EDITORIAL

SECOND EUROPEAN MULTI-DISCIPLINARY CONFERENCE OF NATIONAL STRATEGIES FOR *CHLAMYDIA TRACHOMATIS* AND HUMAN PAPILLOMAVIRUS (NSCP CONFERENCE) IN BERLIN, 2013 – ENHANCED DETECTION, MANAGEMENT AND SURVEILLANCE OF SEXUALLY TRANSMITTED INFECTIONS IN EUROPE ARE ESSENTIAL!

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There is a need for updated guidance on detection, management and surveillance of sexually transmitted infections (STIs). Chlamydia, gonorrhoea and syphilis reporting needs to be mandatory in more European countries to aid collection of data. More widespread Chlamydia screening is needed in many countries as this is the only way to reduce complications. The role of Human Papillomavirus (HPV) screening in a situation where the prevalence of HPV infection has dropped significantly was also discussed in the context of the high cost of screening, the need for a relatively complex infrastructure, particularly in developing countries, and falling vaccination costs. An integrated HPV vaccination and screening policy could be the most appropriate with vaccination at 9-13 years as recommended by WHO and a single HPV screen at 35-39 years, possibly repeated thereafter every 10 years. Female and male HPV vaccination programmes could lead to near elimination of genital warts in both females and males. Surveillance of STIs should be intensified where needed; additional or better quality data should be collected including reasons for testing, denominator data to estimate positivity rates, diagnostic methods, concurrent STIs, sexual orientation and country of acquisition; more analytical rather than descriptive epidemiology is needed.

In 2008, the World Health Organization (WHO) estimated 499 million cases among adults of the non-viral treatable sexually transmitted infections (STIs) trichomoniasis, gonorrhoea, *Chlamydia trachomatis* infections, and syphilis globally. Accordingly, those STIs, including their severe complications, cause substantial morbidity and economic costs, and represent major public health concerns globally (1, 2). Across European countries, there are large variations in the reported incidences of those and other STIs. This can be partly explained by the different health care systems including provision of testing and management of STIs, STI laboratory diagnostic methods used (type, performance characteristics and quality assurance), clinical and laboratory reporting mechanisms, type, functioning

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and completeness of surveillance systems and availability of epidemiological and microbiological data on rates of STIs.

This paper reports discussions and outcomes of the 2nd European Conference on National Strategies for *C. trachomatis* and Human Papillomavirus (NSCP) in Berlin, Germany, May 23-24, 2013. The NSCP is an international multi-disciplinary conference that invites STI clinicians, microbiologists, public health experts, epidemiologists, sexual health and behavioural scientists, as well as basic scientists, to share knowledge and expertise in order to collaboratively find effective tools to combat the spread and burden of STIs internationally. Since 2009, STI surveillance in the European Union/European Economic Area (EU/EEA) has been coordinated by the European Centre for Disease Prevention and Control (ECDC). However, in the EU/EEA, as well as in many other regions worldwide, the reported incidences of *C. trachomatis* infections are underestimated, due to the suboptimal diagnostics, testing coverage, and incomplete case reporting and epidemiological surveillance performed in many countries. Accordingly, the substantially higher incidences of those and other STIs in some countries are certainly highly affected by a more effective case detection, better diagnostic tools, greater awareness of clinicians, and improved surveillance systems as well as the introduction or expansion of chlamydia screening programmes in a few countries (2, 3).

The conclusions of the meeting were that an integrated surveillance system for *C. trachomatis* infections, gonorrhoea and syphilis should be implemented in all European countries. Implementation of the ECDC surveillance mechanisms for STIs in all EU/EEA countries is highly recommended (4). It is also crucial to substantially increase the access and performance of testing, and optimize the quality of diagnostics, case management, reporting, screening and surveillance of non-viral STIs (2).

