

# Sexually Transmitted Infections

## Editorials

### Farewell to Gutenberg?

I too find it difficult to imagine life without a novel on the beach or the *BMJ* in the loo. But the very nature of the imaginative process roots it in the familiar. I fear we are about to enter a world unfamiliar to most of us over the age of 30. Gutenberg is giving way to Gates. And I urge myself to embrace it with a grin. Electronic *Sexually Transmitted Infections (STI Online)* was born in September alongside other illustrious journals at HighWire Press, a division of the Stanford University's Green Library, whose mission is to "foster research and instruction by providing a more direct link between the writers and readers of scholarly materials".<sup>1</sup> This is not a gimmick, but an effort to stay one step ahead of the inevitable. As a 19th century philosopher once said, freedom is the recognition of necessity. We chose this path freely but, as pioneers, we want also to influence how things develop.

As with most revolutions the e-revolution is essentially unavoidable. This one has come about because the scientific community believes that scientific research belongs to all. Some original papers are already being put on the web, for all to see, on sites such as the NIH's PubMed Central. It is not a wild guess that in a few years this practice will become universal. Where the peer review process will fit in with this attempt at openness is a subject to which I will return at a later date. Here I hope to whet your appetite.

*STI Online* contains full text of articles plus tables and figures, published at the same time as the paper version, thus beating the postman by days or even weeks. Personal subscribers to the paper *STI* will receive *STI Online* without additional cost or can subscribe the online version for a reduced rate. Institutional subscribers can subscribe to *STI Online* separately, the price being determined by the size of the institution. *STI Online* allows you to browse and search *STI* archives and access full text of articles from February 1998, as well as abstracts and table of contents for earlier issues. References are hyperlinked to Medline abstracts and *free* full text links are available to journals

hosted by HighWire Press. This is clearly a transitional period. In the longer term the paper version and *STI Online* will diverge into two different beings, as befits their different natures. We cannot crystal ball gaze too adventurously at this stage, but a recent brainstorming session<sup>2</sup> came up with some visions. What follows is the output of those brains in "storm" mode.

*STI Online* will experiment with a more open peer review process, invite readers to comment on selected papers in a more interactive way, invite e-letters, and aim to introduce an interactive continuing medical education (CME) programme, which will be coordinated by Sarah Edwards (consultant in genitourinary medicine, West Suffolk Hospital, UK). As HighWire currently hosts over 200 journals including the *BMJ* and some of the BMJ specialist journals we can create hyperlinks to the full text with related articles in these. We are currently negotiating with our sister journals to see if we can create more direct and dynamic crosslinks between us. Instant free access to Medline could also be augmented by the *STI@lert* which will alert readers to important related publications in other journals and to important new websites. These will replace the Current Publications section of the journal. We will create direct links to conference sites allowing instant access to abstracts. There will also be more room for cases of instructive (and not just rarity) value—though concerns for confidentiality and consent become even more acute.

In the more distant future we will experiment with a "journal club," where selected authors will be asked to summarise their paper, placing it in the context of existing knowledge and how it might change current practice. The electronic format may also allow "chat rooms" on topics of particular interest or controversy. Conference reporting will also be quicker and more direct. We will experiment in summarising some of the more important presentations in Power Point format. The electronic format will also make it easier to expand the "From bench to bedside" (basic science for the clinician) series.

The paper *STI* will initially mirror the electronic form in its essential outlines, but with some streamlining. We will try and banish long, indigestible, tables to *STI Online*. The “Global views” section will have the abstract in paper form and a longer manuscript than at present in e-format. We will do the same for articles dealing with operational issues, with an important but geographically limited audience. This will come under the heading of “In practice”. We will be able to make much more adventurous use of colour.

