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Epidemiological and Clinical Aspects of Syphilis Incidence in the Russian Federation and the Republic of Uzbekistan: A Comparative Analysis

© Margarita R. Rakhmatulina[1], Delya F. Porsokhonova[2], Elena Yu. Novoselova[1]*, Avaz Sh. Inoyatov[2]

[1] State Research Center of Dermatovenereology and Cosmetology, Moscow, Russia
[2] Republican Specialized Scientific and Practical Medical Center of Dermatovenereology and Cosmetology of the Republic of Uzbekistan, Tashkent, Republic of Uzbekistan

The Soviet model of healthcare was characterized by the centralization of state medicine, which made it possible to effectively deal with mass epidemics, including sexually transmitted infections (STIs). After the USSR collapse, the dermatovenereological services of the Russian Federation and the Republic of Uzbekistan actively developed and improved, working out new effective methods for treatment and prevention of skin diseases and STIs and introducing them into the healthcare practice, which ensured the maintenance of epidemiological well-being. The article presents the results of a retrospective comparative study of syphilis incidence rates in two countries, including an analysis of the earliest, most epidemiologically dangerous clinical forms. It was found that starting from 2019, the incidence of early syphilis in the Republic of Uzbekistan began to exceed the same rate in the Russian Federation, while previously this rate had been higher in Russia. An analysis of syphilis cases in different age and sex populations by clinical forms of the disease demonstrated an increase in late and unspecified forms in Russia among the male population over the age of 40, while in Uzbekistan there was an increase in the number of cases of early latent syphilis in the same age group. As a result of the study of normative documents regulating algorithms and principles of management of patients with syphilis, differences in laboratory diagnostic algorithms and treatment regimens were revealed, namely lower dosages of drugs and shorter treatment courses for patients with syphilis in the Republic of Uzbekistan compared with those in the Russian Federation.

Keywords: **epidemiology; diagnostics; therapy of syphilis; congenital syphilis; neurosyphilis**

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Эпидемиологические и клинические аспекты заболеваемости сифилисом в Российской Федерации и Республике Узбекистан: сравнительный анализ

© Рахматулина М.Р.[1], Порсохонова Д.Ф.[2], Новоселова Е.Ю.[1]*, Иноятов А.Ш.[2]

[1] Государственный научный центр дерматовенерологии и косметологии, Москва, Россия
[2] Республиканский специализированный научно-практический медицинский центр дерматовенерологии и косметологии Республики Узбекистан, Ташкент, Республика Узбекистан

Советская модель здравоохранения характеризовалась централизацией государственной медицины, позволяющей эффективно справляться с массовыми эпидемиями, в том числе инфекций, передаваемых половым путем (ИППП). После распада СССР дерматовенерологические службы Российской Федерации и Республики Узбекистан активно развивались и совершенствовались, разрабатывая новые эффективные методы лечения и профилактики кожных заболеваний и ИППП и внедряя их в практику здравоохранения, что обеспечивало поддержание эпидемиологического благополучия. В статье представлены результаты ретроспективного сравнительного исследования показателей заболеваемости сифилисом в двух странах, включая анализ ранних, наиболее опасных с эпидемиологической точки зрения клинических форм. Установлено, что начиная с 2019 г. в Республике Узбекистан заболеваемость ранним сифилисом стала превышать аналогичный показатель в Российской Федерации, в то время как ранее этот показатель был выше в России. Анализ случаев сифилиса в различных возрастных и гендерных популяциях по клиническим формам заболевания продемонстрировал рост поздних и неуточненных форм в России среди мужского населения в возрасте старше 40 лет, в то время как в Узбекистане наблюдалось увеличение числа случаев раннего скрытого сифилиса среди той же возрастной группы. В результате изучения нормативных правовых документов, регламентирующих алгоритмы и принципы ведения пациентов с сифилисом, были выявлены различия в алгоритмах лабораторной диагностики и схемах терапии, а именно более низкие дозировки лекарственных препаратов и менее продолжительные курсы лечения больных сифилисом в Республике Узбекистан по сравнению с таковыми в Российской Федерации.

Ключевые слова: **эпидемиология; диагностика; терапия сифилиса; врожденный сифилис; нейросифилис**

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Introduction

The forms of organization of national health care systems are diverse, and each country in the global community creates and develops its own models of health care delivery to the population. The Soviet model of health care was characterized by the centralization of state medicine, was based on the principles of universal accessibility and comprehensive free medical care, and had a preventive orientation, which made it possible to effectively cope with mass epidemics, including sexually transmitted infections (STIs). After the collapse of the Soviet Union, a significant increase in the incidence of STIs, including syphilis, was observed in the new independent states as a result of the deterioration of the financial and economic situation of the population, drastic social stratification and criminalization of society, which required the introduction of new legislative acts concerning the principles of patient management and based on more advanced approaches and methods [1–4].

After the disintegration of the USSR, the Russian dermatovenerology service continued to develop actively, taking into account the preservation and augmentation of the best national traditions and achievements of global science, developing new effective methods of treatment and prevention of STIs and widely introducing them into public healthcare practice. At present, examination for syphilis and treatment of subjects in the Russian Federation are regulated by the clinical guidelines “Syphilis” approved by the Scientific and Practical Council of the Ministry of Health of Russia, standards of medical care for syphilis, and by Order of the Ministry of Health of Russia dated March 26, 2001, No. 87 “On Improvement of Serological Diagnosis of Syphilis”, which sets approaches to the diagnosis of this disease [5–7].

Over the years of independence of the Republic of Uzbekistan, significant changes have also occurred in the public healthcare system, including in the organization of medical care in the field of dermatovenerology: the structure of medical institutions has been improved, their facilities and resources has been modernized, human resources have been strengthened, and international cooperation has been developed. To date, Order of the Ministry of Health of the Republic of Uzbekistan dated May 10, 2012 No. 128 “On the Organization of Preventive Examination for Syphilis in Medical and Preventive Treatment Facilities”, which defines the examination procedure for syphilis, and the “National Clinical Protocol for the Management of Patients with Early Forms of Syphilis”, which regulates the algorithms of diagnosis and treatment of this disease, are in force in the country [8–12].

Analysis of the incidence of syphilis in the Russian Federation and the Republic of Uzbekistan

In 1980, during the existence of the Soviet Union, the incidence of syphilis in the Russian Soviet Federative Socialist Republic (RSFSR) was 23.1 cases per 100 thsd population, 2.1-fold higher than in the Uzbek Soviet Socialist Republic (11.0 cases per 100 thsd population). In 1980–1989, the incidence of syphilis in both republics tended to decrease: 5.4-fold in the RSFSR (to 4.3 cases per 100 thsd population) and 3.5-fold in the Uzbek SSR (to 3.1 cases per 100 thsd population). The achievement of such low rates was the result of a strict complex of anti-epidemic activities in the USSR, including criminal and administrative responsibility of syphilis patients for evading treatment and/or concealing contact persons.

