ORIGINAL ARTICLE

Chlamydia trachomatis infections in eastern Europe: legal aspects, epidemiology, diagnosis, and treatment

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Objectives: Knowledge concerning genital *Chlamydia trachomatis* infections in eastern Europe is scarce. Data on the legal aspects, epidemiology, diagnosis, and treatment of the infection have never been collected, summarised, and presented to the international scientific community. The aim of this study was to present the current situation on the main aspects of chlamydial infections in the countries of eastern Europe.

Methods: Written questionnaires concerning legal aspects, epidemiology, diagnosis, and treatment of the infection were distributed among national STI operating administrators as well as researchers who had presented papers at earlier meetings of European chlamydia or STI societies.

Results: Most of the countries have not legalised reporting of chlamydial infections and in those who have done so, the quality of the reporting system is poor. Contact tracing is mostly done on a voluntary basis. Reported chlamydia incidence varies from 21 to 276 per 100 000 inhabitants. The most commonly used diagnostic test remains the direct immunofluorescence test; however, some tendencies towards nucleic acid amplification are in evidence. Diagnostic services are paid for by the patient himself, while treatment in many countries is partially or completely covered by public insurance.

Conclusions: This is the first report summarising data concerning the situation on *C trachomatis* infections in eastern Europe. The reporting system and diagnosis of *C trachomatis* infections remain suboptimal, which allows neither control of the epidemiological situation nor optimal treatment of the patients. The most urgent work currently necessary is the education of professionals and the general population.

Genital infections caused by *Chlamydia trachomatis* and the important sequelae of these infections are well documented in the developed Western countries, with articles in which the epidemiology, diagnosis, treatment, and other management issues related to chlamydial infections are discussed.

During the initial period of reorganisation of the healthcare systems in the "newborn" countries, after the collapse of the USSR, questions concerning sexual health were mostly ignored. During national as well as international meetings, healthcare administrators did not address issues concerning sexually transmitted infections (STIs). One reason for this was that for many years specialised institutions managed tuberculosis as well as HIV and other STIs. Furthermore, there were no internationally available publications discussing STI issues of this region. Moreover, without the epidemic of syphilis, the situation would probably have remained unchanged. However, the alarming syphilis situation resulted in several publications in international journals and World Health Organization activities contributed to the presentation and analysis of the epidemic.[1–4] But, the situation concerning the most prevalent bacterial STI, *Chlamydia trachomatis* infections, is still largely unknown.

Before the fourth meeting of the International Society for Chlamydia Research in Helsinki, August 2000, the booklet *Chlamydia trachomatis infections in Eastern Europe* was prepared.[5] Here representatives from each country described the local situation. This paper summarises these reports on the management of chlamydial infections in 13 countries of eastern Europe.

METHODS

Gynaecologists, venereologists, and microbiologists, from Byelorussia, Bulgaria, Croatia, Czech, Estonia, Hungary, Latvia, Lithuania, Poland, Russia, Slovenia, Ukraine, and Yugoslavia were invited to participate in the study. "Country representatives" were chosen, national STI operating administrators or the people they suggested, as well as researchers who had presented papers at earlier meetings of European chlamydia or STI societies. One representative per country was selected and asked to involve relevant collaborators, if needed. The exception was Russia where, in addition to the general Russian representative providing information concerning the whole country, regional representatives from St Petersburg, Middle Ural (Ekaterinburg, former Sverdlovsk), and western Siberia (Novosibirsk) were also invited.

Study participants were instructed to give standardised answers to questions concerning legal aspects (history of, traditions, quality of, partner tracing), epidemiology (reported cases, prevalence), diagnosis (tests used, cost coverage, testing costs), and treatment (costs for different treatment regimens used, cost coverage, partner treatment, post cure testing) of genital chlamydial infections.

RESULTS

Legal aspects

In all participating countries, notification of syphilis cases has been done for at least 20–30 years. Notification of *Neisseria gonorrhoeae* is also done by most of them.

C trachomatis was not a notifiable disease until the early 1990s. The situation started to change when first Estonia (1991), Latvia (1992), Russia (1993), Lithuania (1994), Slovenia (1995), and then Hungary (1998) legislated on the notification of *C trachomatis.*

Notification reports include information about the sex and age of the patient and are performed on a monthly basis.