On a longer perspective we think the written journal will not only become slimmer, but it will change fundamentally in character from a journal of fact to something more like what one of our editorial board members called for—a “one stop” journal. One attendee at the brainstorming session, in answer to the question “what do you see the paper journal doing in the future?” after some thought came out with: “nothing!” That may be too revolutionary but it contains an inescapable truth. “*pSTI*”, or for that matter “p-anything” will be unimaginably different from what you have in your hands as you read this—assuming you’ve got this far. If for no other reason than that there may be less money to take it to the printers! The *pSTI* of the future may resemble a cross between *TV Times*, *Sight and Sound*, and the *New York Review of Books*. Experts summarising the

state of the art, articles from *STI* and other journals abstracted with an expert’s commentary placing it in the context of current knowledge and practice, regular commissioned short reviews of recent advances in specific areas, research methodology, debates, updated lists of websites of interest, etc . . .

It is an exciting world we are entering. I have agreed to stay on as editor till December 2002. We have already expanded the hanging committee and will need to make other adjustments to meet the new challenges. We are asking the editorial board to become actively involved in moulding the new journal. We hope, and believe, the changes will make *STI* even more useful to you, the reader. Yet without your input these thoughts will be like raw eggs, nourishing, but crude. So please let us have your views—“p” or “e”!

MOHSEN SHAHMANESH

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1 About HighWire Press. [Highwire.stanford.edu/about.shtml](http://Highwire.stanford.edu/about.shtml)

2 In attendance were Michelle Dimler, Tony Delamothe, Sarah Edwards, Richard Lau, Rob Miller, Janet O’Flaherty, Jonathan Ross, Mohsen Shahmanesh, Helen Ward, Alex Williamson, and Jonathan Zenilman (by phone). Annemiek de Ruiter and Simon Barton could not attend but sent their views.

## Sexually transmitted infections in women who have sex with women: who cares?

What is known about the occurrence of sexually transmitted infections (STI) in women who have sex with women (WSW), and should it matter? Demographically, this is not a trivial issue: estimates of lifetime same sex behaviour among women range from 8% to 20%, and between 1.4% and 4.3% of all women may be WSW on the basis either of behaviour or self defined identity.<sup>1–3</sup> WSW have traditionally been viewed as “low risk” for STI, including HIV, and data from several small studies seem to support this belief.<sup>4–9</sup> However, as is often the case when one attempts to categorise any group by a descriptive “measurement” as complex as sexual behaviour, the real situation is of course more complicated.

As several studies have reported, the sexual practices of WSW present a reasonable means for vagina to vagina transmission of infected cervicovaginal secretions,<sup>10–12</sup> a concept most directly supported by documentation of trichomoniasis being sexually transmitted between women.<sup>13</sup> There is strong evidence that transmission of human papillomavirus (HPV) between female sex partners occurs, as HPV and associated squamous intraepithelial lesions (SIL) have been detected in WSW who reported no previous sex with men.<sup>10 14 15</sup> Bacterial vaginosis (BV), a condition associated with pelvic inflammatory disease and adverse outcomes of pregnancy,<sup>16</sup> occurs in 24% to 51% of WSW,<sup>5 9 12 17 18</sup> and sexual transmission of some responsible factor has been debated.<sup>12 17</sup> Although uncommon, transmission of HIV and hepatitis B between female sex partners has been reported.<sup>19–23</sup> Many WSW are also at risk for STI acquisition from male partners. Even when surveyed outside STI clinic settings, most WSW report having had sex with men, and many (20–30%) continue to have sex with men as well as women.<sup>24</sup> Female adolescents who have sex with other females may be especially likely to engage in unprotected sex with both male and female partners.<sup>25</sup>

