MEDICAL UNIVERSITY - PLEVEN

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Clinical-epidemiological analysis of the prevalence of syphilis in the Pleven region

ABSTRACT OF A DISSERTATION PAPER

TO OBTAIN THE EDUCATIONAL AND SCIENTIFIC DEGREE "DOCTOR (PhD)"

Doctoral program: Dermatology and venereology

Professional direction: 7.1. Medicine

Field of higher education: 7. Health care and sports

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Pleven, 2024

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Abbreviations used

STIs / STDs	-	Sexually transmitted infections/diseases
STI / STB	-	Sexually transmitted infections/diseases
STIs / STDs	-	Sexually transmitted infections/diseases
MSM / MSM	-	Men who have sex with men
UIN	-	Injecting drug users
HIV / HIV	-	Human immunodeficiency virus
AIDS	-	Acquired immune deficiency syndrome
EC	-	European Union
EEA	-	European Economic Area
RZI	-	Regional Health Inspection
NCZI	-	National Center for Health Information
NSI	-	National Statistical Institute
WHO	-	World Health Organization / World Health Organization
HIV	-	Human immunodeficiency virus
FSW	-	Female sex worker
MSM	-	Men who have sex with men
ECDC	-	European Center for Disease Prevention and Control
EU/EEA	-	European Union / European Economic Area
TPHA	-	Treponema Pallidum Haemagglutination Assay
RPR	-	Rapid Plasma Reagin test
VDRL	-	Venereal Disease Research Laboratory test
ELISA	-	Enzyme-Linked Immunosorbent Assay
PCR	-	Polymerase Chain Reaction
IgM/IgG	-	Immunoglobulin M / Immunoglobulin G

I. INTRODUCTION

Sexually transmitted infections (STIs, STIs) are transmitted from person to person primarily through sexual contact. Some of these, such as syphilis and AIDS, can be transplacentally transmitted from a mother to her unborn child. STIs are among the most common diseases in the world and have significant health, social and economic consequences for millions of men, women and children. The scope of their distribution, the increasing frequency of people who use injecting drugs (IDU) and HIV infection, as well as the dramatically developing biological and social phenomenon related to the increase in the number of homes- and transsexual individuals and recognition of the so-called third gender and "gender ideology" is a global and paramount public health problem for two reasons :

1. STIs lead to serious negative medical and psycho-social effects in the infected person. If the infected are women, there is an additional risk of infection and disease of the fetus and
2. STIs facilitate the transmission of HIV between sexual partners.

Syphilis causes inflammatory genital, oral, and anal lesions and ulcers that provide a gateway for transmission of HIV and increase the risk of developing AIDS. Therefore, prevention and treatment of STIs and syphilis is a key component in the strategy to prevent HIV transmission. There is a global tendency to increase the prevalence of syphilis among the risk group M With M (Men who have sex with men), including in association with HIV.

In the process of health reform, which started in 1997 in Bulgaria, some problems related to the existence of financial, administrative-organizational and normative barriers to the use of health services by persons related to their sexual health stood out. At the same time, in the last 10 years, the role of social networks and dating apps has grown, associated with an increase in the number of risky sexual contacts.

In 2019 and 2022, due to increasing trends in the prevalence of syphilis in the European Union / European Economic Area, especially among MSM and at the request of Member States, the European Center for Disease Prevention and Control (ECDC) published a comprehensive epidemiological analysis for the period 2007–2018. Moreover, in 2022, public health response options and recommendations will be formulated that are still valid today.

In general, prevention and control activities should include, on the one hand, active detection of the infected and their contacts, improved diagnosis, treatment, registration and reporting of cases, expanded testing of persons from risk groups, and on the other hand, educational activities aimed at the whole population, populations at risk and health care providers.

Depending on the regional epidemiological situation, increased screening of risk groups (e.g. ethnic minorities, marginalized populations, sex workers, people who inject drugs) is recommended.

These facts motivated us to present a detailed clinical-epidemiological analysis of the prevalence, clinical forms and characteristics of syphilis, diagnosis, treatment, sexual behavioural patterns and other indicators of the disease, comparing our results with the data published for Bulgaria and the European Union.

II. PURPOSE AND OBJECTIVES OF SCIENTIFIC DEVELOPMENT

II.1. Target of the study:

To make a clinical-epidemiological analysis of the general incidence of syphilis in the Pleven region for 15 years (2008 – 2022)

To achieve our goal, we set the following tasks:

II.2. Tasks:

1. To make a general epidemiological characterization of the spread of syphilis cases in the Pleven region, patients will be divided by gender, age, place of residence, educational status, family status, and social status.
2. To study the risk factors for STIs, the main patterns of sexual behaviour and the transmissibility category of the registered cases.
3. To analyze cases of syphilis and co-infection with HIV.
4. To study the frequency of clinical stages of syphilis and indicate the most common clinical manifestations.
5. To compare the data on the incidence of syphilis in the Pleven region with those for Bulgaria and the Eurozone countries for the same period.
6. To analyze therapy and seronegative laboratory test results depending on the treatment administered.

III. MATERIAL AND METHODS. SCIENTIFIC METHODOLOGY RESEARCH

III.1. Clinical material

- With different forms of syphilis in the period 2008 - 2022. Three hundred twenty-three patients were diagnosed, treated and followed up. The age range of the patients is from 0 to 82 years old. The average age is 32.92 ± 13.918 years. There were 192 (59.4%) men with a mean age of 35.11 ± 14.31. There were 131 (40.6%) women with an average age of 29.71 ± 12.71.
- For the study of infection in men who have sex with men (MSM), a subpopulation of 50 individuals, all male, aged between 16 and 55 years, with a mean age of 31.44 ± 8.96 years, was selected.

- The study of the infection among the Roma community in the Pleven region is a selected subpopulation of 113 persons, aged between 0 and 63 years, with a mean age of 28.50 ± 11.80 years. There were 51 (45.1%) men with a mean age of 28.33 ± 11.95. Women 62 (54.9%) mean age 28.63 ± 11.80.
- In the study of the infection among the Roma community and to compare the indicators of the Roma with the representatives of other ethnic groups in the district, the subpopulation of 210 persons, aged between 0 and 82 years, with an average age of 35.30 ± 14.40 years, was also selected. There were 141 (67.1%) men with a mean age of 37.30 ± 14.34. There were 69 (32.9%) women with a mean age of 28.63 ± 11.80. ***(Fig.1)***

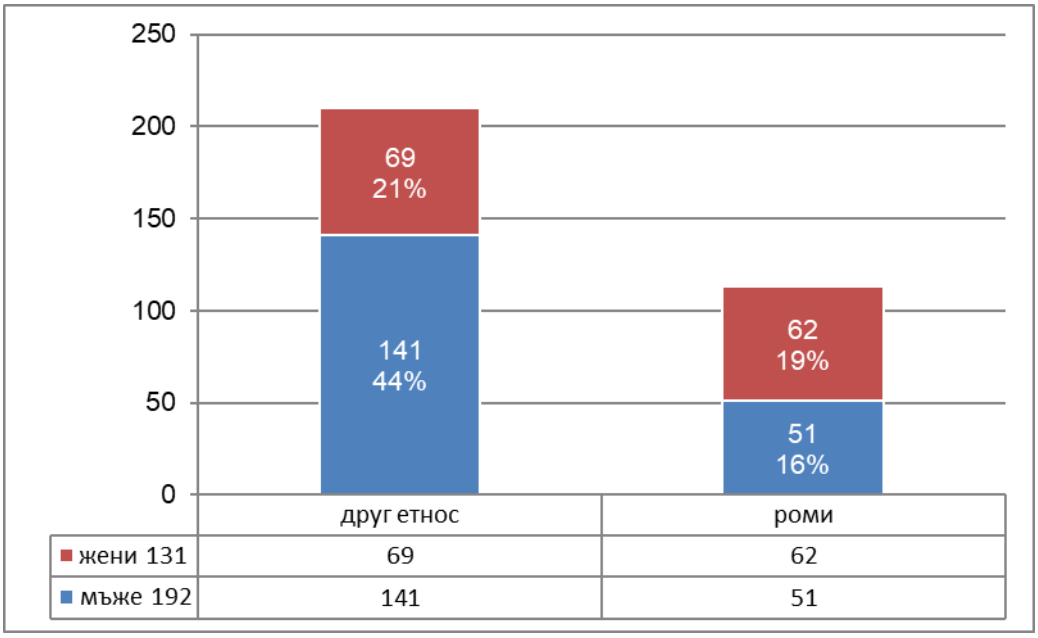


Figure 1: Distribution of the two ethnicities by gender (men in blue column, women in red)

III.2. Methods

III.2.1. Epidemiological analysis - for the analysis, the information was extracted from a registration card valid throughout the country for the needs of dispensation of patients with venereal diseases. The doctor fills out the card, which contains data on the patient's history, demographic characteristics, clinical features, prescribed treatment, and follow-up until the moment of discharge.

- Retrospective epidemiological analysis to determine the frequency of syphilis in patients, distributed by sex, age, ethnicity (Roma and others), place of residence, education, social status, and marital status. For the study, the subjects were divided into the following age ranges – 1-14 years, 15-19 years, and 20-24 years. and so on at five-year intervals until "over 50 years." For more convenience in determining the frequency of infection in some of the studies, age groups are combined into ten-year periods, even into five-year periods (2008-2012, 2013-2017, 2018-2022). The social environment is defined in the following categories: learners (children, pupils, students), working, unemployed, pensioners, prisoners,

prostitutes, etc. Marital status includes married, single (never married), divorced, cohabiting, widowed/widowed.

  - A cross-sectional analysis to determine the incidence, epidemiology and clinic of syphilis among men who have sex with men (MSM).
  - Cross-sectional analysis to determine the incidence, epidemiology and clinic of syphilis among sick representatives of the Roma ethnic group.
  - Comparative analysis of the results obtained during the survey of the Roma with those that characterize the other ethnic group (united Bulgarians, Turks and one foreigner)

- A retrospective epidemiological analysis to determine the mode of infection and diagnosis of syphilis. Transplacental, heterosexual, homosexual and no information was noted as "Mode of transmission". The patients were diagnosed in the course of a clinical examination on the occasion of prophylactic examinations (blood donation, pregnancy, childbirth, etc.), persons indicated as contacts as the source of the infection. Data on number of sexual partners, frequency of sexual contacts, available comorbidities and co-infections were analyzed. Based on the extracted characteristics, two cross-sectional and one comparative analysis of the subpopulations mentioned above were carried out.

III.2.2. Clinical-morphological analysis

The clinical-morphological characteristics of the disease were studied, and the analysis was also based on indications from the accompanying documentation. The results are interpreted according to the clinical picture, and the patients are grouped into the different clinical stages of treponematosis development according to the clinical morphology of the lesions.

Anamnesis is related to data on past rashes, subjective sensations, hypersensitivity to medications, accompanying and past diseases, current therapy, etc.

Dermatological status to determine the presence or absence of pathological skin and mucosal lesions and adenopathy. The localization of the rash syndrome has been described as genital, anorectal, oropharyngeal, unknown. On this basis, the periods of development of syphilis are diagnosed - primary, secondary, early latent, late latent syphilis, some forms of involvement of systemic organs (neurolysis, late syphilis of the cardiovascular system), and congenital syphilis.

III.2.3. Laboratory serological methods for screening and diagnosis

III .2.3.1. Non-specific rapid micro flocculation tests

(for qualitative and semi-quantitative detection of reagin, cardiolipin, non-treponemal antibodies:

- VDRL (Venereal Disease Research Laboratory) is a nonspecific, rapid and easy-to-perform syphilis test that serves as mass screening. The reaction is less specific but highly sensitive. It was introduced in 1946. Furthermore, it was practically implemented in Bulgaria until the end of 2013.
- RPR (Rapid Plasma Reagin) is a nontreponemal slide agglutination test for the qualitative and semi-quantitative detection of plasma reagins in human

serum. Reagins are a group of antibodies against certain components of the damaged tissues of patients infected with T. pallidum. This microorganism causes the release of some tissue fragments from the liver and heart, and the patient's immune system produces antibodies against these fragments. The assay is useful for monitoring response to antibiotic therapy.

III.2.3.2. Specific treponemal methods

- Treponema Pallidum Haemagglutination Assay (TPHA) is a diagnostic indirect hemagglutination test for qualitative and semi-quantitative detection of specific antibodies. The principle of the test is based on the ability of the specific anti-treponemal antibodies in the patient's serum to agglutinate sensitized/conjugated / with T. pallidum strain Nicole lamb or bird erythrocytes. The test was introduced to diagnose syphilis in 1948. It is highly specific, sensitive and mandatory to confirm the diagnosis of syphilis.
- Enzyme immunoassay SYPHILIS IgM is a solid-phase enzyme immunoassay for the qualitative determination of antitreponema pallidum IgM antibodies in human serum/plasma. It was introduced into laboratory practice in 2004. The test has a diagnostic sensitivity of 100% and a specificity of 100%. The clinical relevance of the method is based on the fact that IgM antibodies are associated with active disease and are positive in 70-90% of early forms. They disappear after treatment of primary syphilis in about 3-9 months in late forms in about 12-18 months. IgM-at appears again in reinfection. Sometimes untreated, inadequately treated or reinfection of syphilis can be proven only on the basis of IgM-antibodies. The study of IgM antibodies is mandatory for establishing the diagnosis of congenital syphilis.
- The ETI Treponema screen IgM/IgG enzyme immunoassay is an enzyme immunoassay for the detection of total antibodies against T. pallidum in human serum or plasma. The test was introduced into laboratory practice in 2002 and is based on a competitive principle for screening antibodies of the IgG- and IgM-immunoglobulin classes against T. Pallidum. It has a diagnostic sensitivity of 100% and a specificity of 100%.

III.2.3.3. Serological diagnosis of HIV 1/2 infection

- HIV 1/2 Human Immunodeficiency Virus Rapid Test is an immunochromatographic rapid test for the detection of antibodies against HIV ½ in human serum/plasma. The diagnosis of HIV1/2 infection was introduced in the Clinic for Skin and Venereal Diseases in Pleven in 1992 by the ELISA method with the Labsystems equipment. The test is used for the rapid qualitative determination of IgA, IgM and IgG antibodies against HIV-1 and HIV-2 in human serum, plasma and whole blood for the early diagnosis of AIDS, but it has no quantitative value and cannot be used to measure the antibody titer in dynamics. The test should not be used as the sole criterion for HIV diagnosis. A negative result does not exclude the possibility of HIV infection. If a positive result is confirmed, the steps under Ordinance No. 47/11.12.2009 are carried out. Of the Ministry of Health on the terms and

conditions for testing, reporting and reporting of infection with the acquired immune deficiency syndrome virus.

III.2.4. Statistical methods

The accumulated information was entered and analyzed using IBM SPSS Statistics 26.0.0 statistical software. $p < 0.05$ was chosen as the level of significance at which the null hypothesis was rejected. Part of the research data was processed using the EXCEL program. The results are presented through tables, graphs and numerical indicators such as percentages, coefficients, average values, standard deviation and others.

The following description of qualitative and quantitative variables, descriptive statistics, correlation analysis (Pearson's correlation coefficient - r, odds ratio - OR), parametric (T-test, ANOVA) and non-parametric (Pearson chi-square and the Kruskall - Wallis test) hypothesis testing methods.

Table 1: Selection of statistical tests for analysis

Rock	Two samples		Three or more samples	
	Superlatives	Dependent	Independents	Dependent
Nominal	Chi-square (also for 1 group)	McNemar's test	Chi-square	Cochran's test
Ordinal	U-criterion of Mann-Whitney	Wilcoxon test	Kruskal-Wallis test	Friedman test
Interval or Proportional	z or t-test (unpaired)	z or t-test (correlated)(paired)	Analysis of variance – Fisher's F test	

III.2.5. Photo documentation

A Canon PowerShot A310 digital camera was used for photo-documentation of the pathological skin lesions with automatic mode, use of macro-mode for the close-focus photos and comparable illumination and distance of the objects. The photos taken have a resolution of 1600 x 1200 pixels and file sizes between 340 and 670 KB.

III. 2.6. Ethical aspects

The study is conducted in accordance with national and international requirements for the preservation of the anonymity of the participants and the non-disclosure of their personal information. This study used secondary data and did not need ethical approval.