CONTROL PROGRAMMES, INCLUDING SCREENING, FOR *CHLAMYDIA TRACHOMATIS*

European countries with adequate diagnostic capacity, testing volume and coverage, and well-functioning surveillance systems typically have high reported incidences of *C. trachomatis* (5). Dr. Torvald Ripa of Sweden discussed the history of control programmes for *C. trachomatis* in Sweden, depicting the importance of opportunistic screening (defined as offering a test to patients attending health care or other defined settings for any healthcare reason) to influence the number of infections and importantly also complications, increased testing in general and using nucleic acid amplification tests (NAATs) in particular, effective cases detection and reporting, and high awareness of *C. trachomatis* infections among general population as well as professionals. Dr. Ripa also suggested to divide the epidemiology of *C. trachomatis* into three "phases": 1) "Non-treated hyper endemic phase": no diagnostic facilities, rudimentary knowledge; 2) "Treated hyper endemic phase": testing and treatment of symptomatic patients; 3) "Epidemiologic treatment phase": testing and treatment of symptomatic patients and "case finding" of asymptomatic individuals. Phase 3 is required to truly influence the epidemic and is the way to control the burden of *C. trachomatis* infections provided adequate coverage can be reached (5).

Nevertheless, challenges to provide effective control programmes and STI surveillance remain in many countries, including those countries with adequate diagnostic capacity. For example, in Germany cases of *C. trachomatis* infections are still not mandatorily reported. However, in 2008 an opportunistic *C. trachomatis* screening programme for women <25 years of age (OCS) was introduced in Germany and subsequently a concomitant voluntary laboratory surveillance system tried to gather information. The results from this surveillance system showed that the proportion of young women testing positive for *C. trachomatis* was high and that OCS coverage remained insufficient. OCS should be promoted, using e.g. awareness campaigns, among the target population and physicians (6). In Germany, the Robert Koch-Institut has also assessed available data on *C. trachomatis* prevalence and positivity rates (PR), using five specific data sources, and defined the need for further surveillance and research. The data sources were: two health surveys in the general population, data from a laboratory sentinel system and two surveys among sex workers and men who have sex with men (MSM).

Accordingly, some epidemiological data regarding *C. trachomatis* infections in Germany are available, but the data are incomplete. Statutory surveillance or at least the continuation of the laboratory sentinel surveillance would allow identifying time trends, and those data should be supplemented by repeated sexual behavioural surveys (7).

Most European countries have no complete control programme for *C. trachomatis* infections and it is crucial to enhance the diagnostics, testing volume, and surveillance system in many countries. However, the cost-effectiveness of screening programmes and opportunistic testing strategies need to be appropriately evaluated, which will form the basis for decision makers in times of financial deprivation. The ECDC can provide information regarding optimized and standardized surveillance and control programmes for *C. trachomatis* infections, and early next year ECDC will have its updated guidance on Chlamydia control available (3).

IMPROVED AND NOVEL STRATEGIES ARE NEEDED TO TRULY INFLUENCE THE EPIDEMIOLOGY OF *CHLAMYDIA TRACHOMATIS* INFECTIONS

As mentioned above, screening, adequate testing and treatment of symptomatic patients and "case finding" of asymptomatic patients are important to truly affect the epidemics of *C. trachomatis* infections (5). However, screening and strategies for prevention of chlamydial infections are usually based on the assumption that the infections are uniformly spread, particularly in the young population. In many countries a small proportion of young people are responsible for a large number of chlamydia cases. This clearly shows the importance of linking and subsequently evaluating data from *C. trachomatis* diagnostics, surveillance, prevention, and sexual health and behaviour. An appropriate "risk assessment model" has the potential to create awareness about risk factors and promote testing the identified high-risk populations through online self-identification and in clinical settings. In Sweden, risk factors such as age, number of sexual partners, negative experience of sex or experience of unwanted sex, receiving reimbursement for sex (8), or hazardous alcohol consumption (9), have been identified in some studies. Furthermore, as Dr. Ruth Verbrugge of Belgium stated appropriate analyses on notification rate (NR), testing rate (TR) and test positivity rate (TP) are highly important. Worryingly, in many programmes the groups with the highest TP are not sufficiently tested and it is crucial to develop programmes, which include appropriate methods for partner notification, for those groups (10).