After gaining sovereignty in the newly independent states, the incidence of syphilis began to grow rapidly and by 1997 reached the maximum limit values for the last 25 years: 277.3 cases per 100 thsd population in the Russian Federation and 46.9 cases per 100 thsd population in the Republic of Uzbekistan. In the following years, the implementation of a complex of measures aimed at preventing the spread of the disease, including the development of effective methods and algorithms for syphilis diagnosis as well as preventive measures, made it possible to stabilize the epidemiological situation in each of the countries.

In the Russian Federation, in 1997–2019 the incidence of syphilis decreased 18.4-fold (to 15.1 cases per 100 thsd population) in the setting of a stable annual trend towards decrease (on average by 12.3 % per year). In 2020, the pandemic of a new coronavirus disease COVID-19 conditioned the introduction of anti-epidemic measures in the country, completely canceled only in 2022, which expectedly affected an uncharacteristic distribution of incidence rates [13]. In 2023, syphilis incidence rate was 17.6 cases per 100 thsd population, 6.9 % lower than the same rate in 2022 (18.9 cases per 100 thsd population), but 16.5 % higher than the pre-COVID rate in 2019.

In the Republic of Uzbekistan, syphilis incidence, after reaching its peak in 1997, also tended to decrease annually until 2011 (to 7.0 cases per 100 thsd population). In 2012–2017, there was a stabilization of the epidemiological process with the maintenance of incidence rates in the range between 6.9 and 7.4 cases per 100 thsd population, which was largely due to the introduction of Order of the Ministry of Health of the Republic of Uzbekistan from March 31, 2010 № 99 “On Measures for Optimization of Dermatovenerological Care to the Population of the Republic of Uzbekistan” [14]. Thereafter (2018–2023), syphilis incidence had dynamic fluctuations with periods of increase and decrease, including those due to restrictive measures during the COVID-19 pandemic (Figure 1). In 2023, the syphilis incidence rate in Uzbekistan was 8.9 cases per 100 thsd population, which is 49.4 % lower than that in Russia.

The structure of syphilis incidence in the two countries was analyzed separately.

In the Russian Federation, in 2008–2023 significant changes occurred regarding the redistribution of clinical forms of syphilis in the overall disease structure: the proportion of late forms increased 12.1-fold (from 3.2 to 38.8 %), that of other and unspecified forms increased 6.5-fold (from 3.3 to 21.4 %), while the proportion of early forms of syphilis decreased 2.3-fold (from 93.2 to 39.7 %). In the structure of early syphilis over the same period, the proportion of primary syphilis decreased by 48.9 % (13.7 to 7.0 %), while the proportion of secondary syphilis increased by 1.8 % (32.8 to 33.4 %) and the proportion of early latent syphilis increased by 11.4 % (53.5 to 59.6 %). Congenital syphilis accounted for less than 0.1 % (12 cases) in 2023, which is 83.3 % lower than that in 2008 (249 cases; 0.3 %). An increase in the proportion of late and other unspecified forms of syphilis was largely due to 2.8-fold increase in the number of cases of latent syphilis (from 5010 cases in 2008 to 14,112 cases in 2023). The negative trend of increase in cases of neurosyphilis (from 518 cases in 2008 to 555 cases in 2023) with a peak in 2017 (1263 cases) and cases of cardiovascular syphilis (from 15 cases in 2008 to 177 cases in 2023) with a peak in 2022 (207 cases) is also noteworthy. Late and other unspecified forms of syphilis

Fig. 1. Syphilis incidence (all forms) in the Russian Federation and the Republic of Uzbekistan, 1980–2023, per 100 000 population
Рис. 1. Заболеваемость сифилисом (все формы) в Российской Федерации и Республике Узбекистан, 1980–2023 гг., на 100 тыс. населения

are known to be diagnosed many years after infecting and are actively detected mainly during medical examinations and investigations in somatic hospitals. The increase in the proportion of these forms of the disease may suggest both an inadequate history of diagnosis and therapy and existing deficiencies in the disease prevention system.

Of the total number of syphilis cases reported in the Republic of Uzbekistan in 2008–2023, the proportion of early disease forms ranged between 99.6 % and 99.9 %, and others and unspecified forms accounted for less than 0.4 %. While the proportion of cases of early latent syphilis increased by 51.8 % (from 56.0 % in 2008 to 85.0 % in 2023), the proportion of cases of primary and secondary syphilis decreased by 60.4 % (from 13.3 % in 2008 to 5.3 % in 2023) and 68.2 % (from 30.7 % in 2008 to 9.8 % in 2023), respectively. Congenital syphilis and late forms of syphilis, including neurosyphilis and cardiovascular syphilis, were not reported in the country during the study period. On the one hand, the lack of detection of late syphilis positively characterizes the work of the dermatovenerology service, but on the other hand, there is a possibility of neglected diagnosis of cardiovascular syphilis and neurosyphilis due to the lack of pronounced and pathognomonic symptoms of these clinical forms. In addition, cerebrospinal fluid testing to confirm neurosyphilis is often associated with difficulties in obtaining subject's consent, which may result in untimely diagnosis and incomplete treatment due to insufficient strength of antibacterials required for therapy of neurosyphilis.

Taking into account the fact that early forms of syphilis pose the greatest epidemiological danger, contributing to active spread of infection, it seems appropriate to analyze the incidence of early syphilis in terms of its clinical forms in the two countries.

In the Russian Federation, in 2008–2018 there was a decrease in the incidence of early syphilis by 84.6 % (from 55.7 to 8.6 cases per 100 thsd population); the rate of decrease was quite pronounced, averaging 16.9 % per year. As a result, the incidence rate in Russia became equal to that in the Republic of Uzbekistan, while in 2008 the difference between these rates was 5.4 times. Further on, the incidence rate in the country varied between 5.3 and 7.2 cases per 100 thsd population but did not exceed that in Uzbekistan. In general, over the period between 2008 and 2023, the incidence of all forms of early syphilis in the Russian Federation decreased by 87.4 % (to 7.0 cases per 100 thsd population).

In 2023, the incidence of primary syphilis in Russia was 0.46 cases per 100 thsd population, which is 93.9 % lower than that in 2008 (7.6 cases per 100 thsd population) and corresponds to the incidence rate in the Republic of Uzbekistan (0.47 cases per 100 thsd population). The incidence of secondary syphilis decreased by 87.2 % (from 7.60 to 0.46 cases per 100 thsd population) over 2008–2023, and while in 2008 the incidence rate of secondary syphilis in the Russian Federation was 5.8-fold higher than in the Republic of Uzbekistan, the difference between the two rates had almost halved by 2023. In 2008–2023, the incidence of early latent syphilis also decreased, and despite an increase in the post-COVID period (+21.7 % over 2021–2022), the incidence rate in 2023, being 4.2 cases per 100 thsd population, remained lower than the pre-COVID rate in 2019 by 16.0 % (5.0 cases per 100 thsd population). It is noteworthy that in 2008, the incidence of early latent syphilis in the Russian Federation (29.8 cases per 100 thsd population) was 5.2-fold higher than that in the Republic of Uzbekistan (5.74 cases per 100 thsd population); however, by 2018, these rates had become comparably equivalent, and in 2023, the incidence of early latent syphilis in Russia became 1.8-fold lower than that in Uzbekistan (Figure 2–5).