When registering and monitoring the patients, the requirements of the regulations in the country are complied with - Ordinance No. 3 of May 26, 2016. on the terms and conditions for diagnosis, prevention and control of syphilis, gonorrhoea and urogenital chlamydia infection and the National program for the prevention and control of HIV and sexually transmitted infections in the Republic of Bulgaria 2021 - 2025.

III.3. Research methodology related to the main objective :

- Analysis of accounting documentation - Individual card of a Syphilis patient in the Clinic of Dermatology and Venereology - UMHAT, Pleven
- Analysis of laboratory results - cases with Syphilis and HIV in the Laboratory for the Study of Sexually Transmitted Infections in the Clinic for Skin and Venereal Diseases - UMHAT, Pleven
- The main epidemiological characteristics of Syphilis incidence are represented by:
  - Extensive metrics – structure metrics – relative shares and through
  - Intensive indicators – frequency indicators per 100,000 people in the Pleven region, using the average annual population in the Pleven region.

III.4. Data Sources

- Accounting documentation from the Venereal Sector is stored in the University Clinic for Skin and Venereal Diseases in Pleven.
- Laboratory logs for serological tests are carried out on request, after a doctor's consultation, or on persons referred from other settlements and are designated as the source or contact of the infection.
- Intra-hospital information system - data on women in labour and cases of congenital syphilis.
- Data systems include the National Center for Health Information, National Statistical Institute, World Health Organization (WHO), and European Center for Disease Prevention and Control (ECDC).

IV. RESULTS OF OWN RESEARCH

IV.1 Analysis of the incidence of syphilis in the Pleven region for 15 years (2008 – 2022)

The study aims to analyze the development of syphilis incidence over 15 years (2008 – 2022) in the Pleven region and to compare the results with national and international data.

To achieve our goal, we set **tasks** to determine the socio-demographic characteristics of the studied population (gender, age, ethnicity, education, professional status), the clinical forms of the disease, the therapeutic schemes applied for treatment, tracking over time the achieved effect on test seronegative ratio.

Material and methods - A retrospective clinical-epidemiological analysis of 323 patients with syphilis, treated and dispensed for 15 years (2008-2022) in the clinic for skin and venereal diseases of the university hospital "Dr G. Stranski" - Pleven. The demographic (gender, age group, ethnicity, place of residence, marital status, level of education, profession) and clinical-therapeutic data of the patients (periods and clinic of syphilis, research methods, cases of Lewis-HIV co-infection, administered therapy, follow-up of individuals until seronegative results). Epidemiological and

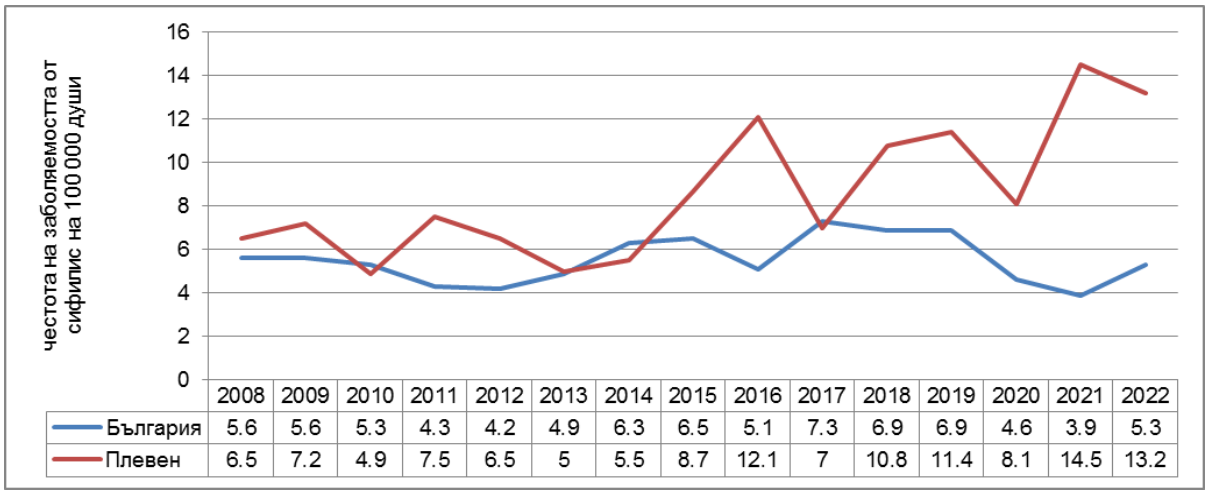
clinical data are included in a personal file, according to the requirements of the regulations in the country.

Patients were tested with the non-treponemal rapid plasma reagin (RPR), specific TPHA (Treponema pallidum hemagglutination test) and ELISA IgM/IgG, through which seronegative results at the sixth month, 1st, 2nd and 3rd year followed the effect of the applied treatment. The rarer cases of congenital and late, unspecified syphilis were followed for 5 years or more. All dispensary persons are also examined for carrying the AIDS virus.

Statistical analysis was performed using SPSS statistical software (version 26.0; IBM Corp.) with a significance level of alpha (α)=0.05 and 95% CI (confidence interval). Descriptive statistics and the Kolmogorov-Smirnov parametric test (K–S test) for normal data distribution with a statistically significant Lilliefors level were applied. Numbers and percentages indicate variables. Results are presented as mean ± standard deviation (SD). A p-value <0.05 was accepted for statistical significance, which is considered indicative of rejecting the null hypothesis (H_o)

Results

During the period 2008-2022 in the Pleven region (291695 inhabitants in 2008 - 220345 inhabitants in 2022), the average incidence of syphilis was 8.59 new cases per 100,000 inhabitants. In this period, the incidence of syphilis ranged from a low of 4.9/100,000 in 2010 to a maximum of 14.5 new cases/100,000 in 2021. For the same period in R. Bulgaria, the frequency varies from a minimum of 4.2 in 2012. up to 7.3 in 2017, an average of 5.5 cases/100,000. The growth of morbidity in the Pleven region during the third five-year period (2018-2022) is striking, as this growth is 2-3 times higher in comparison with the one in the country. ***(Fig.2)***



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
България	5.6	5.6	5.3	4.3	4.2	4.9	6.3	6.5	5.1	7.3	6.9	6.9	4.6	3.9	5.3
Плевен	6.5	7.2	4.9	7.5	6.5	5	5.5	8.7	12.1	7	10.8	11.4	8.1	14.5	13.2

Figure 2: Syphilis trend per 100,000 people 2008 – 2022. (Pleven in red line, Bulgaria in blue line)

The mean (± SD) age of persons diagnosed with syphilis was 32.92 ± 13.92 years, and 69.1% belonged to the age group of 15-39 years. The majority of patients with syphilis were men (59.4%); the most affected age is 20-29 years. – 34%, followed by 30-39 years. – 25%; living in urban areas is 65.3% the risk of illness is 3.55 higher

than persons living in small settlements (OR 3.55; 95%CI: 2.5668 to 4.9076; p<0.00 0 1); 35% are of Roma origin; with secondary and secondary special education are 61.3%, 13.3% are university graduates; 37.8% are unmarried, and 29% are cohabiting without marriage; 38.4% are employed, 34.7% are unemployed, 5.6% are prostitutes, all of whom are women. ***(Table 2)***

Of the 323 patients with syphilis, 17 were co-infected with HIV, all men (5.3%). In this category, 13 patients declared themselves to be MSM (76.5%) and four were heterosexual. In the "syphilis-HIV co-infection" group of patients, an upward progressive distribution was found after 2016. (13 cases). There are five people with acute condylomas (1.5%), three with chlamydia infection (0.9%), and two with gonorrhoea (0.6%). The group of "other systemic diseases" (19.2%) includes mainly chronic diseases requiring periodic medical control and research, some of which diagnosed the infection. This indicator is most common in the age group of 20-39 years. (9.3%) and over 40 years. (9%). ***(Table 3)***

Table 2: Sociodemographic indicators of 323 patients with different forms of syphilis

indicators	**number**	**per cent**	**P**
gender			< 0.001
men	192	59.4	
women	131	40.6	
Total	323	100.0	
Age group			< 0.001
< 1 year	7	2.2	
1-14	6	1.9	
15-19	23	7.1	
20-24	54	16.7	
25-29	65	20.1	
30-34	45	13.9	
35-39	36	11.1	
40-44	30	9.3	
45-50	11	3,4	
> 50 years	46	14.2	
Total	323	100.0	
Ethnicity			< 0.001
Bulgarians	209	64.7	
Roma	113	35.0	
a foreigner	1	,3	
Total	323	100.0	
Residence			< 0.001
City	211	65.3	
village/small town	112	34.7	
Total	323	100.0	
Education			< 0.001
without (children under 7)	10	3.1	
initially	11	3,4	
basically	61	18.9	
average	139	43.0	
average specially	59	18.3	
higher	43	13.3	

Total	323	100.0	
Marital status			< 0.001
family	64	19.8	
Unmarried (never married)	122	37.8	
divorced	18	5,6	
a widower	11	3,4	
cohabitation	96	29.7	
child	12	3.7	
Total	323	100.0	
Social status			< 0.001
child	10	3.1	
student	9	2.8	
a student	8	2.5	
working	124	38.4	
free profession	16	5.0	
a prisoner	7	2.2	
pensioner	17	5.3	
others	2	,6	
prostitutes	18	5,6	
unemployed	112	34.7	
Total	323	100.0	

Table 3: Frequency of the cases of co-infections and co-morbidity

Diseases	Frequency	Per cent	Valid Percent	Cumulative Percent
gonorrhea	2	.6	.6	.6
chlamydia	3	.9	.9	1.5
candidiasis	2	.6	.6	2.2
herpes	1	.3	.3	2.5
papilloma virus	5	1.5	1.5	4.0
HIV	17	5.3	5.3	9.3
other systemic	62	19.2	19.2	28.5
there isn't	231	71.5	71.5	100.0
Total	323	100.0	100.0	

Analyzing the periods of syphilis, the highest frequency of early latent syphilis is reported (48.9%), followed by secondary (18.3%) and primary syphilis (16.7%). ***(Fig.3)***

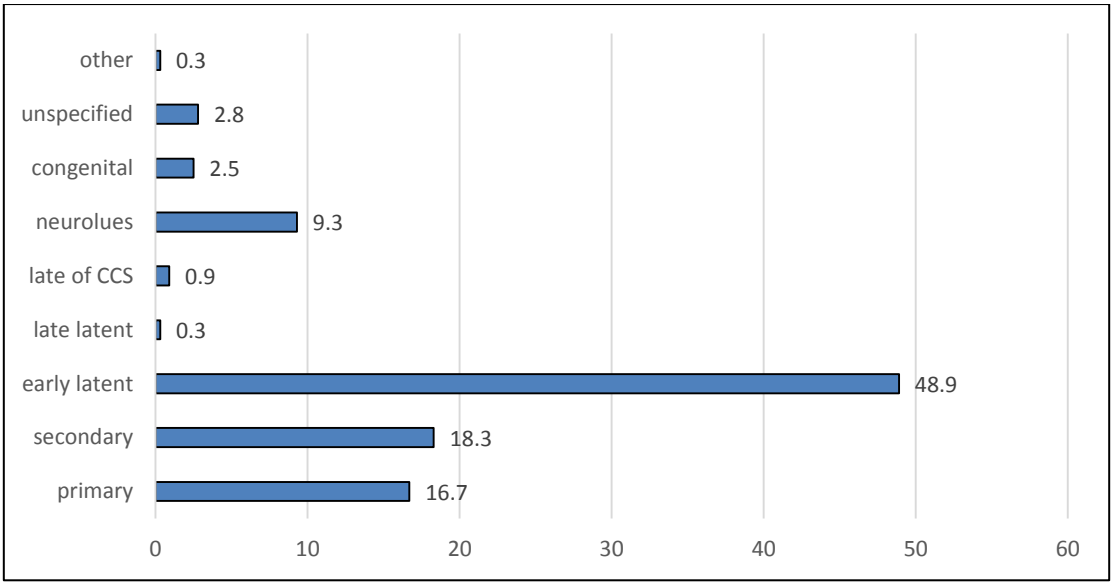


Figure 3: Incidence (in per cent) of different periods of syphilis in 323 patients in the period 2008–2022.

Among 323 patients with syphilis, 125 (40%) had clinical symptoms of the infection. A hard chancre is present in all cases of diagnosed primary Lues and in single cases of primo-secondary syphilis (19.5% of all symptoms). Macular and papular lesions, typical of the second period of the disease, accounted for 49.7% of the clinical manifestations, with more than one symptom occurring in most patients. There are 194 (60%) patients without a clinical picture, and they have latent forms of the infection. ***(Fig. 4 and Fig. 5)***

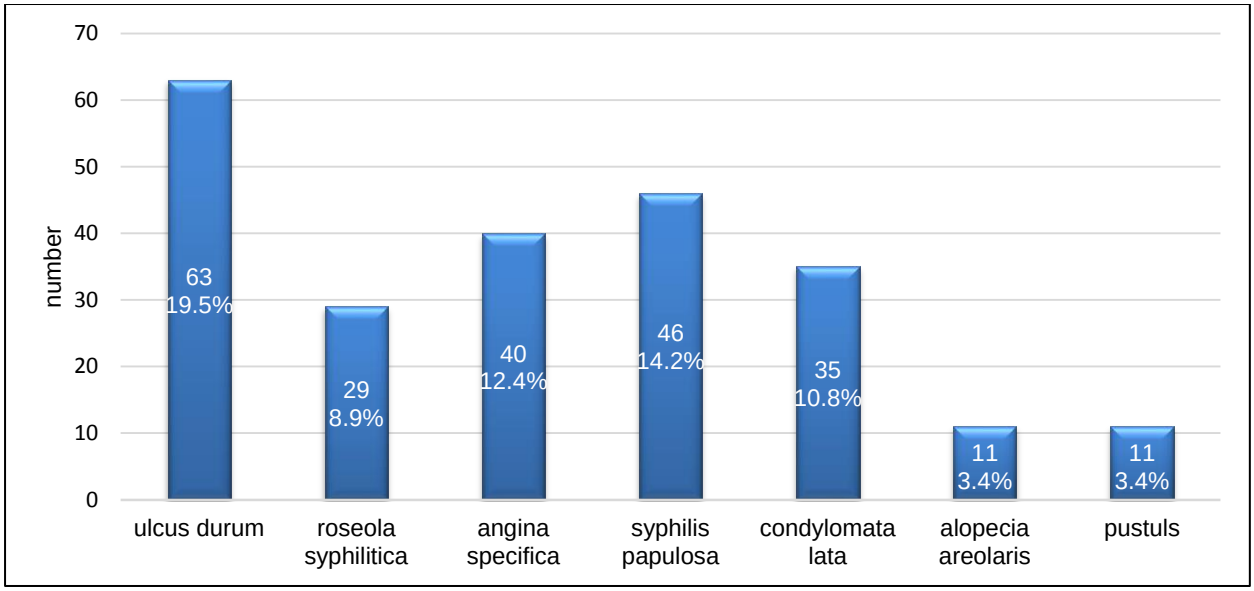


Figure 4: Frequency of different clinical signs of syphilis in patients with primary and secondary syphilis.

Figure 5: Pathological skin-mucosal manifestations in syphilis *(personal archive)*
A – ulcus durum, B – roseola syphilitica, C – papula syphilitica, D – condylomata lata,
E – angina specifica et plaque mucosae, F – alopecia areolaris

Regarding the method of detection, 32.8% of cases were diagnosed by clinical examination, and 6.5% were indicated as a contact person and as a source of infection. Most often, the reason for serological testing is during preventive or mandatory examinations (54.2%). In this regard, through blood donation - 16.1%, during pregnancy, 9.6%, during childbirth, 6.5%, and 5.6% each through research conducted during hospitalization and accompanying other diseases, 4.3% during marriage. The fact that only nine persons (2.8%) were tested voluntarily is disturbing. 45% were serologically diagnosed on occasions other than standard prophylaxis or referred with the diagnosis from other settlements. ***(Table 4)***

Table 4: Registered cases of syphilis diagnosed in the course of preventive examinations and at the request of the persons.

