Sexually Transmitted Infections

Editorials

Use of nucleic acid amplification tests in investigating child sexual abuse

Because of the medical-legal implications, the identification of a sexually transmitted disease, especially *Chlamydia trachomatis* and *Neisseria gonorrhoeae,* in a prepubertal child requires the use of methods with the highest specificity. Diagnosis of *C trachomatis* infection in this setting has been based on isolation of the organism in tissue culture. Culture requires careful specimen collection and stringent transport conditions with maintenance of the cold chain and requires 48–72 hours to perform. In addition, culture methods for *C trachomatis* are not standardised and there can be significant variation in performance from laboratory to laboratory.[1] Obtaining appropriate specimens requires a vaginal swab in children. Similarly, the definitive diagnosis of gonorrhoea has been based on culture of *N gonorrhoeae,* which entails isolation on selective media. Although culture of *N gonorrhoeae* is relatively inexpensive and highly sensitive, it is logistically complicated. As with the collection of specimens for culture of chlamydia, detection of *N gonorrhoeae* also requires vaginal swabs in children. The invasive nature of the specimens needed creates additional trauma for victims of sexual assault.

The introduction of nucleic acid amplification tests (NAAs) has been the most important advance in the field of chlamydia diagnostics since tissue culture replaced inoculation of eggs for culture and isolation of *C trachomatis* from clinical specimens. Because nucleic acid amplification is exquisitely sensitive, theoretically capable of detecting as little as a single gene copy, and highly specific, it offers the opportunity to use non-invasive sampling—that is, urine. There are now four NAAs approved by the US Food and Drug Administration (FDA) for the detection of *C trachomatis* in clinical specimens: polymerase chain reaction (PCR), Amplicor *Chlamydia trachomatis* test (Roche Molecular Diagnostics), ligase chain reaction (LCR), LCx *Chlamydia trachomatis* Assay (Abbott Diagnostics), transcription mediated amplification (TMA) (GenProbe), and strand displacement amplification (SDA) (ProbeTec, Becton Dickson). PCR, LCR, and SDA are DNA amplification tests; TMA is an RNA amplification assay. Currently NAAs are approved for cervical swabs from women, urethral swabs from men, and urine from men and women. None of these tests are approved or recommended by the manufacturers for rectal specimens from adults and they are not approved for rectogenital specimens from children.

NAAs are more sensitive than culture for detection of *C trachomatis* in genital specimens in adults, detecting an additional 25–30% over culture.[2] Multiple studies in adults have demonstrated sensitivities of >80–100% compared with 65–88% for culture, while maintaining high specificities (95–100%).[2] Although all these assays are approved for use with urine from women, the sensitivities are lower than those of endocervical swabs.[3–8] Practically all of these studies have been done in high prevalence populations (3–15%). However, despite high sensitivities and specificities, false positive and false negative results can occur. False negatives due to inhibitors of DNA polymerase are more of a problem than false positives because of Amplicon carryover. Inhibitors appear to be more frequent in cervical specimens. LCR appears to be less susceptible to inhibitors than PCR. Of note, SDA is the only currently available assay that includes inhibition controls.

There is less experience with the use of NAAs for detection of *N gonorrhoeae* in clinical specimens. Unlike *C trachomatis*, culture of *N gonorrhoeae* is well standardised and widely available. However, there have always been concerns about the loss of viability during transport to the laboratory. The following NAAs now have FDA approval for detection of *N gonorrhoeae* in genital swabs and urine from men and women—LCR, PCR, TMA, and SDA. Unlike the experience with NAAs for detection of *C trachomatis,* the performance of these assays has not been dramatically better than standard culture methods for detection of *N gonorrhoeae*.[3–6 8]

The use of urine for the detection of *C trachomatis* and *N gonorrhoeae* in children who are being evaluated for suspected sexual abuse is very attractive. However, are NAA tests of sufficient sensitivity and, most importantly, specificity, to be used in non-invasive specimens from prepubertal girls? Although one can probably extrapolate from the performance of these tests with urine specimens from adult women to adolescent women, one may not be able to do so for younger girls. Most of the evaluations in adults have been done in high prevalence populations (>5%). Performance in low prevalence populations has not been as good, especially for detection of *N gonorrhoeae*.[6] The prevalence of infection with *C trachomatis* and *N gonorrhoeae* in prepubertal girls who are suspected victims of sexual abuse has generally been ⩽2%. Everett *et al* reported prevalences of genital infection with *C trachomatis* and *N gonorrhoeae* of 1.3 and 2%, respectively in 2973 girls evaluated for sexual abuse over a 16 year period.[9] Data on use of NAAs with vaginal specimens from prepubertal girls are very limited. A Canadian study compared PCR with culture of vaginal wash specimens for detection of *C trachomatis* from 25 prepubertal girls.[10] Four of 25 (16%) samples were positive by PCR and were confirmed by a second PCR using different primers. Two of the four specimens were culture positive in vaginal wash and vaginal swabs, two were culture negative. Recently, a US study evaluated PCR (Amplicor) compared with culture in 95

