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Chlamydia and Gonorrhoea Re-infection among Males: A Systematic Review of Data to Evaluate the Need for Re-testing

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ABSTRACT

Objective: To systematically review and describe the evidence on chlamydia (CT) and gonorrhoea (GC) re-infection among males, and to evaluate the need for re-testing recommendations in men.

Methods: We searched PubMed and STI conference abstract books from January, 1995 to October, 2006 to identify studies on CT and GC re-infection among males using CT and GC nucleic acid amplification tests or GC culture. Studies were categorized as using either active or passive follow-up methods. We calculated proportions of male CT and GC re-infection for each study and reported summary medians.

Results: Repeat CT among males had a median re-infection probability of 11.3%. Repeat GC among men had a median re-infection probability of 7.0%. Studies with active follow-up had moderate rates of CT and GC re-infection among men, with respective medians of 10.9% and 7.0%. Studies with passive follow-up had higher proportions of both CT and GC re-infections among men with respective medians of 17.4% and 8.5%. Proportions of CT and GC re-infection among men were comparable to those among women. Re-infection among men was strongly associated with previous STD history and younger age while inconsistently associated with risky sexual behavior.

Conclusions: We found substantial repeat CT and GC in men comparable to rates in women. Re-testing recommendations in men are appropriate given the high rate of re-infection. To optimize re-testing guidelines, we suggest further research to determine effective re-testing methods and establish factors associated with re-infection among males.

INTRODUCTION

Chlamydia and gonorrhea are the two most common bacterial sexually transmitted infections (STIs) in the United States with 929,462 (319.6 per 100,000 population) and 330,132 (113.5 per 100,000 population) respective reported cases in the United States and District of Columbia during the year 2004.¹ Serious complications associated with chlamydia and gonorrhea include chronic pelvic pain, infertility, ectopic pregnancy, and pelvic inflammatory disease (PID) in women, as well as proctitis and epididymitis in men.²⁻⁶ While the treatment efficacy of first-line drugs for both chlamydia and gonorrhea infection is high,^{2,3,7-11} the problem of re-infection remains.^{2,3,12}

The prevalence of recurrent chlamydial infection is especially well documented in young and unmarried women, ranging between 6%-23% within 6 months of treatment.¹³⁻¹⁹ As a result, the 2002 United States Centers for Disease Control and Prevention (CDC) Treatment Guidelines recommended that all women with chlamydial infection be tested for re-infection – different from test of cure - at 3-4 months after treatment.²⁰ While some local health departments recommend re-testing men for STIs, there are no established national re-testing guidelines for either gonococcal infection in women or chlamydial or gonococcal infection in men, in part due to the limited data available for guideline development.

In the United States, there has been a 46.6% increase in reported cases of chlamydia in men from 1999 through 2004,¹ likely as a result of increased screening and diagnoses of chlamydial infections with the advent of highly sensitive and non-invasive nucleic acid amplification tests (NAATs). Although incident chlamydia tends to be higher in women,¹ some recent studies have found that the prevalence of chlamydial infection in young men is comparable to that of young women at 7-15%.²¹⁻²⁷

Focusing screening and treatment only on women will not effectively reduce the overall prevalence of both chlamydia and gonorrhea in the United States because their male partners might remain infected.^{2,3,25,28} Given that untreated male partners are a likely source of re-infection in women following treatment and that men exhibit high rates of asymptomatic infections, it is important to evaluate the need for extending screening guidelines for chlamydial and gonococcal re-infection to men as a means of reducing recurrent chlamydial and gonococcal infection in both men and women. Although several studies implementing expedited partner treatment (EPT) have demonstrated significant decrease in re-infection of females, a considerable proportion of re-infection occurred despite treating existing partners.^{29,30} Thus re-testing males might be another important prevention strategy.

Older literature from the 1970's and 1980's has examined the role of re-testing in reducing morbidity from gonorrhea re-infection during those decades.³¹⁻³⁴ However, there exists no recent compilation of the literature about gonococcal re-infection in men and no review has been published to date about chlamydial re-infection in men. We systematically reviewed and described the current evidence of recurrent chlamydial and gonococcal infection in men, focusing on studies using the most sensitive and specific tests. Our results might be useful in developing re-testing guidelines for men.