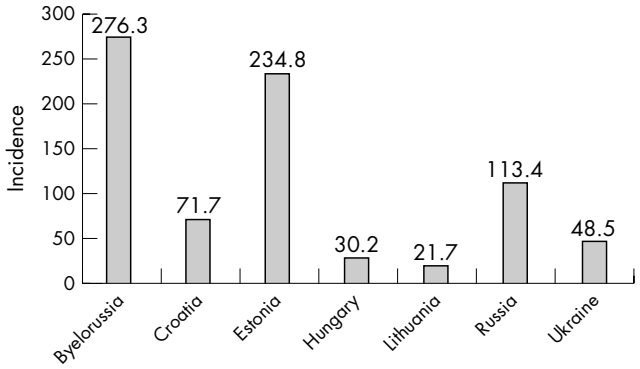

Figure 1 Reported incidence of *C trachomatis* infections per 100 000 inhabitants in eastern Europe, 1999.

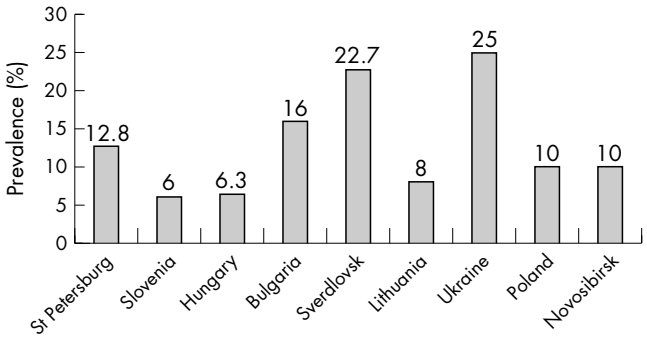

Figure 2 Prevalence of genital *C trachomatis* infections in women consulting outpatient gynaecological clinics (data from the literature).

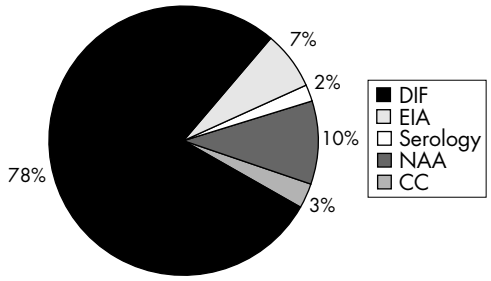

Figure 3 Frequency (%) of diagnostic tests used to detect genital *C trachomatis* infections in eastern European countries, 1999.

Reports are sent to a central dermatovenereological department, STI, or public health centre.

In none of the countries, with the exception of Hungary, is the number of samples recorded, as there has been no laboratory reporting system introduced.

With the exception of Latvia, partner notification and tracing is not compulsory. It is mostly applied to regular partners. "Patients inform their partners without direct involvement of the physician" (Latvia) or "We are trying to tell patients that the partner may also be infected and that it would be best if they were both tested and treated" (Russia).

Epidemiology

Reported incidence of genital *C trachomatis* infections per 100 000 inhabitants in seven east European countries, Byelorussia, Estonia, Russia, Croatia, Ukraine, Latvia, and Lithuania, is presented in figure 1. As one can see, the highest incidence was reported in Byelorussia and Estonia, comprising 35% and 29% of all reported *C trachomatis* cases in these seven countries. Russia reported 14%, Croatia 9%, Ukraine 6%, Latvia 6%, and Lithuania 3% of all of the respective cases of *C trachomatis*.

Three countries, Estonia, Russia, and the Ukraine, presented the dynamics of the annually reported incidence of chlamydial infections. In Estonia, data have been available since 1991. This year, the reported incidence of chlamydial infections was 26.8. Until 1995, a gradual increase had been observed culminating in 360.4 cases, which was followed by a subsequent slow decline to 234.8 cases in 1999. The reported incidence for Russia in 1993 was 37.0. In 1997, it reached 115.6 and has remained at this level since then. In the Ukraine in 1994, the reported incidence was only 17.0, while in 1998 the number had more than doubled—that is, to 48.5.

The most comparable data obtainable came from the four Russian regions, St Petersburg, Sverdlovsk, Novosibirsk, and Murmansk. Three of them had quite similar reported incidence of *C trachomatis* infections in 1999—that is, 210–250 new cases per 100 000 inhabitants. The exception was Murmansk with a reported incidence of chlamydial infections of over 350 per 100 000 inhabitants.