vaginal specimens from girls being evaluated for suspected sexual abuse.[11] The overall prevalence of *C trachomatis* infection was 12.6%. The specific age of these girls was not given, but the range was 4–16 years, with a mean age of 10.7 years, suggesting that most were probably adolescents, and adolescents have some of the highest rates of *C trachomatis* infection. Nine vaginal specimens were culture and PCR positive, two were culture negative and PCR positive, and one was culture indeterminant and PCR positive, giving a sensitivity of 100% and a specificity of 98%. The positive predictive value (PPV) was 83%. Only one of 30 rectal specimens was PCR and culture positive, one was PCR positive and culture negative and two were PCR negative but culture positive, giving a sensitivity of 33%, specificity of 96% and a PPV of 50%. No discrepant analysis or confirmatory testing was done on the culture negative, PCR positive specimens. These numbers are clearly too small to recommend use of PCR in this setting, especially for rectal specimens.

There are no data on the use of NAAs for detection of *N gonorrhoeae* from either vaginal specimens or urines from prepubertal girls. Although specificity of NAAs may exceed 99%, the adequacy of positive predictive values in populations with a low prevalence of gonorrhoea—for example, 1–3%, has not been fully determined. In one study of the use of the coamplification PCR with genital and urine specimens from of men and women attending STD clinics in the United States, the sensitivities and specificities for detection of *N gonorrhoeae* in urine from males and females compared with culture were 94.4 and 98.5%, and 90% and 95.9%, respectively.[3] The prevalences of gonorrhoea among men and women were 17.4% and 7.8%, respectively. Discrepant specimens were all resolved by repeat PCR testing with a confirmatory 16SrRNA assay. However, another multicentre evaluation from Europe of over 3000 women attending non-sexually transmitted disease clinics where the prevalence of *N gonorrhoeae* was only 0.3%, found only nine positive samples by coamplification PCR.[6] None of the positive PCR results could be confirmed by the16SrRNA PCR.

If one assumes a prevalence of 2% for gonorrhoea and *C trachomatis* in sexually abused children, and sensitivities and specificities of an NAA of urine from women based on published data, PPV of a positive urine NAA would range from 35% when the sensitivity and specificity was 82% and 97%, respectively, to 66%, when the sensitivity and specificity was 97% and 99%, respectively. The PPV is dependent on the specificity and prevalence. Thus, even with a very sensitive and specific test, the PPVs of NAAs may not be adequate for detection of either *C trachomatis* or *N gonorrhoeae* in sexually abused children. The 1998 guidelines for the treatment of sexually transmitted diseases from the US Centers for Disease Control (CDC)[12] suggested that NAAs could be an alternative for detection of *C trachomatis,* if confirmation is available but culture was unavailable. However, all the confirmatory tests are in-house assays and are not commercially available or FDA approved. One could conceivably confirm a positive NAA result with another approved assay, which uses a different genetic target, but most laboratories only use one test. Even in adults, there have been problems with reproducibility of PCR and LCR[13 14] for detection of *C trachomatis* and *N gonorrhoeae*. Although we are concerned about missing possible sexual abuse, it is important to remember that a false positive test for a sexually transmitted disease can lead to erroneous reports of sexual abuse and possibly unjustified prosecution and incarceration. In the absence of a comprehensive, prospective evaluation of NAAs compared with culture for detection of *C trachomatis* and *N gonorrhoeae* in children who are suspected victims of sexual abuse and the lack of commercially available confirmation tests, it would be premature to recommend the use of these assays for this indication at this time.

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Chlamydia trachomatis and cancer

Genital *Chlamydia trachomatis* infections have been recognised as a major public health problem. The World Health Organization (WHO) estimates that 50 million cases of *C trachomatis* infection occur each year worldwide.[1] *C trachomatis* is the major cause of mucopurulent cervicitis, pelvic inflammatory disease, tubal factor infertility, and ectopic pregnancy.[2–5] Thus, the healthcare costs due to complications caused by *C trachomatis* infections are enormous.

