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Preventive human papillomavirus vaccination

M Lehtinen and J Dillner

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Social epidemiology

Understanding racial-ethnic and societal differentials in STI

S O Aral

Do we need to move beyond behavioural epidemiology?

Prevalence and incidence of sexually transmitted infections (STIs) vary across societies \(^1\) and across subpopulations defined by age, race-ethnicity, and socioeconomic status. \(^2\) The efforts to account for such variation and explain it, that can be found in the STD literature, have in general not differentiated between individual and population level health, or between population and individual level determinants of individual STD outcomes. \(^4\) Perhaps this pattern reflects the predominant paradigm in modern epidemiology which has been termed the “risk factor” paradigm and has been linked to “biomedical individualism” as its underlying theoretical foundation. \(^5\) This theoretical approach views populations simply as reflective of individual cases while considering social determinants of disease to be at best secondary, if not irrelevant. \(^7\) In the past several years, the risk factor paradigm in epidemiology has been seriously challenged by leading epidemiologists \(^8\) \(^9\) and a new paradigm that would emphasise the broader context of individual risk factors has been called for. It has been suggested that whereas traditional epidemiologists ask the question “Why are some individuals healthy and others not?” the social epidemiologist is concerned with the question “Why are some societies healthy while others are not?” \(^10\) Social epidemiology has focused on features of the economy, culture, politics, and the law. Examples of societal characteristics that have received attention include macroeconomic factors such as poverty, unemployment, and income distribution; and features of social relationships such as social cohesion, social exclusion, and sex and race relationships. \(^11\) Also, a renewed interest in effects of neighbourhood environments on morbidity and mortality has emerged. \(^12\) \(^14\)

Work in social epidemiology has emphasised neighbourhoods and the community; and considerations of social capital and collective efficacy have usually been applied to chronic diseases, mortality, violence, and mental health as health outcomes. Infectious diseases and, particularly, their modes of transmission are often ignored in this literature. Moreover, the social epidemiological approach is often successful in the description of social correlates of morbidity and mortality; identification of mechanisms of action through which social determinants influence levels and distribution of morbidity in populations tends to be more difficult.

Social epidemiological approaches may have a lot to offer to the explanation of STD differentials within and across societies. Conversely, STD epidemiology, with its distinct transmission dynamics may provide detailed examples of mechanisms of action through which social determinants operate. What follows is a description of one possible way in which relations among social determinants, their mechanisms of action, and their impact on STD morbidity may be conceptualised.

THE SOCIAL NETWORKS APPROACH IN STD EPIDEMIOLOGY

During the past decade an important trend in STD epidemiology research has focused on the role of sexual networks in the spread of STIs in populations. Findings demonstrated that in the United States, the higher rates of sexual contact between the “core” group and the “periphery” among African Americans facilitate the spread of infection overflow into the African American general population; whereas the “sexual segregation” of African Americans from other racial-ethnic groups results in STIs remaining inside this population. \(^15\) \(^16\) Other studies have shown that linkages between sexual networks are necessary for the spread of STIs across sexual networks; \(^27\) that so called “core groups” appear to be important in the spread of STIs and in their prevention \(^28\) \(^29\), and that the sexual transmission of sexually transmitted diseases (STDs) and HIV beyond core groups may depend on people who have sexual intercourse with members of core groups and with members of the general population—so called “bridge populations.” \(^31\) Studies in Thailand and other populations revealed that large proportions of men in certain occupations, such as truck drivers, the police, and the military tend to function as “bridges” between female sex workers and their wives or girlfriends. \(^32\) \(^33\) However, one study conducted in Seattle found the proportion of infection attributable to bridge populations to be remarkably small; with most of the disease burden for gonococcal and chlamydial infections in both high prevalence and low prevalence subpopulations being attributable to mixing within the subpopulation or to direct mixing with members of high prevalence subpopulations. \(^34\) It appears that bridge populations play a very prominent role in the introduction of infection into subpopulations, once the infection is introduced, most of the disease burden is attributable to mixing within the subpopulation.