Prevalence data obtained from studies testing gynaecological patients in the different countries are presented in figure 2. A survey of national data concerning the prevalence of genital *C trachomatis* infections revealed that in a majority of the countries the population most tested for chlamydia is that of women attending their gynaecologist. We could not properly compare the prevalence figures from different countries. In some of the articles, the description of methods used and population characteristics are missing. Based on extracted prevalence figures we could divide the countries into those having low (<10%), middle (11–20%), and high (>21%) prevalence of chlamydial infections among attendees at gynaecologists. Of the nine countries where such data were available, four fell within the low prevalence group. These were Slovenia (6%), Hungary (6.3%), Lithuania (8%), Poland, and also the Novosibirsk region (10%). Both the St Petersburg region (12.8%) and Bulgaria (16%) belonged to the middle prevalence category; while the Sverdlovsk region of Russia (22.1%) and Ukraine (25%) fell into the high prevalence group. Owing to the previously mentioned lack of information, it was impossible to make any useful comparison.

Diagnosis

The distribution of diagnostic systems used expressed as percentages is presented in figure 3. The most commonly used diagnostic system was direct immunofluorescence (DIF) test, followed by nucleic acid analysis (NAA), enzyme immunoassays (EIA), cell culture (CC) and serology. In a few places, staining by Giemsa is still in use.

Mean salaries (obtained from the national statistical departments) and the testing costs using different diagnostic systems in the different countries are presented in table 1. As one can see, the prices of the diagnostic system were higher in countries with higher incomes and vice versa. In Lithuania, for example, more expensive commercial diagnostic systems imported from the Western world are used, while in Russia, domestic products are preferred. Thus, a Bulgarian, who would like to be chlamydia tested by DIF, would have to use 12% of his monthly income, a Russian 10%, a Croatian 8%, a Czech, and a Slovakian 3.6%, a Lithuanian 2.2%, and an Estonian 1.8%, respectively.

In Slovenia, Hungary, and Estonia diagnosis is free of charge—that is, covered by public insurance.

Treatment

In Croatia, Czech Republic, and Slovenia, treatment of genital *C trachomatis* infections is free of charge. In Estonia, insurance covers 50% of all—and in Hungary 50% of treatment expenses with doxycycline, respectively. In Lithuania, since 1999, people younger than 25 years of age receive treatment with doxycycline free of charge.

After laboratory results (1–3 days in Russia, Hungary, Lithuania, Ukraine, Latvia, one week in Slovenia, Czech

Table 1 Median monthly salary and the costs for diagnostic services for diagnosing *Chlamydia trachomatis* infection in eastern European countries, 1999

Country	Salary (US$)	Diagnostic costs (US$)	
		Cost	Method
Bulgaria	105	10–15	NI
Croatia	320	25.0	DIF
Estonia	270	5.0	Cell culture
		4.2	DIF
		5–14	Ab test
		9.0	PCR
Lithuania	250	6.0	DIF
		5.0	ELISA
		9.0	Cell culture
		14.0	DNA HC
		12.5–14	LCR
Russia	74	3.1	DIF
		6.2	Cell culture
		2.0–3.0	ELISA Ab
		2.0–3.0	MIF
		2.0–4.0	PCR
Slovenia	833	27.0	DIF
		31.0	Serology
		36.0	Cell culture
		44.0	PCR

NI = unknown.

Table 2 Treatment costs for genital *C trachomatis* infections using doxycycline and azithromycin in different east European countries, 1999

Country	Median salary (US$)	Treatment	
		Doxycycline	Azithromycin
Bulgaria	105	3.0	14.0
Croatia	320	3.0*	20.0*
Estonia	270	4.0–5.0	11.0–12.0†
Hungary	258	0.9‡	14.0§
Lithuania	250	1.25¶	15.0
Russia	74	0.5–2.0	10.0

*Covered by insurance; †50% covered by insurance; ‡0.5 covered by insurance; §5.0 covered by insurance; ¶0.6 covered <25 years.

Republic, and Bulgaria) the patient is invited for a second visit and medication is not prescribed until then. In most cases partner treatment is advised and prescribed without even the suggestion of testing.

In Latvia and Russia *test of cure* is performed 3–4 weeks after the end of treatment.

In countries where treatment is paid for by the patient, he is given an option to choose the medicine he can afford. As is demonstrated in table 2, there is a considerable price difference between treatments with doxycycline and azithromycin.

DISCUSSION

Although compulsory, reporting is mostly done by public institutions (mainly venereological departments) and it is not complete. As a rule, private physicians do not report cases. Lithuania is a good illustration of this. In 1999, 650 cases of *C trachomatis* infection were reported in a country with almost four million inhabitants! This obvious under-reporting may reflect the fact that there are no legal measures to control the performance of reporting. In an effort to improve reporting, Estonia has recently introduced a financial penalty for physicians who violate the law.