METHODS

We searched for published or presented scientific literature regarding chlamydial and gonococcal infection, re-infection, re-testing and screening recommendations for men. In the National Center for Biotechnology Information PubMed, we used combinations of search terms including “repeat gonorrhoea chlamydia,” “recurrent gonorrhoea chlamydia,” “repeat gonorrhoea,” “repeat chlamydia,” “persistent gonorrhoea,” “persistent chlamydia,” “rescreening gonorrhoea,” “rescreening chlamydia,” “retesting gonorrhoea” and “retesting chlamydia” to find literature published between January, 1995 and October, 2006. Literature from previous decades was excluded because of differences between current and past disease trends. We searched scientific abstracts from United States and International STI conferences from January 2000 through August 2006. For relevant conference abstracts, actual posters and/or presentations were reviewed to facilitate data abstraction. To maximize the search, we examined articles of persons known to be involved in chlamydia and gonorrhoea research and searched the bibliographies of relevant papers. Finally, we contacted 8 authors of relevant articles to acquire any unpublished data.

All studies included men and reported chlamydia, gonorrhoea, or chlamydia and gonorrhoea combined data as well as gender-specific data. Included studies also had a follow-up period starting at least 2 weeks after treatment of initial infection and used nucleic acid amplification tests (NAATs) for chlamydia and NAATs or culture for gonorrhoea in order to ensure consistent sensitivity and specificity of test results. There is a significant difference in test performance of chlamydia NAATs and of older chlamydia tests,^{2,35} but little difference between gonorrhoea NAATs and gonorrhoea culture.^{2,36,37} However, studies varied in whether there were age restrictions for their participants or restrictions by gender of partners. Several studies were excluded for not including gender-specific data,³⁸ not restricting to laboratory confirmed CT and/or GC at baseline,³⁹ and not including organism-specific data.⁴⁰⁻⁴²

Studies were classified on the basis of follow-up method: active follow-up as in a prospective cohort study design versus passive follow-up through disease or clinic registries. To standardize reported measures, we calculated the overall proportion of re-infected individuals and define it as the number of re-infected individuals per followed-up enrollees. Data abstracted from studies were summarized in tables. We report the median as the measure of central tendency to account for the variation in studies, but also report the range. We plotted estimates of proportions of re-infection by study.

RESULTS

Our initial search of PubMed returned 71 articles for “repeat gonorrhoea chlamydia,” 19 articles for “recurrent gonorrhoea chlamydia,” 53 articles for “repeat gonorrhoea,” 108 articles for “repeat chlamydia,” 51 articles for “persistent gonorrhoea,” 417 articles for “persistent chlamydia,” 5 articles for “rescreening gonorrhoea,” 9 articles for “rescreening chlamydia,” 6 articles for “retesting gonorrhoea,” and 31 articles for “retesting chlamydia.” Numerous duplicates were found among the various search terms.

Of these, 12 published articles tested men and met our inclusion criteria of having a follow-up period and using NAATs for chlamydia testing, but NAAT or culture for gonorrhea testing.²⁹ In addition, one presentation and one poster from national and international STI conferences met our inclusion criteria.^{54,55} Reviewed studies were published or presented between 2000 and 2006 with data collected from the year 1992 to 2004. Tables 1 and 2 provide a select summary of the 14 reports.^{29,43-55}

Of the 14 studies, 5 investigated both chlamydial and gonococcal re-infections, 4 studied only chlamydial re-infection, and 3 studied only gonococcal re-infection. The proportion of males with repeat chlamydia ranged from 9.8%⁴³ to 18.3%⁵¹ with a median of 11.3% (Fig. 1). The proportion of males with repeat gonorrhea ranged from 0%^{46,54} to 30.8%⁴⁴ with a median of 7.0% (Fig. 2).

Follow-up periods for the studies with active follow-up ranged from 10 weeks⁴⁶ to 24 weeks⁴⁷ with a median of 4 months. In contrast, the studies with passive follow-up allowed for repeat infection definitions up to a maximum of 4.8 years⁵⁰ from initial infection. The studies with active follow-up had moderate proportions of repeat chlamydia and gonorrhea among males, with respective medians of 10.9% and 7.0%. Follow-up rates to obtain these estimates ranged from 24.3%⁴⁴ to 83.3%^{43,47} with a median of 62.4%. The studies with passive follow-up had higher proportions of both chlamydia and gonorrhea re-infection among males with respective medians of 17.4% and 8.5%. The follow-up rate of the studies using passive follow-up was indeterminable.

