Enfermedades Infecciosas y Microbiología Clínica 40 (2022) 470–472

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Editorial

A challenging future in the sexually transmitted infection diagnostics landscape: *Chlamydia trachomatis* as model

Un futuro desafiante en el diagnóstico de las infecciones de transmisión sexual: *Chlamydia trachomatis* como modelo

The last WHO report estimated 374 million new sexually transmitted infections (STI) per year in the world; or in other words, more than one million per day.[1] The highest incidences observed were for four infectious agents, chlamydia, gonorrhea, syphilis and trichomoniasis. In Spain, the STI incidence was decreasing during the last years of the twentieth century. However, the trend reversed in the first decade of the 21st century and a most worrying increase in chlamydia and gonorrhea has been observed since 2015.[2] In the absence of well-designed and targeted screening programs, several factors are contributing to the continuous increase in the STI incidence in industrialized countries. Among these are changes in the sexual behavioral including age at first sexual intercourse or the high percentage of extragenital infections which are usually asymptomatic, the scope of mobile apps used for sexual contacts, recreational drugs (chemsex and/or slamming), or the decrease in the use of condoms related to prophylaxis pre-exposition (PrEP) against HIV infection. In addition to these new social and health realities, other situations have not yet been resolved such as the difficulties in access to early diagnosis and treatment in some populations. In Spain, the national incidence of chlamydia (44.18/100,000) is still well-below the European average (146/100,000)[3] suggesting an underdiagnosis of *C. trachomatis* cases. In fact, in those countries, such as the UK, with excellent programs of surveillance, the incidence reaches 365/100,000 population revealing that Spanish screening strategies should be revised.[4] HIV and STI are interrelated sharing transmission mechanisms and the target population. For this reason, the WHO Global Strategy for the Health Sector for the prevention of HIV, STIs and viral hepatitis has integrated all these infections for the first time to optimize their impact.[5] Following these recommendations, the Spanish Plan for prevention and control of HIV and STI infection 2021–2030, has designed combined strategies against HIV and STI,[6] focused in 4 objectives: prevention, early diagnosis, and treatment but also equal treatment and opportunities.

The chlamydial epidemiological setting is particularly complex as two different population profiles can be identified. The first, affects younger people ranging from 15 to 24 years old, especially heterosexual women, in percentages from 65 to 80% compared to men and 70% of the genital infections. The other population profile is related to men ranging from 25 to 44 years old, more frequently found in men who have sex with men (MSM) with extragenital infection in around 70% of cases.[2] In the MSM group, the invasive genotypes of *Chlamydia trachomatis,* related to lymphogranuloma venereum, are the most detected, and for these genotypes the MSM: women ratio is 100:1. Consequently the screening strategies must be planned according to both epidemiological profiles.

In the current journal, López-de Munain et al. analyzed the clinical and epidemiological characteristics of patients infected by C. *trachomatis*.[7] They suggest the implementation of opportunistic screening in women under 25-years-old, with and without symptoms, because of 25% of people with STI were included in this age group and 70% were described in asymptomatic patients. Their recommendations go hand to hand with those from the US Center for Disease Control and Prevention (CDC), who also include a test of cure at 3 months post-treatment, especially in pregnant women.[8] In the UK, when the promotional campaigns were implemented, the overall number of the screened young population increased, but surprisingly the positivity rates have not increased in the same way,[9] suggesting the simultaneous need for a comprehensive approach to sexual health together with several other perspectives. For instance, the European Center for Disease Prevention and Control (ECDC) proposes to work in three lines, such as formation for healthcare professionals, facilitate access to rapid diagnosis, such as the availability of point-of-care for syphilis chlamydia and gonorrhea in the emergency department; and auto-sampling for those patients with cultural or language barriers.[4] In Spain, where there is low social awareness of the need for testing, several initiatives have been explored such as educational programs for young people, including preservative use (under 30% or 60% in occasional intercourse between men and women or MSM respectively), to implement periodic screening until reaching 70–80%, auto-sampling or online questionnaires with telemedicine assistance. CDC has directed a marketing campaign for self-tests, and the messages include a weblink for an online ordering portal inside the Federal Ending of the HIV Epidemic program (EHE).

