Author's response to reviews

Title: Predictors of incident herpes simplex virus type 2 infections in young women at risk for unintended pregnancy in San Francisco

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Author's response to reviews: see over
August 6, 2007

Editor

BMC Infectious Diseases

Dear Editor,

Please find attached our revised manuscript entitled “Predictors of incident type 2 herpes simplex virus infections in young women at risk for unintended pregnancy in San Francisco” submitted for publication as a major article. This manuscript is a secondary analysis of a previously published randomized control trial (RCT) on emergency contraceptive use. This trial did not have a registration number as it occurred before the RCT registration system began.

Below are our point-by-point responses to the concerns addressed by reviewers Adrian Mindel and Christopher Fairley.

Reviewer #1:

Reviewer's report
Title: Predictors of incident herpes simplex virus type 2 infections in young women at risk for unintended pregnancy in San Francisco
Version: 2 Date: 6 July 2007
Reviewer: Adrian Mindel
Reviewer's report: General

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. The first problem I have with the paper relates to the selection of the test used for HSV serology. The majority of epidemiological studies that have been conducted in relation to HSV 2 serology have not used this method choosing instead the Focus ELISA test and/or Western blot. Some justification for the use of this test is required.

We expanded on why the POCKit test was chosen for the study. This paragraph was added to the methods:

“Participants were then tested for HSV-2 antibodies by POCKit HSV-2 rapid point-of-care test (Diagnology Inc, Belfast, Northern Ireland) on fingerstick whole blood samples. POCKit tests were donated by the manufacturer for study use and the test was considered less invasive than venipuncture and thus more acceptable for study participants. This test is now available as "biokitHSV-2 Rapid Test" from Biokit USA, Lexington, MA or as "SureVue-HSV-2" Rapid Test..."
from Fisher HealthCare, Houston, TX. Premarket evaluation of this test against culture-
documented and Western blot confirmed HSV-2 negative (n=50) and HSV-2 positive (n = 253)
showed POCKit HSV-2 test sensitivity was 96% and specificity was 98% [11] Sensitivity for
HSV-2 was not affected by the presence of HSV-1 antibodies. In this premarket evaluation,
discordant specimens were further examined by repeat Western blot testing. POCKit falsely
identified one specimen as positive for HSV-2 (unknown reason for false positive) and falsely
identified eight specimens as negative for HSV-2 (due to low titre levels in the specimens).”

2. Background, sentence 2: currently reads: “There currently is no cure for the HSV-2 and clinical
manifestations must be controlled with periodic or long-term suppressive medical therapy.” I believe
“must” is a little strong. Something like “can” or "should" is better.

We changed “must” to “may.”

3. Discussion, page 11, paragraph 2: The authors talk about targeted screening. Some definition of
precisely what this means is required.

We added a sentence clarifying targeted screening:

“Targeted screening could include women who are African American or who report multiple sex partners
within the last six months.”

4. References 14 and 15: These refer to the same data set and re-examine these data in a slightly
different way. I am doubtful whether it is pertinent to include both references.

These two references do not refer to the same data set. There were two concurrent doubleblind,
randomized, placebo-controlled efficacy trials of a recombinant HSV subunit vaccine for protection
against HSV-2 acquisition. In the JAMA 2001 manuscript, Wald et al describes one study of 528
monogamous discordant couples and in the Ann Intern Med 2005 manuscript Wald et al describes the
other study of 1862 different HSV-2 seronegative individuals. The manuscripts also use different analytic
methods.

We have left the two references in place. Below is the abstract from the vaccine efficacy trial outlining
the two concurrent studies:


Recombinant glycoprotein vaccine for the prevention of genital HSV-2 infection:
two randomized controlled trials. Chiron HSV Vaccine Study Group.

Corey L, Langenberg AG, Ashley R, Sekulovich RE, Izu AE, Douglas JM, Handsfield
RL, Leong WP, Straus SE.