In the studies accounting for infection in both sexes, the proportions of repeat chlamydia and gonorrhea among males were comparable to those among women. The proportions of chlamydial re-infection among males was only slightly less,^{29,43,47,49,51} and in two studies, higher,^{46,54} than those among women. A study in three major US cities with active follow-up by a scheduled 3 month STD clinic visit found a repeat chlamydia proportion among men of 9.8% comparable to that among women at 10.7%.⁴³ A study with passive follow-up found a similar trend with a chlamydia re-infection proportion among men at 18.3% only slightly lower than among women at 23.2%.⁵¹

The proportions of repeat gonorrhea among males were either nearly equal²⁹ or slightly above those among women.^{44,48,50} A study with active follow-up by scheduled clinic visit or disease investigation specialist found a repeat gonorrhea proportion among men at 30.8% to be slightly higher than that among women at 28.9%.⁴⁴ Similarly, a passive study found gonorrhea re-infection among males at 5.0% to be greater than that among women at 4.1%.⁴⁸

Some studies only presented combined chlamydial or gonococcal re-infection data. In these studies, combined chlamydial or gonococcal re-infections among men were either equal⁵² to or even higher than among women.⁵³ One study with passive follow-up in North Carolina found repeat infection among men to be higher than among women, with respective re-infection proportions of 28.3% and 19.0%.⁵³

One study specifically focused on the effect of partner treatment on re-infections rates and showed that increased partner treatment reduced the amount of chlamydial and gonococcal re-infection among in men.²⁹ This study found that with standard referral, repeat chlamydia in men and women was nearly equivalent at 12% and 13% respectively, and with expedited partner treatment, repeat chlamydia in men at 7% was lower than that in women at 11%.

Table 1. Male Chlamydia and Gonorrhea Re-Infection Data Abstracted from Studies with Active Follow-Up.

Author, year (reference #)	Population	n	Follow-up Method	Follow-up Period	% of Enrolled Men with Follow-up	% of Men with Repeat CT	% of Men with Repeat GC	% of Men with Repeat GC/CT	Female Data
Peterman et al, 2006 (43)	STD clinic-based								
	Newark, Denver, and Long Beach: CT and/or GC subset of 2,419 clinic patients age 15-39 enrolled in HIV prevention counseling study	246 M 133 F	scheduled 3 month follow-up visit at respective STD clinic	3 months ¹	83.3% (205/246)	9.8% (n=112)	14.9% (n=68)	20.0% ² (n=25)	CT: 10.7% (n=84) GC: 3.6% (n=30)
Bernstein et al, 2006 (44)	STD clinic-based								
	Baltimore, MD: persons diagnosed with GC at public STD clinic	548 M 119 F	scheduled follow-up visit or follow-up by disease investigation specialists	3 months	24.3% (133/548)	NA	30.8% (41/133)	NA	GC: 28.9% (13/45)
Ellen et al, 2006 (45)	Various venues								
	Baltimore and Denver: Asymptomatic CT and/or GC infected men aged 13-25	314 M	scheduled follow-up visits at 1 month and 4 months	4 months	44.3% ³ (139/314)	NA	NA	6.5% ⁴ (9/139)	NA
Golden et al, 6/2005 (54)	Population-based								
	King County, WA: partner-notified heterosexuals who returned mailed re-screening kits	57 M 124 F	mailed re-testing kit 3 months after treatment	3 months	35.8% ⁵ (221/618)	10.7% (6/56)	0.0% (0/14)	NA	CT: 7.6% (11/144) GC: 16.7% (2/12)
Golden et al, 2/2005 (29)	Population-based								
	King County, WA: GC and/or CT infected women and heterosexual men with untreated partners	646 M 2105 F	reinterview and re-test	19 weeks	61.3% (396/646)	10.1% (27/267)	7.0% (11/157)	9.1% ³ (37/396)	CT: 12.3% GC: 7.0% CT/GC: 12.0%
Sparks et al, 2004 (46)	STD clinic-based								
	King County, WA: asymptomatic CT and/or GC infected heterosexual men and women ≥ 14 years old	84 M 38 F	mailed or clinic re-testing 10-24 weeks after treatment	24 weeks	63.4% (71/112)	16.0% (6/38)	0.0% (0/9)	NA	CT: 0% (0/20) GC: 25% (1/4)
Dunne et al, 2004 (55)	Various venues								
	Baltimore, Denver, and San Francisco: CT-infected men	361 M	scheduled follow-up visits at 1 and 4 months	4 months	76.0% (272/358)	11.4% (31/272)	NA	NA	NA
Kjaer et al, 2000 (47)	Population-based								
	Ringkjobing, Denmark: CT infected general practice patients ≥ 18 years old who had not been treated with antibiotics in previous 4 weeks	12 M 30 F	serial mailed specimens collected at 2, 4, 8, 12 and 24 weeks	24 weeks	83.3% ⁷ (10/12)	11.1% ⁸ (1/9)	NA	NA	12.0% ⁸ (3/25)