Indicators	Frequency	Per cent	Valid Percent	Cumulative Percent
Reason for the study				
clinical examination	106	32.8	32.8	32.8
prof. research	175	54.2	54.2	87.0
cited as source	21	6.5	6.5	93.5
listed as contact	21	6.5	6.5	100.0
Total	323	100.0	100.0	
Research profile				
pregnancy	31	9.6	9.6	9.6
marriage	14	4.3	4.3	13.9
abortion	1	.3	.3	14.2
blood donation	52	16.1	16.1	30.3
nursery school	7	2.2	2.2	32.5
for work	5	1.5	1.5	34.1
hospitalization	18	5.6	5.6	39.6
another disease	18	5.6	5.6	45.2
sexual violence	2	.6	.6	45.8
at will	9	2.8	2.8	48.6
childbirth	21	6.5	6.5	55.1

another occasion	145	44.9	44.9	100.0
Total	323	100.0	100.0	

Congenital syphilis is a public health burden, and its eradication is a significant public health and women's health goal worldwide. In this regard, among our patients, there are 52 pregnancies - 31 (9.6% of all 323 patients) pregnant women and 21 (6.5%) women in labour, which represent 16.1% of all patients and 39.7% of sick women. The result of these pregnancies was - 2 abortions (3.8% of 52 women), 15 stillbirths (28.8%), seven sick newborns (13.5%), 25 healthy newborns (48%), one sterility (1 .9%) and in two women (3.8%) the outcome is unknown. The Friedman test for comparing the frequency distributions of pregnancies and the effect of pregnancy shows statistically significant differences in the distribution - $\gamma^2(1)=321.00$, $p<0.001$.
In the process of diagnosis, follow-up and treatment of syphilis, the guidelines of the Ministry of Health are followed and adapted to each stage of the development of the infection.
In the last decade, there has been a transition from the classical scheme of monotherapy with depot penicillin - B benzathine Benzylpenicillin, Penicillin G Benzathine (total for the period 29.1%) and crystalline penicillin Penicillin G (total for the period 5.6%) to combined therapies (total for the period 54.8%), mainly with crystalline penicillin (Penicillin G and Ceftriaxone IV) with a subsequent course of depot penicillin (Penicillin G Benzatin IM), Doxycycline and less often Azithromycin.
Response to treatment with negative serology was assessed at 6 months, 1st, 2nd, and 3rd year of treatment, and cases with persistently positive serological results were also reported. Combined therapies lead to negative test results up to the third year in 35% of cases, but the large number of persons for whom there is no information, mostly for subjective reasons – 41% is striking. ***(Table 5)***

Table 5: Treatment performed and negative serological reactions followed over time

Deadlines			Penicillin G	Penicillin G Benzathine	Ceftriaxone	Doxycycline	Combined	Total
Negative serology	Up to 6 m.	number	1	7	0	7	6	21
		%	0.3%	2.2%	0.0%	2.2%	1.9%	6.5%
	up to 1 year	number	5	11	1	1	25	43
		%	1.5%	3.4%	0.3%	0.3%	7.7%	13.3%
	up to 2 years	number	0	10	1	0	22	33
		%	0.0%	3.1%	0.3%	0.0%	6.8%	10.2%
	up to 3 years	number	1	1	0	0	14	16
		%	0.3%	0.3%	0.0%	0.0%	4.3%	5.0%
	persists	number	1	21	1	4	51	78
		%	0.3%	6.5%	0.3%	1.2%	15.8%	24.1%
	There is no information	number	10	44	6	13	59	132
		%	3.1%	13.6%	1.9%	4.0%	18.3%	40.9%

Total	number	18	94	9	25	177	323
	%	5.6%	29.1%	2.8%	7.7%	54.8%	100.0%

In conclusion, the incidence of syphilis from 2008 until 2022 in the Pleven region varies between 4.9 and 14.5 per 100,000 inhabitants. After 2016, an increasing trend in the incidence of the disease was observed, with values exceeding two to four times the national data. The demographic profile of a syphilis patient in the Pleven region is aged 20-35, living in a city, with secondary education (grades 9-12), single, working or unemployed. After 2016, cases of syphilis-HIV co-infection are progressively increasing. In recent years, due to the lack of medication, first-line therapy with B benzathine Benzyl p penicillin, Penicillin G Benzatin / Penicillin G has been supplemented with cephalosporins, doxycycline and azithromycin. Applying adequate treatment (alone or in combination) leads to negative results within 2 years.

IV.2. Clinico-epidemiological analysis of syphilis among men who have sex with men (MSM) in the Pleven region (2008-2022)

The study aimed to investigate the epidemiology and different clinical features of syphilis in men who have sex with men (MSM).

In order to achieve our goal, the following **tasks were completed** :

1. To determine the frequency of MSM patients with a diagnosis of syphilis among dispensary persons with Lues, with the patients being distributed by age, place of residence, education and professional environment;
2. In connection with the spread of STDs, to study the risk factors for the MSM population - harmful addictions, number of partners and frequency of sexual contacts accompanying diseases;
3. With a thorough clinical examination, dermatological status and serological studies to determine the clinical stages of the disease, the frequency and localization of the clinical symptoms of the infection. After the diagnosis and prescribed antibiotic therapy, the effect of the treatment should be monitored over time;

Material and methods

Material - For the period 2008 - 2022 at the University Clinic for Skin and Venereal Diseases, 323 patients with different forms of syphilis were diagnosed and treated in Pleven. From them, 50 persons who had sexual contact with the same sex (MSM) were selected. They were aged between 16 and 53 years (mean age 31.53 ± 9.026) self-identified as "male". All signed informed consent for the use of clinical data without publication of personal information.

Methods - In the course of a retrospective and prospective epidemiological study, through cross-sectional analysis, to determine the frequency and percentage of MSM, with patients distributed by age, ethnicity, place of residence, family status,

education, and profession. An analysis of the risk factors for the spread of STIs among the MSM population was made.

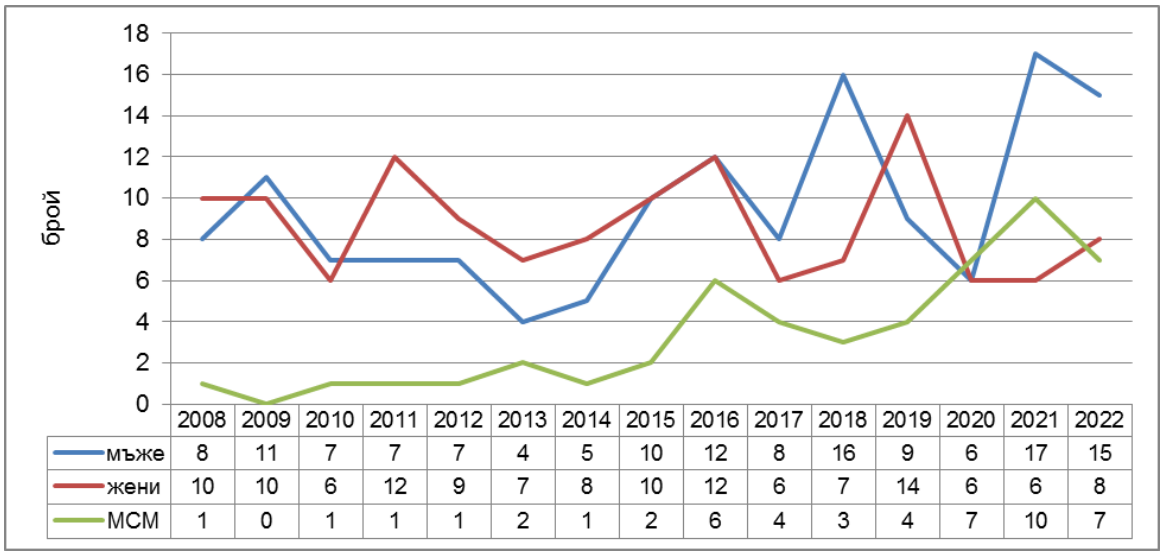
The clinical method is carried out by taking a detailed history, a thorough clinical examination and a dermatological status with a description of the clinical symptoms of the infection. The different clinical stages of the disease are registered - primary, secondary, and latent. Antibiotic therapy was prescribed, the effect of which was monitored over time by negating the serological samples, and patients with syphilis/HIV co-infection were referred to an infectious diseases clinic for treatment.

Laboratory methods for diagnosis and control include the serological tests RPR (rapid plasma reagin), TPHA (Treponema Pallidum Hemagglutination Assay) and ELISA IgM-IgG for syphilis, and for HIV carrier ELISA HIV1/2 Ag-Ab and HIV1/2 Rapid test are applied.

The results obtained were processed using the statistical program SPSS v.26 and EXCEL. They are described through tables, graphs and numerical values (percentages, coefficients, average values, standard deviation, etc.). The statistical methods used to analyze the results are descriptive statistics, variation and correlation analysis. The level of significance was $p < 0.05$.

Results

For 15 years (2008-2022), 323 persons of both sexes with different forms of syphilis were diagnosed, registered and treated - 192 men and 131 women (1.5: 1). The MSM population of 50 men represented 15.5% of the total treated patients with the same diagnosis and 26% of the affected men. ***(Fig. 6)***



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
мъже	8	11	7	7	7	4	5	10	12	8	16	9	6	17	15
жени	10	10	6	12	9	7	8	10	12	6	7	14	6	6	8
МСМ	1	0	1	1	1	2	1	2	6	4	3	4	7	10	7

Figure 6: Syphilis trend over the years, with distribution by gender (men blue line, women red line) and MSM (green line)

The high number of homosexual individuals registered after 2016 is striking. (41 patients, 82% of all), with 24, 48% of all, during the COVID-19 pandemic - 2020-2022.

Patients were aged between 16 and 53 years (mean age 31.53 ± 9.026). The demographic characteristics of MSM are shown in the **Table 6**

Table 6: Sociodemographic characteristics of MSM

Indicators		Frequency	Per cent	Valid Percent	Cumulative Percent
Age group	16-20	2	4.0	4.0	4.0
	20-29	27	54.0	54.0	58.0
	30-39	11	22.0	22.0	80.0
	40-49	6	12.0	12.0	92.0
	> 50	4	8.0	8.0	100.0
	Total	50	100.0	100.0	
Ethnicity	Bulgarians	39	78.0	78.0	78.0
	Roma	11	22.0	22.0	100.0
	Total	50	100.0	100.0	
Indicators		Frequency	Per cent	Valid Percent	Cumulative Percent
Place of residence	City	41	82.0	82.0	82.0
	Village / small town	9	18.0	18.0	100.0
	Total	50	100.0	100.0	
Education	First and foremost	4	8.0	8.0	8.0
	average	19	38.0	38.0	46.0
	Medium special	10	20.0	20.0	66.0
	Higher	17	34.0	34.0	100.0
	Total	50	100.0	100.0	
Family status	Family	2	4.0	4.0	4.0
	Unmarried	42	84.0	84.0	88.0
	Divorced	4	8.0	8.0	96.0
	Coexistence	1	2.0	2.0	98.0
	A child	1	2.0	2.0	100.0
	Total	50	100.0	100.0	
Employment	A student	4	8.0	8.0	8.0
	Working	28	56.0	56.0	64.0
	Free profession	5	10.0	10.0	74.0
	Prisoner	2	4.0	4.0	78.0
	A male gigolo	1	2.0	2.0	80.0
	Unemployed	10	20.0	20.0	100.0
	Total	50	100.0	100.0	

According to the age of 50 MSM, the 20-29 age group is the most affected. (54%), followed by 30-39 year olds. (22%). 78% are of Bulgarian ethnic origin, 82% of them live in large and medium-sized cities, 92% of them have secondary and above

secondary education (34% are university graduates), 84% are single, 56% are professionals in their work, and 20% are unemployed.
When assessing the risk factors, it is striking that 28% abuse alcohol, cigarettes and narcotic substances at the same time, 32% with alcohol and only 12% do not report any harmful habits. Data related to sexual activities indicated that 88% of them had two or more sexual contacts, 30% had a permanent partner, and 70% reported casual contacts. For 62%, the last sexual act was up to 3 months old, with 24% from 3 to 6 months. ***(Table 7)*** Risk calculations show that MSM who abuse alcohol or combine alcohol with drugs are more than 2 times more likely to be infected (OR 2.25; 95%CI: 1.0108-5.0083; p<0.05), and those who had contact with a casual partner were at risk of treponemal infection 5.5 times compared to those with a regular partner (OR 5.4; 95%CI: 2.3145-12.8072; p<0.001).

Table 7: Epidemiology of syphilis in MSM

Indicators		Frequency	Per cent	Valid Percent	Cumulative Percent
Risk factors	It does not report	6	12.0	12.0	12.0
	Alcohol	16	32.0	32.0	44.0
	Cigarettes	13	26.0	26.0	70.0
	Drugs	1	2.0	2.0	72.0
	Everyone	14	28.0	28.0	100.0
	Total	50	100.0	100.0	
Sex. contacts	disposable	6	12.0	12.0	12.0
	plural	44	88.0	88.0	100.0
	Total	50	100.0	100.0	
Sex. partner	Random	35	70.0	70.0	70.0
	constant	15	30.0	30.0	100.0
	Total	50	100.0	100.0	
Last sex. contact	< 3 months	31	62.0	62.0	62.0
	3-6 months	12	24.0	24.0	86.0
	> 6 months	7	14.0	14.0	100.0
	Total	50	100.0	100.0	

More than half of the patients (52%) have no accompanying diseases; there are only a few cases of co-infection with chlamydia, candida and papillomavirus, but 13 (26%) combine with HIV carriers. For comparison, out of a total of 323 individuals registered, 17 (5.3%) had syphilis/HIV co-infection.
58% actively sought medical help, 8% indicated as a source, and 6% as a contact. In the course of preventive examinations, 28% of them were found - 8% during blood donation, 12% during examinations for other systemic diseases and only 4% by request). All patients were serologically verified with the screening RPR test and the syphilis-specific TPHA and ELISA IgM-IgG. They were also tested for HIV. 20% of RPR tests are negative, and tests with a titer of 1:16 (24%) and 1:32 (26%) are the

most common. The diagnosis in negative screening tests, as in all others, was confirmed by TPHA. ***(Table 8)*** No correlative dependence of the titer in the screening RPR test with the clinical form of syphilis was found (p > 0.05).