DOIs of original articles: https://doi.org/10.1016/j.eimc.2021.06.004, https://doi.org/10.1016/j.eimc.2021.03.016, https://doi.org/10.1016/j.eimc.2021.02.005

https://doi.org/10.1016/j.eimc.2022.03.003

López-de Munain et al. propose the sampling from genital and extragenital samples as an optimal strategy (around 20% of patients had *C. trachomatis* in more than one localization); their data showed that 70% of *C. trachomatis* infections in MSM and 15% in females were detected in extragenital localization (such as rectum and pharynx). These extragenital infections are mainly detected in asymptomatic patients, revealing that we should also be proactive in the identification of these patients. However, other authors have questioned the potential beneficial effects (more diagnoses) of increasing screening frequency in asymptomatic patients. Several reasons are argued. Among them, the denominated arrested immunity hypothesis; according to this hypothesis early diagnosis and treatment of asymptomatic infections could abrogate the development of an effective immune response and the subsequent intact susceptibility to reinfection, paradoxically increasing the number of infections among vulnerable population,[10] but also if 12–57% of extragenital *C. trachomatis* clear spontaneously yet excessive use of antibiotics could contribute to increased antibiotic resistance.[11] In our opinion, the long duration of infection in asymptomatic patients (weeks or months) probably contributes to high levels of transmission and therefore, with the current scientific evidence, we consider that screening in the asymptomatic high-risk population, such as patients on PrEP should be undertaken.

The introduction of a PrEP program preventing HIV infection has demonstrated its cost-effectiveness, but the efforts for reducing HIV transmission are also contributing to a reduction in condom use and the expansion of a global STI epidemic.[12] In order to avoid that worrying scenario, the STI screening will be increased in the next months or years and new cost-effective studies will be necessary. Currently, CDC and several European institutions recommend STI screening every 3–6 months for MSM using PrEP (https://www.cdc.gov/std/treatment-guidelines/screening-recommendations.htm). A Dutch study analyzed the cost-effectiveness of those screening strategies based on 3 or 6 months, over a 10-year period. Although they detected 18,230 *C. trachomatis* and *N. gonorrhoeae* infections in the 3-monthly screening, this strategy is not cost-effectiveness[13] and probably should be evaluated to extended screening intervals. Furthermore, substantial gaps exist between international recommendations for STI screening during PrEP care in current clinical practice, particularly for rectal and pharyngeal exposure because only 2 out of 3 PrEP users are screened for STI in those locations.[14] In this group, the genotyping of *C. trachomatis* is necessary to detect invasive genotypes such as lymphogranuloma venereum (LGV), as LGV was diagnosed > 20% of anorectal positive *C. trachomatis* from MSM.[15] A correct diagnosis of LGV is important because of the distressing morbidities, such as perirectal abscesses severe proctitis, proctocolitis, rectal bleeding, etc. Moreover, the treatment required is longer than non-invasive *C. trachomatis* genotypes.

Another reason for the detection of *C. trachomatis* is related to the impact in the reproductive health of women because around 9–20% of women with prolonged *C. trachomatis* infection could evolve to pelvic inflammatory disease (PID) and among the untreated women 5–10% could evolve toward tubal pathology, infertility or ectopic pregnancy.[16] PID is clinically difficult to define, but the estimations suggest that the burden of this disease associated to PID affect around 2.1–2.4 million reproductive-aged US women. Several microorganisms have been involved, especially those related to STI, but *C. trachomatis* infection is probably the main risk factor for developing PID, which is the gateway to the appearance of reproductive sequalae.[17] For this reason, the detection and treatment of *C. trachomatis* infections will prevent or interrupt reproductive tract morbidity, but unfortunately, many times, the persistent infections are asymptomatic. Two works are published in the current volume of this journal. One of them, analyzes the rapid diagnosis for dual detection of *C. trachomatis* and *N. gonorroheae*,[18] and the second study reports the *C. trachomatis* genotypes detected in men with infertile women as sexual partners.[19] The point-of-care (PoC) for detection of *C. trachomatis* and *N. gonorrhoeae* in PID cases concluded that the presence of CT/NG was not a risk factor for a complicated clinical course, and the PID management should be based on clinical features, irrespectively of the presence or absence of *C. trachomatis* or *N. gonorrhoeae.* However, we have commented the lack of specificity in the clinical diagnosis of PID. Several groups are working to identify non-invasive biomarkers, which will help us with better identification of PID cases. A downward trend in PID since 2007 has been observed, which could be related to increased screening, especially for *C. trachomatis* in women < 20 years old with low or no impact in the female population over 25 years.[20] In the PoC work, the studied population was > 25 years and probably this selected population could have affected their conclusion.