In this issue of *Sexually Transmitted Infections*, Fethers and colleagues report (p 345) a case-control study of 1432 WSW attending a public STI and HIV clinic in Sydney for routine sexual health screen.<sup>26</sup> Almost one in 10 women attending these clinics were WSW; only two thirds of these were screened for STI. Why those unscreened sought care at the clinic, and what determinants went into the decision not to screen them, is not described. More common among WSW relative to matched heterosexual controls were BV, previous diagnosis of STI, and seropositivity to hepatitis B and C; less common was a report of previous genital warts. Equally prevalent were gonorrhoea, chlamydia, HIV, and Papanicolaou smear evidence of SIL. *Trichomonas vaginalis*, *Chlamydia trachomatis*, and HIV infections were detected in WSW reporting sex exclusively with women in the previous year. WSW more commonly reported having had sex with men who have sex with men (MSM) and injecting drug users (IDU), as well as a higher number of lifetime partners, ever having exchanged sex for money, and being IDU themselves. As the authors note, the prevalence of BV (8%) was low relative to that seen in other studies of WSW, possibly because one third of WSW attending the clinic were not screened for BV.

This report is important for two major reasons. Firstly, while case-control studies have their own set of limitations, they offer one approach to circumvent some of the methodological challenges inherent in studying WSW. As eloquently reviewed in a discussion on research in sexual minorities by a multidisciplinary task force report on lesbian, “gay,” bisexual, and transgendered health,<sup>27</sup> the methodological considerations underlying population selection, subject sampling, and recruitment are complex. Precisely defining a reproducible study group, while simultaneously acknowledging and accounting for the inherent heterogeneity in most populations, is especially challenging when studying

sexual behaviour and its attendant risks and outcomes. Well controlled studies in reproducible populations can surmount some of these challenges; the case-control methodology employed by Fethers and colleagues in studying their STI clinic population is a good example.

Secondly, and more importantly, this is now the third study to show an alarming prevalence of HIV related risk behaviours in WSW who report sex with men during a visit to an STI clinic. These risks include sex with homosexual or bisexual men, use of injection drugs and of crack cocaine, and exchange of sex for drugs or money.<sup>28–29</sup> In our analysis of WSW attending our STI clinic in Seattle, Washington, WSW who reported sex with both male and female partners in the preceding 2 months had a high prevalence of risk behaviour for HIV acquisition, and women reporting sex only with other women in the preceding 2 months more commonly reported ever having had sex with a homosexual or bisexual man.<sup>29</sup> Further, among 550 WSW queried in a community survey done in San Francisco, 40% reported unprotected vaginal or anal sex with men during the past 3 years, including men who had sex with men and male IDU.<sup>30</sup> A large, cross sectional, community based study of sociometric networks among IDU found that same sex behaviour among women was independently associated with a twofold increase in the likelihood of HIV infection.<sup>31</sup> Thus, the proportion of HIV infected women who have sex with women may be substantial, while use of barrier methods to prevent STI transmission in such encounters may be low.<sup>32</sup> In summary, these WSW could theoretically function as a “bridge” population: one with sexual links to men (possibly men at higher risk for STI/HIV by virtue of either being IDU or having sex with other men) and to WSW who are sexually active only with women. Such exposures could prove significant for WSW who may be classified as “low risk” when they later report exclusive same sex behaviour.

Despite this provocative and diverse evidence, we have only a limited understanding of the frequency and range of behaviours that put WSW at risk for STI acquisition, and no generalisable estimates of the epidemiology of STI in WSW. Why don't we know more? Attempts to use national or local surveillance data to estimate the prevalence of STI among WSW are limited in that many risk classifications have either excluded same gender sex among women or subsumed it under a hierarchy of other behaviours viewed as conferring greater risk.<sup>33</sup> Few STI reporting systems routinely collect information on same sex behaviour among women. The situation is further complicated by the question of whether sexual minority women receive appropriate preventive health care,<sup>34–35</sup> and thus are even likely to access systems which might capture incident STI or consequent syndromes. For example, WSW probably do not receive Papanicolaou smear screening according to recommended guidelines; whether this relates to erroneous beliefs about personal risk for HPV and cervical cancer, or because providers do not appropriately screen WSW, is not known.<sup>10 36 37</sup>