Analysis of the clinical picture and serological diagnosis objectified 22% with primary syphilis, 34% each for secondary and early latent and 6% for late latent. The localization of the pathological skin-mucosal changes has the highest frequency in the genital area (34%), in the anorectal (10%), in the oropharyngeal (8%), with other extragenital localization in 8% and 40% it cannot be established in the course of the latent forms of the disease. ***(Table 9)***

Table 8: Diagnosis of syphilis in MSM

Indicators		Frequency	Per cent	Valid Percent	Cumulative Percent
Reason for the study	Clinical examination	29	58.0	58.0	58.0
	Prof. research	14	28.0	28.0	86.0
	Cited as a source	4	8.0	8.0	94.0
	Listed as a contact	3	6.0	6.0	100.0
	Total	50	100.0	100.0	
Profile of the research	Blood donation	4	8.0	8.0	8.0
	Hospitalization	2	4.0	4.0	12.0
	For work	1	2.0	2.0	14.0
	Another disease	6	12.0	12.0	26.0
	Own desire	2	4.0	4.0	30.0
	There is no information	35	70.0	70.0	100.0
	Total	50	100.0	100.0	
RPR test-titer	negative	10	20.0	20.0	20.0
	1:4	6	12.0	12.0	32.0
	1:8	8	16.0	16.0	48.0
	1:16 a.m	12	24.0	24.0	72.0
	1:32	13	26.0	26.0	98.0
	1:128	1	2.0	2.0	100.0
	Total	50	100.0	100.0	

Table 9: Clinical characteristics of syphilis in MSM

		Frequency	Per cent	Valid Percent	Cumulative Percent
Clinical stage	Primary	11	22.0	22.0	22.0
	Secondary	17	34.0	34.0	56.0
	Early latent	17	34.0	34.0	90.0
	Neurolues	1	2.0	2.0	92.0
	Late latent	3	6.0	6.0	98.0
	Another	1	2.0	2.0	100.0

	Total	50	100.0	100.0	
Localization of clinical changes	Genital	17	34.0	34.0	34.0
	Anorectal	5	10.0	10.0	44.0
	Oropharyngeal	4	8.0	8.0	52.0
	Unknown	20	40.0	40.0	92.0
	another	4	8.0	8.0	100.0
	Total	50	100.0	100.0	

Clinical symptoms were hard chancre in 28.6%, macular syphilides (roseolae and angina) in 49%, and papular syphilides (papules and flat condylomas) in 45% of the 50 MSM. The sum of the percentages is greater than 100% due to the fact that patients had more than one symptom. ***(Fig. 7)***

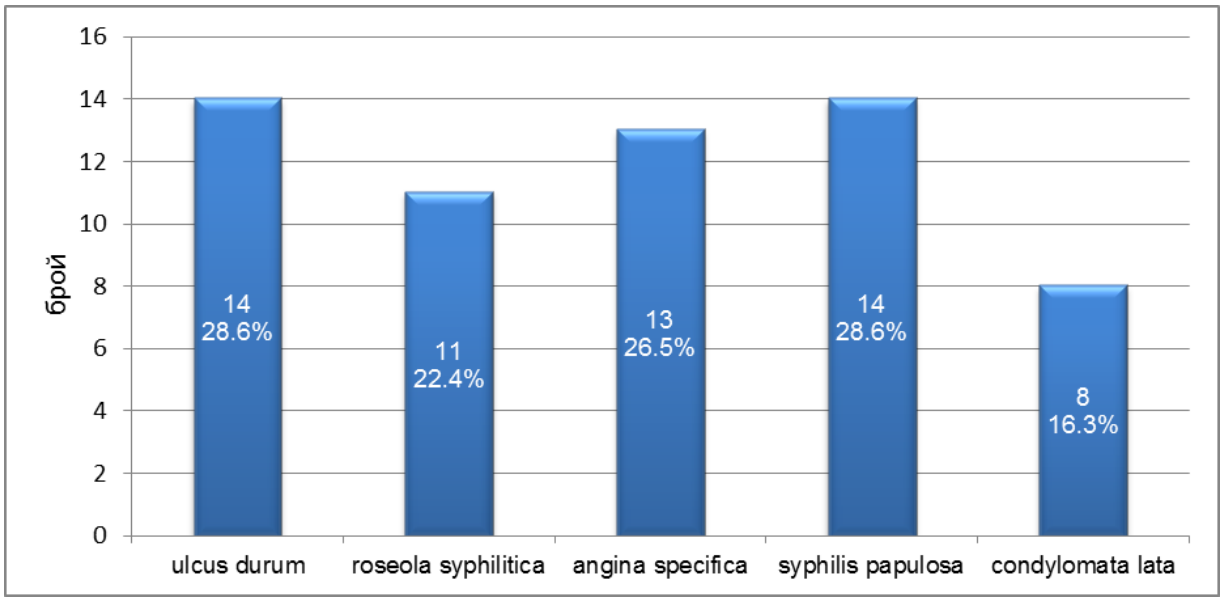


Figure 7: Clinical symptoms in 50 MSM patients with syphilis

A significant correlation was found between the clinical form of the disease and the localization of the pathological skin-mucosal lesions ($r=0.628$; $p<0.001$; $N=50$), as well as the relationship between the clinical symptoms and the clinical form - ulcus durum with primary syphilis ($r=0.811$; $p<0.001$; $N=50$), the macular ($r=0.912$, $p<0.001$, $N=50$) and papular syphilides ($r=0.681$, $p<0.001$, $N=50$) with the secondary period.

Therapy included treatment with depot penicillin 2,400,000 IU once weekly in 34% of patients, as well as a combination of antibiotics in 60% of them. The treatment effect was monitored periodically, with 58% having follow-up examinations and tests 1 to 3 times, 28% 4 to 7 times, and 6% 8 to 10 times, as a result of adequate antibiotic therapy, 8% negative their positive serology by the 6th month, 12% by the 12th month, 28% by the 24th month. At the same time, there is no data for 34% of luetic

patients due to interrupted contact with the clinic (change of residence, departure abroad, of their own accord, etc.). ***(Table 10)***

In conclusion, the results of our study show that the number of diagnosed and treated syphilis cases at the Pleven Dermatology Clinic increased after 2016. The percentage of infected MSM is also increasing. Worryingly, the number of homosexual individuals with syphilis/HIV co-infection is increasing. These facts correspond to the data published in the scientific literature in the last 10 years. A qualified medical approach is needed in the course of a clinical examination to identify the infection and ensure adequate treatment is followed until the specific serology becomes negative. Assessment of sexual risk, recommendations for safe sex restriction of sexual contacts, and regular testing for sexually transmitted infections are only part of the activity for the prevention and control of syphilis among the MSM population.

Table 10: Treatment of syphilis in MSM

		Frequency	Per cent	Valid Percent	Cumulative Percent
Antibiotics	Penicillin G	1	2.0	2.0	2.0
	Penicillin Depot	17	34.0	34.0	36.0
	Cephalosporin	1	2.0	2.0	38.0
	Doxycycline	1	2.0	2.0	40.0
	Combined	30	60.0	60.0	100.0
	Total	50	100.0	100.0	
Number of control visits	1-3	29	58.0	58.0	58.0
	4 -7	14	28.0	28.0	86.0
	8 -10	6	12.0	12.0	98.0
	> 10	1	2.0	2.0	100.0
	Total	50	100.0	100.0	
Negative serology	1-6 months	4	8.0	8.0	8.0
	6 m. – 1 year	6	12.0	12.0	20.0
	1 – 2 years	14	28.0	28.0	48.0
	2 – 3 Mr.	1	2.0	2.0	50.0
	> 3 years	8	16.0	16.0	66.0
	There is no information	17	34.0	34.0	100.0
	Total	50	100.0	100.0	

IV.3. Clinical-epidemiological analysis of syphilis among the Roma ethnic community in the Pleven region (2008-2022)

The study aims to determine the frequency of syphilis among the Roma ethnic group in the Pleven region and to describe the socio-demographic and clinical characteristics of the affected Roma.

Material and methods

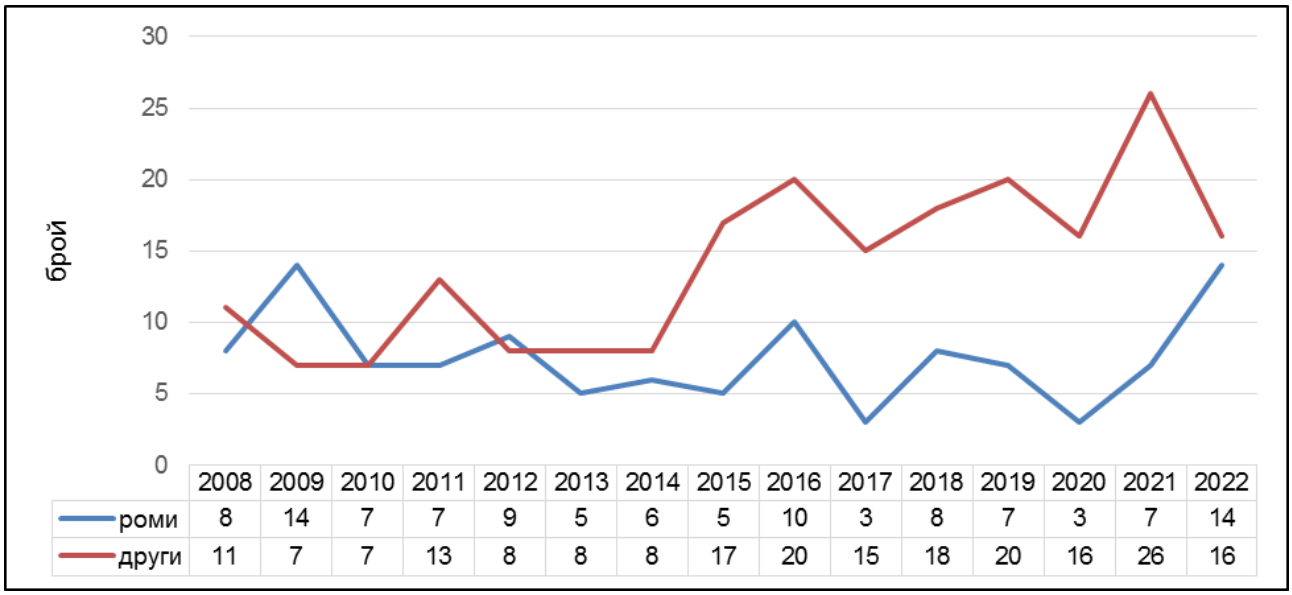
In the period 2008-2022, 113 patients of Roma origin, suffering from various forms of syphilis, were diagnosed and treated in the clinic for skin and venereal diseases at the University Hospital in Pleven. Their average age is 28.50 ± 11.80; men are 51

(45.13%), and women are 62 (54.87%). The diagnosis is based on the patient's history and physical examination and is confirmed with serological diagnostic methods. Data on the demographic characteristics of Roma patients (age, gender, place of residence, marital status, education, employment and sexual orientation) were retrospectively extracted from their registration cards, the completion of which is mandatory according to the regulations in the Republic of. Bulgaria. When processing the data, descriptive statistics and comparative analysis (χ^2 test and Fisher's exact test) were applied. All P values are based on two-tailed tests, and $p<0.05$ is considered significant.

Results

During the period 2008–2022, Roma represents, on average, 35% of all registered cases of syphilis. The frequency of syphilis among them and other ethnic groups of the population of the Pleven region is presented by year in **Figure 8**.

Based on the data from the last two population censuses in Bulgaria (2011 and 2021), the share of Roma in the total population of the Pleven region varies between 4.09% - 3.09%, and the infection is more common among them. Compared to the rest of the patients from the population of the region - 13 times more often in 2011. and 10 times in 2021.



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
роми	8	14	7	7	9	5	6	5	10	3	8	7	3	7	14
други	11	7	7	13	8	8	8	17	20	15	18	20	16	26	16

Figure 8: Incidence of syphilis among the Roma population (blue line) and other ethnic groups (red line) in the district over the years

The frequency of syphilis among the Roma and other ethnic groups of the population of the Pleven region, presented by five years, shows a significant difference in the frequency distribution of patients from the two subpopulations for the three 5-year periods - $\chi^2(2)=11.68$, $p=0.003$, $N=323$. ***(Table 11)***

Table 11: Incidence of syphilis among the Roma population and other ethnic groups in the Pleven region for the three five-year periods from 2008 to 2022.

Incidence of syphilis		Roma ethnicity		Another ethnicity		P value
		Count	%	Count	%	
In 5 years						< 0.005
	2008-2012	45	39.8	46	21.9	
	2013-2017	29	25.7	68	32.4	
	2018-2022	39	34.5	96	45.7	
Total		113	100	210	100	

Among Roma with syphilis, 45.13% are men, and 54.87% are women. They ranged in age from 0 to 63 years (mean age 28 ± 11.8 vs. 35.30 ± 14.4 in the other patients). The most affected age is 20–29 years (44.2%). 32.7% are unmarried, and 48.8% are cohabiting without marriage. 48.7% have primary and basic education, 54% are unemployed, 82.3% are heterosexual. Roma men who declared themselves homosexual represent 9.7% of all patients and 21.5% of men. Among Roma women, 11.5% were prostitutes, 14% were pregnant, and 15% were in labour. Early syphilis (8 with primary, 24 with secondary and 61 with early latent) is 82.3%, and cases of congenital syphilis are 5 (4.4%). There are significant differences in almost all observed characteristics between Roma patients and other patient's ethnic groups. ***(Table 12)***

Table 12: Socio-demographic characteristics of Syphilis-afflicted Roma and persons from other ethnic groups in Pleven region for the period 2008-2022.

Indicators	Roma		Another ethnicity		P value
	number	%	number	%	
gender					< 0.001
men	51	45.13	141	67.14	
women	62	54.87	69	32.86	
Age groups					< 0.05
< 15	6	5.3	7	3.3	
16-19	13	11.5	9	4.3	
20-29	50	44.2	70	33.3	
30-39	28	24.8	53	25.3	
40-49	9	8.0	31	14.8	
> 50	7	6.2	40	19.0	
Residence					< 0.001
City	56	49.55	155	73.8	
Village / small town	57	50.45	55	22.2	
Education					< 0.001
Without (<7 years)	5	4.5	5	2.4	
Basic (7-14 years)	55	48.7	17	8.1	

Average (15-19 years)	52	46.0	146	69.5	
Higher	1	0.8	42	20.0	
Family status					< 0.001
Family	17	15.1	47	22.4	
Unmarried	37	32.7	97	46.2	
Divorced	3	2.6	15	7.1	
Widower/widow	1	0.8	10	4.8	
In cohabitation	55	48.8	41	19.5	
Employment					< 0.001
Child/pupil/student	8	7.1	19	9.2	
Working	24	21.3	116	55.3	
Unemployed	61	54.0	63	30.0	
Prisoners	5	4.5	2	0.9	
Prostitutes*	13	11.5	5	2.4	
Pensioners	2	1.6	15	7.2	
Sexual orientation					> 0.05
Heterosexual	93	82.3	161	76.6	
Homosexual**	11	9.7	39	18.6	
They refuse to answer	4	3.5	5	2.4	
Not applicable (children)	5	4.5	5	2.4	

* all prostitutes are women ** all homosexuals are MSM

The results show that Roma are younger, less educated, more often cohabiting without marriage and unemployed. In the study population, among the Roma, there are more female prostitutes (11.5% vs. 2.4%) and a smaller percentage of homosexuals (9.7% vs. 18.6%).

Harmful habits, sexual behaviour, and frequency of sexual contact are described in Table 13, and when comparing the sick Roma with the other subpopulation, statistically significant differences in the distribution are found in two of the groups of indicators: for "frequency of sexual contacts" χ^2 (2) = 25.626, p<0.00 1; for "last sexual contact" χ^2 (3)=11.636; p<0.0 1 ***(Table 13)***

Table 13: Risk factors and accompanying diseases in infected Roma

Indicators		**Roma**	**Another ethnicity**	**Total**	**r**
Harmful habits					> 0. 0 5
alcohol	number	27	52	79	
	% of all	8.40%	16.10%	24.50%	
cigarettes	number	31	46	77	
	% of all	9.60%	14.20%	23.80%	
drugs	number	3	2	5	
	% of all	0.90%	0.60%	1.50%	
everyone	number	15	27	42	
	% of all	4.60%	8.40%	13.00%	

none	number	37	83	120	
	% of all	11.40%	25.70%	37.10%	
Total	number	113	210	323	
	% of all	35.00%	65.00%	100.00%	
Frequency of sexual contact					< 0.001
No (children)	number	5	5	10	
	% of all	1.50%	1.50%	3.10%	
one time	number	22	101	123	
	% of all	6.80%	31.30%	38.10%	
repeatedly	number	86	104	190	
	% of all	26.60%	32.20%	58.80%	
Total	number	113	210	323	
	% of all	35.00%	65.00%	100.00%	
Partners					> 0. 0 5
No (children)	number	5	5	10	
	% of all	1.50%	1.50%	3.10%	
random	number	61	131	192	
	% of all	18.90%	40.60%	59.40%	
constant	number	47	74	121	
	% of all	14.60%	22.90%	37.50%	
Total	number	113	210	323	
	% of all	35.00%	65.00%	100.00%	
Last sexual contact					< 0.0 1
No (children)	number	5	5	10	
	% of all	1.50%	1.50%	3.10%	
Up to 3 m.	number	64	101	165	
	% of all	19.80%	31.30%	51.10%	
3-6 m.	number	33	51	84	
	% of all	10.20%	15.80%	26.00%	
Over 6 m.	number	11	53	64	
	% of all	3.40%	16.40%	19.80%	
Total	number	113	210	323	
	% of all	35.00%	65.00%	100.00%	
Comorbidities					> 0.05
Gonorrhea	number	2	0	2	
	% of all	0.60%	0.00%	0.60%	
Chlamydia	number	1	2	3	
	% of all	0.30%	0.60%	0.90%	
Candidiasis	number	0	2	2	
	% of all	0.00%	0.60%	0.60%	
Herpes	number	0	1	1	
	% of all	0.00%	0.30%	0.30%	
Papilloma	number	1	4	5	
	% of all	0.30%	1.20%	1.50%	
HIV	number	1	16	17	
	% of all	0.30%	5.00%	5.30%	

other systemic	number	21	41	62	
	% of all	6.50%	12.70%	19.20%	
there isn't	number	87	144	231	
	% of all	26.90%	44.60%	71.50%	
Total	number	113	210	323	
	% of all	35.00%	65.00%	100.00%	

Harmful habits are the same for both subpopulations, as smoking and drinking alcohol are traditional for the Bulgarian way of life, the use of narcotic substances is usually not recognized, and a high percentage of those who indicated that they do not have any harmful habit is certainly false. 86 Roma (76% of them and 27% of all) indicated frequent multiple sexual contact. For 61 (54% of Roma), these contacts were with a casual partner, and for 64 of them (56.6%), the last sexual act was within a period of up to 3 months. Syphilis co-infection with other STIs is low to absent – one heterosexual with HIV, one with chlamydia and two with gonorrhoea.