We agree that the clinical and molecular PID diagnosis should be improved. A few groups are suspecting, as do Munrós et al., that the only molecular detection of *C. trachomatis* is not sufficient to infer the clinical evolution or pathogenesis. The quantification of gene pgp3 (or the protein corresponding) encoded in chlamydial plasmid could improve our understanding of the chlamydial pathogenesis.[21] For instance, the high antibodies level against Pgp3 was 2–3-fold more frequent in PID and infertile women[22] and the introduction of serological testing in young reproductive-aged women could help in the management. On the other hand, we know that PID is a polymicrobial infection involving STI microorganisms such as *Mycoplasma genitalium* or anaerobic bacteria associated to bacterial vaginosis, which many times are not analyzed. A risk score for acute endometritis was developed combining the detection and quantification of anaerobic bacteria such as *Atopobium vaginae* (associated with increased risk of endometritis) and normal flora such as *Lactobacillus crispatus* (negatively associated).[23] These strategies could help to improve the laboratory role in the management of PID cases.

In industrialized countries, approximately 15–20% of reproductive age couples are infertile, and in 30% of the cases, fertility problems are due solely to the male partner.[24] *C. trachomatis* has long been associated to women-infertility, but its role in male infertility has been largely controversial. In the last years, several groups have found evidence that *C. trachomatis* infection of Sertoli cells has a pathophysiological mechanism for male infertility, compromising spermatogenesis, reduced sperm count and motility of mature spermatozoa.[25] López-Hurtado et al. found similar results with a significant association between chlamydia infections and the number of spermatozoa and volume of semen, confirming the correlation between chlamydia and male infertility. In addition, this group studied the *C. trachomatis* genotypes detected in those infected patients who were couples of infertile women. The prevalence of characterized genotypes is different to the general population in which genotype E is the most prevalent compared to genotype F in infertile men. This is also the most prevalent in infertile women,[26] but we cannot exclude any bias in the selection of samples. As to the estimated probability of transmission of *C. trachomatis* in a single sexual act (~10%) and the concordance of infection between partners is 75%,[27] the question should be, if it is necessary to screen infertile men for *C. trachomatis*. Although screening for *C. trachomatis* among infertile men is widely practiced it is not endorsed by the American Society for Reproductive Medicine. However, in the model proposed, couples of infertile women, the results shown in this study revealed the interest of this screening in those high-risk populations but large cost-effectiveness studies are required.

Because the spread of STIs has to do with biological, behavioral, and structural factors effective preventive interventions should include them all. Strengthening training among health professionals to increase STI screening for all sexually active people, especially

among high-risk behaviors. In the current complex scenario, the Point of Care technologies may play a crucial role in facilitating access to diagnosis and treatment for many STIs, including HIV and HCV. Sexual education among young people should be increased by facilitating through social networks or advertising access to diagnostic tests or self-sampling. Moreover, self-testing and self-sampling strategies have been proven feasible and effective among many vulnerable populations. As a matter of fact, the experience generated by the SARS-CoV-2 pandemic could help us to implement these strategies both at the community and formal health system level. Another strategy requiring our implication will be contact tracing in decreasing the incidence of STIs. As yet all these strategies are underused in our context.

The health system in general needs to integrate all STIs together with these new approaches to increase access and effectiveness in diagnosing and treating STIs as soon as possible. The current STI epidemics are a paradigmatic example of the need to review and coordinate the role of public health community-based programs, formal health systems, and laboratories. by means of an integrated and combined prevention approach across all the continuum of care.