Cervical cancer is the most common cancer in women worldwide. Epidemiological studies have shown that early sexual activity is a risk factor for cervical cancer.[6] High risk human papillomavirus (HPV) types are found in practically all cervical carcinomas.[7] The evidence linking oncogenic HPV types in the aetiology of cervical carcinoma is beyond doubt. HPV DNA based longitudinal studies have confirmed the seroepidemiological findings

that past HPV infection predisposes to the development of cervical carcinoma.[8 9] Since *C trachomatis* infection is also a marker of sexual activity, an association between *C trachomatis* and cervical cancer has been suggested. Previous case-control studies have found cytological or serological evidence of the role of *C trachomatis* in cervical neoplasia.[10–12] Recent longitudinal seroepidemiological studies also shown that *C trachomatis* infection is associated with cervical carcinoma.[13 14] This association remains after adjustment for smoking and serum antibodies to the high risk HPV types.[15] The association was specific for squamous cell carcinoma, and not for adenocarcinoma.[15] Of specific *C trachomatis* serotypes, serotype G was most strongly associated with cervical squamous cell carcinoma.[16] Furthermore, the presence of serum IgG antibodies to more than one serotype increased the risk.[17] The link between *C trachomatis* and squamous cell carcinoma is unexpected since it is well known that the targets for *C trachomatis* are endocervical glandular cells, and that women with cervical ectopy are more susceptible to *C trachomatis* than women without cervical ectopy. However, the endocervical epithelium of the transformation zone undergoes a process known as squamous metaplasia, and metaplastic cells are also targets for *C trachomatis*. In fact, persistent chlamydial infection may be one of the factors inducing squamous metaplasia and metaplastic cell atypia.[12 18]

No association has been shown between the presence of *C trachomatis* antibodies and the development of non-cervical anogenital cancers.[19]

The incidence of ovarian cancer is increasing. Ovarian cancer is the number one killer among gynaecological malignancies. The aetiology of ovarian cancer is unknown. Incessant ovulation and exposure to high gonadotrophin concentrations increase the risk of ovarian cancer while pregnancy, breast feeding, oral contraceptive use, and tubal ligation all protect against ovarian cancer. Concern about the risk for ovarian cancer associated with infertility or infertility treatment has been heightened by several reports.[17 20–22] However, although the association has become less convincing based on many subsequent larger studies,[23–27] it is tempting to speculate that a common cause of salpingitis, oophoritis, and infertility such as *C trachomatis* infection might explain the link between infertility and ovarian cancer found in some studies (fig 1). Interestingly, one study of cancer incidence correlations suggests that cervical cancer and ovarian cancer might have common aetiological factors.[28] However, the presence or absence of HPV DNA or *C trachomatis* DNA in benign or malignant ovarian tumours has not been extensively studied. It is well known that chlamydial pelvic inflammatory disease (PID) is associated with elevated serum levels of ovarian cancer associated tumour markers CA-125 and TATI (tumour associated trypsin inhibitor).[29 30] These tumour markers may reflect the tissue damage and disruption of the basement membrane seen in severe oophoritis. An association between self reported PID and subsequent ovarian cancer has been reported in one case-control study of histologically verified epithelial ovarian cancer cases.[31] Using the overall odds ratio and the estimated lifetime prevalence of history of PID, the authors calculated that approximately 9% of ovarian cancer in the population could be due to past PID. However, another recent study did not confirm these results.[32] Epidemiological studies linking past history of PID and epithelial ovarian cancer in later life are problematic, because the self reported history of PID is unreliable and because chlamydial antibody levels decrease over time. Thus, the available epidemiological evidence to date is far from convincing.

The link between chlamydia and cancer is biologically plausible because many other chronic bacterial infections have been linked to the development of malignant diseases.[33]

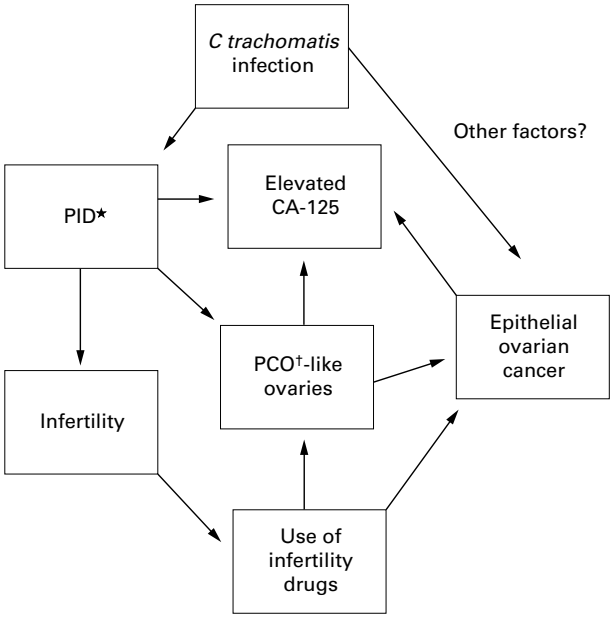

*Figure 1 Hypothetical link between C trachomatis and epithelial ovarian cancer. *PID = pelvic inflammatory disease; †PCO = polycystic ovaries.*