In the Republic of Uzbekistan, over 2008–2023, the incidence of early syphilis decreased by 13.6 % (from 10.3 to 8.9 cases per 100 thsd. population) with a minimum value in 2020 (6.1 cases per 100 thsd population), when restrictive measures were introduced due to the COVID-19 pandemic. During the analyzed period, there was a trend towards decrease in the incidence of primary (by 65.7 %, from 1.37 to 0.47 cases per 100 thsd population) and secondary (by 72.4 %, from 3.15 to 0.87 cases per 100 thsd population) syphilis. And, despite a slight increase in the rates in the

post-COVID period, in 2023 the incidence rates of primary and secondary syphilis decreased by 11.3 % and 53.5 %, respectively, relative to the pre-COVID 2019. In contrast to Russia, in Uzbekistan, the incidence of early latent syphilis increased by 31.5 % (from 5.74 cases in 2008 to 7.55 cases in 2023), demonstrating the most pronounced growth dynamics since 2018, when the incidence rate was 6.25 cases per 100 thsd population, exceeding previous values in the country. The incidence growth continued in 2019 to 6.58 cases per 100 thsd population (+5.3 % to 2018), after which it expectedly decreased by 32.5 % (to 4.44 cases in 2020) as a result of the anti-epidemic measures taken in the country during the coronavirus pandemic. During the period of gradual removal of restrictive measures in 2021-2022, the incidence of early latent syphilis continued to increase, with a cumulative increase of 51.4% in these two years relative to 2020. In 2023, the incidence of early latent syphilis was 7.55 cases per 100 thsd population, which is 7.9 % higher than the incidence in 2022 and 14.7 % higher than the pre-COVID 2019 rate (see Figures 2–5).

The current situation related to the increased incidence of early latent syphilis in Uzbekistan in the pre- and post-COVID period can be explained by the following reasons. In 2017, in order to strengthen and supplement the range of

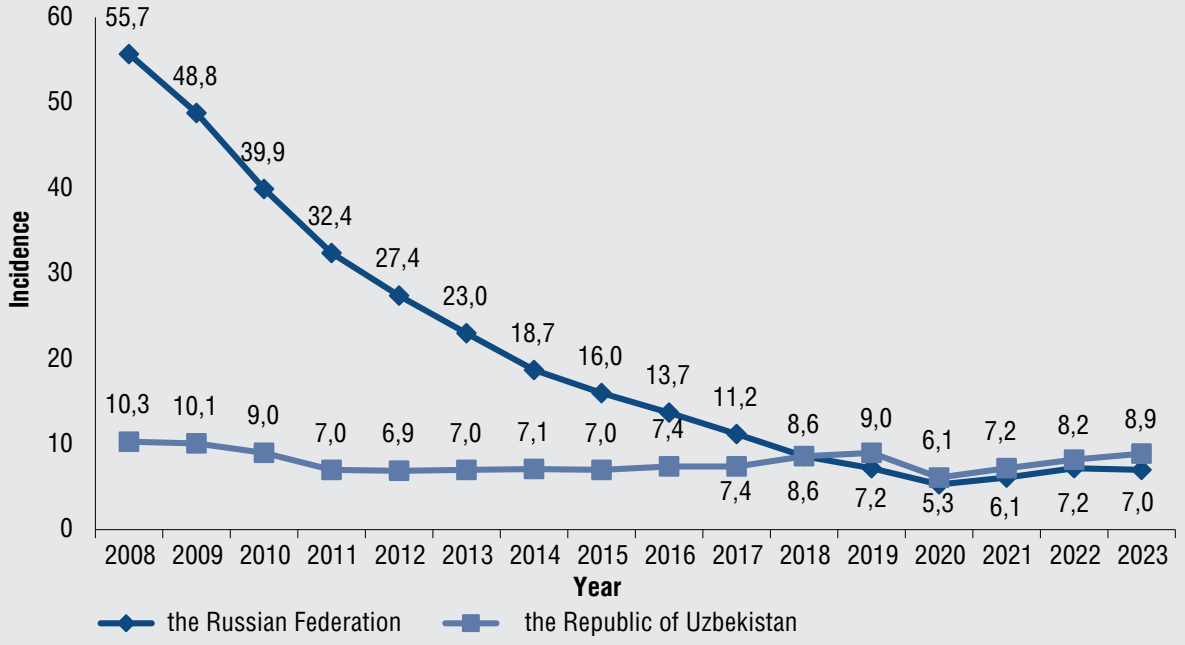


Fig. 2. Incidence of early syphilis in the Russian Federation and the Republic of Uzbekistan, 2008–2023, per 100 000 population
Рис. 2. Заболеваемость ранними формами сифилиса в Российской Федерации и Республике Узбекистан, 2008–2023 гг., на 100 тыс. населения

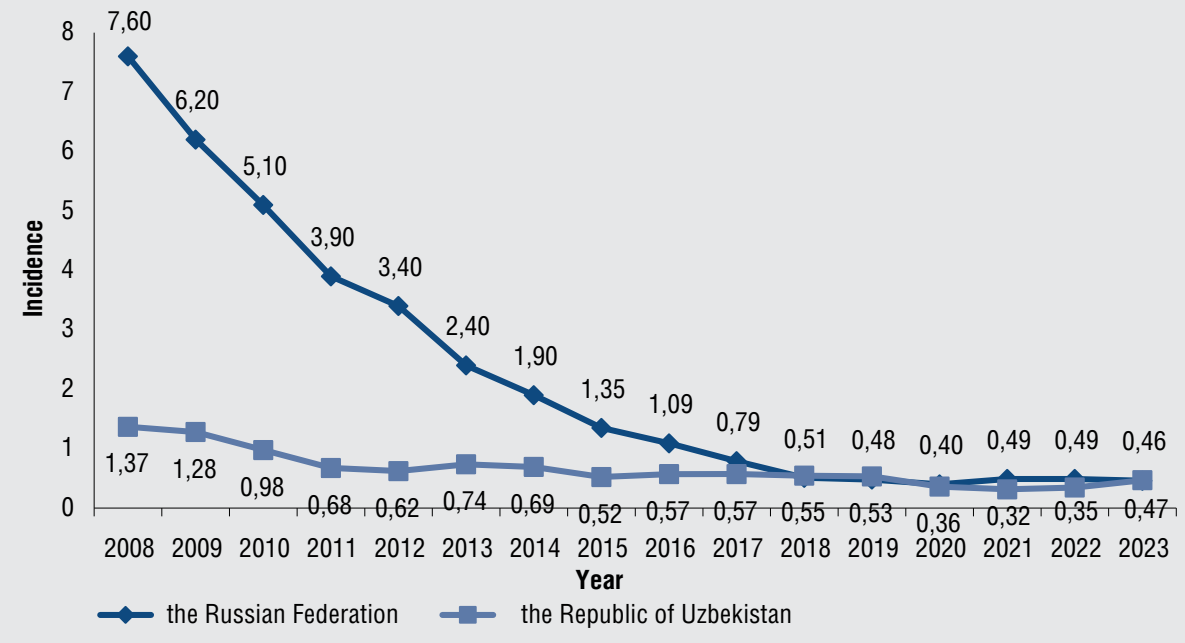


Fig. 3. Incidence of primary syphilis in the Russian Federation and the Republic of Uzbekistan, 2008–2023, per 100 000 population
Рис. 3. Заболеваемость первичным сифилисом в Российской Федерации и Республике Узбекистан, 2008–2023 гг., на 100 тыс. населения