¹ Follow-up period was for 1 year, but abstracted data is limited to first follow-up at 3 months.

² Repeat CT/GC infection defined as either CT or GC infection in men co-infected with CT and GC at baseline.

³ Follow-up is defined as participants with at least one follow-up visit. If 1 month visit was not available, 4 month visit was used.

⁴ Repeat CT/GC infection defined as CT infection at follow-up in men with CT at baseline or GC infection at follow-up in men with GC at baseline.

⁵ Repeat CT/GC infection defined as CT infection at follow-up in men with CT at baseline or GC infection at follow-up in men with GC at baseline or either infection in men co-infected with CT and GC at baseline.

⁶ Measure is overall follow-up rate. Male specific data was not available.

⁷ Defined as at least 1 mailed specimen collected 2-24 weeks after baseline mailed specimen.

⁸ Reported re-infection data is defined as a new infection between 2 and 12 weeks after initial infection.

Table 2. Male Chlamydia and Gonorrhea Re-Infection Data Abstracted from Studies with Passive Follow-Up.

Author, year (reference #)	Population	n	Repeat Case Definition	% of Men with Repeat CT	% of Men with Repeat GC	% of Men with Repeat GC/CT	Female Data
Gunn et al, 2004 (48)	Population-based San Diego County, CA: persons with reported cases of GC	6243 M 4747 F	1/1995-12/2001: 2 or more GC infections for same name and DOB within 30-365 day time frame plus trailing 12 month repeats	NA	5.0% (311/6243)	NA	GC: 4.1% (196/4747)
Lee et al, 2004 (49)	STD clinic-based Portsmouth, UK: men and women diagnosed with CT	214 M 861 F	9/1999-8/2000: subsequent CT at any visit within a 3 year follow-up period	16.4% (10/61)	NA	NA	CT: 20.5% (46/224)
Mehta et al, 2003 (50)	STD clinic-based Baltimore, MD: heterosexuals ≥12 years diagnosed with GC	1717 M 6610 F	1/1994-10/1998: first incident GC infection at least 3 months after initial visit to a max of 4.8 years	NA	11.9% (788/6610)	NA	GC: 7.1% (122/1717)
Rietmeijer et al, 2002 (51)	STD clinic-based Denver, CO: patients screened for CT more than once	2097 M 1470 F	1/1997-6/1999: more than one positive CT test > 30 days apart	18.3% (56/306)	NA	NA	CT: 23.2% (43/185)
Gunn et al, 2000 (52)	STD clinic-based San Diego County, CA: patients with a new STI or a history of STI in the past 5 years	2612 M	2-7/1995: subsequent STD reported by client or communicable disease investigator between 45-365 days after treatment	NA	NA	6.3% (39/620)	CT/GC: 6.3% (15/239)
Thomas et al, 2000 (53)	STD clinic-based Step County, NC: patients diagnosed with CT and/or GC	626 M 574 F	8/1992-1/1994: subsequent CT and/or GC infection in clinic or private practice >14 days and <17 months after index infection	NA	NA	28.3% (177/626)	GC/CT: 19.0% (109/574)

Analysis of factors associated with chlamydial and gonococcal re-infection among men found that a previous history of STIs was consistently predictive of re-infection of either or both infections.^{43,52,53,55} Re-infection in either sex was also strongly associated with having untreated partners^{43,44,48,54} and the demographic factors of younger age,^{29,48,50,51,53} and non-white race.^{43,53} High-risk sexual behavior, including non-use of condoms, change in partners, and higher number of sex partners inconsistently was associated with an increased risk for repeat infection.^{29,43,49,50}