What are the challenges and tasks for those working in this area and those responsible for directing STI research and policy? As noted by Fethers and colleagues, traditional assumptions about the sexual practices between women have generally implied that such activities confer low or no risk. Such generalisations are often made categorically, without specific knowledge of sexual practices. At best, they are informed by disinterest, or by a lack of willingness to believe that the area is worthy of further study; at worst, homophobia and sexism contribute to these views. Such premature conclusions about STI risk among WSW adversely affect our ability to gather data that would illuminate our lack of knowledge. This “early

closure” is deleterious not only for research directly related to STI in WSW; in large studies of more “traditional” health outcomes, such as breast cancer and heart disease, data on sexual orientation are not routinely collected despite the importance of measurements related to women's reproductive health histories. A tendency to dismiss the value of studying STI in WSW may certainly adversely affect the likelihood that research proposals are funded, and that research findings are published in journals with relatively wide readership in the scientific community.

Why study STI in WSW? Reasons for testing any scientific hypothesis should *not* be because it is politically mandated, because it is politically expedient, or because “it hasn't been studied.” Research and funding priorities should be based on sound hypotheses and solid data. In the United States, the Institute of Medicine report on research priorities for lesbian health confirmed the need for more extensive data on sexual practices and healthcare seeking behaviours that put women who have sex with women at risk for STI.<sup>38</sup> The work of Fethers and colleagues adds to the growing body of evidence that supports this line of scientific inquiry. It also reminds us that our attempts to categorise people by “sexual behaviour” into risk groups that neatly predict STI epidemiology and transmission must account for the complexity and subtleties that characterise human sexual behaviour.

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## Postal research: too many problems?

Postal research is a valuable means of collecting health related information. Although the majority of mailed research is in the form of questionnaires, postal services have also been used to report the results of home tests or to obtain clinical specimens.<sup>1–7</sup> This approach has been shown to be valuable in certain screening programmes. For example, home testing for glycosuria and subsequent reporting of the results is a simple and effective way of population screening for diabetes mellitus.<sup>1</sup> For genitourinary medicine physicians the concept of postal screening may provide an acceptable method of screening low risk populations for certain sexually transmitted infections. A number of studies have already investigated the potential for postal screening for *Chlamydia trachomatis* infection using mailed specimens including first void urine and vaginal flush samples.<sup>3–7</sup>

On the surface, postal research would appear to provide a simple, cost efficient means of reaching a widely dispersed population, many of whom would not normally attend a healthcare setting. However, there are a number of factors that need to be considered in the design of the survey and careful interpretation of the information obtained is essential to ensure the validity of results.

### Response rates

One of the major problems with mailed research is that response rates tend to be low. Response rates will vary depending on the type of survey and the persistence of the investigators in terms of both the number and type of contacts with the subjects.<sup>1 3 8 9</sup>

Higher response rates are seen when repeat mailings are sent to subjects. In their study investigating non-response bias in postal surveys, Tennant and Badley report an 87% response rate after four mailings of the survey.<sup>8</sup> The first mailing saw a 57% response, increasing to 73% after the second mailing and 81% after the third.

Macleod *et al* surveyed a mixed population of 200 subjects, requesting mailed urine samples to screen for *C trachomatis* infection.<sup>3</sup> They report a response rate of 93% from the 68% of the original subject group who were confirmed to be resident at the address registered with their general practitioner. To achieve this response rate they sent out two mailed packages by recorded delivery and subsequently telephoned or visited non-responders.

The request made by the study can influence participation. Etter *et al*<sup>9</sup> set out to establish whether asking subjects to provide a saliva sample in conjunction with a survey

would influence response rate. They found an 11% lower response rate than when participants were asked only to complete a questionnaire related to smoking habits. It was proposed that the lower response may have arisen as a result of participants' concern that tests other than those specified may have been performed on the samples, such as HIV testing or drug screening. Alternatively, participants may not have felt adequately compensated for providing a specimen.