Already in 1936 lymphogranuloma venereum (LGV) caused by L2 strain of *C trachomatis* was linked to cancer.[34] Furthermore, another common microbe, *Helicobacter pylori* has been associated with the development of gastric cancer.[35 36] The outcome and sequelae of chronic or subclinical chlamydial infection can be influenced by the host immune response. Chlamydial heat shock proteins (HSPs) induce deleterious humoral and cell mediated immune responses in individuals developing long term sequelae.[37] Thus, cervical chlamydial infection may result in local immune perturbation favouring persistence or progression of infection caused by the high risk HPV types. Poor immune response may lead to the persistence of the organism and the development of immunologically mediated tissue injury which increases the risk for malignant transformation. Serotype G has been associated with symptomatic infections and upper genital tract infections.[38 39] Serotype G was also associated with cervical carcinoma.[16] Thus, specific *C trachomatis* serotypes might be more virulent than others, and perhaps less sensitive to appropriate antimicrobials, and could thus play a part in carcinogenesis.

The development of carcinoma takes several years, probably decades. The link between bacterial infections and carcinogenesis is not clear, but genetic damage and neoplastic changes can be induced in vitro by co-culturing cells with activated inflammatory cells.[33] Release of nitric oxide occurs in *C trachomatis* infections.[40] Recent studies have shown that *C trachomatis* inhibits host cell apoptosis by specific mechanisms.[41] In chronic chlamydial infections these mechanisms could initiate or promote carcinogenesis. Both the serotype specific differences and the fact that the risk was higher in women exposed to more than one serotype suggest that *C trachomatis* may in some way have a role in cervical carcinogenesis. It is tempting to speculate on the potential molecular mechanisms explaining this association—for instance, if specific determinants related to specific chlamydial serotypes could be directly or indirectly carcinogenic. However, until confirmatory evidence of an association has been demonstrated it is premature to conclude that *C trachomatis* is causally related to these cancers.

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Sector-wide approaches and STI control in Africa

Allocation of aid from international agencies to the health sector in developing countries has usually involved funding of specific projects. This process enabled donors to suggest priorities and to monitor accountability of spending. More recently, a different system using sector-wide approaches (SWAps) has been adopted by an increasing number of funders including the World Bank, World Health Organization, and the Department for International Development. Through SWAps, funds are given to the entire health sector for priorities determined by ministries of health rather than to specific projects.[1] In theory the system should lead to greater efficiency through reduction of duplicative mechanisms that may occur through multiagency support.

Most of the UN agencies now recognise HIV increasingly as a societal problem. This belief would therefore seem to justify the allocation of HIV prevention funds to the whole health sector across the board. SWAps also appear justified by the contention that HIV/AIDS is associated with poverty and that the poor are more likely to access services that can be delivered at the primary healthcare level. Furthermore, this approach offers all HIV interested parties or stakeholders an opportunity to obtain funds from a central pool and have an input into HIV prevention strategies.

Serious doubts remain, however, about whether SWAps are effective.[2] No evaluation of SWAps in STI control has been undertaken. While the role of STI in preventing HIV is now well established, there are still conflicting opinions and uncertainty about how STI services for the population are best delivered. Clear policy directives are even more difficult to justify following the contrasting results of the Mwanza and Rakai studies in which both STI control strategies and the relative effects of the interventions differed significantly.[3 4] Given these uncertainties, will SWAps be a good idea for improving STI control in developing countries, and, more importantly, those communities with significant STI/HIV problems?

To answer this one must firstly look at the wider public health aspects of STI control and acknowledge the diversity of the HIV and STI epidemics. In Africa the prevalence of STIs appears to vary significantly between countries and populations. The prevalence of genital ulcer disease is higher in the countries worst affected by HIV in Africa.[5] Clearly, in some countries STI are a major problem and require a special focus while in others they are of lesser importance. In countries with significant STI/HIV epidemics, some of the potential concerns in adopting SWAps are as follows.