Analyzing the periods of syphilis, the highest frequency of early latent syphilis is reported (54%), followed by secondary (21.2%) and late latent syphilis (10.6%). Latent forms represent 64.6% of all, and logically, the localization of the clinical stigmata of the disease remains unknown in 68.1% of sick Roma. Usually, genital localization is the most common - 18.6%, followed by the oropharyngeal - 8% ***(Table. 14 and Fig. 9)***

Table 14: Clinical stage of syphilis and localization of pathological changes in Roma

Indicators		Frequency	Per cent	Valid Percent	Cumulative Percent
Clinical form	primary	8	7.1	7.1	7.1
	secondary	24	21.2	21.2	28.3
	early latent	61	54.0	54.0	82.3
	neurosyphilis	1	,9	,9	83.2
	late latent	12	10.6	10.6	93.8
	unspecified	2	1.8	1.8	95.6
	congenital	5	4.4	4.4	100.0
	Total	113	100.0	100.0	
Localization	genital	21	18.6	18.6	18.6
	anorectal	3	2.7	2.7	21.2
	pharyngeal	9	8.0	8.0	29.2
	unknown	77	68.1	68.1	97.3
	another	3	2.7	2.7	100.0
	Total	113	100.0	100.0	

When comparing sick Roma with the other subpopulation, a significant statistical difference was found in the frequency distribution of rash localization between the groups - $\chi^2(4)=20.379$; p=0.000

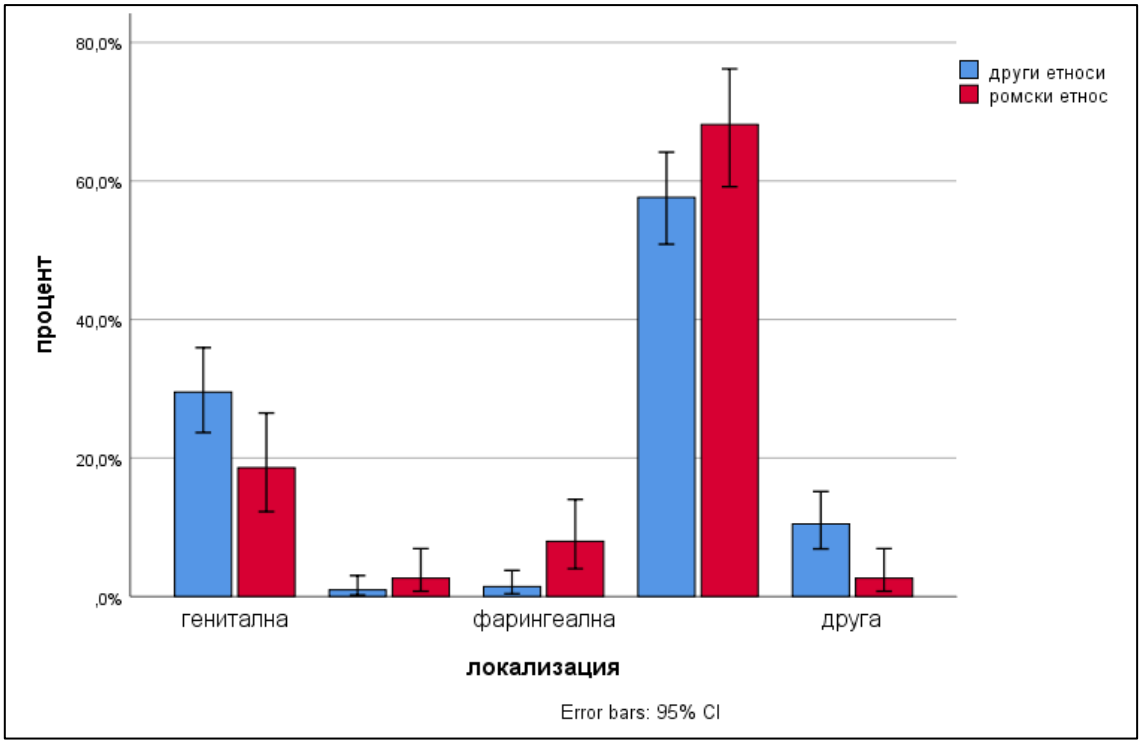


Figure 9: Distribution of the localization of pathological lesions (genital, anorectal, oropharyngeal and others) in the two subpopulations (Roma in red column, another group in blue)

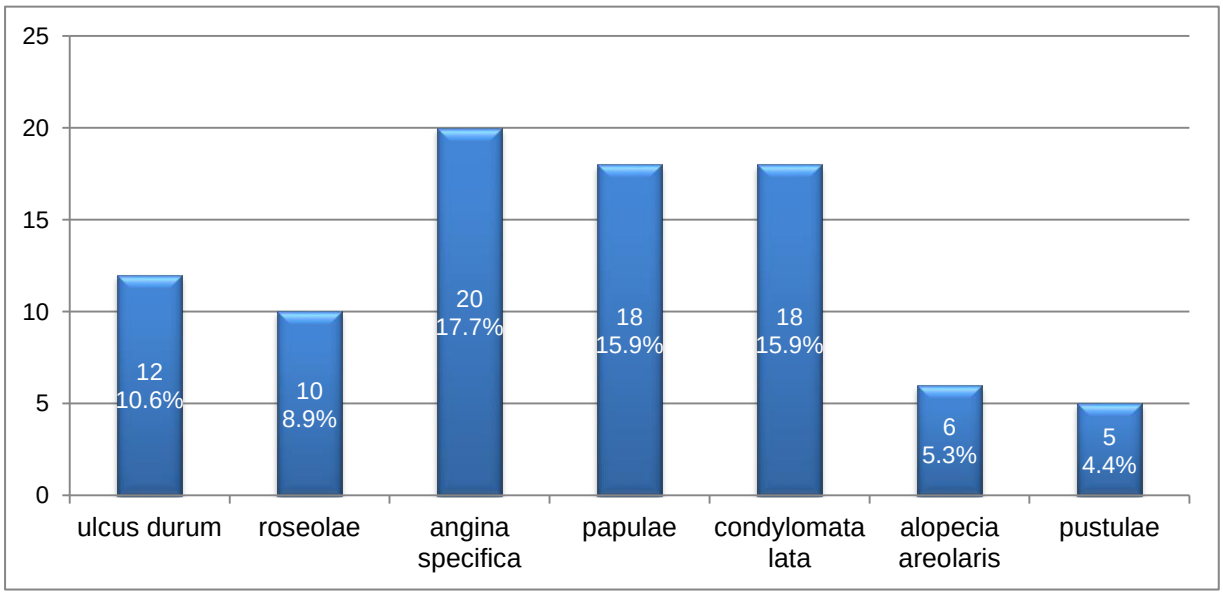


Figure 10: Clinical characteristics of syphilis in Roma

Through clinical examination, 26.3% of the infected Roma were found, and 59.3% through prophylactic and mandatory fasting. There are 16 (14.2%) pregnant Roma women, 17 (15%) women who have given birth, 13 (11.5%) were found to have donated blood. Only three (2.7%) were examined at their own will, which is an extremely worrying fact. ***(Table 15)***

Table 15: Diagnosis of syphilis among the Roma

Indicators		Frequency	Per cent	Valid Percent	Cumulative Percent
Reason for the study	clinical examination	30	26.5	26.5	26.5
	prof. research	67	59.3	59.3	85.8
	cited as source	11	9.7	9.7	95.6
	listed as contact	5	4.4	4.4	100.0
	Total	113	100.0	100.0	
Research profile	pregnancy	16	14.2	14.2	14.2
	marriage	6	5.3	5.3	19.5
	blood donation	13	11.5	11.5	31.0
	nursery school	2	1.8	1.8	32.7
	hospitalization	4	3.5	3.5	36.3
	another disease	7	6.2	6.2	42.5
	sexual violence	1	,9	,9	43.4
	at will	3	2.7	2.7	46.0
	childbirth	17	15.0	15.0	61.1
	NP	44	38.9	38.9	100.0
	Total	113	100.0	100.0	

The effect of these data is indicated in Table 16 - abortion (3.5% of registered Roma), 14 stillbirths (12.4%), five sick newborn children (4.4%), and five sterility (4.4%). The newborn 30 healthy children (26.5%) are the result of effective treatment during pregnancy. ***(Table 16)***

Table 16: Birth anamnesis among Roma compared with that of other ethnic groups

Birth history		**Roma**	**Another ethnicity**	**Total**
abortion	Count	4	4	8
	% within the birth history	50.0%	50.0%	100.0%
	% within Roma	3.5%	1.9%	2.5%
	% of Total	1.2%	1.2%	2.5%
stillbirth	Count	14	2	16
	% within the birth history	87.5%	12.5%	100.0%
	% within Roma	12.4%	1.0%	5.0%
	% of Total	4.3%	0.6%	5.0%
born sick	Count	5	4	9
	% within the birth history	55.6%	44.4%	100.0%

	% within Roma	4.4%	1.9%	2.8%
	% of Total	1.5%	1.2%	2.8%
born healthy	Count	30	34	64
	% within the birth history	46.9%	53.1%	100.0%
	% within Roma	26.5%	16.2%	19.8%
	% of Total	9.3%	10.5%	19.8%
sterility	Count	5	8	13
	% within the birth history	38.5%	61.5%	100.0%
	% within Roma	4.4%	3.8%	4.0%
	% of Total	1.5%	2.5%	4.0%
Not applicable (men and children)	Count	55	158	213
	% within the birth history	25.8%	74.2%	100.0%
	% within Roma	48.7%	75.2%	65.9%
	% of Total	17.0%	48.9%	65.9%
Total	Count	113	210	323
	% within the birth history	35.0%	65.0%	100.0%
	% within Roma	100.0%	100.0%	100.0%
	% of Total	35.0%	65.0%	100.0%

In the treatment of syphilis and follow-up of the effect of the therapy, all the guidelines of the Ministry of Health, adapted to each stage of the development of the infection, are followed - pregnant women and newborns are treated with crystalline Penicillin G (8%). Monotherapy with depot Penicillins (Benzathine Benzylpenicillin, Penicillin G Benzatin) was applied in 22.1% of cases. The scheme of combined treatment was most often applied after a period of penicillin therapy, and the treatment continued with cephalosporins, Doxycyclin, or Azithromycin. (54%). There are only a few cases of intravenous therapy with Ceftriaxone at the beginning, followed by a subsequent course of depot penicillin with intramuscular application. Response to treatment with negative serology was assessed at 6 months, 1st, 2nd, and 3rd year of treatment, and cases with persistently positive serological results were also reported. Combined therapies lead to negative tests by the third year in 9.7% of cases, and after the third year, positive serology persists in 23.9%. As with the analysis of the entire population suffering from syphilis in the Pleven region, the large number of persons for whom there is "no information" is striking, mostly for subjective reasons - 47.8%. ***(Table 17)*** In this regard, for this indicator, we made a comparison between the two subpopulations - 78 persons from other ethnicities (37.15%) and 54 Roma (47.8%), and with the Mann-Whitney U test it was found that there is a significant difference in the distribution of the indicator for representatives

of other ethnic groups (average rank 153.17) and for Roma (average rank 178.41), U = 10011.0, p = 0.015, with a smaller than typical effect size – r = 0.14.

Table 17: Treatment and treatment effect of syphilis in Roma

Deadlines			Type of treatment					Total
			Penicillin G	Penicillin G Benzathine	Ceftriaxone	Doxycycline	Combined	
Negative serology	1 to 6 m.	number	0	1	0	4	1	6
		%	0.0%	0.9%	0.0%	3.5%	0.9%	5.3%
	up to 1 year	number	3	0	0	0	5	8
		%	2.7%	0.0%	0.0%	0.0%	4.4%	7.1%
	up to 2 years	number	0	3	0	0	4	7
		%	0.0%	2.7%	0.0%	0.0%	3.5%	6.2%
	up to 3 years	number	1	1	0	0	9	11
		%	0.9%	0.9%	0.0%	0.0%	8.0%	9.7%
	persists	number	1	6	1	0	19	27
		%	0.9%	5.3%	0.9%	0.0%	16.8%	23.9%
	There is no information	number	4	14	5	8	23	54
		%	3.5%	12.4%	4.4%	7.1%	20.4%	47.8%
Total		number	9	25	6	12	61	113
		%	8.0%	22.1%	5.3%	10.6%	54.0%	100.0%

The results of our study for the Roma ethnic group show that the number of diagnosed and treated cases of syphilis among them at the Pleven Dermatology Clinic increased after 2018. Roma with Lues are younger, less educated, and more often unemployed, most in the age group of 20-29. Moreover, the rate of infection is 10-13 times higher than other ethnicities living in the district. These facts correspond to the data published in the last 15 years in the scientific literature by other authors from Central and Eastern Europe. The Balkans, where about 70% of the Roma population of the continent live. In general, the social, economic, household and health problems of Roma societies represent a significant problem for public health in various countries in the quest for Roma integration. Limiting the sexual risk through recommendations to reduce the number of sexual contacts, safe sex, and regular testing for sexually transmitted infections are only part of the activity for the prevention and control not only of syphilis but also of other STIs among the Roma population.

IV.4. Description of clinical cases

IV.4.1. Syphilitic uveitis in an HIV-positive patient

We present the case of a 27-year-old homosexual man of Roma ethnicity, hospitalized in the Ophthalmology Clinic with a diagnosis of uveitis and a three-month history of reduced vision and floating black spots in the left eye, accompanied by severe headache. In recent weeks, his vision has also been impaired on the right. He reports that a year ago (January 2014), he had a painless penile ulcer that resolved spontaneously without treatment. In September 2014, I noticed swelling of the neck glands, high fever, fatigue, and sore throat. Treated with Paracetamol for 3-4 days. Gradually, the peripheral lymph nodes increased - under the armpits and lower jaw, in the groin. In October 2014, is referred to a haematologist with suspected lymphoma or infectious mononucleosis. An excisional biopsy of a neck lymph node is performed. Then, he noticed a progressive visual impairment, mainly on the left. ***(Table 18)***

Table 18: History of the disease and evolution of clinical manifestations in the patient

Periods	Symptoms	State dynamics
January 2014	Genital ulcer (Ulcus durum)	It passed spontaneously without treatment.
September 2014	Fever, fatigue, sore throat, enlarged lymph nodes in the neck - primary clinical complex	Taking Paracetamol for 3-4 days
October 2014	With a clinic of acute HIV infection, disseminated lymphadenomegaly gradually develops	Consultation with a hematologist and biopsy from LV – LV-lymphoma is excluded; morphological picture closest to Infectious mononucleosis
December 2014	Progressive visual disturbances on the left	From PKK - anaemic syndrome and monocytosis
January 2015	Uveitis of both eyes	Hospitalization in an eye clinic
	Diagnosed with syphilis and HIV infection	Consultation with a dermatologist, serological examination

Dermatological status: Genitalia – intact, no postlesional cicatrix of the penis. Oral mucosa – enanthema of tonsils, palatal arches, tongue, one central longitudinal furrow and hypertrophic lesion with irregular shape and whitish plaques on the tongue. Skin – single papular and pustular lesions in the beard area. Skin appendages – no change. Lymph nodes are greatly enlarged, dense, not fused and with the surrounding skin, mobile, and painless in the occipital, submandibular, axillary, and inguinal regions. ***(Figs. 11A and 11B)***

Ophthalmological status: On the corneal endothelium - fine non-confluent precipitates. PC – deep. Tyndall /+/ positive. Pupil - central, clear. Lens - transparent. Vitreous opacities and effusion. Vessels with inflammatory infiltrate - punctate exudate along the course of the vessels. Macula - scattered light reflexes without

foveolar reflex. VOD = 1.0; VOS = 0.15; TOD = 14 mmHg; TOS = 13 mmHg ***(Fig. 11C)***

Figure 11: Clinical picture: A – pathological changes on the mucous membrane of the tongue; B – cicatrix after extirpation of a lymph node in order to rule out lymphoproliferative disease; C – Biomicroscopic picture of panuveitis

Laboratory tests: Proved the presence of active Syphilis and co-infection with the AIDS virus. ***(Table 19)*** PKK – anaemic syndrome and monocytosis. Histological examination of a neck lymph node objectified a morphological picture closest to infectious mononucleosis. Electroencephalography (EEG) was performed, which was within normal limits. The patient refused a lumbar puncture.