CONTEXT: In the last 3 decades, herpes simplex virus type 2 (HSV-2) infection
seroprevalence and neonatal herpes have increased substantially. An effective
vaccine for the prevention of genital herpes could help control this epidemic.
OBJECTIVE: To evaluate the efficacy of a vaccine for prevention of HSV-2
infection. DESIGN: Two randomized, double-blind, placebo-controlled multicenter
trials of a recombinant subunit vaccine containing 30 microg each of 2 major
HSV-2 surface glycoproteins (gB2 and gD2) against which neutralizing antibodies are directed, administered at months 0, 1, and 6. Control subjects were given a citrate buffer vehicle. Participants were followed up for 1 year after the third immunization. SETTING AND PARTICIPANTS: We enrolled 2393 persons from December 10, 1993, to April 4, 1995, who were HSV-2 and human immunodeficiency virus seronegative. One trial with 18 centers enrolled 531 HSV-2-seronegative partners of HSV-2-infected persons; the other, with 22 centers, enrolled 1862 persons attending sexually transmitted disease clinics. A total of 2268 (94.8%) met inclusion criteria and were included in the analysis with 1135 randomized to placebo and 1202 to vaccine. MAIN OUTCOME MEASURE: Time to acquisition of HSV-2 infection, defined by seroconversion or isolation of HSV-2 in culture during the study period by randomization group. RESULTS: Time-to-event curves indicated a 50% lower acquisition rate among vaccine vs placebo recipients during the initial 5 months of the trial; however, overall vaccine efficacy was 9% (95% confidence interval, -29% to 36%). Acquisition rates of HSV-2 were 4.6 and 4.2 per 100 patient-years in the placebo and vaccine recipients, respectively (P = .58). Follow-up of vaccine recipients acquiring HSV-2 infection showed vaccination had no significant influence on duration of clinical first genital HSV-2 episodes (vaccine, median of 7.1 days; placebo, 6.5 days; P > .10) or subsequent frequency of reactivation (median monthly recurrence rate with vaccine, 0.2; with placebo, 0.3; P > .10). The vaccine induced high levels of HSV-2-specific neutralizing antibodies in vaccinated persons who did and did not develop genital herpes. CONCLUSIONS: Efficient and sustained protection from sexual acquisition of HSV-2 infection will require more than high titers of specific neutralizing antibodies. Protection against sexually transmitted viruses involving exposure over a prolonged period will require a higher degree of vaccine efficacy than that achieved in this study.

Discretionary Revisions (which the author can choose to ignore)
What next?: Accept after minor essential revisions
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer #2:

Reviewer's report
Title: Predictors of incident herpes simplex virus type 2 infections in young women at risk for unintended pregnancy in San Francisco
Version: 2 Date: 24 June 2007
Reviewer: Christopher K Fairley
Reviewer's report: General
This is a well written and clearly presented paper. I've suggested some things for the editors and authors to consider.
1. Given the uncertainly over HSV serology and its critical importance (i.e. it is the outcome measure here) the paper may be improved by more than just a few words about the sensitivity and specificity of the test. With a low incidence, even a few false positives may be important. In the methods a paragraph should be included that discusses this and also a paragraph in the discussion. Data may also be available about retesting of the same samples or other quality control measures.

We added a paragraph to both the methods (as discussed above with reviewer #1’s comments) and discussion on the performance and limitation of using the POCKit rapid HSV-2 test. In addition the following sentence was added to the methods:

“Women with positive rapid HSV-2 antibody results were told they could seek confirmatory testing at their discretion, however confirmatory test results were not recorded as a part of this study.”

Methods:

“Participants were then tested for HSV-2 antibodies by POCKit HSV-2 rapid point-of-care test (Diagnology Inc, Belfast, Northern Ireland) on fingerstick whole blood samples. POCKit tests were donated by the manufacturer for study use and the test was considered less invasive than venipuncture and thus more acceptable for study participants. This test is now available as "biokitHSV-2 Rapid Test" from Biokit USA, Lexington, MA or as "SureVue-HSV-2" Rapid Test from Fisher HealthCare, Houston, TX. Premarket evaluation of this test against culture-documented and Western blot confirmed HSV-2 negative (n=50) and HSV-2 positive (n = 253) showed POCKit HSV-2 test sensitivity was 96% and specificity was 98% [11] Sensitivity for HSV-2 was not affected by the presence of HSV-1 antibodies. In this premarket evaluation, discordant specimens were further examined by repeat Western blot testing. POCKit falsely identified one specimen as positive for HSV-2 (unknown reason for false positive) and falsely identified eight specimens as negative for HSV-2 (due to low titre levels in the specimens).”

Discussion:

“Finally, although the rapid point-of-care test we used to identify HSV-2 infection has a documented high sensitivity (96%) and specificity (98%), it is not as accurate as Western blot. A few women may have been falsely identified as HSV-2 positive while others may have been falsely identified as HSV-2 negative, especially if they had low HSV-2 titre levels. This would result in non-directional misclassification and would bias our findings towards not finding significant predictors of HSV-2 infection. Therefore our findings may have been stronger if we had used a more accurate test.”

2. Odds Ratios and 95% confidence intervals should be included in table one (baseline analysis), not just p values

Table 1 shows prevalence of HSV-2 by select demographic and behavioral factors at baseline. We performed Chi-squared (dichotomous variables) and General Chi-squared (multilevel variables) analyses for this table and recorded the p-value of those tests. Odds Ratios were used for incident HSV-2 infection analyses and both crude and adjusted ORs are shown for incident infection in Table 2. We clarified the p-values in Table 1 were from Chi-squared analysis and did not make other changes.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the
author can be trusted to correct)
1. Abstract should include 14% loss to follow up— it is plus for the study and a pity not to include it.

This was added to the abstract.

Discretionary Revisions (which the author can choose to ignore)
What next?: Accept after minor essential revisions
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

In addition we made a few other minor revisions to correct and clarify previous statements.

Thank you for your consideration.

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