References

1. Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull. World Health Organ. 2019;97:548–62, http://dx.doi.org/10.2471/BLT.18.228486.
2. Unidad de vigilancia de VIH, ITS y hepatitis B y C. Vigilancia epidemiológica de las infecciones de transmisión sexual, 2019. Centro Nacional de Epidemiología, Instituto de Salud Carlos III/Plan Nacional sobre el Sida, Dirección General de Salud Pública; 2021.
3. European Centre for Disease Prevention and Control. Chlamydia infection. In: ECDC. Annual epidemiological report for 2018. Stockholm: ECDC; 2020.
4. European Centre for Disease Prevention and Control. Technical Report: Technologies, strategies and approaches for testing populations at risk of sexually transmitted infections in the EU/EEA. Stockholm: ECDC; 2021.
5. https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/strategies/global-health-sector-strategies.
6. Ministerio de Sanidad. 2021. Plan de Prevención de la infección por el VIH y las ITS 2021–2030 en España. Available from: https://www.sanidad.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/planNalSida/Plan_de_Prevencion_y_Control1.pdf.
7. López-de Munain J, Cámara-Pérez MDM, López-Martinez M, Alava-Menica JA, Hernandez-Ragpa L, Imaz-Pérez M, et al. Clinical and epidemiological characteristics of Chlamydia trachomatis infection among sexually transmitted infection clinics patients [Características clínicas y epidemiológicas de la infección por Chlamydia trachomatis en pacientes de consultas de infecciones de transmisión sexual]. Enferm Infecc Microbiol Clin (Engl Ed). 2022;40:359–66.
8. Screening Recommendations and Considerations Referenced in Treatment Guidelines and Original Sources. Available from: https://www.cdc.gov/std/treatment-guidelines/screening-recommendations.htm [accessed 20.12.21].
9. Pearce E, Jolly K, Harris IM, Adriano A, Moore D, Price M, et al. What is the effectiveness of community-based health promotion campaigns on chlamydia screening uptake in young people and what barriers and facilitators have been identified? A mixed-methods systematic review. Sex. Transm. Infect. 2022;98:62–9, http://dx.doi.org/10.1136/sextrans-2021-055142. Epub 2021 Aug 26.
10. Marcus U, Mirandola M, Schink SB, Gios L, Schmidt AJ. Changes in the prevalence of self-reported sexually transmitted bacterial infections from 2010 and 2017 in two large European samples of men having sex with men – is it time to re-evaluate STI-screening as a control strategy? PLOS ONE. 2021;16:e0248582, http://dx.doi.org/10.1371/journal.pone.0248582.
11. Kenyon C, Vanbaelen T, Van Dijck C. Recent insights suggest the need for the STI field to embrace a more eco-social conceptual framework: a viewpoint. Int. J. STD AIDS. 2022;4, http://dx.doi.org/10.1177/09564624211064133, 9564624211064133.
12. Traeger MW, Schroeder SE, Wright EJ, Hellard ME, Cornelisse VJ, Doyle JS, et al. Effects of pre-exposure prophylaxis for the prevention of human immunodeficiency virus infection on sexual risk behavior in men who have sex with men: a systematic review and meta-analysis. Clin. Infect. Dis. 2018;67:676–86, http://dx.doi.org/10.1093/cid/ciy182.
13. van Wifferen F, Hoornenborg E, Schim van der Loeff MF, Heijne J, van Hoek AJ. Cost-effectiveness of two screening strategies for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* as part of the PrEP programme in the Netherlands: a modelling study. Sex. Transm. Infect. 2021;97:607–12, http://dx.doi.org/10.1136/sextrans-2020-054741.
14. Chandra C, Weiss KM, Kelley CF, Marcus JL, Jenness SM. Gaps in sexually transmitted infection screening among men who have sex with men in pre-exposure prophylaxis (PrEP) care in the United States. Clin. Infect. Dis. 2021;73:e2261–9, http://dx.doi.org/10.1093/cid/ciaa1033.