Based on the clinical data and laboratory test results, the diagnosis of Secondary syphilis, panuveitis and co-infection with HIV was confirmed.

Intravenous treatment with Penicillin G - 12,000,000 IU daily / 4 x 3 million IU / for 14 days was carried out, followed by depot penicillin preparation Benzatin benzylpenicillin 2,400,000 IU IM weekly - 5 weeks. The patient was referred for antiretroviral therapy.

Table 19: Laboratory tests and results

Test	Result
PKK	Hb – 97.0 g/l; Er – 3.43; Mo – 11.1%
RPR (Rapid Plasma Reagin - nontreponemal)	positive (4+); titer 1:32
TPHA (Treponema pallidum haemagglutination assay)	positive (4+)
Rapid HIV test ELISA (BIO-RAD, Genscreen Ultra HIV Ag-Ab)	positive positive
Western blot (InnoLia HIVI/II Score)	positive for HIV-1
Immunophenotyping of lymphocyte populations	Ly – 1373 (norm 1600-2400) CD4+ – 16.3 (normal 36-46) Lowered Th / Ts ratio
Histological examination of a lymph node	Follicular hyperplasia with enlarged paracortex and numerous CD20+ large lymphoid cells; CD30+; CD10-; EMA + cells

The described case of a young homosexual man with a leading clinical manifestation of syphilitic uveitis and co-infection with the AIDS virus is a demonstration of the diverse symptomatology of syphilis as systemic vasculitis. It aims to direct our attention to the need for screening tests for sexually transmitted infections in diagnostic and treatment algorithms.

IV.4.2. A case of early congenital syphilis - dead fetus

We present a 24-year-old woman of the Roma ethnicity, pregnant in the VII-VIII lunar month; she was admitted urgently to the Maternity Ward, where she gave birth to a dead, macerated fetus. The woman did not visit a gynaecologist during pregnancy. She was not tested for syphilis. There are four live births and two aborted pregnancies. The prostitute lives on a family basis with a man diagnosed with latent syphilis. The source of the infection is a foreigner. After consultation with a dermatologist and serological examination, Early secondary syphilis was established with characteristic, contagious rashes and highly positive serological tests: VDRL /4+/; TPHA /4+/; ELISA IgM / IgG positive. Dermatological status: Disseminated on the trunk and extremities, round, hypopigmented macules without desquamation – Leucoderma syphilis; Single nummular, erythematous papules in the axilla and genital area – Condylomata lata; Variegated, erythematous, peripherally desquamated, papular syphilides on palms and soles - Syphilis papulosa psoriasiformis ; Diffuse, pronounced oedema and enanthema of the tonsils, palatal arches and uvula - Angina syphilitica catarrhalis; Erythematic, erosive, depilatory plaques on the tongue - Plaques muqueuses. ***(Fig.12)*** Enlarged lymph nodes in different areasyou – Polyadenitis specifica.

Figure 12: A – Leucoderma syphilitica, Condylomata lata; B – Syphilis papulosa psoriasiformis ; C – Plaques muqueuses et Angina specifica ; D – Condylomata lata axillae

Pathological-anatomical diagnosis of the dead fetus:

Malformative stillborn fetus of female gender in VII - VIII lunar months with external features – hydrops fetalis, brachycephalic skull, flat face and occiput, horizontal eye slits, low-set large ears, cleft upper lip, short neck, subluxation of the wrist joint and quadrifinger furrow on the left. The pathoanatomical and histological examination proved a large inter-atrial defect of the "ostium secundum " type and foramen ovale apertum, generalized oedema, cyanosis of internal organs, and ascites fluid in the abdominal cavity. In the internal organs, liver, adrenal glands, kidneys, and brain, a pronounced lymphoplasmacytic infiltrate, focal necrotic fields, thickened vascular walls, and vascular hyperemia were found. With Giemsa staining, Treponema pallidum is not visualized (a positive result in this study does not exceed 10% and is defined as highly specific but low sensitive. ***(Fig. 13)***

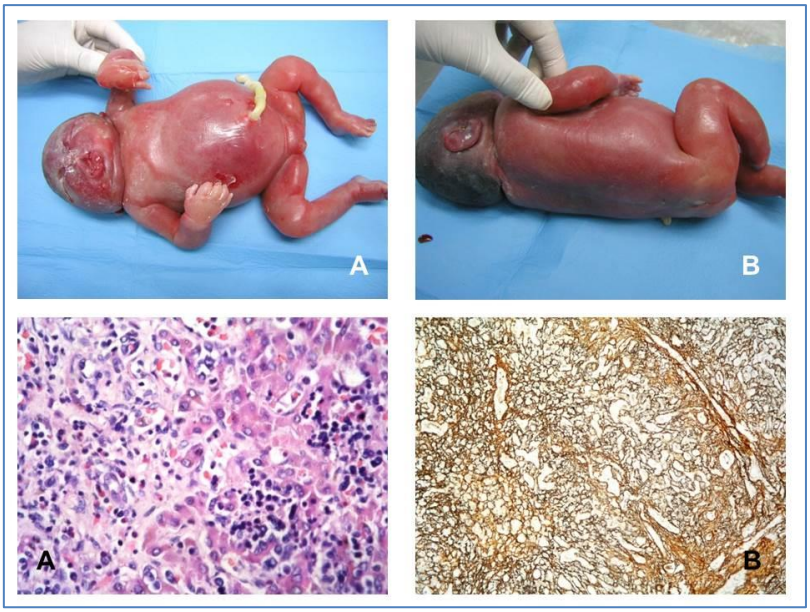


Figure 13: Top – malformation dead fetus (A and B); bottom – histopathology of the liver: A - HE stain, B - Giemsa stain.

The presented case demonstrates stillbirth of a fetus weighing 1350 g, severe hydrops and maceration, multiorgan failure, specific histopathological evidence of intrauterine infection, born to a mother with serologically and clinically proven secondary syphilis at 28 weeks of gestation.

V. DISCUSSION OF STUDY RESULTS

V.1. Discussion of the results of the analysis of the incidence of syphilis in Pleven region in the period 2008-2022.

In 2023, The World Health Organization published data on the frequency of STIs, according to which more than 1 million inhabitants of the planet get sick daily from STIs, and for syphilis, the frequency is 7.1 million people.

Syphilis (Lewes, Hoffman's disease) is a sexually transmitted infection caused by the bacterium Treponema pallidum. It is transmitted through sexual contact (genital, oral, anal, or combinations thereof), through the blood route (blood transfusion or organ transplant), or transplacentally from an infected mother to the fetus (vertical transmission). The incubation period is 10-90 days, after which the primary syphilis is clinically manifested - the primary effect (painless ulcus durum) appears at the site of the entrance to the infection. After a short latent period, a series of rashes on the mucous membranes and skin follows - secondary syphilis, after which a latent period of varying duration follows again. Many years after the initial infection, tertiary nodular and gummoid lesions of syphilis may appear along with visceral multiorgan involvement, including severe vascular and neurological damage. Although Lues can be effectively cured, latent forms are a sign of untreated infection and are defined as early latent syphilis (acquired < 1 year) and late latent (acquired > 1 year). Congenital syphilis, if not treated in time, leads to stillbirth or early neonatal death. Also, through the clinical presentation of genital and or anorectal ulcers, syphilis may increase the risk of HIV transmission and acquisition, particularly among MSM.

Syphilis is a complex infectious disease with periods of exacerbation and remission, whose clinical manifestations have been described for centuries. It is found worldwide, and the incidence varies greatly by geographic location. The causative agent, T. pallidum, is a microorganism first described in 1905. Infection occurs primarily through sexual contact and affects persons of all ages, and in congenital syphilis, the infection is transplacentally transmitted from a sick mother to the fetus. In the last decade, there has been a worldwide tendency to increase the spread of the disease among the risk group M With M (men who have sex with men), including in association with HIV. The disease proceeds in several stages. A solid chancre at the site of inoculation and regional lymphomegaly defines the primary stage. The secondary stage is characterized by a polymorphic rash on the skin and mucous membranes, generalized lymphadenopathy and other systemic manifestations. Latent periods are asymptomatic, divided for epidemiological purposes into early (< 1 year) and late (> 1 year) latent lues, according to ECDC. The early stages of syphilis (primary, secondary and early latent) are potentially

infectious. The tertiary stage is the most destructive and is characterized by nodular and gummy lesions that can affect any system and organ, as well as cardiovascular and neurological complications. Congenital infection leads to very early or late skin-mucosal, musculoskeletal and auditory-ocular manifestations.
Due to the extraordinary variety of rash elements, syphilis is called the "great imitator", which can imitate many dermatological conditions (pityriasis rosea, palmoplantar dermatoses, labial and genital herpes, medicament reactions, viral exanthems, erythema multiforme, infectious mononucleosis and others). The infection can have different clinical aspects – from classical to specific forms (seronegative syphilis, syphilitic balanitis, ocular syphilis).
Due to the impossibility of culturing the organism and the limitations of direct microscopy, serological testing is the basis of the laboratory diagnosis of syphilis. Serological tests are non-specific (classical, suitable for mass screening and control of therapy - VDRL and RPR) and specific (treponemal - FTA, TPHA and immunoenzyme ELISA methods IgM/IgG and Western blot).
Unlike many other bacteria that cause infectious diseases, treponema pallor remains sensitive to penicillins, and this fact determines the main therapy used. Since 2011, the Bulgarian pharmaceutical market has been missing Benzathine Benzylpenicillin and Penicillin G Benzatin. This forces patients to obtain these medications from abroad or to apply alternative treatment regimens with some oral antibiotics, such as azithromycin and doxycycline, which may be less effective than classic regimens. These regimens are also used in patients allergic to penicillin.
Although syphilis is a treatable disease with affordable diagnostic tests and treatment, it is still a serious public health problem. In this direction, the dramatically developing biological and social phenomenon related to the increase in the number of homo- and transsexual individuals, recognition of the so-called third gender and "gender ideology", which is a global problem of modern times.
To limit the spread of syphilis and other STIs, as well as the dependence on the epidemiological situation in different regions, it is recommended that increased screening of risk groups (ethnic minorities, marginalized populations, sex workers, people who inject drugs, unemployed, MSM, HIV positive persons). Currently, diagnostic tests are mandatory in Bulgaria only in cases of marriage, pregnancy, blood donation and contact with a person infected with syphilis.
The data for our country was published in March 2024. the annual epidemiological report of the European Center for Disease Control and Prevention (E CDC) shows that for 2022, the incidence of syphilis in the country is 5.3/100,000 people. For Bulgaria, this number in 2022 remains below the number reported in 2019. (6.9/100,000), but higher than that in 2021. (3.9/100,000) In the Pleven region for 15 years (2008 – 2022), the total incidence of syphilis varies over the years, with the lowest being in 2010. (4.9/100,000), and the highest in 2021. (14.5 new cases/100,000). After 2016, a tendency to increase the incidence of syphilis is observed, which is consistent with national and European data. ***(Table 20)***
It is noteworthy that this frequency for the Pleven region is two to four times higher than the national average, including the logically reduced parameters during the

COVID-19 pandemic, a fact reported by Crane *et al.* for the US, Yan *et al.* for China, Rodríguez and Hernández in Cuba, and K. Evangelou et al. for different geographical regions – Poland, New York, Prague, Bologna, Rome. According to data from the Centers for Disease Control and Prevention (CDC) of sexually transmitted diseases in the United States registered for 2020. One hundred thirty-three thousand nine hundred forty-five cases of syphilis are 52% higher than those detected in 2016, of which 2,148 were cases of congenital Lues, an increase of 235% compared to 2016. When talking about frequency calculated per population, circumstances related to migration must also be taken into account. According to NSI data in 2008. the population in Pleven region is 291,695 inhabitants, while in 2022, it is 220,345 people, i.e. in 15 years, it has decreased by more than 70,000 inhabitants, which to some extent can explain the higher rates of syphilis in the district over the years.

Table 20: Data on the frequency of syphilis over the years, according to the ECDC reports and the registry of the Clinic of Dermatovenereology in Pleven

	EU/EEA*		**Bulgaria**		**Pleven**	
Year	Number cases	Frequency per 100,000	Number cases	Frequency per 100,000	Number cases	Frequency per 100,000
2008	20143	4.6	419	5,6	19	6.5
2009	19797	4.5	420	5,6	21	7.2
2010	18838	4.2	397	5.3	14	4.9
2011	20597	4.6	314	4.3	20	7.5
2012	21262	4.6	309	4.2	17	6.5
2013	23351	4.9	354	4.9	13	5.0
2014	25101	5.3	460	6.3	14	5.5
2015	27976	5.9	465	6.5	22	8.7
2016	29611	**6.0**	367	**5.1**	30	**12.1**
2017	33855	**7.0**	516	**7.3**	17	**7.0**
2018	34112	**7.1**	485	**6.9**	26	**10.8**
2019	35039	**7.4**	480	**6.9**	27	**11.4**
2020	23502	**5,6**	319	**4.6**	19	**8.1**
2021	27074	**6.3**	271	**3.9**	33	**14.5**
2022	35371	**8.5**	361	**5.3**	29	**13.2**

In the population studied by us, the frequency of luetic disease is higher in men (60%), with a male-female ratio of 1.5:1, similar to that reported on a national and European scale - below 3:1 and for the countries of Estonia, Finland, Hungary, Lithuania, Romania and Slovakia. Globally, the risk of syphilis in men is 6-8 times higher than in women, as in Europe in 2013. The male-female ratio will be 8.4:1.6 in 2022. was 8: 1, in the US, it was 15.6: 1.9 in 2016, with the risk of developing the infection being higher for MSM. Overall, the trend in syphilis incidence increased

between 2013 and 2013. Furthermore, 2022, mainly due to an increase in the number of cases among MSM (74% – 77% of those infected in the last 3 years). During the same period, data show little variation in the rate of infection among heterosexual individuals at the European Union level, but 2022. is the first year in ten years with a marked increase in syphilis among heterosexual men and women.

Patients with syphilis in our study live mainly in urban areas (65.3%), where Internet use is more accessible, and all risk factors are present - opportunities for multiple partners, including same-sex, alcohol and drugs, sex without a condom, etc. Of the 50 MSM with syphilis, 82% live in cities. In relation to the epidemiology of the disease in the US and an analysis of the literature, Singh and Romanowski reported that there are also regional differences, with the highest rates in the urban South of the United States, followed by the Northeast and the Midwest. Overall, the highest rates were seen in urban areas, with the combined rates of primary and secondary syphilis for 63 large cities (populations greater than 200,000) representing twice the overall US rate in the 1980s and 1990s. However, a study in North Carolina reported higher rates in rural areas than in urban areas.

Over three-quarters of our patients with syphilis are between the ages of 15 and 45 (78%), with peak incidence between the ages of 20 and 30 (total 37%, average 7.5 cases per 100,000 population). The maximum frequency of the disease in both women and men is in the same age group. In 2022, information on the age of cases in Europe was reported by 26 countries. For the remaining three countries (Belgium, Bulgaria, and Poland), the information was either not submitted or reported in a format unsuitable for analysis. The results showed that the largest proportion of cases were reported in two population groups: 25–34-year-olds (31%) and those over 45 (32%). A reading of the literature confirms the maximum incidence of syphilis in the age groups with more intense sexual activity.

Analyzing the education of syphilis patients during the research period, it was found that 61% of patients had secondary and secondary special education, and 13.3% had university degrees. 22% of syphilis patients have elementary and primary education, among whom we would expect a higher incidence of the disease. Analyzing the marital status of the group, the data show that 38% are single, 20% are married, 30% are cohabiting, and 6% are divorced. These results indicate that about 1/5 of the patients contracted the disease through extramarital relationships ($p = 0.016$).

