

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 indeterminate 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 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 the 16SrRNA 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

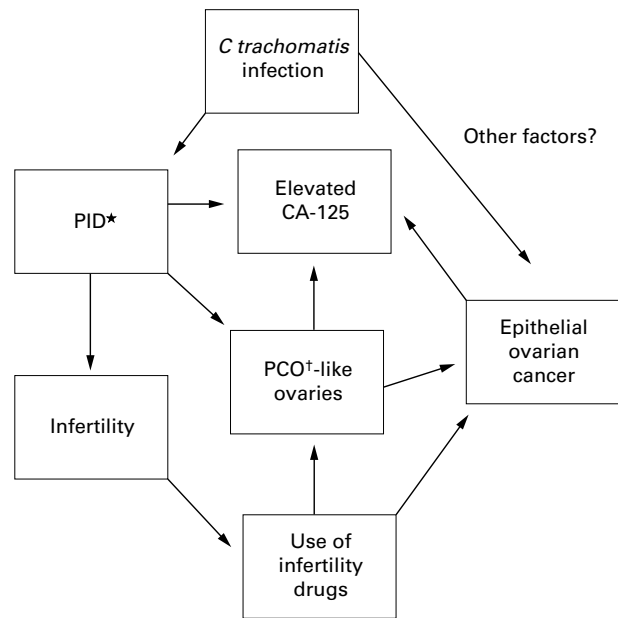


Figure 1 Hypothetical link between *C trachomatis* and epithelial ovarian cancer. *PID = pelvic inflammatory disease; †PCO = polycystic ovaries.

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 (SWAs) has been adopted by an increasing number of funders including the World Bank, World Health Organization, and the Department for International Development. Through SWAs, 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. SWAs 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 SWAs are effective.² No evaluation of SWAs 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 SWAs 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 SWAs 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