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Return of Positive Test Results to Participants in Sexually Transmitted Infection Prevalence Studies: Research Ethics and Responsibilities

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BRIEF SUMMARY

We reviewed 80 studies of the prevalence of sexually transmitted infections and found that more than half did not specify if participants were notified of their laboratory test results.

ABSTRACT

Background: In prevalence studies of sexually transmitted infections (STIs), investigators often provide syndromic management for symptomatic participants, but may not provide specific treatment for asymptomatic individuals with positive laboratory test results due to the delays between sample collection and availability of results as well as logistical constraints in re-contacting study participants.

Methods: To characterize the extent of this issue, 80 prevalence studies from the World Health Organization's *Report on global sexually transmitted infection surveillance, 2018*, were reviewed. Studies were classified as to whether clinically relevant positive results were returned or if this was not specified.

Results: More than half (56%) of the cited studies did not specify if participants were notified of clinically relevant positive STI test results. The percentages were similar for low- and middle-income country populations (57%) and high-income country populations (53%).

Conclusions: The absence of documentation of the provision of test results raises the possibility that in some instances, results may not have been communicated, with potential negative effects for participants, their sexual partners, and newborns. From an ethical perspective, clinically relevant results should be returned to study participants and treating clinicians in a timely fashion to ensure appropriate management of identified infections. Study authors should document if they returned test results to study participants and report on numbers lost to follow-up.

Key words: sexually transmitted infections; research ethics; return of results

INTRODUCTION

Studies of prevalence of sexually transmitted infections (STIs) are needed to understand the burden of infection with etiologic agents of interest in specific populations, which often include vulnerable or marginalized populations with higher rates of infection such as adolescents, sexual minorities, sex workers, racial or ethnic minorities, and those in lower-income countries. STI prevalence studies generally involve screening a large number of individuals at risk for infection, many of whom may have asymptomatic infection. Investigators often provide syndromic management for symptomatic participants but in some cases may not provide specific treatment for asymptomatic individuals with positive test results. Barriers to follow-up and treatment include delays between sample collection and availability of results as well as costs and logistical challenges to confidentially re-contacting study participants.

The implications of not treating curable STIs include complications as serious as pelvic inflammatory disease, infertility, and tertiary syphilis.[1] Furthermore, untreated individuals positive for an STI could transmit the infection to sexual partners and, if pregnant, to their newborns.[1] A 2018 report from the National Academies of Sciences, Engineering, and Medicine underscored the ethical importance of returning individual research test results to participants, particularly when the tests have high validity, the information is valuable to participants, and return is feasible.[2]

In order to determine the potential extent of non-return of clinically relevant test results in STI prevalence studies, we reviewed a large sample of such studies and examined the descriptions of the notification and treatment protocols in these studies' publications.

Methods:

We reviewed the prevalence studies included in the World Health Organization's (WHO) *Report on global sexually transmitted infection surveillance, 2018,* for their notification and treatment protocols as well as the country income level for their research sites.[3] We also selected several publications as illustrative case studies of descriptions of non-return and return of results across different study methodologies and populations.

The WHO report cites two reviews that estimate the global burden of disease for a number of STIs.[4,5] : The two reviews included results of PubMed literature searches and requests to WHO regional STI advisors and members of the International Union against STIs to identify additional published or unpublished studies. Specimen collection dates for the studies ranged from 2005 to 2016. Each review's supplementary data were downloaded to create a list of prevalence studies. The lists were merged and de-duplicated. Papers were excluded if they could not be located, were abstracts only, or were reviews. The remaining papers were reviewed and classified according to the following criteria:

- Returned – Papers explicitly included text indicating: a) provision of treatment for participants who tested positive for curable STIs; or b) referral to a provider for communicating positive test results to infected participants.
- Unspecified – Articles that did not meet at least one of the two criteria for "Returned" were assigned the status "Unspecified."