Other studies conducted in Canada reveal that sexual network patterns involved in STD epidemics vary across phases of epidemics \(^35\) and that during later phases of STD epidemics, the majority of sexual networks involved in the epidemic are not restricted to one geographic area; \(^36\) frequent contact between network members from a small group of northern reserves and individuals in the major southern population centre of Winnipeg have formed bridges of transmission between these communities. Similarly, a study of elimination and reintroduction of primary and secondary syphilis in Seattle showed that characteristics of persons with primary and secondary syphilis varied across epidemic spread, elimination, and reintroduction periods. \(^37\) There were significant differences between cases during the various epidemic phases with respect to age, sex, ethnicity, drug use, and involvement with commercial and anonymous sex. Moreover, during all phases, imported cases differed from locally acquired cases with respect to age, sex, ethnicity, and drug use behaviours.

One network pattern that has received increasing research attention in recent years is concurrent partnerships, or sexual partnerships that overlap over time. \(^38\) Concurrent partnerships accelerate the spread of an STI through a population by removing the protective factors of time and sequence inherent in serial monogamy.

Sexual networks and patterns of sexual partnership formation and dissolution constitute a major mechanism of action through which the political economy and the sociological system influence the rate of spread of STI in a population; availability, accessibility, and utilisation of appropriate health care, and availability and utilisation of condoms being others.

CREATION, MAINTENANCE, AND EVOLUTION OF CORE GROUPS

Sexual networks that are highly critical to the rate of spread of STI include sex

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work; exchange of sex for goods, material needs or drugs; and anonymous sex. The creation, maintenance, and expansion of sex in exchange for money or other goods appears to be highly sensitive to changes in political economy and the sociological system. Internal conflicts, war, economic crises, and social collapse are accompanied by the establishment of major sex markets or the expansion of existing ones. For example, in Moscow, Russia, before the August 1998 economic crisis the number of female sex workers was 15,000–30,000; following the crisis this number increased to 30,000–90,000. Similarly, in Jakarta and Surabaya, Indonesia, between 1997 and 1998—during which time the monetary crisis occurred—the percentage of female sex workers who were less than 125% respectively; the percentage of female sex workers who were less than 130% during the same period in months’ experience increased by 28% and 1998—during which time the monetary crisis occurred—the percentage of female sex workers who were less than 125% respectively; the percentage of female sex workers who were less than 130% during the same period in months’ experience increased by 28% and 130% during the same period in these two cities. A decade of conflict in the Balkan region and the poverty of post communist eastern Europe have created a major network of trafficking in women which reaches across eastern Europe, Balkans, the Middle East, and Western Europe. Globalisation, characterising many social, economic, and behavioural patterns, includes sex work and expands the volume of sex workers.

The political economy and the sociocultural system and any changes in them systematically impact lower socioeconomic status, minority groups to a greater extent than others. Sociological systems tend to reinforce existing hierarchies and protect the privileged. Thus, social parameters often create the context which facilitates the creation, maintenance, and expansion of sexual networks that cause rapid spread of STD among minority racial, ethnic, and socioeconomic groups and in less developed societies. The same context associates longer duration of infection with the less privileged groups and less privileged societies through differential access to, and differential utilisation of, good quality STD care. A detailed description of the sociopolitical context in which African Americans live in the rural southeastern United States powerfully elucidates how contextual features including racism, discrimination, limited employment opportunity, and resultant social and economic inequity may promote sexual network patterns that transmit STIs.