The distribution of patients by stages of the disease is as follows: latent (early 48.9% and late 9.3%), secondary (18.3%), primary (16.7%), congenital syphilis (2.8%), and neurolues (1%). 2.5% of cases remain unspecified. Recent data suggest that without an interdisciplinary approach and specific serological tests, neurosyphilis may remain undiagnosed. At the same time, it should be borne in mind that tertiary syphilis can appear even after 20 years from the moment of infection, mainly in persons of low social and economic status who do not seek medical help and cannot afford any specific treatment. Our results of the distribution by disease stage correspond to already published data from other Balkan and Eastern European countries.

Syphilis of pregnancy is an extremely sensitive topic for any society whose goal is to reduce this category of patients to 0. For the 15 years of our study, 32 pregnant women (24.4% of women), 21 parturients (16% of women) and 9 cases of congenital Lues (2.8% of all infected). Given the possibility of transplacental transmission of the infection from the mother to the fetus the lues of the pregnant woman evolving into congenital syphilis, the presented data are alarming. Because of this, pregnant women need specific therapy that should be started as early as possible to reduce the risk of congenital syphilis. According to data from the ECDC report for the period 2007-2017. of all reported cases of congenital syphilis in Europe, for Bulgaria, the incidence of congenital syphilis has decreased from 49.1 cases/100,000 newborns in 2007 up to 21.5 cases/100,000 births in 2017. Cases have been reduced to 0 in Croatia, Hungary, Slovakia, Slovenia, Latvia, Estonia, the Scandinavian countries and some Western European countries such as Italy and Spain. In the USA in 2020, there were 149 stillbirths and infant deaths, representing a 210 per cent increase from 2016. this way. The data from 2022 show that the contagious forms of syphilis and congenital syphilis continue to increase, with congenital syphilis rising from 1,325 cases in 2018. to 3755 in 2022, i.e. 183% and an average value for the period of 30.6/100,000 newborns.

The therapy provided to the patients is in accordance with the regulatory documents of the Ministry of Health and the European guidelines for the treatment of syphilis and is adapted to each stage of the disease. Alternative therapies with cephalosporins and doxycycline are recommended for penicillin allergy, as well, due to the lack of benzathine-penicillin G on the Bulgarian pharmaceutical market. During the studied period, all newly diagnosed pregnant women, cases with congenital syphilis and neurolues, were treated with crystalline penicillin, and patients with primary, secondary, early and late latent syphilis were treated with depot penicillin. After the decision of the treating team, combined regimens of fast-acting and depo-penicillins or with the other specified oral antibiotics were administered. During the follow-up of the treatment effect, seronegativity was achieved in the sixth month at 6.5%, by 1 year at 13.3%, and by the end of the second year at 10.2%. These individuals were treated with penicillin and doxycycline in combination. The fact that 41% remain unfollowed due to non-appearance of control examinations, migration and other mostly subjective reasons is disturbing. In relation to therapy, Cao et al. reported that after 6 months of treatment of primary, secondary and early latent syphilis, the effect of cephalosporins compared to that achieved with benzathine penicillin G was approximately similar (78% vs. 90.2%).

In the 1970s, published evidence showed that syphilis was a common disease among men who have sex with men (MSM). Numerous local epidemics have been described in different countries of the world. At the same time, the wide range of sexual practices, the public tolerance of same-sex sexual relationships and the high efficiency of transmission of the treponemal infection make it possible to increase the number of people infected with syphilis.

Over the past twenty years, the percentage of MSM with syphilis/HIV co-infection has also increased. The most common reason for this is that the primary affection

and syphilitic ulcers disrupt the integrity of the genital epithelium, thus becoming a gateway for HIV. A challenge of co-infection is the bidirectional synergistic effect that facilitates both the acquisition and transmission of both infections, altering the clinical progression of the diseases.
Given that Treponema pallidum divides in 30–33 hours, depot penicillin preparations (benzathine penicillin and) are sufficiently effective and preferred in the treatment of patients with syphilis. However, outbreaks of the disease continue to occur worldwide, primarily in urban environments and among the MSM population.

V.2. Discussion of the results of the analysis of syphilis among MSM in the Pleven region for the period 2008-2022.

Because of their risky sexual behaviour, Men who have sex with men (MSM) are a risk group for the spread of STIs due to multiple sexual partners, often casual sexual contact, inconsistent condom use, and drug use. In recent years, the number of syphilis/HIV co-infections has been increasing among this population. The results for the Pleven region show that MSM are 50 men (15.5%) of the total treated patients with the same diagnosis and 26% of the diseased men. They have an average age of 31.53 ± 9.026, with the predominant age group being in the range of 20 to 30 years (54%). The high number of homosexual individuals registered after 2016 is striking. (82% of all), as 48% of them are during the COVID-19 pandemic - 2020-2022. According to an analysis by Cusini et al. (2021), for the first year of the pandemic, in two centres in Lombardy, the number of STI cases decreased, but the number of acute bacterial infections associated with MSM increased. The conclusion has to be drawn that despite the imposed social and physical distancing measures, the COVID-19 pandemic has not prevented the risky behaviour of MSM. In our study, MSM with syphilis/HIV co-infection after 2013. a total of 26% were registered, while during the pandemic, it was only 6%. The rate of syphilis/HIV co-infection among MSM has been increasing over the past decade, a phenomenon of particular concern because of the biological and epidemiological associations between syphilis and HIV infection. The two infections interact synergistically to accelerate the progression of AIDS and increase the incidence of therapeutic resistance to the disease.
The trend of increasing the number of syphilis cases in the 29 countries of the European Union has been published in the latest report of the European Center for Disease Prevention and Control in 2022. – from 27,976 cases in 2015. to 35,039 in 2019. Among registered persons, the incidence of syphilis in men is nine times higher than in women. The peak incidence is in the male age group 25–34 years. 74% of syphilis cases are reported in men who have sex with men (MSM). According to experts, the increase in the incidence of syphilis among men between 2010 and 2017 was due to an increase in the number of cases among MSM.
Our data indicate that during the study period in the clinic, the male: female ratio was 1.5: 1, and MSM were 26% of the male patients. This ratio corresponds to the one published in the report for Bulgaria, but the data on the frequency of syphilis among

heterosexual men and MSM are quite different, bearing in mind that we indicate the results from only one centre in the country.

The findings in our study shed light on the prevalent risk factors among men who have sex with men (MSM) and the alarming rates of syphilis infection in this demographic. In the study, the predominant age group among MSM falls in the 20 to 30-year range (54%). Similar data have been reported in other studies that indicate the susceptibility of the youth of this age to high-risk behaviours such as multiple sexual partners, unsafe sex, and substance abuse. The fact is that with the advancement of technology, MSM is increasingly using social networks to search for sexual partners, which also increases the risk of STIs. In fact, 88% of the participants in our study showed behaviours associated with a sufficiently high risk - 78% shared multiple sexual contacts, and 70% admitted to having contacts with casual partners, 84% of MSM patients were single. Our results correspond to those published by Pereira Nogueira et al. in 2022

It is noteworthy that during the COVID-19 pandemic (2020-2022), 24 MSM with syphilis were registered in our centre (48%). For comparison, the remaining 26 patients were selected for a much longer period - 2008-2019. According to an analysis by Cusini et al. (2021), for the first year of the pandemic, in two centres in Lombardy, the number of STI cases decreased, but the number of acute bacterial infections associated with MSM increased. It has to be concluded that despite the imposed social and physical distancing measures, the COVID-19 pandemic has not prevented risky behaviour, especially by MSM. The claim is also supported by Evangelou et al. (2022), who published a summary of results from epidemiological studies conducted in six different locations around the world. A generally noticeable increase in syphilis cases has been observed everywhere, which supports the hypothesis that the restrictive measures against COVID-19 have not been able to suppress the transmission of syphilis effectively.

In our study, MSM with syphilis /HIV co-infection after 2013. a total of 26% were registered, while during the pandemic, it was only 6%. The rate of syphilis/HIV co-infection among MSM has been increasing over the past decade. This phenomenon is of particular concern because of the biological and epidemiological associations between syphilis and HIV infection. The two infections interact synergistically to accelerate the progression of AIDS and increase the incidence of therapeutic resistance to the disease. Studies have shown that the immune response in syphilis stimulates and directs to the site of infection-activated macrophages, CD4 and CD8 T cells that can facilitate the acquisition of HIV infection, and that acute luteal infection can increase the risk of HIV seroconversion up to 2,5 times.

According to the clinical form of the disease in our study, 22% had primary, 34% secondary, 34% early latent syphilis, and 10% late latent and other unspecified – frequencies reported in large cohort studies over the years. Back in 2011, Jebbari et al. analyzed the epidemiology of syphilis in 11,838 patients in England and Wales who had the disease between 1998 and 2008. They report that 73% of cases were observed in MSM, a percentage much higher than that in our patients. Primary

syphilis was reported in 43% of cases, secondary in 33%, and early latent in 24%, which results are comparable to ours.
Usually, genital involvement has the highest frequency, but involvement in extragenital areas is increasingly reported. Our data speak of 34% genital, 10% anorectal, 8% oropharyngeal involvement, and 48% without clinical manifestation corresponding to the latent forms. We found a high correlation of the clinical form with the localization of the pathological lesions ($p<0.001$), as well as of the hard chancre with primary syphilis ($p<0.001$), and of the macular (roseolae and specific angina) and papular (palmoplantar papules and condylomas) lesions with the secondary (also $p<0.001$) which corresponds to the theoretical knowledge of syphilis.
In connection with the different sexual patterns practised by MSM, the frequency of the extragenital localization of the hard chancre is significantly increasing. However, due to the fact that patients are not always inclined to share their sexual preferences, it is difficult to determine the exact affected anatomical area.
The treatment we provide is in accordance with national and international guidelines for the various stages of the disease. 48 enrolled patients underwent outpatient therapy, and only two were hospitalized for intravenous therapy with Penicillin G (500,000 IU 5 times daily) and Ceftriaxone 2.0 grams daily. Benzathine benzylpenicillin 2,400,000 IU IM weekly was administered as the first course of treatment for 3-5 weeks in different sessions in 47 patients. In 30 of them, therapy was continued with the oral antibiotic Doxycyclin 2 x 100 mg. daily for 20 days, depending on the dynamics of the serological results, and the patients were followed until the non-specific RPR reactions became negative (48% by the end of the second year). Disturbing is the fact that 34% of patients lost contact with the clinic, a phenomenon that occurs mainly in regions with a mixed population.
This study has some limitations. The results reflect the experience of one clinic in treating patients with syphilis, and we are not aware of similar specific studies investigating the trends of infectious syphilis among Bulgarian patients, including MSM, in other regions of the country. They are not finding out about the modern pathomorphosis of syphilis throughout the country, but they are supported by data published in the world scientific periodical.

V.3. Discussion of the results of the analysis of syphilis among the Roma community in the Pleven region for the period 2008-2022.

The Roma are the largest and most vulnerable minority in Europe. In total, about 9-11 million Roma live in Europe, and approximately 70% of them live in Central and Eastern European countries and the republics of the former Soviet Union. A significant number of the Roma population lives in Bulgaria, Hungary and Romania, where Roma poverty, according to the study, is greatest.
According to data from the National Statistical Institute in Bulgaria, the population census in the country shows that in 2011, 7,364,570 people lived there, 4.9% of whom were Roma. Two hundred thirty-seven thousand five hundred eighty-nine people live in the Pleven region, with Roma making up 4.09%. Data from the last census in 2021. talk about a decrease in the number of the country's population, as

well as the number of Roma - 6,519,789 inhabitants, with 4.4% of people identifying themselves as the third largest Roma ethnic group. The relative share of the population from this ethnic group decreased by 0.5% compared to 2011. For the Pleven district with 226,120 inhabitants, the Roma are 3.09%, i.e. the decrease in 10 years is 1%, but it should be taken into account that some Roma do not identify themselves as part of the ethnic group.

It is a well-known fact that the Roma minority is the most vulnerable due to poverty, poor hygiene, poor living conditions, inadequate nutrition, lack of education, high unemployment, high birth rate and active migration. Due to their risky sexual behaviour, Roma are at high risk of sexually transmitted infections (STIs). Kabakchieva et al. (2002 and 2006) examined levels of sexual risk among young men in R. Bulgaria and in the capital, Sofia and found that most men of Roma origin use drugs, have multiple partners, rarely use condoms, and often engage in sexual intercourse with other men. According to studies by the World Bank (2005), about 11 million Roma are living in Europe, and about 70% of them are in Central and Eastern European countries. Although the data varies over the years, studies on the frequency of Roma communities by place of residence are similar - for Bulgaria 4.4%, for Romania 3.8%, for Budapest 2%, for Serbia 2.05%, for Belgrade 1.6 %, Czech Republic 2-3%, Slovakia 2%.

The Roma ethnic group is the most vulnerable minority due to poverty, poor living conditions, inadequate nutrition, limited access to healthcare, lack of education, high unemployment, and discrimination. At the same time, the risky sexual behaviour of Roma makes them at risk of STDs – early onset of sexual life, promiscuity, failure to use protective equipment, use of alcohol and drugs, sex workers, bisexual behaviour, paid oral and especially anal sex. In relation to the risk of HIV infection and STIs, Kabakchieva et al. (2006) studied young Roma men in Sofia, Bulgaria and found that 21.7% of them had at least one sexually transmitted disease, 3.5% had syphilis, with rates of syphilis among them 312 times the national level. Amirkhanian et al. (2013) assessed high-risk sexual behaviour and risk factors in HIV/STI prevalence among young men of Gypsy origin in Bulgaria. The study was conducted by the same group of researchers and found much lower rates of infection. For the Pleven district, the incidence of syphilis has increased from two to four times compared to the national average, and in 2011, the infection was 13 times more common among Roma compared to the rest of the district's population, and in 2021, 10 times.

Historically, conservative patriarchal norms characterized the Roma community and influenced the sexual behaviour of individuals. Traditionally, Roma men have more power and control in relationships, have sexual freedom before and during marriage, and often engage in sexual practices with multiple partners. Romani women are expected to maintain their virginity and be monogamous after marriage. The risk of STIs in Roma communities is largely determined by the behaviour of men, who also suffer from venereal diseases more often. At the same time, with the changes in Europe that occurred after 1990, traditional patriarchal norms weakened social values and norms of behaviour, which led to riskier sexual behaviour in the Roma

community and facilitated the spread of STIs. Among Roma women, problems arise, such as early onset of sexual life, teenage pregnancy, low levels of contraceptive use, high frequency of abortions, and prostitution. In our study, among Roma patients with syphilis, there are more women than men (54.87% to 45.13%). In confirmation of the above data, the most affected age group among Romani women is 15-25 years. (20.4% vs. 10.6% for men). The higher frequency of Romani women with syphilis can be explained by the fact that 14.2% are pregnant and 15% are women in labour.

In general, our results show that in the Pleven region, Roma with Lues is younger, less educated, and more often unemployed compared to patients of other ethnicities, which corresponds to the published data of Kabakchieva et al. (2006) for the city of Sofia, as well as Knezevic (2013) for Belgrade. In the conditions of poverty and unemployment, it is not surprising that 11.5% of Roma women and only 2.4% of the other cases declared that they were sex workers. Among our syphilis patients, 9.8% of Roma men identified themselves as MSM versus 18.6% of other cases, with some studies showing a significantly lower percentage of Roma men admitting their homosexual orientation. Contrary to numerous publications about a high incidence of syphilis-HIV co-infection among MSM, we did not detect co-infection among our studied Roma with syphilis.

The results of our study show that the number of diagnosed and treated cases of syphilis among the Roma ethnic group at the Pleven Dermatology Clinic increased after 2018. Roma with Lues are younger, less educated, and more often unemployed, most in the age group of 20-29. Furthermore, the rate of infection is 10-13 times higher than other ethnicities living in the district. These facts correspond to the data published in the last 15 years in the scientific literature by other authors from Central and Eastern Europe. The Balkans, where about 70% of the Roma population of the continent live. In general, the social, economic, household and health problems of Roma societies represent a significant problem for public health in various countries in the quest for Roma integration. Limiting the sexual risk through recommendations to reduce the number of sexual contacts, safe sex, and regular testing for sexually transmitted infections are only part of the activity for the prevention and control not only of syphilis but also of other STIs among the Roma population.

This study has some limitations. The study is based on the data from the mandatory registration of syphilis patients and the results of anamnesis and clinical examination. Although the registration process takes place in the presence of a doctor, the history data on the personal behaviour of the Roma patient is potentially inaccurate or even purposefully false.