DISCUSSION

The reviewed studies provide strong evidence for the substantial incidence of chlamydial and gonococcal re-infection among males. The proportions of repeat chlamydial infection among males had a median of 11.3% and ranged from 9.8% to 18.3%. Proportions of repeat chlamydia among males were similar to those among women. Such data are especially significant because current re-testing guidelines only recommend chlamydia re-screening in women 3 months after initial infection.²⁰ While initial incident chlamydial infection may be higher in women than men,¹ likely due to shorter duration of natural clearing of infections in males, the re-infection data suggest that chlamydial re-infection rates among males is similar to that among women, and may contribute to continued female infections.

The proportions of repeat gonococcal infection among males in the reviewed studies had a median of 7.0% and ranged from 0% to 30.8%. Proportions of repeat gonorrhea among males were similar to those among women. There are currently no gonorrhea re-testing guidelines for either men or women, likely due to the decreased reported national gonorrhea incidence and more limited recent data about re-infection. Because the studies we reviewed indicated that proportions of repeat gonococcal infection among males are equal if not higher than those of repeat chlamydia among females, re-testing men after initial treatment might be effective for reducing gonorrhea prevalence among both sexes.

A previous history of STIs and the demographic factors of younger age, and non-white race were strongly associated with chlamydial and gonococcal re-infection. Data from the studies indicate an inconsistent association between re-infection and risky sexual behaviors such as increased number of partners and non-use of condoms. Because no specific behavioral factors predict re-infection, all chlamydia or gonorrhea-infected men should be re-tested for re-infection.

Certain factors limited the findings of this review. The search strategy could have possibly overlooked relevant studies, although numerous steps were taken to prevent this oversight. The search on PubMed was limited to English-only sources, thus possibly excluding studies from non-English speaking countries with high chlamydia prevalence. Most importantly, there is little published literature documenting repeat chlamydial and gonococcal infection.

Major discrepancies in reported re-infection proportions were due to the variation of study designs. Studies had either active or passive follow-up in their design and so used a wide range of different follow-up periods. The longer follow-up periods for many

passive studies compared to active follow-up studies (years versus months) allowed more people to become re-infected with time, yielding higher median re-infection proportions in passive studies than in active follow-up studies. In addition, all study designs might be impacted by a differential return for follow-up among symptomatic and asymptomatic individuals. Given that symptomatic persons are more likely to return than asymptomatic persons, this would cause an overestimate of the true rate of re-infection. Studies with passive follow-up, which depend upon persons seeking services, are especially vulnerable to this bias.⁵⁶ In addition, the studies with active follow-up experienced variable follow-up rates ranging from 24.3% to 83.3%, which may also differentially account for asymptomatic infections.

Although current recommended therapies for both chlamydia and gonorrhea show low instances of treatment failure,^{2,3,7-11} all studies attempted to account for persistent chlamydia or gonorrhea infection due to treatment failure by eliminating data within certain time periods of initial treatment. The majority of our reviewed studies looked at very high-risk populations, which may limit widespread generalizability of our results. Most data was collected at or from records of public STD clinics where only a minority of reported cases of infection are detected in men: 36% of chlamydia and 45% of gonorrhea reported cases.¹

Despite these limitations, our review clearly established the considerable proportion of repeat chlamydia and gonorrhea among males comparable to that among women. While one of the studies suggests effective reduction of repeat chlamydial and gonococcal infection with expedited-partner treatment (EPT),²⁹ a substantial proportion of repeat infection remains. Even with the widespread implementation of EPT, proportions and incidences of both chlamydial and gonococcal re-infection might remain high.

Given limited resources and the need for focused interventions, targeting previously-infected males for re-testing might disproportionately reduce chlamydia and gonorrhea transmission, thereby reducing re-infection in females and their subsequent adverse sequelae. Our analysis of the current body of literature established substantial proportions and incidences of repeat chlamydia and gonorrhea among men that are similar to those among women consistent across studies, suggesting that re-testing of all chlamydia and gonorrhea-infected men at 3 months after initial treatment should be recommended. We recognize the challenge in implementing successful re-testing programs^{38,54} and suggest additional research to optimize re-testing procedures and establish rates of repeat infection in other populations as means to further refine re-testing guidelines for chlamydial and gonococcal infections among males.