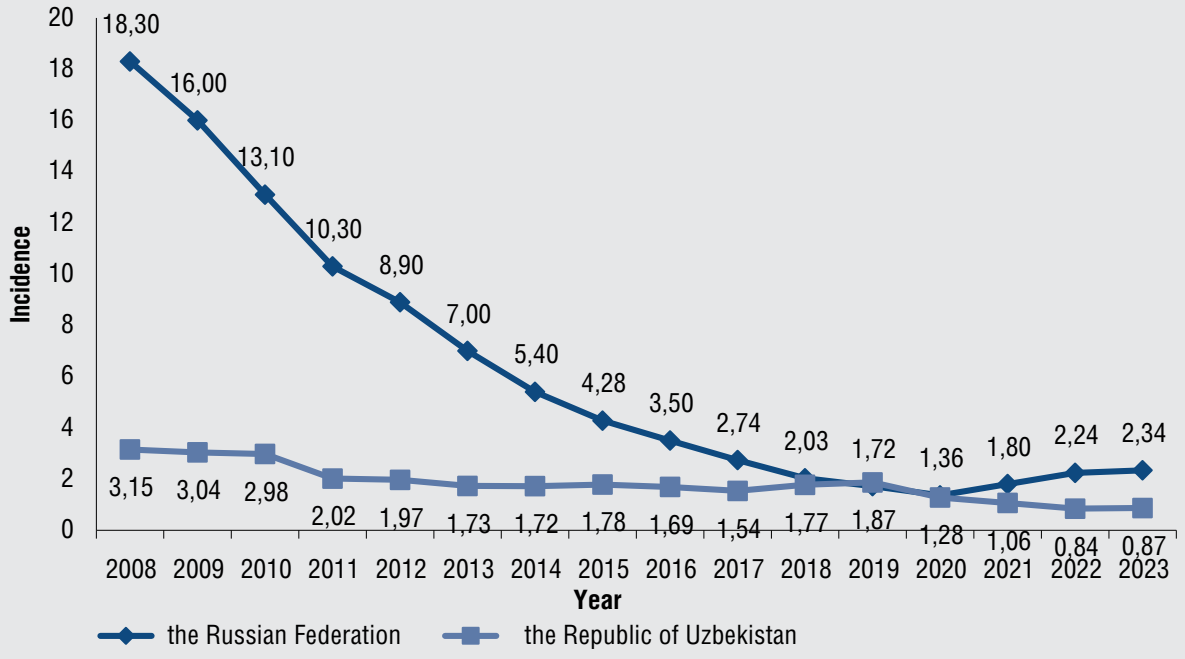


Fig. 4. Incidence of secondary syphilis in the Russian Federation and the Republic of Uzbekistan, 2008–2023, per 100 000 population
Рис. 4. Заболеваемость вторичным сифилисом в Российской Федерации и Республике Узбекистан, 2008–2023 гг., на 100 тыс. населения

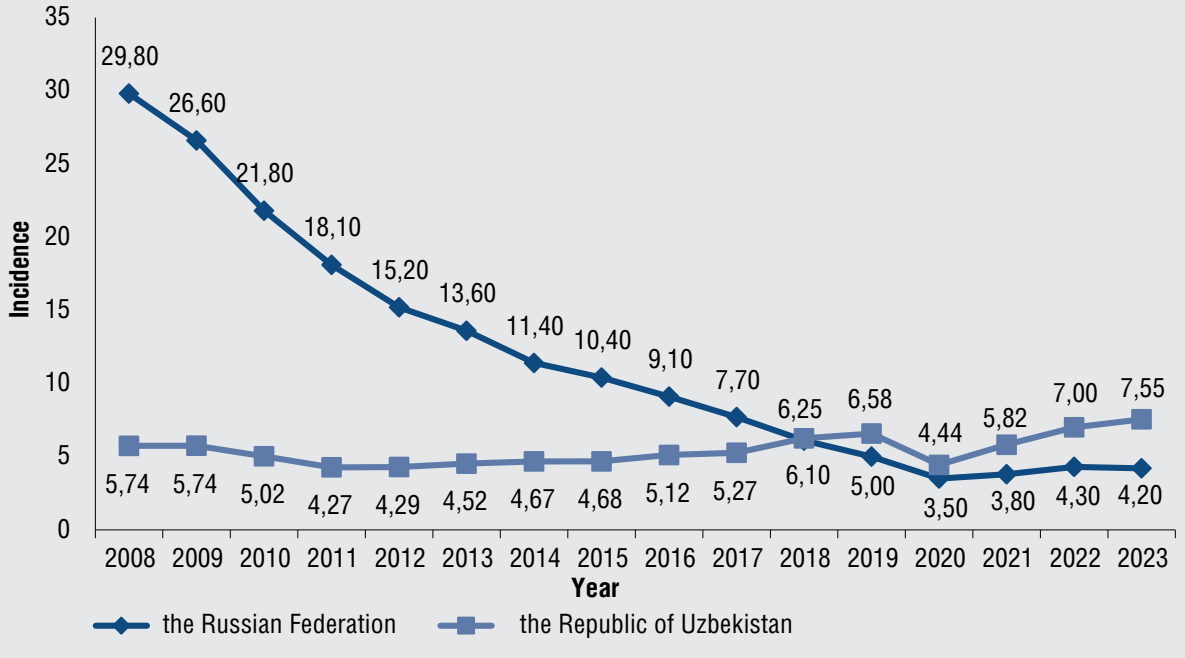


Fig. 5. Incidence of early latent syphilis in the Russian Federation and the Republic of Uzbekistan, 2008–2023, per 100 000 population
Рис. 5. Заболеваемость ранним скрытым сифилисом в Российской Федерации и Республике Узбекистан, 2008–2023 гг., на 100 тыс. населения

medical services provided by public health care institutions, Resolution of the President of the Republic of Uzbekistan No. ПП-2863 “On Measures for Further Development of the Private Health Care Sector” was adopted [15], according to which medical organizations of non-state ownership were granted the right to provide services for laboratory diagnosis of STIs, including syphilis. Due to the increased availability of medical services with the use of modern high-tech diagnostic methods for the general population, the detection of difficult to recognize latent forms of syphilis has increased, which has brought about an increase in the disease incidence in the country. At the same time, diagnosis of early latent syphilis based on the interpretation of serological tests may be associated with false-positive serological reactions. An uncontrolled use of antibacterials available in pharmacy stores by subjects practicing self-treatment at the onset of the first symptoms of syphilitic infection cannot be ruled out.

When the sex and age characteristics of subjects with syphilis were assessed in the two countries, the following results were obtained.