During the population census, some Roma do not self-identify as such, which is why only declared Roma can be scientifically studied, a fact we have taken into account.

The results reflect the experience of one clinic and the socio-demographic characteristics of sick Roma from the Pleven region, which may be different for Roma communities or other populations in the country. We are not aware of such specific studies investigating syphilis prevalence trends among the Bulgarian Roma

over the last 10 years, but our results are supported by data published in world scientific periodicals.

V.4. Discussion of the described clinical cases

V.4.1. Discussion of syphilitic uveitis in an HIV-positive patient

The involvement of the Central Nervous System (CNS) and the eyes can occur during all periods of syphilis, even during the primary hematogenous dissemination of the treponema and manifestation of the secondary or latent stage. The infection is long, chronic, in attacks, and often individual periods cannot be differentiated. Ocular manifestations of syphilis are grouped under the term "ocular syphilis," and while the disease can occur in any part of the eye, uveitis is the most common manifestation, and its increasing incidence of syphilitic uveitis requires a multidisciplinary approach. The Centers for Disease Control and Prevention (CDC) defines ocular syphilis as “clinical symptoms or signs consistent with ocular disease (i.e., uveitis, panuveitis, decreased visual acuity, blindness, optic neuropathy, interstitial keratitis, anterior uveitis, and vasculitis of the retina) with syphilis of any stage.

A case of ocular syphilis was defined as an individual with clinical symptoms or signs consistent with eye disease (i.e., uveitis, panuveitis, reduced visual acuity, blindness, optic neuropathy, interstitial keratitis, anterior uveitis, and retinal vasculitis) and with syphilis in every stage. However, it is unclear whether syphilitic uveitis should be treated as a manifestation of secondary syphilis or early neurosyphilis. Coinfection with the AIDS virus (Human Immunodeficiency Virus) contributes to the more severe course of syphilis and its systemic manifestations and can disrupt the usual periodicity of the infectious process.

Uveitis is an inflammatory disease of the vascular lining of the eyeball (uvea), leading to impaired vision or blindness. Uveitis can be anterior (iritis – inflammation of the iris and iridocyclitis – inflammation of the iris and ciliary body) and posterior (choroiditis – inflammation of the back of the middle shell of the eye). Inflammation of the entire vascular sheath of the eyeball is called panuveitis. Prerequisites for the development of uveitis are genetically determined or acquired defects of the immune system (including AIDS), acute and chronic inflammatory processes in the body, autoimmune diseases, endocrine diseases (diabetes), infectious agents of viral, bacterial and fungal origin, and trauma.

During the second period of syphilis, the CNS can be affected, with pathological cerebrospinal fluid (CSF) with positive specific samples for syphilis being present in 15% of cases. Patients have headaches and, less commonly, meningitis and cranial nerve palsy. The other systemic manifestations of secondary syphilis include – panuveitis, periostitis, glomerulonephritis, hepatitis, gastritis, and myocarditis.

Ocular manifestations of syphilis are rare, but the appearance of uveitis at the beginning of the disease can lead to severe vision loss, which, in the absence of other symptoms, may not be recognized by the clinician as a systemic sexually transmitted infection. This fact requires a multidisciplinary approach and screening for sexually transmitted infections, especially syphilis and AIDS, in young people with

severe, unusual manifestations of eye disease. Early detection and treatment with optimal doses of penicillin are important for good clinical outcomes and prognosis.
According to a number of authors, syphilis is the most common bacterial cause of uveitis in HIV-positive patients. Syphilitic uveitis can cause severe vision loss, so effective treatment with intravenous penicillin is recommended.
Epidemiological data show an increase in the incidence of syphilis among young people/especially homosexual men/ in developed countries, often in association with other sexually transmitted diseases and HIV. Impressive are the data in a retrospective analysis published by Amaratunge et al. (2010), for all cases reported in the English-language literature for the period 1984-2008, 143 patients with diagnosed syphilitic uveitis were found, of which 65% were HIV positive.
In conclusion, the described case of a young homosexual man with a leading clinical manifestation of syphilitic uveitis and co-infection with the AIDS virus is a demonstration of the diverse symptomatology of syphilis as systemic vasculitis. It aims to direct our attention to the need for screening studies for sexually transmitted infections in diagnostic and treatment algorithms.

V.4.2. Discussion of early congenital syphilis

T. pallidum infection may also be transmitted vertically, from an infected mother to the fetus, through transplacental transmission or contact with a maternal lesion during delivery. Worldwide, perinatal syphilis is the second leading cause of stillbirth and is associated with significant morbidity and mortality among affected newborns with congenital syphilis.
Cases of clinically apparent congenital syphilis and fetal syphilis in Bulgaria are minimized and rarely observed. This is due to serological screening during pregnancy and after delivery, antiluetic treatment of undiagnosed pregnant women with this infection, and the more often observed latent forms of unknown duration, allowing the birth of clinically healthy, seropositive children. According to the law of M . Kassowitz (1875), the fresher, the more massive and virulent the mother's infection, the more severe the damage to the fetus and vice versa. Transmission of the infection to the fetus occurs mainly during the first 2-3 years of the disease. Over the past 5 years, 8,544 pregnant women were examined at the Clinic for Dermatology and Venereology, Pleven, of which 144 had different periods of past and newly diagnosed syphilis. According to data from the National Center for Public Health and Analyzes in 2014. Twenty-six cases of congenital syphilis were reported in Bulgaria.
According to the Guideline for the Diagnosis and Management of Congenital Syphilis, a confirmed case of syphilis is considered when Treponema pallidum is identified by dark-field microscopy, fluorescent antibody, or other specific methods in specimens from lesions, placenta, placental cord, or autopsy material. A suspected case of congenital syphilis is accepted when one of the following conditions is met: Any child born to a mother with untreated syphilis; any child who has a reactive treponemal test for syphilis and one of the following evidence—objective evidence of

syphilis on physical examination, specific radiographic changes of a long bone, reactive VDRL CSF, increased CSF cell count and protein in the absence of another cause, quantitative VDRL titer fourfold higher than maternal, reactive IgM test antibodies.

A stillborn fetus with syphilis is considered fetal death when a mother with syphilis was not treated or was inadequately treated. The birth occurred after 20 weeks of gestation, and the fetus weighed more than 500 g. Antenatal death is the most common outcome, occurring in 40% to 70% of pregnancies in mothers with untreated or inadequately treated syphilis; most live neonates are asymptomatic but may develop manifestations later. Clinical signs may appear earlier or later, and their presentation varies considerably. Any organ of the fetus can be affected, but most often, the disease affects the liver, kidneys, bone marrow, pancreas, spleen, lungs, heart and brain. In the most characteristic histological picture of congenital syphilis, which resembles that of acquired syphilis, the disease manifests as obliterating endarteritis with a perivascular infiltrate of lymphocytes and plasmatic cells accompanied by intimal hyperplasia. Fibrosis and goitres are often present. Changes in the placenta include focal infiltration by maternal lymphocytes and plasma cells, as well as focal necrosis.

Optimizing prenatal testing and treatment is at the heart of prenatal care. Data show that many people from vulnerable populations, including those living in poverty, victims of domestic violence, substance abusers, the uneducated, the victims of racism and discrimination, lack the awareness to control their pregnancy and birth due to lack of health literacy and limited understanding the risks of sexually transmitted infections.

VI. CONCLUSION

After the political and socio-economic changes in the countries of Eastern Europe that followed in the 1990s, as well as the long and incompletely regulated healthcare reforms, there were significant difficulties in the registration of many socially significant diseases, including sexually transmitted diseases. The data on the newly registered cases in the Skin and Venereology Clinics, Departments and Centers do not correspond to the real number of syphilis cases. With the subsequent decentralization of patient care and the uncontrolled development of the private sector, research, diagnosis, and treatment of these diseases have been allowed to be carried out in various laboratories, private offices, clinics, and by specialists from other specialities. The main problem remains self-medication and the dispensing of medicines, especially antibiotics, without a doctor's prescription in pharmacies.

Syphilis is undoubtedly a serious public health problem. The efforts of the state, in the form of the Ministry of Health, to exercise and manage control over the spread of the infection are also indisputable. We believe that education aimed at the general population and increased screening of at-risk populations would be helpful in raising awareness of the problem. The growing diversity of different gender categories must also be taken into account, which is far from being due to self-determination by

individuals. The standard for at-risk groups is also rising – HIV-positive MSM; HIV-negative MSM engaged in high-risk sexual practices, with multiple partners, or with a previous diagnosis of syphilis; HIV-positive heterosexual individuals; ethnic minorities; sex workers; people who use intravenous drugs. National prenatal screening programs must be optimized, as well as the control of syphilis transmission among the heterosexual population.

The results obtained and described by us from the present scientific study on the frequency and distribution of patients diagnosed with syphilis in the Pleven region for the period 2008-2022 confirm the main trends characteristic of the EU member states and the Eurozone.

- There is an alarming trend of increasing incidence of syphilis (from 5.9/100,000 in 2010 to 13.2/100,000 in 2022)
- Predominance of the male sex, as in the area infected men in 2021. They are 82% of patients.
- A high frequency prevails among the age group of 20-34 years old (51%), but also a relatively high frequency in the age group of 50+ years (14%).
- Regarding the transmissible category, over the last 5 years, there has been an increase in the number of MSM - 62% of homosexuals registered in KDV-Pleven.
- Increasingly alarming is the increasing trend in the number of MSM with syphilis/HIV co-infection (26% in the district)

A similar study of clinical-epidemiological characteristics of the spread of syphilis in the country, including an analysis of the disease among two of the most at-risk groups - MSM and the Roma ethnic community, is being carried out for the first time in Bulgaria. The results we obtained for one geographical region (Pleven district) are similar to those published for the countries of Europe and the Balkans, which is why we accept our data as reliable.

VII. CONCLUSIONS AND CONTRIBUTIONS OF THE DISSERTATION

VII.1. Conclusions

1. For the period 2008-2022, 323 cases of syphilis were registered in Pleven district (average age 32.92 ± 13.92 years). Men are 59% on average. Age 35.11 ± 14.31, and women are 41% on average. age 29.71 ± 12.71. The most affected age is 20-35 years. 65% of patients live in cities. 74% have an education above secondary level, and 13.5% have a university degree. 38% are unmarried, and 30% live in cohabitation without marriage. 34% are unemployed, 6% are prostitutes, and all are women.
2. The study of risk factors, patterns of sexual behaviour and the mode of transmission of the infection shows regular intake of alcohol and smoking in 49% of patients, and 13% also take drugs. The risk of infection was 2.4 times higher in those individuals who had multiple contacts ($p<0.001$). Sex with a

casual partner was circumcised by 59%, in which the risk of infection was 2.5 times higher (p<0.001), and in MSM this risk was 5.4 times (p<0.001).

3. Syphilis/HIV co-infection cases are 5.3% of all reported cases, 76% of which are in men who have sex with men (MSM).
4. The frequency of early latent syphilis is highest (48.9%), followed by secondary (18.3%) and primary syphilis (16.7%). Congenital syphilis is 3%. Clinical symptoms are present in 40% - hard chancre in 19.5%, macular and papular syphilides in 50%. There are 60% without a clinic, all with latent forms of the infection. The clinical picture correlates with the stage of the disease ($r = 0.432$, $p < 0.001$, $N = 323$)
5. The comparison of the data on the incidence of syphilis in the Pleven region, Bulgaria and the countries of the Eurozone for the observed period shows that during the period 2008-2022. in the Pleven region, the average incidence of syphilis is 8.59/100,000 inhabitants. For the same period, the average incidence of the infection in Bulgaria is 5.5/100,000, and in the countries of the European Union, it is 5.8/100,000 people. In all three sources, the incidence of syphilis increased after 2018.
6. Monotherapy with depot penicillin was administered in 29% of cases, with crystalline penicillin Penicillin G in 6% and combined therapies (penicillins and other antibiotics) in 54%. Negative results by the end of the first year were found in 13% of patients, by the end of the second year in 10% of them, and after the third year, serology remained positive in 24% of cases.

VII. 2. Contributions

VII.2.1. Original contributions

1. For the first time in Bulgaria, a clinical-epidemiological analysis of men suffering from syphilis who have sex with men has been carried out.
2. For the first time in Bulgaria, the clinical characteristics of syphilis among the Roma ethnic group are described.

VII.2. 2. Scientific-theoretical

1. For the first time in the country, the demographic and clinical data of persons suffering from syphilis in the Pleven region are described.
2. The follow-up of the effect of the applied treatment to negate the results of the serological tests for diagnosis.

VII. 2. 3. Scientific-practical and confirmatory

1. The fact that the Roma ethnic group and the MSM contingent are risk groups for STIs is confirmed.
2. Multiple sexual contacts increase the risk of receiving and transmitting the infection up to 5.5 times more often.
3. The obtained results are similar to those published in scientific periodicals in the last 15 years.

SCIENTIFIC PRODUCTION RELATED TO THE TOPIC OF THE DISSERTATION

Publications

1. **Haidudova HV,** Karcheva MD, Gospodinov DK. Analysis of the incidence of syphilis in the Pleven region for 15 years (2008 – 2022) Dermatology and venereology. 2024; 63(2): 20-30. ISSN: 0417-0792.
2. **Haidudova HV,** Karcheva MD, Balabanov ChB, Lukanov TC, Gospodinov DK. Syphilitic uveitis in an HIV-positive patient. Dermatology and Venereology, 2017; 56(4): 58–62; ISSN: 0417-0792 (print)
3. **Haydudova HV**, Gospodinov DK, Karcheva MD, Syphilis in the Pleven region, Bulgaria: a retrospective study, Acta Dermatovenerologica Alpina, Pannonica et Adriatica, 2020, 29(2): 63-66; ISSN:1318-4458 (Scopus, SJR 2020 0.376; Q3)

Participation in scientific forums

At national conferences and congresses:

1. **Hajdudova H.** , V. Gincheva, B. Duhlenski, S. Kitanova, I. Yordanova, D. Gospodinov Syphilis secundaria recidiva and aphonia, X National Congress of Bulgarian Dermatovenereologists, November 02-05, 2023, Sofia.
2. **Hajdudova H.** Clinical-epidemiological analysis of the spread of syphilis in Pleven region, XXIV Scientific and Practical Conference of BDD, November 30 - December 3, 2023, Tryavna.
3. Karcheva M, **Haidudova H**, Gospodinova K, Pakov I, Nacheva M. Epidemiological profile of persons with syphilis and HIV in Pleven region, Bulgaria. 6th National Conference on Epidemiology "Challenges and Prevention of Infectious Diseases". 27-29.09.2024, Varna (report)
4. Petrakieva M., Tomova V., Atanasova V., Popovska S., Gospodinova K, **Haidudova H**, Gospodinov D. Syphilis of the newborn with a fatal outcome. XXI Scientific Conference "Clinical Dermatology - Rarely Observed Clinical Cases - Annual Sofia Dermatology Days" Prof. Asen Durmishev" 31.10.2024 – 3.11.2024, Sofia (report)
5. Petrakieva M, Tomova V, Dimitrov T, Valcheva K, Gospodinova K, **Haidudova H**, Gospodinov D. Syphilitic uveitis. XXI Scientific Conference "Clinical Dermatology - Rarely Observed Clinical Cases - Annual Sofia Dermatology Days" Prof. Asen Durmishev" 31.10.2024 – 3.11.2024, Sofia (report)
6. Gospodinov D. **Hajdudova H**, Gospodinova K. Treatment of syphilis. XXV Scientific-practical conference on Dermatology and Venereology 28 November - 01 December 2024, Tryavna (report)

At scientific forums abroad:

7. Popov A, **Haydudova H**, Gospodinov D.. Skin sarcoidosis. Case report, Cosmetic Surgery Forum, 04-07 December 2019, Nashville, Tennessee, USA. (oral presentation)
8. **Haidudova H**, Balabanov C, Gospodinov D, Lukanov T, Karcheva M. Syphilitic Uveitis in Human Immunodeficiency Virus-infected patients. 34th Balkan Medical Week, Bucharest, Romania, 7-8 October 2016 (poster)
9. Variaah G, **Haydudova H**, Gospodinov D. A case of stillbirth congenital syphilis 6th Congress of Dermatovenereologists of Macedonia with international participation, 27-30. 09. 2017, Ohrid, Macedonia. (oral presentation)