Partner notification and tracing was reported to be compulsory only in Latvia. However, in other post-Soviet Union countries, it is accomplished via an "unofficial law" with the venereologists "trying" to complete their task. However, reporting and contact tracing are done exceptionally, on a voluntary basis by other doctors as well as patients. The patient often "refuses to remember" his contact or the contact "is not interested in being treated" and thus is never investigated. In many situations, a recommendation for treatment (if the patient is positive) or drug supplementation is the best the physician can do. It all depends upon the "partner-patient relationship" and the "goodwill" of the patient.

Owing to lack of information, patients have difficulty in understanding the importance of partner treatment. In particular, young people often admit the lack of such knowledge.[6] In our survey, only 8% of the young adults admitted that the main source of their knowledge concerning STIs is school and more than 20% were "educated" by their friends.

It is difficult to persuade partners to be tested, since in most countries patients must pay for the laboratory test as well as the treatment. Even when these costs are covered, resources intended for STI care are limited. In Estonia, for example, the public insurance system is supposed to cover the cost of diagnosis. However, venereological departments are given a fixed monthly sum of money regardless of the number of patients attending. So, if the number of patients exceeds the budget of a given month, the patient is simply asked to return the next month.

In many countries, the "law of infectious disease control" is presently being revised, which will affect STI management.

It is extremely difficult to compare the incidence of *C trachomatis* infections in different countries. Some only conduct perfunctory statistical surveys (not required by law). Countries with mandatory registration do not present the number of samples examined. Consequently, any shift in the number of positives is impossible to evaluate. It could be the result of a real increase/decrease or an artefact of a change in testing volume.

Statistics on the reported incidence of *C trachomatis* infections in the east European countries studied evidence a number of sources of possible error. The most important would be the weaknesses of the notification system: allowing physicians to choose between reporting and not reporting, and whether or not the contacts should be traced. In addition, it would appear that only Estonia is in the process of taking administrative measures to control compliance with the law. The major reason, however, for the misinterpretation of the epidemiological situation is the quality of the diagnostic procedures, which in most countries is suboptimal.

Since 1999, we have been conducting a project in Lithuania on optimisation of the laboratory diagnosis of *C trachomatis* infections using DIF (Syva's MicroTrack). Before initiation of the training programme, laboratory estimate placed the prevalence of chlamydial infection in a population of women consulting gynaecologists to be 24%. After a series of training courses at the laboratory, the prevalence of infection in the same population during the same year "decreased" to 8% (M Domeika, unpublished data). Therefore, even if a functional reporting system had been in place at that time, the prevalence would still have been highly overestimated.

We conducted a survey of the national literature to find the population most extensively tested for *C trachomatis* infections. This was found to be women seeking gynaecological advice. However, owing to the fact that in many cases, both the population and the tests used were poorly described, it is impossible to make an intercountry comparison.

Regarding diagnosis, the first problem addressed by most of the countries is that the lack of resources does not allow the use of well established Western high quality test systems. In many countries there is a belief that nucleic acid amplification technologies would give a better diagnostic quality for *C trachomatis*.

The wish to change DIF or EIA to Western produced nucleic acid amplification technologies is simply motivated by the

ideology that "it is what they use in the West." Costs to the healthcare system or to the patient are not evaluated. One often neglected aspect is the enormous difference between wages in the West and the East. The West seeks more automated technologies to be able to reduce the amount of staff hours. In the East, the hourly wage is comparatively low and the major part of the diagnostic cost is the kit. Thus, an experienced microscopist with a reasonable microscope often could do a better job for society than the expensive nucleic acid amplification technologies. Being too expensive, nucleic acid amplification technologies are sometimes used too infrequently to allow an established laboratory routine, and this strongly affects diagnostic quality. On the other hand, today the economy in some of the Western countries—namely, the United States, also dictates the preferable use of cheaper tests instead of the prestigious NAA technologies.[7 8]

The Russian situation is unique in that the enormous market potential attracts Western test kit producers. At the same time, the weak economy limits access to these tests. Consequently, several diagnostic systems for DIF, PCR, CC are produced in Russia. To date, comparative evaluations are absent; so all questions regarding quality and standardisation are unanswered.

In Russia, polymerase chain reaction (PCR) is almost the cheapest diagnostic alternative. Locally produced diagnostic kits are widely available and thus chosen by many laboratories. Again, questions regarding contamination and other possible failures (for example, kit standardisation) have not been properly analysed. This implies a considerable risk for hyperdiagnosis.