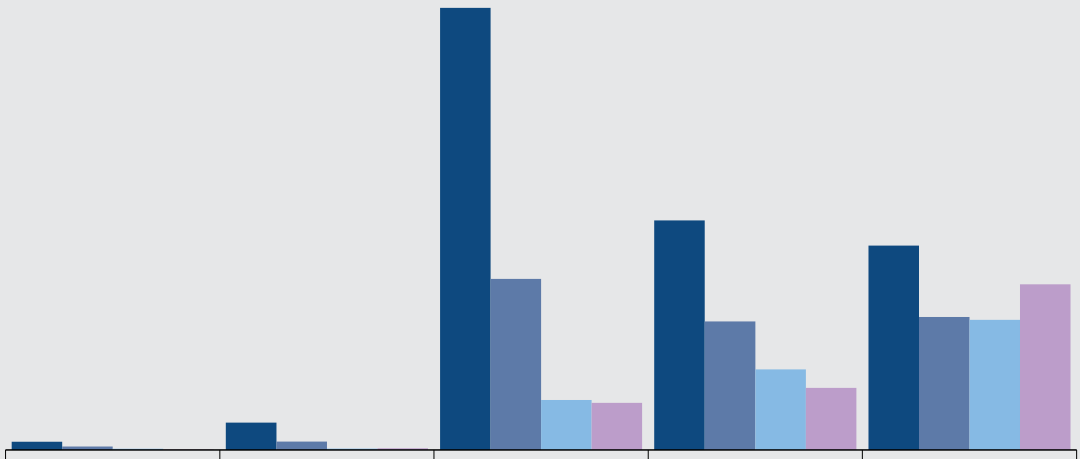
In the Russian Federation, in 2008–2023, there was a decrease in the number of syphilis cases in all age groups: by 95.6 % (from 766 to 34 cases) in the paediatric population 0 to 14 years of age; by 93.8 % (from 2555 to 159 cases) in the adolescent population 15 to 17 years of age; by 89.3% (from 41,229 to 4388 cases) in the population 18 to 29 years of age; by 73.0 % (from 21,414 to 5790 cases) in the population 30 to 39 years of age; and by 18.9% (from 19,054 to 15,452 cases) in the population over 40 years of age. It is noteworthy that in the disease structure, the proportion of syphilis increased 2.7-fold among the population over 40 years of age (from 22.4 % in 2008 to 59.8% in 2023) due to an increase in the number of cases of late and other unspecified disease forms among male population, which may be associated, as indicated earlier, with untimely diagnosis and inadequate treatment of the disease (Figure 6).

In the Republic of Uzbekistan, similar changes were observed in the paediatric population over the same period: the number of syphilis cases in the age group of 0–14 years old decreased by 88.9 % (from 9 to 1 case); that in the age group of 15–17 years old decreased by 86.4 % (from 22 to 3 cases); that in the age groups of 18–29 years old and 30–39 years old decreased by 53.7 % (from 1144 cases in 2008 to 530 cases in 2023) and by 18.6 % (from 787 cases in 2008 to 641 cases in 2023), respectively. As in Russia, a significant increase (2.4-fold) in the number of syphilis cases among individuals over 40 years of age (from 853 to 2067 cases) was reported in the country in 2008–2023 (Figure 7).

In 2023, of the total number of syphilis cases in the Russian Federation, that in males accounted for 65.2 %, which is 30.1 % higher than in 2008 (50.1 %); the proportion of females decreased expectedly from 49.9 % in 2008 to 34.8 % in 2023. An increase in the proportion of syphilis in the male population was observed in adolescent population 15–17 years of age (+78.8 %); individuals 18–29 years of age (+56.4 %); individuals 30–39 years of age (+27.6 %) and individuals over 40 years of age (+3.6 %). However, in the structure of clinical forms of the disease detected in these age groups, there was a trend towards increase the proportion of the number of cases of late and other unspecified forms: by 8.0 % (from 1.0 % in 2008 to 8.0 % in 2023 in the group of juniors 15–17 years of age; 10.9-fold (from 2.1 % in 2008 to 22.9 % in 2023 in the group of individuals 18–29 years of age; 6.3-fold (from 7.0 % in 2008 to 43.9 % in 2023) in the group of individuals 30–39 years of age and 6.1-fold (from 11.7 % in 2008 to 71.7 % in 2023) in the group of individuals 40 years of age.

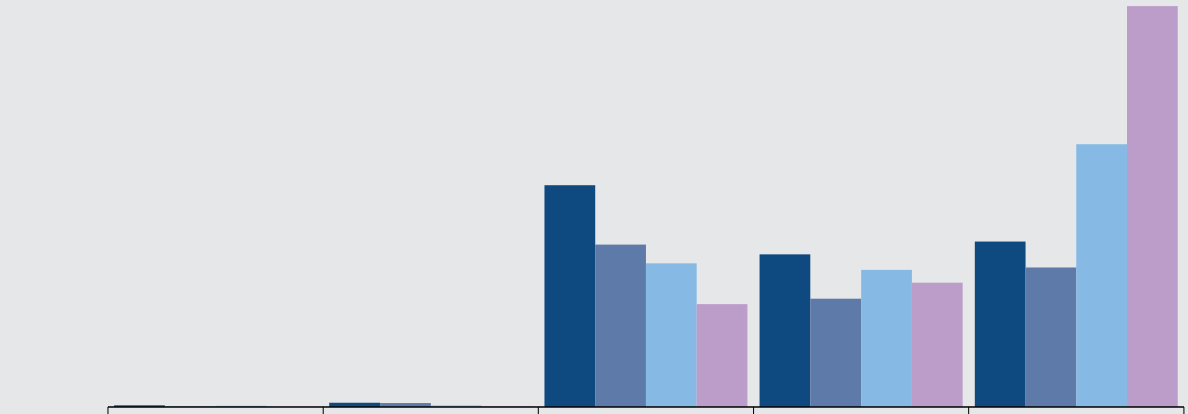
Analysis of the number of syphilis cases in the gender-specific aspect in the Republic of Uzbekistan over 2008–2023 also showed the prevalence of men among syphilis patients, the proportion of which varied from 57.0 % to 65.0%. A similar trend was observed in all age groups, except for the group of adolescents 15 to 17 years of age, where the ratio of boys to girls was approximately the same throughout the analyzed period.

Thus, in 2023, the incidence of syphilis in the Russian Federation (17.6 cases per 100 thsd population) was 2.0-fold higher than that in the Republic of Uzbekistan (8.9 cases per 100 thsd population), which is comparable to the difference in indicators in the Soviet period. Overall, over 1997–2023, the incidence of syphilis decreased 15.7-fold in the Russian Federation and 5.3-fold in the Republic of Uzbekistan. There was also a redistribution of clinical forms of the disease in the two countries: in Russia — towards the growth of late and other unspecified forms of syphilis reported mainly among the male population over 40 years of age; in Uzbekistan — towards an increase in the number of cases of early latent syphilis, also detected among the population over 40 years of age. A significant difference



	0–14 years of age	15–17 years of age	18–29 years of age	30–39 years of age	over 40 years of age
2008	766	2555	41 229	21 414	19 054
2013	324	783	15 954	11 989	12 405
2018	112	135	4668	7508	12 140
2023	34	159	4388	5790	15 452

Fig. 6. The number of cases of syphilis in the different age group in the Russian Federation, 2008, 2013, 2018, 2023, abs.
Рис. 6. Число случаев сифилиса в различных возрастных группах в Российской Федерации, 2008, 2013, 2018, 2023 гг., абс.