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Figure 1. Percent of CT Re-infection among Males by Study

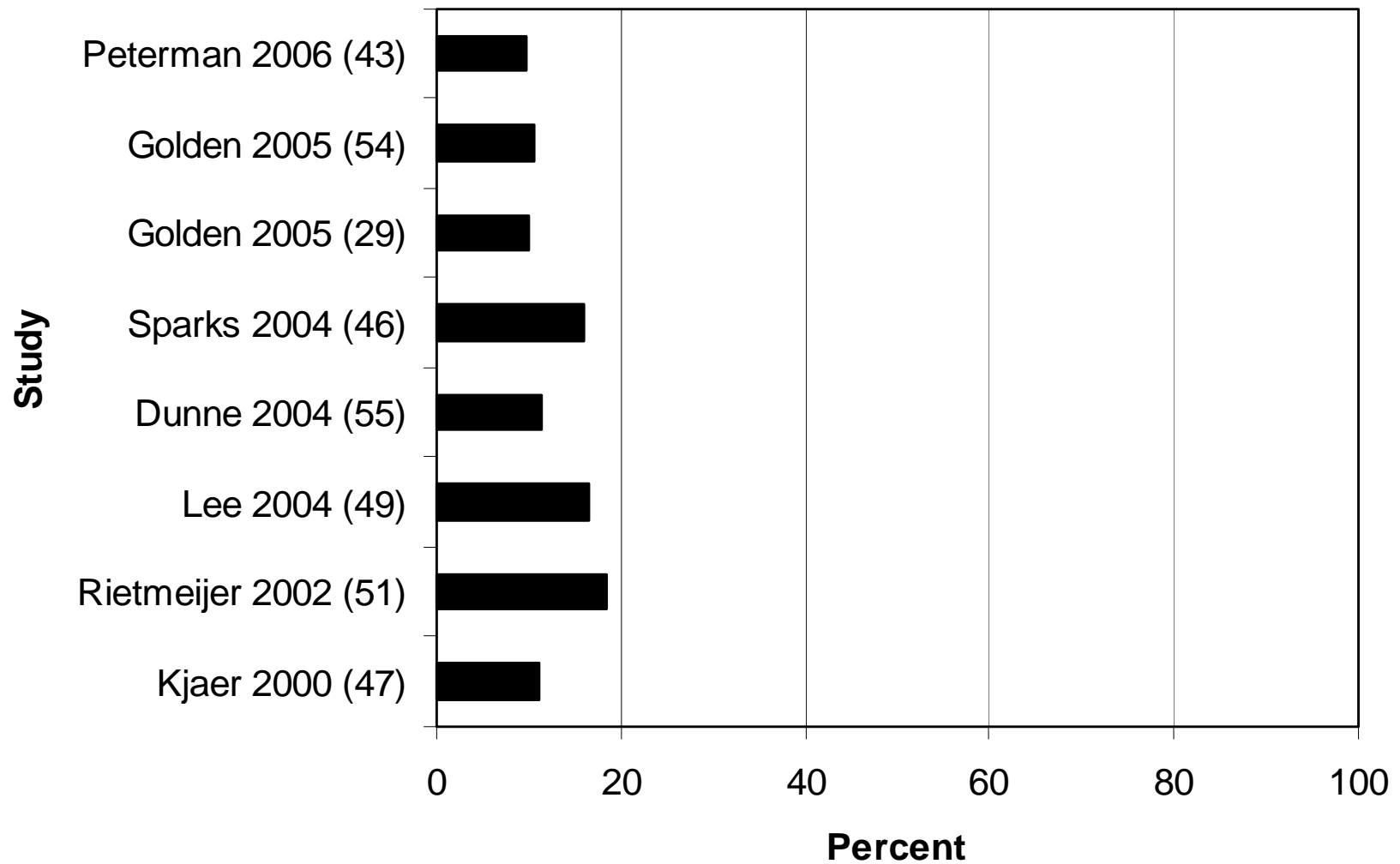


Figure 2. Percent of GC Re-infection among Males by Study