A low response rate will also be seen if address databases are not regularly updated, particularly where highly mobile populations such as students are being surveyed. Macleod *et al*<sup>3</sup> reported that 32% of subjects aged 18–45 were no longer living at their GP registered address in their postal survey. Others have also reported the inadequacy of family practitioner committees' lists, and noted that screening programmes will fail if population registers are not improved.<sup>10</sup>

### Incentives

Numerous incentives designed to improve response rates have been evaluated, and it would appear that a combination of these incentives is most effective.

Spry *et al*<sup>11</sup> found that prenotification in combination with a lottery incentive significantly improved response rates and that prenotification by telephone, although more expensive, was more effective than by postcard. The lottery incentive alone did not increase response rates significantly. Reminders in the form of a letter or postcard, or as a repeat mailing of the questionnaire, have been shown to increase response. This effect tends to decline after the second mailing.<sup>11</sup>

It is generally perceived that shorter questionnaires are more likely to be completed than longer ones, and some investigators reduce the length of questionnaires in an attempt to enhance response at the expense of the amount of information obtained. However, Spry *et al*<sup>11</sup> compared an eight page survey with a two page survey and found that the length of these questionnaires did not appear to influence response rates. Hoffman *et al*<sup>12</sup> found similar results.

A meta-analysis of mail survey response rate by Fox *et al* reported that the largest increase in response rate was seen with university sponsorship of the study, prenotification by letter, and stamped return postage.<sup>13</sup> First class outgoing postage and the colour of the questionnaire were other factors identified.

Table 1 International Air Transport Association 602 Packaging Regulations: a summary of the main recommendations

- Primary receptacles (specimen containers) must be glass, metal, or plastic and resistant to any chemical or other action of the sample. Seals must be leak proof—eg heat seal, skirted stopper, metal crimp seal. Screw caps, if used, must be reinforced with overtape.
  - The primary container should be surrounded with sufficient material to absorb the entire contents of the primary receptacles. Multiple samples must be individually wrapped. This must be packed in a watertight secondary container.
  - The secondary receptacles must not contain more than 50 ml or 50 g.
  - The outer packaging must be of adequate strength and at least 100 mm in the smallest overall external dimension.
  - An itemised list of contents (pathology forms) must be placed between the secondary and outer packaging.
- Outer labelling must include:
- A Class 6 transport label for infectious substances.
  - UN packaging specification marks.
  - The name and address of the sender, the recipient, and a contact name and emergency number.
  - A shipping name label.

It is important to note that incentives that are effective in one population may not be transferable to another. A number of postal surveys have incorporated in their design a means of investigating which incentives provide the best response. A “randomised phase” is initially undertaken and analysed. The incentive inducing the greatest response is then adopted for the “most effective intervention” stage of the survey.<sup>14</sup>

### Bias in postal surveys

As with any other study, bias can influence the results of postal surveys. Sampling bias can be introduced to a postal survey if subjects selected are not truly representative of the population targeted. The study may aim to represent the general population—for example, subjects selected from GP patient lists, or a select population such as university students or adolescents attending a genitourinary medicine clinic. Sampling techniques and random selection procedures are used to determine a representative study sample. Within that sample, certain people may be more likely to respond to a particular survey than others. This may result in selection of a subset of the targeted population being represented.

The possibility of incentives introducing bias needs to be considered. Incentives may introduce selection bias by encouraging a certain subgroup of the population to respond to the survey, or they may introduce information bias by influencing the participants’ responses.

### Prevalence studies

The objective of many postal surveys is to determine prevalence. Incomplete response to a survey can introduce uncertainty as to the true prevalence of a condition. Simple extrapolation of the results assumes that there is no difference in prevalence between the responders and the non-responders and consequently may lead to an underestimation or overestimation of the prevalence. This may be particularly important in surveys dealing with sexually transmitted infections where the prevalence of a condition may be strongly influenced by a small “core group” at high risk of acquiring an STI. If this group is underrepresented or overrepresented among respondents there will be a significant impact on the results.

### Mailing clinical specimens

There are specific issues which need to be addressed when requesting clinical specimens from subjects via the postal services. However, few studies that have involved the postage of pathological specimens have described the packaging used during transport. A discussion of this would aid future researchers aiming to undertake similar studies.