	0–14 years of age	15–17 years of age	18–29 years of age	30–39 years of age	over 40 years of age
2008	9	22	1144	787	853
2013	2	20	837	558	719
2018	6	8	741	707	1355
2023	1	3	530	641	2067

Fig. 7. The number of cases of syphilis in the different age group in the Republic of Uzbekistan, 2008, 2013, 2018, 2023, abs.
Рис. 7. Число случаев сифилиса в различных возрастных группах в Республике Узбекистан, 2008, 2013, 2018, 2023 гг., абс.

between the distribution of clinical forms in the disease structure in the both countries requires further analysis, including a comparison of approaches to investigations for diagnosis of neurosyphilis and late forms of syphilis.

Laboratory diagnosis of syphilis in the Russian Federation and the Republic of Uzbekistan

Serological methods take a leading place in the laboratory diagnosis of syphilis, as they make it possible to detect various, including latent, forms of infection and neurosyphilis, as well as to assess the treatment efficacy. The presence of a significant number of serological reactions used in syphilis serodiagnosis is due to a complex polyantigenic composition of the Treponema pallidum, due to which antibodies of different classes and specificity are produced in patient's body [16–19].

The main serological tests used in the diagnosis of syphilis are nontreponemal (reaction for microprecipitation with cardiolipin antigen (RMP), Veneral Disease Research Laboratories (VDRL), Rapid Plasma Reagin (RPR) test) and treponemal (Treponema Pallidum Hemagglutination Assay (TPHA), enzyme-linked immunosorbent assay (ELISA), Fluorescent Treponemal Antibody test (FTAP), Treponema pallidum hemagglutination test (TPHT), immunoblotting (IB), chemiluminescence immunoassay (CLIA), immunochromatographic assay (ICA)) tests.

In the Russian Federation, nontreponemal tests are used for mass screening of the population to detect syphilis. A combination of nontreponemal and treponemal tests is used to detect syphilitic infection in special target groups, such as pregnant women including those referred for abortion, blood, sperm and tissue donors, psychiatric, neurologic, cardiac, ophthalmologic and otorhinolaryngologic patients, and HIV-infected individuals. $ELISA_{IgM}$, $ELISA_{IgM+IgG}$, $RIF_{abs/200}$, and $IB_{IgM+IgG}$ are used to examine individuals who have been in sexual and close household contact with a syphilis subject when the last contact was not more than 2 months ago. To confirm the diagnosis of early syphilis, a combination of a nontreponemal test in the quantitative version of performance together with one treponemal test is used: TPHA, or $ELISA_{IgM+IgG}$, or IB, or CLIA, or ICA. To diagnose latent and late forms of syphilis, including suspected late congenital syphilis, at least two serological tests are used: TPHA and/or $ELISA_{IgM+IgG}$, and/or $FTAP_{abs/200}$, and/or $IB_{IgM+IgG}$, and/or TPHT, and/or CLIA [7].

In the Republic of Uzbekistan, according to Order No. 128 "On the Organization of Prophylactic Examination for Syphilis in Medical and Preventive Treatment Facilities", all serological reactions are divided into three groups: screening reactions (RMP, RPR, RW, TPHA, ELISA, ICA), diagnostic reactions (FTAP, TPHA, ELISA, TPHT, ICA) and reactions used to monitor the therapy efficacy (CFT with cardiolipin antigen, RMP). Taking into account different sensitivity, specificity and complexity of the reactions, and depending on the financial capacities of local health authorities, screening reactions, including both nontreponemal and treponemal reactions, are used to screen the population for syphilis. According to the National Clinical Protocol for the Management of Patients with Early Syphilis, adopted in Uzbekistan in 2021, laboratory tests performed to establish the diagnosis, including in special target populations, are similar to those used in the Russian Federation. To diagnose latent and late forms of the disease, one nontreponemal test and at least two of the following treponemal tests are used: TPHA, $ELISA_{IgM+IgG}$, $FTAP_{abs/200}$, TPHT, CLIA [7]. This spectrum of investigations, according to the above order, can be performed only in regional and republican specialized institutions corresponding to the third (III) and fourth (IV) levels. While in district and municipal facilities corresponding to level one (I) and level two (II), RMP is performed among the compulsory investigations and ICA and TPHA among the recommended investigations.

To diagnose neurosyphilis in the Russian Federation and the Republic of Uzbekistan, cytologic examination of cerebrospinal fluid in combination with serological tests (RMP, FTAP with whole liquor, TPHA, $ELISA_{IgM+IgG}$ and IB) is

performed. The indications for cerebrospinal puncture and cerebrospinal fluid examination do not differ between the two countries. They include:

- Presence of neurologic, ophthalmologic, otologic symptoms and psychiatric disorders in syphilis patients regardless of the disease stage;
- Combination of syphilis and HIV infection, especially if the blood CD4+ T-lymphocyte count is ≤ 350/mm^3, and/or the serum RMP/RPR titer is
- Latent and late forms of syphilis;
- Malignant course of early syphilis even in the absence of neurologic symptoms;
- Secondary syphilis with manifestations in the form of leukoderma, alopecia (especially when combined);
- Presence of early and late specific lesions of visceral organs;
- Suspected congenital syphilis;
- Absence of negative reactions of nontreponemal tests after specific therapy for early syphilis;
- Increase in the positivity degree or titer of serological tests in patients during clinical and serological control (follow-up) after the treatment of late and unspecified forms of syphilis;
- De-registration of subjects with neurosyphilis and serological resistance.

In Russia, serological diagnosis of syphilis is performed in medical institutions and laboratories of any type of ownership that have a license for this type of medical activity. Quality control of laboratory diagnostics in the country is performed by the Federal Service for Surveillance in Healthcare. Laboratories of all types of ownership use Russian, French, Israeli, Korean, Chinese and Austrian test systems registered in the unified register of medical devices of Federal Service for Surveillance in Healthcare for serological diagnosis of syphilis.

In Uzbekistan, screening examination for syphilis is performed by both state and private medical institutions and laboratories, however, the diagnosis is verified exclusively in the laboratories of skin and venereological institutions of municipal, regional and republican significance. Interlaboratory comparative quality control performed by the Central Serological Laboratory with PCR diagnosis takes place twice a year on the basis of the Republican Specialized Scientific and Practical Medical Center of Dermatology and Venereology. In the laboratories of non-state ownership, only one-step immunochromatographic determination of anti-*Treponema pallidum* antibodies in human serum, plasma or whole blood using Chinese One step Anti-TP test system is performed to screen the population for syphilis. State centralized laboratories mainly use Russian test systems by ECOlab CJSC, Vector-Best JSC, as well as German and Chinese kits for detection of anti-Treponema pallidum antibodies.

Thus, in the Russian Federation, examination for syphilis is performed in both public and private medical institutions and begins with nontreponemal tests. In the Republic of Uzbekistan, both nontreponemal and treponemal reactions can be used as qualifying tests, followed by a confirmatory test, which is not inferior to the qualifying test in sensitivity and belongs to a different group of methods; diagnosis is confirmed only in state medical institutions.