Lack of advocacy

In Africa there are few specialist physicians in STI/HIV. Historically, the majority of African countries have accorded little importance to STI in health budgets. This may reflect a state of denial and a belief that because STIs are not life threatening, individuals who brought such problems upon themselves did not merit special treatment and deserved to be punished for their immoral actions. Such notions are well established in many communities

and may be resistant to change, despite the recent evidence supporting STI interventions against HIV. If the project based approach is to be abandoned, ring fencing of funds for STI control activities may well be required.

The importance of advocacy is well demonstrated by the current situation in South Africa where local policymakers have adopted a low key approach to STI/ HIV/AIDS. HIV is still not accepted as a major problem despite antenatal prevalences of more than 30% in some provinces.[6] This denial at the highest governmental level is causing considerable distress and confusion among professionals working in the HIV field and the population at large.

Dilution of expertise

Responsibility for STI control may rest with a number of agencies including AIDS/HIV prevention, clinical services and reproductive health (RH), and others. The expanded concept of joint services for STI and RH has received strong political support, not least because they are directed mainly at women who are perceived to be victims of the HIV epidemic. However, in assessing whether integration is the way forward, limitations as well as benefits should be acknowledged.[7] While recognising that RH clinics may provide expertise designed for primary health care, they have little experience of providing specialised services for men. It is also worrying that the limited numbers of medical posts in STI have already been reduced in some areas following decentralisation of services.[8]

Targeting HIV core groups will be curtailed

Traditionally targeting has focused on groups such as sex workers and their clients, truck drivers and the military. As the epidemic expands out to the general population, new core groups at high risk of HIV must be identified in the community. One such group is STI clinic attenders—in some areas there is evidence that 77% of men with genital ulcers[9] and more than 60% of routine attenders are HIV positive.[10] STI services for men, a crucial group for targeting in urban settings, need dramatic improvement.[11] Designated clinics are also justified for a number of reasons, including enhanced surveillance, antibiotic susceptibility testing, training and education, referral of problem cases, evaluation of syndromic management protocols, and as a centre to develop expertise for an STI control programme.

A limited number of multisectoral STI interventions—for example, the Mwanza project, have been implemented usually through donor funding. The Mwanza intervention involved vertical and horizontal programmes but was undertaken in a rural population with a relatively low HIV prevalence for sub-Saharan Africa (4%). Whether the favourable results seen in this study would be replicated elsewhere in countries with worse HIV epidemics is unknown.

Providing scope for targeted interventions is a crucial component of a successful strategy for many countries.[12] However, SWAps are likely to limit the acceptance of targeting which is recognised as among the most cost effective strategies for STI/ HIV prevention. In Thailand, new STI clinics were opened and contributed to the success of the 100% condom use campaign. While the dynamics of the spread of HIV in Thailand are different in Africa, there is a strong case to be made for increasing the number of STI clinics in urban centres in the latter. In South Africa, targeted programmes for sex workers and miners brought about significant reductions in STI incidence.[13] Other established services for vulnerable and possibly illegal core groups such as sex workers, street kids, and injecting drug users could also suffer through SWAps. Again, ring fencing of funds by policymakers would appear to be necessary to assist these groups through STI and HIV prevention projects.

Supply and distribution of STI drugs

The importance of STI drugs in supporting a programme should not be underestimated. Drug shortages can quickly lead to both a loss of credibility of a programme and falling morale among service providers. Also, the potential for slippage (theft) of drugs may be considerable. Demand for STI drugs may be almost inexhaustible if used prophylactically. STI drugs provided for distribution to the whole health sector would be very difficult to track. Effective monitoring of drug use is paramount and should also be capable of standing up to rigid assessment through independent evaluation.

Conclusion

We are still not clear what is the best approach to improve STI control. The evidence base and what constitutes good governance in STI control varies significantly between populations. While SWAps support the horizontal approach to STI control by strengthening primary healthcare services, sometimes at the expense of designated specialist services, there is no evidence that this is the best strategy. Perhaps STI programme planners should take note of how health sector reform may affect tuberculosis control. Decentralisation of tuberculosis services into primary health care in Zambia has led to a marked reduction in funding and a deterioration in services for people with tuberculosis.[14] Optimal use of scarce resources for STI control probably requires a combination of approaches involving aspects of both the horizontal and vertical systems taking into account their strengths and weaknesses.[15 16] The tried and trusted methods in reducing STIs that have been poorly implemented in many African countries with severe STI/HIV problems should not be ignored in deference to SWAps until a full evaluation of its effectiveness has been undertaken.

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