Each paper was reviewed by two authors of this paper. If discordant interpretations could not be resolved by the two authors, a third author served as a tiebreaker. Study populations were coded as residing in low- and middle-income countries (LMIC), high-income countries (HIC), or both in accordance with World Bank Income and Lending Groups. We also compared the page lengths of publications coded as "Returned" vs. "Unspecified" using the Mann-Whitney U-Test.

Results:

The reviews included 105 unduplicated STI prevalence studies. Of them, the publication for 12 studies could not be found, and 13 publications were either abstracts only or reviews, leaving 80 studies for analysis. The majority of studies tested for *Chlamydia trachomatis* alone or together with other curable STIs (papers per STI – *C. trachomatis*: 66, *Neisseria gonorrhoeae*: 47, *Trichomonas vaginalis*: 37, *Treponema pallidum*: 26, *Mycoplasma genitalium*: 5). Of the 80 studies, 45 (56%) did not specify if participants with positive STI test results were notified and treated. One of these used unlinked anonymous testing. Most of the publications' study populations (79%) were in LMICs; 19% were in HICs; 2.5% screened populations in both LMICs and HICs. Provision of information about return of results was similar across country income groups: 57% in LMICs, 53% in HICs, and one out of the two studies (50%) with participants from both LMICs and HICs did not specify whether results were returned. Papers coded as "Returned" had a non-significantly, slightly longer page count than those that were "Unspecified" (median of 7 vs. 6 pages, p=0.1).

Select case studies are presented in the panel for illustrative purposes; these are not intended to identify or criticize any of the reviewed studies specifically. References to these studies are

therefore not included.

Case Studies:

T. vaginalis *and* Candida albicans *Screening in a Middle-Income Country (Unspecified Return of Results)*
The study population comprised 252 women who consented to giving a urine sample at a selected primary clinic. Samples were stored and transported to another site in the same city for testing. The results showed a prevalence of 23% for *T. vaginalis* and 39% for *C. albicans*. The publication did not discuss syndromic management or treatment after testing. The majority of women who tested positive were asymptomatic.
C. trachomatis *and HPV Screenings in a Middle-Income Country (Unspecified Return of Results)*
Sexually active women presenting for regular cervical cancer screening were invited to participate in a study on *C. trachomatis* from 2008 to 2012. Approximately 10% of participants (N = 1,134) tested positive for *C. trachomatis*. The published paper did not specify syndromic management or treatment of positive cases.
T. pallidum, N. gonorrhoeae, *and* C. trachomatis *Screening in a High-Income Country (Unspecified Return of Results)*
Men and women in the general population (N = 1,612) presenting to select health centers completed a survey on sexual behavior and provided blood and urine samples to test for *T. pallidum*, *N. gonorrhoeae*, and *C. trachomatis*. Samples were immediately sent to a central laboratory for processing. The most prevalent STI was *C. trachomatis* (6%), followed by *N. gonorrhoeae* (0.4%), and *T. pallidum* (0.4%). The authors did not specify if syndromic management or treatment of positive cases was provided.

Screening Adolescent Females for C. trachomatis, N. gonorrhoeae, T. vaginalis, *and other STIs in a Middle-Income Country (Results Returned)*
Adolescent females (N = 298) were recruited in the community and evaluated at one of two research centers. The most prevalent curable STIs were *C. trachomatis* (30%), *N. gonorrhoeae* (8%), and *T. vaginalis* (5%). The study publication methods state that treatment was provided immediately to all women with a vaginal discharge syndrome according to national STI management guidelines and that those who were asymptomatic but had positive laboratory results were recalled for treatment. Furthermore, women were given the choice of patient- or provider-initiated partner notification or treatment. Treatment follow-up rates were not reported.

DISCUSSION

Most (56%) of the prevalence studies in our sample did not specify if positive test results were returned and treatment given to study participants with positive test results. This observation was similar between studies when sorted by country income group, although the majority of publications reported on study sites in LMICs. The case studies provide examples of unspecified return of results with different pathogens and in different study populations, e.g., men, women, LMIC, and HIC.