Procedure for medical examinations in the Russian Federation and the Republic of Uzbekistan

Medical examinations, which are a set of medical activities, are performed both to detect abnormal conditions, diseases and risk factors for their occurrence and to prevent the occurrence and spread of infections and infestations among the population. In Russia and Uzbekistan, medical institutions, regardless of their form of ownership and departmental affiliation, that have a license for this type of medical activity have the right to perform all types of medical examinations and medical assessment.

To date, the procedure, scope and frequency of medical examinations in order to determine the health status of workers, timely detect diseases and initial forms of occupational diseases are regulated in the two countries: by Order of the Ministry of Health of the Russian Federation dated January 28, 2021 No. 29н "On Approval of the Procedure for Mandatory Preliminary and Periodic Medical Examinations of Employees…" in the Russian Federation; by Order of the Minister of Health of the Republic of Uzbekistan dated July 10, 2012 No. 200 "On Approval of the Regulation on the Procedure of Medical Examination of Employees" in the Republic of Uzbekistan. Decreed population groups engaged in medicine, manufacturing, storage, transportation and marketing of food products and drinking water, upbringing and education of children, communal and household services pose the greatest risk for infectious diseases. There are certain requirements for this population, including laboratory investigations for syphilis [20–24]. The frequency of medical examinations of individuals of decreed professions in Russia and Uzbekistan is given in Table 1.

In 2011–2023, 2.3 to 3.4 % of the total number of syphilis cases were detected during periodic medical examinations of workers in the Russian Federation, while in the Republic of Uzbekistan the similar indicator was between 10.0 and 17.5 % (Table 2).

It is noteworthy that during preliminary medical examinations in Uzbekistan, single cases were detected, while in the Russian Federation there was a trend towards an increase in the proportion of syphilis cases detected at entry to work (from 5.6 % in 2011 to 31.0 % in 2023). This was largely due to an increase in detected cases of syphilis among foreign migrant citizens (from 3001 cases in 2011 to 7991 cases in 2023) who underwent medical assessment, which is regulated by Order of the Ministry of Health of Russia dated November 19, 2021 No. 1079н "On Approval of the Procedure for Medical Assessment...". [25]. Under this order, blood investigation for syphilis is performed using three serological reactions (ELISA$_{IgG}$, TPHA and RMP) for differential diagnosis of all forms of the disease as well as to exclude false-positive results.

In the structure of the number of early syphilis cases among migrants during the same period, the proportion of primary syphilis decreased by 39.1 % (2.3 to 1.4 %) and the proportion of secondary syphilis decreased by 49.0 % (10.0 to 5.1 %), while the proportion of early latent syphilis increased by 6.7 % (87.7 to 93.6 %). In 2023, 9866 cases of syphilis (1599 (16.2 %) cases of early syphilis, 5622 (57.0%) cases of late syphilis, and 2645 (26.8%) cases of other and unspecified forms of the disease) were detected among foreign migrant citizens in Russia, of which 2877 (29.2 %) cases were among foreign citizens from Uzbekistan. Over 2011–2023, the proportion of early syphilis detected during medical assessments in foreign migrant citizens decreased 4.6-fold (from 74.8 to 16.2 %), while the proportion of late syphilis naturally increased 3.1-fold (from 18.5 to 57.0 %), and the proportion of other and unspecified forms of the disease increased 4.0-fold (from 6.7 to 26.8 %) (Table 3).

Table 1. Frequency of syphilis testing as part of mandatory preliminary and periodic medical examinations of employees
Таблица 1. Периодичность обследования на сифилис в рамках обязательных предварительных и периодических медицинских осмотров работников

Works performed	Frequency of medical examination and syphilis testing, times/year	
	The Russian Federation	The Republic of Uzbekistan
Works where there is contact with food products in the process of manufacturing, storage, transportation and sales thereof (in institutions of food and processing industries, agriculture, points, bases, warehouses of storage and sales, in transport institutions, trade organizations, public catering institutions, in food units of all institutions and organizations).	1	2
Works on water supply facilities directly related to water treatment and maintenance of water supply networks	1	1
Works in institutions which activity is related to the upbringing and education of children	1	1
Works in institutions which activity is related to public utilities and consumer services to the population	1	2
Works in medical institutions	1	1

In 2023, 3242 cases of syphilis were reported in the Republic of Uzbekistan, which is comparable to the number of syphilis cases detected in foreign citizens from Uzbekistan who underwent medical assessment in the Russian Federation. Of the total number of syphilis cases reported in Uzbekistan, other unspecified forms of syphilis were detected only in isolated cases, varying from 1 case in 2021 to 12 cases in 2011, and no late forms of the disease were reported.

Thus, despite the lower incidence rates of syphilis (predominantly early forms — 99 % of all syphilis cases) in the Republic of Uzbekistan, a comparable number of cases was detected in the Russian Federation during medical assessment of the citizens of Uzbekistan, with late and other unspecified forms being detected in 83.8 % of cases. This may be related to both problems in diagnosis of late forms of syphilis in Uzbekistan and the overestimation of the indicator in the Russian Federation due to cases when a foreign citizen reports having had the disease during the medical assessment, but does not have the relevant medical documents confirming treatment, and

Table 2. Number of syphilis cases detected in the Russian Federation and the Republic of Uzbekistan during periodic medical examinations in 2011–2023
Таблица 2. Число случаев сифилиса, выявленных в Российской Федерации и Республике Узбекистан при периодических медицинских осмотрах в 2011–2023 гг.

Year	The Russian Federation		The Republic of Uzbekistan	
	Number of syphilis cases	Of them detected during periodic medical examinations, *n* (%)	Number of syphilis cases	Of them detected during periodic medical examinations, *n* (%)
2011	53 773	1833 (3,4)	2073	260 (12,5)
2012	47 268	1614 (3,4)	2071	207 (10,0)
2013	41 455	1451 (3,5)	2136	247 (11,6)
2014	36 606	1322 (3,6)	2182	286 (13,1)
2015	34 426	1253 (3,6)	2168	342 (15,8)
2016	31 143	1139 (3,7)	2384	362 (15,2)
2017	28 639	991 (3,5)	2378	361 (15,2)
2018	24 563	867 (3,5)	2817	400 (14,2)
2019	22 032	697 (3,2)	3020	393 (13,0)
2020	15 313	557 (3,6)	2042	220 (10,8)
2021	21 152	805 (3,8)	2456	276 (11,2)
2022	27 930	643 (2,3)	2965	518 (17,5)
2023	25 823	793 (3,1)	3242	418 (12,9)

Table 3. Syphilis cases detected in the Russian Federation among foreign migrant citizens during medical examinations in 2011–2023
Таблица 3. Случаи сифилиса, выявленные в Российской Федерации среди иностранных граждан-мигрантов при медицинских освидетельствованиях в 2011–2023 гг.