Despite the powerful effects of social context and social determinants embedded in political economy and sociological systems on the level and distribution of STDs, most of our research and surveillance attention focuses on the STDs themselves and to a limited extent on the individual behaviours associated with STD acquisition. It is important to develop standard techniques for summarising the behaviour and nature of sex work within populations and for determining the size and nature of the interactions among core groups, bridge populations, and the general population. Moreover, most research and surveillance activity tends to be conducted within local boundaries, without much attention to sexual links that relate many local sexual networks to each other. Given that prevalence of sex work seems dependent on global forces, and that sex workers seem to be highly mobile across geographic areas, it may be important to consider the establishment of surveillance systems that include monitoring of contextual parameters and social determinants at regional and global levels. STD prevention programmes may be more effective if informed about the local, regional, and global context in which STD rates rise and fall; and which create the inequalities in STD incidence across societies and across groups defined by race-ethnicity and socioeconomic status.

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Vaccination

Preventive human papillomavirus vaccination

M Lehtinen, J Dillner

Considerable gains at the individual and societal level would be obtained if cervical cancer could be prevented

The cancer burden causally associated with human papillomavirus (HPV) infections is high. Cervical cancer is the second most common cancer among females in the world, with 500,000 new cases and 300,000 premature deaths a year. Because of the long preclinical period cervical cancer can be prevented by screening, diagnosis, and treatment of premalignant cervical lesions, but for developing countries preventive vaccination may be the only possibility to significantly reduce cervical cancer incidence. Also in the developed countries considerable gains at the individual and societal level would be obtained, if a significant proportion of cervical cancer and its precursor lesions could be prevented if cervical cancer could be prevented

Considerable gains at the individual and societal level would be obtained if cervical cancer could be prevented.

In phase I and II trials HPV VLPs have proved to be safe and highly immunogenic. HPV VLP immunisation induces approximately 100-fold higher neutralising antibody titres than natural infection. The level of mucosal immunoglobulin G (IgG) is 10% but it varies following the menstrual cycle and is lowest at the time of ovulation. The prevailing theory of the mode of action of the vaccine, however, suggests that this variation may not be a major problem. In natural infection the entry of HPV into the basal cells of the epithelium, which support the initial stages of viral replication, is facilitated by a microscopic trauma resulting from, for example, sexual intercourse. Following this microtrauma, circulating antibodies leak to the epithelial surface and neutralise the virus.

The L1 antibodies recognise a conformational, type specific epitope, and have shown close to a 100% protection in animal studies against homologous challenges with both HPV and animal papillomaviruses. While the increasingly large number of oncogenic HPV types (16, 18, 31, 33, 35, 45, 51, 52, 58, 59) that associate with cervical cancer may make it impossible to achieve 100% protection against cervical cancer, it is relatively easy to include the most prevalent oncogenic HPVs (HPV16 and HPV18) into a multivalent VLP vaccine, however, suggests that this variation may not be a major problem. In natural infection the entry of HPV into the basal cells of the epithelium, which support the initial stages of viral replication, is facilitated by a microscopic trauma resulting from, for example, sexual intercourse. Following this microtrauma, circulating antibodies leak to the epithelial surface and neutralise the virus.

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Analogously to hepatitis B virus (HBV) vaccine HPV VLPs also induce cytotoxic T cell (CTL) responses by entering the MHC class I pathway. If the antibodies fail to neutralise all HPV virions, CTLs recognising viral capsids bound for as long as 10–12 hours to more or less specific cellular receptors (integrin and/or heparan sulphate proteoglycans) might block spread of the virus at its most primateal stage in the initially infected cells. Production of new virions takes place in the upper layers of the epithelium, and CTLs targeting these cells might effectively reduce spread of the virus. Indication of this has, however, been shown only for the non-oncogenic HPV VLPs, and it is not clear whether such a response is able to eliminate oncogenic HPVs from the basal cells.

CVLPs may offer a significant advantage in this regard. The expression of various early HPV proteins responsible for viral replication (E1), transcription (E2), and onogenesis (E6, E7) is abundant both in the basal and the differentiating epithelial cells providing good targets for the CTLs. Two vaccines based on different gene constructs—HPV16 L1, L2 truncated E2–E7 CVLP (by an NIH group) and HPV16 L1–E7 CVLP (by Medigene)—have passed or are passing safety and immunogenicity tests.