Lack of information about follow-up or treatment of study participants with asymptomatic infection does not necessarily mean that it was not provided. Absence of evidence is not in itself evidence of absence. Treatment may have been provided, but the details not deemed relevant by the authors. We hypothesized that some researchers may have treated asymptomatic infections but did not report this due to space considerations. However, papers coded as "Returned" had

only a slightly longer median page count than those that were unspecified, and the difference was not statistically significant. There may also be instances where syndromic treatment only was provided, and it was considered too cumbersome or too late to ensure treatment of asymptomatic infection once laboratory test results were available. Studies often rely on off-site laboratory services or ship frozen samples to other countries for processing, thus increasing the geographical distance between sample collection and testing and further impeding the return of results to patients. Two of us (PHK and CAR) have experience as researchers with the challenges in timely return of STI test results and providing treatment to asymptomatic individuals in diverse settings worldwide. In roles as research ethics reviewer, manuscript referee, and journal editor we have also observed instances where studies did not ensure return of positive test results and treatment of study participants with documented asymptomatic infection.

This investigation is subject to a number of limitations. The studies included may not be representative of the numerous STI prevalence studies conducted each year worldwide. We did not contact the study authors and cannot definitively conclude that test results were not returned when this was not specified. The clinical significance of untreated asymptomatic infections may vary depending on the pathogen and the participant population, but treatment is indicated for most such infections and should be provided to study participants in nearly all circumstances.

Debate remains over the exact scope of an ethical obligation to return individual research results to participants.[6] This debate extends to prevalence studies of STIs.[7] However, there is widespread agreement that under certain conditions such an obligation obtains. These conditions are, roughly, that the results are accurate, that return is feasible, and that there is substantial value

to the participants from receiving the results.[2,8] The obligation can be grounded in the principles of beneficence and justice.[9] Beneficence supports returning results insofar as the cost of doing so is relatively low and the benefits to the recipients are high—hence the conditions just described. Justice supports returning results insofar as doing so is a reasonable way to reciprocate the contribution made by individuals through their research participation.

The potential for non-return of results and lack of treatment for study participants with asymptomatic STI therefore raises ethical concerns. Potential complications of these STIs include pelvic inflammatory disease, infertility, and tertiary syphilis, as well as potential transmission of infections to sexual partners and newborns.[1] Given that the tests for these STIs are validated and—with planning—it would often be feasible to return results and for participants to obtain treatment, there is a strong ethical case for returning them. Many STI prevalence studies are conducted in vulnerable or marginalized populations with higher rates of infection, including adolescents, sexual minorities, sex workers, and racial or ethnic minorities. Given the history of ethical lapses in the field of sexually transmitted disease research, special vigilance is indicated for the conduct of STI studies.[10]

The following steps should be taken to reduce ambiguity and ensure appropriate return of results and treatment of STIs in research studies:

1. Investigators should design studies to ensure return of clinically relevant results and treatment of identified STIs according to national guidelines. This may necessitate building local laboratory capacity and the use of laboratory tests with relevant regulatory

approval. Storing specimens for delayed testing, e.g., at the end of study enrollment, should be avoided. Procedures, roles, and responsibilities should be included in study protocols for ensuring reporting of results back to clinicians and for recalling and treating participants who did not already receive adequate treatment. Study case records should include whether participant recall and treatment were completed, including partner treatment where relevant. Study manuscripts should include participant notification and treatment procedures in the methods and treatment status in the results. Notification and treatment may not be indicated for some conditions, e.g., laboratory evidence of bacterial vaginosis in the absence of symptoms. Partner notification and treatment by providers may not always be feasible or appropriate, e.g., with marginalized populations such as sex workers.

2. Research ethics committees should communicate this requirement to researchers and not approve studies that do not ensure indicated treatment of all identified STIs unless a convincing case has been made for why the obligation to return results does not apply to the study.
3. Journal editors and reviewers should require reporting of STI treatment procedures in study methods and STI treatment status of study participants as a condition of manuscript acceptance.
4. Relevant professional societies should endorse these steps for their member clinicians, researchers, laboratorians, ethical review board members, and journal editors and reviewers.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

DISCLAIMER

The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the National Institutes of Health or U.S. Department of Health and Human Services.

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