In order for clinical specimens to be carried by postal services in the United Kingdom, the Royal Mail currently require packaging to comply with the International Air Transport Association (IATA) Dangerous Goods regulations and use UN packing instructions 602 for the carriage of samples likely to contain infectious substances and those for microbiological analysis. These regulations apply to all countries. Some countries such as the United States also have their own national regulations. Of note with the new 602 packaging is the specification that the external dimensions of the package must be a minimum of 100 mm in the smallest overall dimension (table 1). This is too large to allow posting through a normal letter box, necessitating that packages are collected from and delivered to a post office, or that a courier service is used. This may prove to deter subjects from participating in studies. Future postal surveys involving specimen collection will also be more expensive than those previously conducted. However, there is currently a debate as to whether these regulations are necessary for all diagnostic specimens. The formerly used UN 650 packaging specifications can be compact enough to allow postage and may still provide sufficient safety for transport of these specimens.

### Sampling and diagnostic accuracy

Posting of specimens can affect the reliability of certain diagnostic tests. Dabbs<sup>2</sup> found that using cotton rolls rather than chewing gum for collection of saliva specimens resulted in an elevation of testosterone levels on testing. Posting of the specimens resulted in an elevation of female salivary testosterone levels, but not those from male subjects. Adequate investigation needs to be undertaken to ensure that factors such as unpredictable temperature storage, delays in collection, and the transport medium for the specimen will not adversely affect the test results.

Parker *et al*<sup>15</sup> assessed the stability of specimens from 1017 women for chlamydia testing by Gen-Probe PACE 2 sent via the US postal system compared with those transported in a controlled environment (by courier). They reported a 99% agreement in results between the two groups even after 50% of the mailed specimens had been subjected to temperatures above 31°C and 44% had been in transit for more than 3 days. These data suggest that swabs remain stable during postal transit, but these findings may not apply to other specimens such as urine.

For studies of sexually transmitted infections, specimens from the urogenital tract are usually required. Consideration therefore needs to be given to the subjects’ ability and willingness to provide such specimens and to how comparable the sensitivity and specificity of self testing compares with physician obtained samples. Ostergaard *et al*<sup>5</sup> found that the diagnostic efficacy of home obtained and mailed vaginal flush and urine specimens was comparable with physician obtained and mailed endocervical and urethral swabs when testing was by ligase chain reaction.

### Ethical issues

Obtaining ethical approval for postal surveys can be difficult, especially when the survey covers a large geographical area involving numerous committee—for example, with national questionnaires. The requirements of each individual ethics committee may vary, resulting in numerous submissions and the associated administration and time costs. This is aptly described by Middle *et al* who completed 1095 protocols and 1116 application forms to undertake a postal survey of a sample of children born in 1988 in England and Wales.<sup>16</sup> Although the newly formed multicentre research ethics committee simplifies the procedure, submissions to local ethics committees are still required.

Another ethical issue that arises when asking participants to provide a clinical sample for a specified test or to report a test result is how to contact the respondent in the event of a positive result. If participants are asked to provide contact details and do not do so, or are not contactable from the information given, the investigators can be left in a difficult position. The participant will be expecting to be contacted if the test result is significant, but on the other hand may consider further action by the investigator (for example, contacting their general practitioner) a breach of confidentiality. Such issues need to be given considerable thought before embarking on such studies.

Postal survey can provide valuable information relating to health issues. However, the design of the study needs to minimise the introduction of bias and give adequate consideration to ethical and practical issues.

Copies of the IATA Dangerous Goods Regulations, 41st edition, 2000, and the IATA Infectious Substances Shipping Guidelines detailing the IATA 602 packaging regulations can be purchased from Danvers International, 36 Court House Road, Finchley, London N12 7PJ, UK (tel: +44 (0) 20 8445 3929; fax: +44 (0) 20 8445 2745).

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