In addition to the induction of high titres of neutralising antibodies, some of which (anti-L2 antibodies) may be cross protective against several HPV types, the CVLP vaccines induce CTL responses against the early proteins in humans. However, in CVLP data on humans are scarce and need to be expanded. CTL responses against the early HPV proteins are important not only in order to provide theoretically improved protection and possible therapeutic effect, but because they may also offer cross protection against several HPV types. The E1 and E2 proteins are particularly well conserved among the HPVs.

The analogy between the different HPV VLP vaccines and the first human cancer vaccine, HBV vaccine, is very encouraging. The HBV vaccine has an overall efficacy of 95%, even when given to infants born to mothers with active hepatitis (HBV-e antigen positive women, the offspring of whom are prone to become chronic HBV carriers) its efficacy exceeds 75%. These figures also fit the available data on long term effects of universal HBV vaccination. The incidence of liver cancer has reduced by 75% among 12–14 year old Taiwanese children 15 years after implementation of the nationwide HBV vaccination programme. This was to be expected on the basis of seroepidemiological data showing that HBs antibody positive
individuals have a reduced risk of liver cancer, whereas HBs antigen positive individuals have an increased risk. This was the first randomised trial proving the efficacy of HBV vaccination against both acute hepatitis B and becoming a chronic HBV carrier. But, however encouraging, analogies should be considered with caution.

While it appears that most of the women treated for the HBV induced premalignant lesions by, for example, laser or loop excision can tackle the residual low amount of virus and eventually clear the infection, recurrences do occur with varying incubation times and for reasons that are not totally understood. Restricting the viral load plays a part, and new strategies for cervical cancer control are also based on identification of women with moderate to high levels but not low levels of oncogenic HPV DNA (for a systematic review see Cuzick et al5). The role of natural infection or vaccine induced VLP antibodies in restricting mucosal HPV infection may, however, be qualitatively different from the central role of circulating HBV antibodies in preventing systemic hepatitis B infection. While HBV antibody positive individuals have an increased risk of liver cancer, the HPV16 VLP antibody positive individuals remain at an increased risk of developing cervical cancer and other HPV16 associated cancers 10–20 years after infection.7 There are no good data to suggest that the antibodies would do any harm—for example, by inducing latency, but we simply do not know to what extent the paradigm on prevention of liver cancer by preventing acute HBV infection and HBV carrier status can be applied in the HPV infection-cervical neoplasia context.

The main effector function of VLP vaccination is neutralising antibodies but these may never be able to induce totally sterilising immunity and the concept of significantly reducing the viral load becomes an issue.8 While the minimum HPV viral load for development of cervical and other cancers is not known, it is likely that HPV vaccine induced neutralising antibodies and/or CTLs will prevent or significantly restrict and aid in clearing of the primary HPV infection, and reduce transmission of the infection to others. Randomised clinical trials will eventually define efficacy of the different vaccines against persistent HPV infection and other surrogate endpoints, such as cervical intraepithelial neoplasia grade II/III. A proof of the principle that HPV vaccines can prevent these necessary steps in cervical carcinogenesis might be considered sufficient to demonstrate efficacy and to compare different vaccines, and limited licensures will be considered probably sooner rather than later.

