

## S11.4 SEROLOGICAL SCREENING FOR SYPHILIS: RESEARCH NEEDS

doi:10.1136/septrans-2011-050102.47

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**Background and problem** The recent development and implementation of serological screening for syphilis using recombinant protein-based immunoassays has resulted in much confusion about the interpretation of positive results, particularly in low prevalence settings. Early experience suggests that a high proportion of positive tests are not confirmed by either non-treponemal or other treponemal tests. Many questions remain about the accuracy and relevance of these results.

**Research needs** We will discuss research questions related to the performance, utility, and effectiveness of these tests.

**Performance of the existing tests** Sensitivity, specificity, and positive predictive value in high- and low-prevalence populations. What gold standard should be used for evaluation of these tests?

Can performance of the existing tests be improved by simple modifications?

Reactivity in persons with past treated syphilis—how can this be determined?

**Effectiveness of using the current tests for screening** Does screening with the EIA tests result in the need for more additional, unnecessary testing? Does the delay in receiving prompt complete serological results result in delayed treatment and increased transmission of syphilis? How much unnecessary treatment results from the use of these tests for screening? What is the impact of EIA screening on public health time and dollars spent on contact tracing? What is the real cost of EIA screening, including the need for additional testing, possibility of additional transmission, and required public health follow-up?

**Biological basis for the unconfirmed reactivity in the existing tests -** Which *Treponema pallidum* antigens are recognised by patient sera that are reactive only in the EIA tests?

Do such antisera have cross-reactivity with antigens of other treponemal species found in humans?

**Next generation recombinant protein-based antibody tests** Are there *T pallidum*-specific antigens? How can we identify them? Are there antigens for which antibody disappears or declines significantly following treatment?

**Conclusions** The increasingly widespread use of recombinant protein-based immunoassays has contributed to much confusion in serological testing for syphilis. Research efforts to understand the source of the problems with these first-generation tests are needed to provide clinicians with appropriate algorithms and tools to accurately and rapidly diagnose untreated syphilis in their patients.

## Symposium 12: Current topics on human papillomavirus

### S12.1 TRANSMISSION OF HUMAN PAPILLOMAVIRUS INFECTIONS

doi:10.1136/septrans-2011-050102.48

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**Background** There have been few studies of the sexual transmission of human papillomavirus (HPV) between partners. Our objective was to estimate transmission rates among persons with docu-

mented sexual exposure to an infected partner and longitudinal follow-up.

**Methods** We analysed data from the HITCH Cohort Study, a study of recently-formed couples. Women aged 18–24 attending a university or junior college in Montreal, Canada and their male partners were eligible. Self-collected vaginal swabs and clinician-obtained swabs of epithelial cells from the penis and scrotum were tested for DNA of 36 HPV types. We analysed follow-up data at visit 2 from 179 couples who were discordant for one or more HPV types at enrolment. We defined the index partner as that which was infected with a type(s) not found in the other partner, and a transmission event as subsequent detection of that HPV type in the non-index partner. Transmission rates are expressed as the number of transmissions per 100 person-months (PM), with 95% CI estimated using Poisson regression.

**Results** Transmission was observed in 73 partnerships. There was little difference between the male-to-female (3.5 per 100PM, 95% CI 2.7 to 4.5) and the female-to-male transmission rate (4.0 per 100PM, 95% CI 3.0 to 5.5). These rates are consistent with a per-partnership transmission probability of 0.20 (95% CI 0.16 to 0.24) over 6 months. Transmission rates did not differ with the lifetime number of partners reported by the non-index partner at enrolment or with the circumcision status of the male partner. Rates were highest when the index partner was still positive for that type at follow-up; rates of male-to-female transmission quadrupled and female-to-male transmission tripled (5.2 and 6.2 per 100PM, respectively), compared to when the index partner was negative at follow-up (1.2 and 1.8 per 100PM, respectively, p<0.05).

**Conclusions** Transmission rates based on follow-up of discordant partners are probably underestimates of the true rate due to clearance in index partner and the depletion of susceptibles. Our results contribute to a small but growing evidence base regarding the natural history of HPV transmission and the probability of transmission. These estimates may be of utility to improve forecasting estimates from mathematical modelling efforts to project the public health impact and cost-effectiveness of HPV vaccination.

### S12.2 SCREENING FOR CERVICAL CANCER IN THE ERA OF HPV VACCINATION

doi:10.1136/septrans-2011-050102.49

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Two efficacious prophylactic vaccines against infections with human papillomavirus (HPV) types 16 and 18 have become available since 2006. Universal pre-exposure HPV vaccination has the potential to reduce the incidence of cervical cancer by up to 75%. Vaccination is also expected to have an impact on the rate of cervical cytological abnormalities and of diagnostic and treatment procedures required to manage women with such precancerous lesions. The traditional paradigm of Pap cytology screening may not be a suitable complementary preventive strategy in the era of HPV vaccination. Once the cohorts of young women who are being vaccinated reach the age of screening the prevalence of Pap smear-detectable abnormalities will decrease substantially, which will ultimately affect the positive predictive value of cytology and decrease its cost-effectiveness. It is now widely accepted that testing cervical exfoliated cells for DNA of high oncogenic risk HPVs is a much more sensitive screening tool than cytology to detect high grade cervical lesions and cervical cancer. Cytologic or HPV-typing triage of HPV-positive women can reveal cases that should undergo colposcopic examination and biopsy and will largely obviate the concerns related to false-positives. With the improved sensitivity to detect existing lesions and the more “upstream” focus on cervical carcinogenesis this strategy could be implemented via longer screening intervals than are currently possible with cytology alone,

and thus be cost-saving especially after HPV testing is deployed as a screening tool. However, it is in the post-vaccination era when the cohorts of women vaccinated in their teens enter screening age that this approach may prove most valuable by permitting a surveillance system that can serve two roles simultaneously: monitoring duration of vaccine protection (with HPV typing for those who are positive) and screening for cervical cancer. The author will present the arguments for an integrated approach that involve the two prevention strategies against this disease: HPV vaccination and molecular testing in cervical cancer screening.