Enhanced *C. trachomatis* testing in general practice (GP) might also be necessary to combat the high incidence of chlamydial infections in many countries. The Australian Chlamydia Control Effectiveness Pilot (ACCEPt) is a cluster randomised controlled trial to evaluate annual *C. trachomatis* screening for 16-29-year-old patients attending GPs. Towns, in which all GP clinics are enrolled, have been randomised to receive a multifaceted intervention to increase Chlamydia testing or continue with usual practice. Nearly twice as many tests have been conducted in intervention clinics and testing rates are still increasing. The high participation rate of clinics in all towns puts the study in a strong position to determine whether a pragmatic intervention involving GP can reduce *C. trachomatis* prevalence (11). Furthermore, the Borough of Lambeth in South London, United Kingdom has successfully integrated *C. trachomatis* screening in GP and GPs are now responsible for 40% of all *C. trachomatis* tests in the Borough of Lambeth. This programme has combined a financial incentive to practices with education outreach and peer support from a local GP (12).

CHLAMYDIA TRACHOMATIS PATHOGENESIS, INFECTION AND VACCINATION

In the past, attempts to obtain a detailed understanding of the interactions between *C. trachomatis* and the human host have been hindered by, e.g., the genetic intractability of chlamydiae and the absence of suitable infection models. However, recently several groups have succeeded to genetically modify chlamydiae, paving the way to test the function of single genes in a sensitive and specific manner, identifying and verifying pathogenicity factors, and many additional issues. This is a ground-breaking step that will be important for understanding the pathogenesis and to optimize

diagnostics, treatment and hopefully for the development of a vaccine. A second major effort will characterize the micro-environment in which *C. trachomatis* infections take place in humans in order to adjust or refine existing infection models to become more physiological. Following the recent technical advancements, it will become possible to detect the metabolic content (metabolomics), the polymicrobial composition (microbiome) and the transcriptional regulation (metatranscriptomics) within clinical samples from the urogenital tract of *C. trachomatis* patients. Using these findings to modify host-pathogen interactions experimentally has already proven successful to characterize environmental conditions that ameliorate *C. trachomatis* progeny and allow the pathogen to escape the host immune response (13). As the first step in the pathogenesis, adhesion between the pathogen and host target is a prerequisite for subsequent steps in the infection process. *C. trachomatis* can infect various cell types, however, the molecular mechanisms of adhesion to and invasion of human cells are still not understood. Nevertheless, the chlamydial adhesin, OmcB, which binds to glycosaminoglycans (GAGs) on host cells, has been characterized. Furthermore, all nine *C. trachomatis* Pmp proteins are adhesins and play an important role in infection (14). All these findings make it more promising that a *C. trachomatis* vaccine will become a reality in the future.

Nevertheless, Peter Timms stressed that many challenges for development of a highly and broadly effective and safe *C. trachomatis* vaccine remain, i.e., i) there are multiple serovars of *C. trachomatis* (antigen(s) covering all of those?); ii) protection of infectious burden does not always equal protection of subsequent pathology in host (type of immune response required?); iii) how to obtain sufficient protection but avoid immunopathology resulting in more severe disease in host particularly on re-infection?; iv) targeting immunity to the reproductive tract (immunization route, antigen and adjuvant?); v) acute as well as persistent/chronic infections to combat; vi) ideal mouse model?; and vii) if developing an effective vaccine, which group (age, sex) should we and will we be allowed to vaccinate? (15). For example, the major outer membrane protein (MOMP) is highly immunogenic, but suffers from substantial serovar and strain diversity, and can also be exposed to recombination (16). Furthermore, recent studies have shown that the vaccine preparation that produces the best reduction in infectious load does not necessarily result in the best reduction in pathology score. The key cytokine responses that underpin each type of protection are however now beginning to be elucidated (15). Robin Bailey stressed that prospective studies on women with genital *C. trachomatis* infections are also required, which are logistically and ethically very difficult to perform. The natural history pathogenesis and immunology of *C. trachomatis* ocular infection has been studied in detail but little is known about these aspects of genital infection. Trachoma vaccine trials carried out in the 1960s showed it was possible to induce protective immunity to *C. trachomatis*. Studies on non-human primates suggested that vaccination may lead to more severe ocular disease on re-challenge, but there was no truly convincing evidence that this happened in the human trachoma vaccine trials. It will be extremely challenging to ensure that vaccination does not lead to more severe disease in the genital tract. Two approaches have been outlined to the study of innate immunity in subjects with trachoma. Microarray analysis of host gene expression in infected eyelids has shown increased expression of components of a series of pathways involved in pathogen sensing and the signalling and effectors of the innate immune response. Analysis of risk effects near the IL-8 locus suggests the possibility that genetically-mediated high levels of IL-8 may increase tissue damage.

