td>
<td>7% - 14% within 12 months</td>
</tr>
<tr>
<td>Niccolai (2007)</td>
<td>Adolescent women in CT (n=411)</td>
<td>57% within mean 4.7 years</td>
</tr>
<tr>
<td>Hosenfeld (2009)</td>
<td>Systematic review of literature (38 studies)</td>
<td>13.9% (~20% within 10 months)</td>
</tr>
</tbody>
</table>
Public health importance of repeat infections

- More closely linked to adverse health outcomes
- “Core transmitters” may be important for maintaining prevalence in the population
- May be increasing

Sources of repeat infections?

- **Source 1:** Inadequately treated same partner
- **Source 2:** Adequately treated but non-monogamous same partner
- **Source 3:** Different partner
**Previous research**

- Often reported that inadequate partner treatment may be the major source of repeat infections
  - “...suggest that re-infection may be predominantly a result of sexual contact with untreated or inadequately treated partners.”
  - “…suggest infection…resulted from re-infection from untreated sex partners…”, “New infection was likely due to resumption of sex with untreated partners…”
  - “…suggesting that the source of the initial infection may also have been the source of the repeat infection.”, “…likely because of re-exposure to untreated partners.”


**Our research question**

- Can we empirically quantify the relative contributions of untreated sex partners and different sex partners to repeat chlamydia infections?
  - Recognizing the importance of multiple partners
  - Recognizing the importance of sexual networks
Why this is important:
Implications for partner treatment, prevention, and retesting

- Untreated partners
  - Alternative partner treatment strategies

- New partners
  - Condom use
  - Reducing number of sex partners
  - Reducing concurrency, increasing “gap length” in sex partnerships

- Non-monogamous partner
  - Condom use
  - Risk perception in sex partnerships

Behavioral and molecular epidemiology of repeat infections

- Objective
  - To determine sources and predictors of repeat chlamydia infections

- Hypotheses
  - Sources of repeat infections are more equally distributed among the range of possible sources than currently recognized.
  - Molecular genotyping of chlamydia bacteria will increase our ability to differentiate between different sources of repeat infections.
**Methods**

- **Design:** Cohort study (baseline, 4m)
- **Population:** Women age 15 or older diagnosed with chlamydia
- **Setting:** Two reproductive health centers in Connecticut
- **Recruitment:** Providers and brochures
- **Data collection:** Jan 2005 – August 2008
- **Reimbursement:** $30 at each study visit

**Data collection - Interview**

- Audio computer assisted survey interview (A-CASI)
- Approximately 60 minutes to complete
- Demographic, sexual histories, sexual risk behaviors, diagnosis
- Partner modules asked about last 3 sex partners in past 3 months
- Follow-up: post-treatment behaviors and changes in partnerships
Molecular epidemiology of *C. trachomatis*

- Major outer membrane protein of *C. trachomatis* bacteria is encoded by the *omp1* gene
- Divides *C. trachomatis* into 18 genotypes
  - 10 genotypes (D-K, Da, Ia) cause urogenital chlamydia infections
- A different genotype at initial and repeat infections would indicate a new source of infection.

Genotyping methods

- Urine or self-obtained vaginal swab
- Isolate genomic DNA
- Amplify *omp1* gene using an initial PCR
- Send PCR product for sequencing
Analysis

- Rate and predictors of repeat infections
  - Multivariate logistic regression \[ \frac{\text{Risk}_e}{\text{Risk}_u} \]

- Sources of repeat infections
  - Frequencies of untreated, new, non-monogamous
  - Population attributable risk percents \[ \frac{(\text{Risk}_{e+u} - \text{Risk}_u)}{\text{Risk}_{e+u}} \]
    - Absolute measure of association
    - Proportion of disease in population that can be attributed to an exposure
    - Public health impact

Results: Recruitment

- 323 screened
- 237 (73%) enrolled
- 183 (77%) followed
Baseline characteristics (n=183)