15. Martínez-García L, Rodríguez-Domínguez M, Lejarraga C, Rodríguez-Jiménez MC, González-Alba JM, Puerta T, et al. The silent epidemic of lymphogranuloma venereum inside the COVID-19 pandemic in Madrid, Spain March 2020 to February 2021. Euro Surveill. 2021;26:2100422, http://dx.doi.org/10.2807/1560-7917.ES.202126.18.2100422.
16. European Centre for Disease Prevention and Control. Chlamydia control in Europe: literature review. Stockholm: ECDC; 2014.
17. Kreisel KM, Llata E, Haderxhanaj L, Pearson WS, Tao G, Wiesenfeld HC, et al. The burden of and trends in pelvic inflammatory disease in the United States, 2006–2016. J. Infect. Dis. 2021;224 Suppl. 2:S103–12, http://dx.doi.org/10.1093/infdis/jiaa771.
18. Munrós J, Vergara A, Bataller E, García-Lorenzo B, Álvarez-Martínez MJ, Bosch J. Performance of a rapid molecular test to detect Chlamydia trachomatis and Neisseria gonorrhoeae in women with pelvic inflammatory disease. Enferm Infecc Microbiol Clin (Engl Ed). 2022;40:377–80.
19. López-Hurtado M, Escarcega-Tame MA, Escobedo-Guerra MR, de Haro-Cruz MJ, Guerra-Infante FM. Identification of Chlamydia trachomatis genotypes in Mexican men with infertile women as sexual partners. Enferm Infecc Microbiol Clin (Engl Ed). 2022;40:353–8.
20. Davis GS, Horner PJ, Price MJ, Mitchell HD, Soldan K. What do diagnoses of pelvic inflammatory disease in specialist sexual health services in England tell us about chlamydia control? J. Infect. Dis. 2021;224 Suppl. 2:S113–20, http://dx.doi.org/10.1093/infdis/jiab175.
21. López-Pintor JM, Martínez-García L, Maruri A, Menéndez B, Puerta T, Rodríguez C, et al. Quantification of plasmid copy number as surrogate marker of virulence among different invasive and non-invasive genotypes of Chlamydia trachomatis. Diagn. Microbiol. Infect. Dis. 2021;102:115610, http://dx.doi.org/10.1016/j.diagmicrobio.2021.115610.
22. Anyalechi GE, Hong J, Danavall DC, Martin DL, Gwyn SE, Horner PJ, et al. High plasmid gene protein 3 (Pgp3) *Chlamydia trachomatis* seropositivity, pelvic inflammatory disease, and infertility among women national health and nutrition examination survey, United States, 2013–2016. Clin. Infect. Dis. 2021;73:1507–16, http://dx.doi.org/10.1093/cid/ciab506.
23. Hillier SL, Meyn MA, Avolia H, Austin M, Cosentino L, Petrina M, et al. Lower genital tract predictors of acute endometritis among women with signs and symptoms of pelvic inflammatory disease. Sex. Transm. Infect. 2019;95:A47.
24. Thoma M, Fledderjohann J, Cox C, Kantum Adageba R. Biological and social aspects of human infertility: a global perspective. In: Oxford research encyclopedia of global public health. Oxford, UK: Oxford University Press; 2021, http://dx.doi.org/10.1093/acrefore/9780190632366.013.184.
25. Bryan ER, Barrero RA, Cheung E, Tickner JAD, Trim LK, Richard D, et al. DNA damage contributes to transcriptional and immunological dysregulation of testicular cells during Chlamydia infection. Am. J. Reprod. Immunol. 2021;86, http://dx.doi.org/10.1111/aji.13400.
26. Casillas VN, Morfín OR, Garcia S, Llaca-Díaz J, Rodríguez NE, Camacho OA, et al. Frequency and genotypes of *Chlamydia trachomatis* in patients attending the obstetrics and gynecology clinics in Jalisco Mexico and correlation with socio-demographic, behavioral, and biological factors. BMC Women's Health. 2017;17:83–91.
27. Rogers SM, Miller WC, Turner CF, Ellen J, Zenilman J, Rothman R, et al. Con-cordance of *Chlamydia trachomatis* infections within sexual partnerships. SexTransm Infect. 2008;84:23–8.

Mario Rodríguez-Domínguez [a,b], Jordi Casabona [b,c], Juan Carlos Galán [a,b,*]

[a] *Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain*

[b] *CIBER en Epidemiología y Salud Pública (CIBERESP), Madrid, Spain*

[c] *Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), Institut Català d'Oncologia, Badalona, Spain*

* Corresponding author.
E-mail address: juancarlos.galan@salud.madrid.org (J.C. Galán).