We conducted a comparative study on 200 symptomatic women attending their gynaecologist, evaluating several commercial systems available in St Petersburg (Russia)—for PCR (St Petersburg), DIF (Orion; Syva), and CC (Syva).[9] The first PCR system tested (based on chlamydial major outer membrane protein, MOMP) had 89% sensitivity; however, the specificity was only 69%. The second PCR system (based on chlamydial cryptic plasmid) was 81% sensitive, but 100% specific. DIF, using both Orion and Syva's DIF kits and read using a Russian microscope (Lomo, St Petersburg), had a sensitivity of 60% and a specificity of 99%. Cell culture, using locally produced reagents and Syva's Direct Chlamydia Kit and Russian optics (Lomo, St Petersburg), had a sensitivity of 40.5% and a specificity of 100%. So, the most relevant (sensitivity, specificity, and price) to use seemed to be a plasmid PCR. Of course, the sensitivity should be higher, and the kit producers are aware of that and are working on its improvement. However, this locally produced PCR is a good "platform to start with."

In the near future, locally produced NAA techniques will be more frequently used. Hopefully, quality control systems will develop simultaneously.

In many former Soviet countries, economic changes have divided the STI clinic populations into those who can and cannot pay for STI testing. Some venereological departments can be divided into the "true" public section (investigation and testing free of charge) and a private section (all costs paid by the patient). One example was the dermatovenereological clinic in Byelorussia.[10] In the state section, genital smears were stained using Giemsa and the incidence of *C trachomatis* infections was 6.7%. In the other part of the same clinic, DIF testing revealed 34% *C trachomatis* positives. Considering the low sensitivity of the Giemsa stain, and the many cases of false positives using DIF (non-standardised antibodies, suboptimal microscope, etc) it is highly doubtful if any patient category could benefit from such testing.

On the other hand, serology is still used in a number of countries for diagnosis as well as for post-treatment testing.

Many countries lack a policy on antibiotics, which can be sold without a prescription. Thus, anyone can go to the pharmacy and receive the desired treatment. Physicians are well aware that self treatment takes place; however, the extent of this is unknown.

There are a number of patients who migrate between physicians and laboratories and who are considered to be carriers of "untreatable" infections. Physicians are often involved in the treatment of these patients, which "could not be cured by another physician." Mostly, this is a problem of overdiagnosis or a test of cure performed too early.

In our recent study, we asked different clinics in St Petersburg to send us 250 samples, which they, using their DIF test systems, regarded as positive or negative. Almost 40% of the samples that tested positive in the clinics turned out to be negative during retesting done using DIF, in Uppsala. Thus, 40% of the patients with a diagnosis of "genital chlamydial infection" did not have any infection. On the other hand, 20% of true chlamydia positives were missed because of suboptimal initial testing. The false positives end up as "patients with untreatable chlamydial infection." On the other hand, owing to false negative reports, a considerable number of the truly infected individuals never received any treatment and were considered not to be infected (M Domeika, A Savitcheva, unpublished data).

In eastern Europe there is a belief that locally produced drugs are of low efficiency and may contribute to the alleged "treatment failures." We have tested several antibiotics, including doxycycline, erythromycin, and azithromycin, comparing them to their Western analogues. There was not a single indication of any difference between the chemical and biological activity found and that described by the manufacturers.[11]

We also compared a number of Russian chlamydia strains to strains isolated in Uppsala (adjusted by serotypes), by their sensitivity to doxycycline and azithromycin. Swedish and Russian strains had very similar MIC values (M Domeika, A Savitcheva, unpublished data).

Thus, the problem with "untreatable" infections is mostly a problem of diagnostic accuracy, which has to be solved by the simultaneous development of new diagnostic systems and quality control measures.

On the other hand, there are some indications that in certain clinical cases we could be facing strains causing persistent infection (MA Gomberg, personal communication, 2001).

To summarise one could state that east European countries lack national policies concerning *C trachomatis*. Healthcare administrators poorly understand the serious medical consequences of this infection. In countries with notification of *C trachomatis* the performance of the reporting system is suboptimal and consequently the true epidemiological situation is unknown.

The best way to improve the situation is education, both on the professional and population levels. One way to reach all parties involved could be analysis and popularisation of data gained from national research studies.

CONTRIBUTORS

MD and AH designed the study, did the intercountry comparisons and analysis, wrote the manuscript; LK, KC, FG, VU, AP, JD, IJ, GL, ZD, VA, MG, AK, AS, IT, NV, MN analysed and provided the national data, contributed to the discussion, and work on the manuscript.

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