To conclude, while still remaining a major challenge, the development of a successful *C. trachomatis* vaccine is starting to look more likely (15).

HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS, SCREENING AND VACCINATION

HPV is the etiological agent of the most frequent STI globally. At least 60% of all sexually active men and women are infected with HPV during their lifespan. HPV infections might result in cervical cancer in women and anogenital, head and neck cancers, anogenital warts and recurrent respiratory papillomatosis in women and men. Invasive cervical

cancer is the second most common cancer among women worldwide and, worryingly, cervical cancers occur frequently in young women. Vaccination against HPV infections represents the most effective way to decrease the burden of cervical cancer, especially among young women. Thus it is highly recommended that HPV vaccination campaigns are implemented in all countries in order to prevent both HPV infections and cervical cancer (17).

HPV screening is a complimentary approach to reduce the cervical cancer burden, which has not yet been widely implemented in many countries and has performed sub-optimally in a few developing countries due to lack of adequate coverage, follow-up and quality assurance. A complimentary strategy involving HPV vaccination of single year cohorts in the age range 9-13 years and HPV screening of women aged 35 years in developing countries will have far reaching impact in preventing cervical cancer in low-resource settings by building up a cohort of women at low-risk for HPV infection and therefore for cervical cancer and at the same time building up a screening infrastructure to care for unvaccinated adults and those who have breakthrough HPV infections. Current research indicates that HPV testing is the most effective cervical cancer screening tool and women negative for HPV at baseline are at very low risk for cervical cancer. The availability of a simple, affordable, fast and accurate HPV test would facilitate wider HPV screening in low-resource settings. Until affordable HPV testing screening strategies become widely available, even visual screening, e.g. visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI), can build up an early detection infrastructure and skills. In conclusion, it is most prudent to implement a complimentary approach involving HPV vaccination and cervical cancer screening, and planned investments for such a combined approach will save many precious lives in developing countries (18).

From mid-2007, in Australia a universal free HPV vaccination programme for young females has been running (19). The significant declines in the proportion of young women found to have genital warts and the absence of genital warts in vaccinated women in 2011 suggests that the human papillomavirus vaccine has a high efficacy outside of the trial setting (20). This programme has achieved high coverage rates and, in 2013, Australia became the first country to extend the free HPV vaccination programme to boys aged 12-13 years (a catch-up programme includes boys aged 14-15). Although there has been a decline in the proportion of young heterosexual men diagnosed with genital warts, suggesting herd immunity, the decline is slower than that of young females and no decline is observed in homosexual/bisexual men. The male vaccination programme will lead to near elimination of genital warts in both females and males in Australia (19).

OUTCOMES AND RECOMMENDATIONS

The main conclusion of the discussions within this conference was the substantial need in many countries to increase the access to appropriate testing, including screening strategies, to optimize the quality of diagnostics, performance of testing, as well as management, reporting and surveillance of detected cases.

The participants appreciated the multidisciplinary approach needed to effectively combat the spread and burden of STIs internationally, and strongly recommended to keep this approach for future conferences. Furthermore, the programme should be structured accordingly and speakers informed about the heterogeneity of the audience to enhance targeted discussion. The next conference should have clear goals and corresponding recommendations should be the outcome of the conference. Guidance on how the targets can be reached should be provided and the steps reached monitored. The organisation of workshops to discuss local recommendations and to plan in realistic time-frames was emphasized.

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