<table>
<thead>
<tr>
<th>Age (mean ± st. dev., range)</th>
<th>20.0 ± 4.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>56%</td>
</tr>
<tr>
<td>Latina</td>
<td>24%</td>
</tr>
<tr>
<td>White</td>
<td>15%</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
</tr>
<tr>
<td>Age at first intercourse (mean ± st. dev.)</td>
<td>15.5 ± 2.1</td>
</tr>
<tr>
<td>Median number of lifetime sex partners</td>
<td>5</td>
</tr>
<tr>
<td>Number of sex partners in past 3 months</td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>66%</td>
</tr>
<tr>
<td>&gt;1</td>
<td>34%</td>
</tr>
<tr>
<td>Previous STI</td>
<td>43%</td>
</tr>
</tbody>
</table>

Post-diagnosis behaviors

- Sexual activity: 84%
- Sex without a condom: 39%
- Untreated partner: 21%
- New partner: 37%
- Non-monogamous partner: 33%
Repeat chlamydia infections

323 screened
237 (73%) enrolled
183 (77%) followed
24 (13%) repeat chlamydia

Predictors of repeat infection
Relative risks from logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 15-19 years</td>
<td>3.2 (1.2 – 8.1)</td>
<td>3.2 (1.2 – 8.3)</td>
</tr>
<tr>
<td>First intercourse &lt;15 years</td>
<td>2.1 (0.8 – 5.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Untreated sex partner</td>
<td>3.3 (1.4 – 8.3)</td>
<td>3.4 (1.3 – 8.6)</td>
</tr>
<tr>
<td>New sex partner</td>
<td>1.8 (0.8 – 4.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Variables examined but not significant: race/ethnicity, lifetime number of partners, recent number sex partners, previous STI, reason for clinic visit, sexual activity during follow-up, sex without a condom during follow-up, non-monogamous partner
Population attributable risk percents
Public health impact

- **Untreated partners**: 26% (95% CI: 3% - 49%)
  - Interpretation: 26% of repeat infections are due to continued sex with an untreated partner

- **New sex partners**: 21% (95% CI: 0% - 50%)
  - Interpretation: 21% of repeat infections are due to new sex partners

- Non-monogamous partners: not estimated

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Distribution of genotypes

![Genotype Distribution Chart]

Legend:
- **Baseline (n=60 samples)**
- **Follow-up (n=24 samples)**
Genotyping data

323 screened

237 (73%) enrolled

183 (77%) followed – 60 genotypes

24 (13%) repeat chlamydia – 24 genotypes

8 had both

5 of 8 (63%) had different genotype

<table>
<thead>
<tr>
<th>Baseline/Follow-up genotypes</th>
<th>Untreated partner</th>
<th>New partner</th>
<th>Non-partner monogamous</th>
<th>Possible sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/E</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>la/la</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>E/E</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>J/K</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>J/E</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>E/J</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>D/E</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>I/E</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- High frequency of repeat infections (13%)
- Continued sex with untreated partners important risk factor (RR=3.4)
- Different sex partner sources (other than untreated sex partners) may contribute substantially to the burden of repeat infections as evidenced by:
  - Frequencies (higher for new and non-monogamous partners)
  - PAR% (~equivalent for untreated and new partners)
  - Genotyping (majority of different type at repeat)

Potential limitations

- Small sample size
  - Especially for genotyping
- Treatment failures
  - Could account for 3% - 8% of repeat infections
- Selection bias
- Self-report
Implications for expedited partner therapy

- EPT is an important public health approach
  - Established efficacy
  - Included in treatment guidelines

- Lack of effectiveness in some studies may be due to different partner sources
  - Future studies should account for this in design
  - Maybe include genotyping

- Necessary but not sufficient

Implications for prevention

- Condoms
  - Initiate and maintain
  - Couple with testing in new partnerships

- Numbers of sex partners

- Risk perception and communication in partnerships

- Social and sexual networks
Implications for retesting

- Remains an important public health priority
- Retesting rates remain low in many settings\(^1\)
  - 43% Job Corp
  - 15% - 38% in STD clinics
  - 21% - 25% in California FP clinics

1. As reviewed by Park et al. JWH 2010.

Future work

- Research
  - Confirm these findings with larger sample size, different population

- Prevention
  - Intervention studies
  - Public health and clinical practice
**Acknowledgments**

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