### S12.3 WHAT IS THE LATEST DATA FROM THE 2 COMMERCIALLY AVAILABLE PROPHYLACTIC CERVICAL CANCER VACCINES?

doi:10.1136/sextrans-2011-050102.50

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Since 2007 two prophylactic HPV vaccines (a bivalent incorporating VLPs 16 and 18, plus a quadrivalent vaccine with VLPs 16, 18, 6, 11) have been licensed for use. This was based on excellent efficacy, immunogenicity and safety data from phase 3 clinical trials. In addition there is also some cross protection for disease for phylogenetically related genotypes. Where these vaccines have been incorporated into public health programs with high coverage, (particularly targeted school based programs), already reductions in those disease those with the shortest incubation periods, are being seen that is, genital warts for the quadrivalent vaccine.

The greatest challenge today is to obtain wide vaccine coverage to those countries with the highest incidence of disease.

### S12.4 GENITAL WARTS: PREVENTION, DIAGNOSIS, TREATMENT AND COUNSELLING

doi:10.1136/sextrans-2011-050102.51

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Genital warts (GW) are one of the most common reasons for consultation at an STI clinic. A majority of partners sexually exposed to GW will develop GW. Half of cases of GW will have cleared within 4 months. Condoms' efficacy has been demonstrated but need high compliance to achieve good protection. When lesions are not clearing reassessment of diagnosis may be necessary. Therapeutic options include patient applied and office base therapies. Some patients may need repeated cycles of therapy or combined modalities. Counselling for smoking cessation and HIV testing should be offered. High level of anxiety and sexual concerns are common. Partner notification is not recommended. Patients with GW and their actual and future partner(s) should be counselled about HPV quadrivalent prophylactic vaccine.

## S13 Respondent-driven sampling: where we are and where should we be going?

### S13.1 RESPONDENT-DRIVEN SAMPLING: USES, ASSUMPTIONS, LIMITS AND PROSPECTS

doi:10.1136/sextrans-2011-050102.52

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Respondent-driven sampling (RDS) is widely used to obtain estimates of quantities such as HIV prevalence, but is also used to examine correlates of infection, and less frequently, to help characterise social networks of individuals in "hidden" populations. The popularity of RDS stems in part from the often rapid recruitment of

individuals from the target population as well as from the potential to obtain (asymptotically) unbiased estimates using information only from the sample. I will review the assumptions required for this potential to be realised, whether these assumptions are broken in practice, and the impact of breaking assumptions on statistical inference. I will also discuss improvements to the design and analysis of RDS studies, including schemes for giving out coupons, obtaining absolute sizes of at-risk populations using capture-recapture, and the utility of detailed social network inventories.

### S13.2 ASSESSING RESPONDENT-DRIVEN SAMPLING

doi:10.1136/sextrans-2011-050102.53

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Respondent-driven sampling is a network-based technique for estimating traits in hard-to-reach populations, for example, the prevalence of HIV among drug injectors. In recent years RDS has been used in more than 120 studies in more than 20 countries, and by leading public health organisations, including the Centers for Disease Control and Prevention in the USA. Despite the widespread use and growing popularity of RDS, there has been little empirical validation of the methodology. In this talk, I investigate the performance of RDS by simulating sampling from 85 known, network populations. Across a variety of traits we find that RDS is substantially less accurate than generally acknowledged, and that reported RDS CI are misleadingly narrow. Moreover, it is unlikely RDS performs any better in practice than in our simulations as we model a best-case scenario in which the theoretical RDS sampling assumptions hold exactly. Notably, the poor performance of RDS is driven not by the bias, but by the high variance of estimates, a possibility that had been largely overlooked in the RDS literature. Given the consistency of our results across networks and our generous sampling conditions, we conclude that RDS as currently practiced may not be suitable for key aspects of public health surveillance where it is now extensively applied. This work is joint with Matthew Salganik.

### S13.3 AN EMPIRICAL EVALUATION OF RESPONDENT-DRIVEN SAMPLING

doi:10.1136/sextrans-2011-050102.54

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**Objective** Respondent-driven sampling (RDS) is an increasingly widely used variant of snowball sampling, that proponents claim can provide unbiased estimates. RDS has not been rigorously evaluated in the field. This study evaluated RDS by comparing estimates from an RDS survey with total-population data.

**Methods** Total-population data on age, tribe, religion, socioeconomic status, sexual activity and HIV status were available on a population of 2402 male household-heads from an open cohort in rural Uganda. An RDS survey was carried out in this population, employing current RDS methods of sampling (RDS-sample) and statistical inference (RDS-estimates). Analyses were repeated for the full RDS sample and a small sample of the first 250 recruits (including 10 seeds).