There are, however, several possible pitfalls that could prevent effective vaccines from actually achieving their expected health benefits. For example, if vaccination is not differentially associated with determinants of progression or if vaccination induces changes in the population biology of the different HPV types. To find out these pieces of information one has to organise a long term follow up of the initial randomised trials. Countries with stable and vaccination prone populations, population based health registers, standardised public health care, and organised mass screening for cervical cancer have the appropriate infrastructure and setting for direct extension of the clinical trials to the invasive cervical cancer (ICC) and cervical intraepithelial neoplasia grade III (CINIII) end points based on registry follow up.9 Population based randomisation and informed consent based linkages of the different study and health registers from the very beginning to death are needed especially to avoid different selection biases, performance bias resulting from “contamination” of the population after licensure of the vaccines,10 and loss to follow up bias. The ultimate proof will be that immunisation with HPV vaccines significantly reduces the incidence of (and mortality from) cervical cancer and its immediate precursors compared to unvaccinated population based references.11 If it turns out that the plain VLP vaccines fail to do it, while the chimeric VLP vaccines are successful we can infer that simple reduction of the HPV load at the port of viral entry is not enough, and that the second barrier of cell mediated immunity against the early viral proteins is also needed. At the moment, however, there is no indication of this and both alternatives should be pursued.

For all end points it would be optimal to target large numbers of young boys and girls who are about to start their sexual activity, since they will have the highest event rates of both HPV infections and associated cancers. Targeting both sexes may, however, not be necessary at this stage since the assumed vaccine efficiency against HPV infection (90%) is high enough to bring the beneficial long term effect to the females.12 With an assumed attack rate of 0.65% and a vaccine efficacy against CINIII+ICC, enrolment of altogether 15 000 such vaccinees and referents for 15–20 years of registry based follow up would give 80% statistical power to judge whether a vaccine which covers two thirds of the oncogenic HPV types protects against CINIII+ICC. Comparison of different HPV vaccines and gradual implementation of the adolescent vaccination into the general vaccination programme using the same setting would bring in considerable synergy and needs to be considered seriously. Last but not least, possible ethical problems associated with ending or discontinuing the early end point clinical trials would be largely solved by the possibility of referring the vaccinees to an organised mass screening.

Pieces of the preventive HPV vaccination puzzle are on the table. If the scientific community, together with the public health authorities and vaccine manufacturers, manages to solve the puzzle the expected health benefits are immense.

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Editorial

The year ahead
Mohsen Shahmanesh

We have introduced some new sections with the aim of adding value to the journal. Update has replaced the Recent Publications section and hopes to bring expert critical summary of topic based important recent publications—pelvic inflammatory disease on this occasion. An impending tropical disease section, edited by David Lewis, will provide state of the art summaries of diagnosis and management of these conditions, embracing also issues faced in resource poor settings.

Later this year we will begin our interactive CME section, based on “grey cases.” Sarah Edwards will be heading this section helped by Richard Lau. We are negotiating with the Royal College of Physicians to gain CPD recognition. Our expanded editorial board have all promised to provide us with either an Update or a review article, and we are waiting for these to roll in.

Impact factor

Finally to the issue of impact factor, with which our funding authorities appear so infatuated. After disappearing into the ether as a result of our name change we have re-emerged with an unprecedented factor of 2.1 (fig 1). For those who may not be too familiar with it let me clarify the mathematical conjuring tricks which resulted in that figure. Impact factors are derived by dividing all the citations of the previous 2 years by the number of articles published in a given journal. There are a few exceptions. For example, letters count as citations but not as articles. When conference abstracts are cited, an increasing and questionable practice, they are considered bona fide citations though the original abstract is not counted as a publication. The same is true for supplements.

You can see where this illogical juggling leads: journals with a large correspondence, or which publish conference abstract and supplements do well. More questionably, clinical journals do worse than pure science journals. This is because clinical research takes longer to perform than laboratory based research. Hence the “impact” of clinical studies is longer—and certainly way beyond the arbitrary 2 year cutoff point. The final point to make is that the impact factor usually reflects the “impact” of one or two articles with high citations and is therefore more realistically the impact factor of an article rather than the journal as a whole. As you see, this is an imperfect measure of the quality of a journal. But it is all we have. The Americans, rightly I think, ignore it. The rest of the world are unnaturally wedded to it.

Figure 1 Impact factor of STI.