Year	Early syphilis	Of them early latent	Late syphilis	Other unspecified forms of syphilis	Total syphilis cases
2011	1799	1578	445	161	2405
2012	1766	1624	896	219	2881
2013	1375	1246	839	276	2490
2014	1347	1225	1053	491	2891
2015	2016	1908	1083	1809	4908
2016	2199	2116	1727	1562	5488
2017	1600	1545	1987	1752	5339
2018	1267	1220	1927	1628	4822
2019	1175	1142	1724	1266	4165
2020	669	634	1050	713	2432
2021	1219	1187	3932	2089	7240
2022	1840	1720	7815	2723	12 378
2023	1599	1496	5622	2645	9866

therefore it is reported as a newly detected patient with a late form of syphilis.

Therapy of syphilis in the Russian Federation and the Republic of Uzbekistan

After establishing and confirming the diagnosis of syphilis, subjects are prescribed with specific therapy, which involves creating a sufficient treponemocidal concentration of an antimicrobial product in the blood and tissues, and in the case of neurosyphilis — in the cerebrospinal fluid. In the Russian Federation, syphilis therapy can be performed by dermatovenerologists of any medical institution licensed for this type of medical activity, regardless of the form of ownership. Contact persons can be notified of the need for examination and treatment either through the subject himself or via health care providers. Treatment is usually performed on an outpatient basis. Admission to a medical institution is provided for pregnant women with syphilis who need specific and preventive treatment; children with congenital syphilis and acquired syphilis up to secondary school age (up to 10 years) and/or in the presence of somatic pathology; subjects with syphilis who require regular treatment procedures.

In the Republic of Uzbekistan, socially disabled citizens and pregnant women with syphilis are treated under inpatient conditions, while other categories of subjects receive therapy on an outpatient basis in territorial dermatovenerologic institutions. An epidemiological group is functioning in dermatovenerological institutions of all healthcare levels to promptly perform a set of anti-epidemic activities, including mandatory examination of contact persons [14].

The products of choice for the treatment of various forms of syphilis in Russia and Uzbekistan are penicillin antibacterials, with benzylpenicillin being the first choice. If subjects have contraindications to their administration or drug intolerance, alternative products of macrolides, tetracyclines and cephalosporins are used (Table 4).

According to the clinical guidelines “Syphilis” of the Russian Federation and the national clinical protocol for the management of syphilis patients in the Republic of Uzbekistan, treatment regimens are regulated for each clinical form of the disease (Table 5).

Therapy for neurosyphilis in both countries is performed by intravenous administration of antibacterials to achieve required levels thereof in the cerebrospinal fluid. The product of choice is benzylpenicillin sodium salt, administered in a daily dose of 24 mln U for 20 days, in the treatment of late neurosyphilis — with a repeated course after 2 weeks. Alternatively, ceftriaxone is used at a daily dose of 2.0 g for 20 days, with the ability to increase the dose up to 4.0 g in severe cases and to repeat the course similarly in late form.

In Russia, longer courses of therapy with higher strengths of drug products are used to treat various forms of syphilis, with the exception of neurosyphilis, than in Uzbekistan. Subjects in the Russian Federation are treated in state and private medical institutions, while in Uzbekistan subjects with syphilis receive treatment only in territorial skin and dermatovenerologic dispensaries.

Clinical and serological control after specific treatment of syphilis in the Russian Federation and the Republic of Uzbekistan

Clinical and serological control is a set of clinical and laboratory activities performed for subjects after syphilis treatment in order to assess the efficacy of the therapy received. In the Russian Federation and the Republic of Uzbekistan, the terms and scope of clinical and serological control after completion of specific treatment are similar: it is performed once every 3 months during the first year of

Table 4. Antibacterial drugs used for the treatment of syphilis in the Russian Federation and the Republic of Uzbekistan
Таблица 4. Антибактериальные препараты, применяемые для лечения сифилиса в Российской Федерации и Республике Узбекистан

Pharmacological group of drugs	Active ingredient	
	The Russian Federation	The Republic of Uzbekistan
Penicillin	Benzathine benzylpenicillin. Benzylpenicillin procaine in combination with benzathine benzylpenicillin. Benzylpenicillin novocaine salt. Benzylpenicillin sodium salt	Benzathine benzylpenicillin. Benzylpenicillin procaine in combination with benzathine benzylpenicillin. Benzylpenicillin novocaine salt. Benzylpenicillin sodium salt. Ampicillin. Oxacillin
Tetracyclines	Doxycycline	Doxycycline
Macrolides	Erythromycin	Erythromycin
Cephalosporins	Ceftriaxone	Ceftriaxone

Table 5. Treatment regimens for various forms of syphilis in the Russian Federation and the Republic of Uzbekistan
Таблица 5. Схемы лечения различных форм сифилиса в Российской Федерации и Республике Узбекистан

Form of syphilis	The Russian Federation	The Republic of Uzbekistan
	Benzathine benzylpenicillin	
Primary	2.4 mln U IM once daily for **5 days**, course — **3 injections**	2.4 mln U IM once daily for **7 days**, course — **2 injections**
Secondary	2.4 mln U IM once daily for **5 days**, course — **6 injections**	2.4 mln U IM once daily for **7 days**, course — **3 injections**
Early latent	—	
	Benzylpenicillin sodium salt	
Primary	1 mln U IM **6** times daily for **14 days**	1 mln U IM **4** times daily **for 10 days** *or* **400 thsd U IM 8 times daily for 10 days**
Secondary Early latent	1 mln U IM **6** times daily for **28 days**	1 mln U IM **4** times daily for **20 days** *or* **400 thsd U IM 8 times daily for 20 days**
Tertiary, late latent	1 mln U IM **6** times daily for 28 days, **after 2 weeks for additional 14 days**	1 mln U IM **4** times daily for 28 days *or* 1 mln U IM **6** times daily **for 20 days**
	Doxycycline	
Primary	0.1 g orally twice daily for 15 days	0.1 g orally twice daily for 15 days
Secondary Early latent	0.1 g orally twice daily for **28 days**	0.1 g orally twice daily for **30 days**
Tertiary, late latent	**0.1 g orally twice daily for 28 days, after 2 weeks for additional 14 days**	—
	Erythromycin	
Primary	0.5 g orally four times daily for **20 days**	0.5 g orally four times daily for **15 days**
Secondary Early latent	0.5 g orally four times daily for 30 days	0.5 g orally four times daily for 30 days
Tertiary, late latent	**0.5 g orally 4 times daily for 28 days,** **after 2 weeks for additional 14 days**	—
	Ceftriaxone	
Primary	1.0 g IM once daily for 10 days	1.0 g IM once daily for 10 days
Secondary Early latent	1.0 g IM once daily for **20 days**	1.0 g IM once daily for **14 days**
Tertiary, late latent	1.0 g IM once daily for 20 days, **after 2 weeks for additional 10 days**	1.0 g IM once daily for 20 days

follow-up and once every 6 months in subsequent years with nontreponemal tests; in case of persistent negative reaction of nontreponemal tests within 12 months, the follow-up may be stopped.

After the end of the follow-up period, subjects undergo a complete examination, including serological diagnostics (RMP or equivalent, TPHA, ELISA, if necessary — TPHT, FTAP) and medical consultations (therapist or pediatrician, neurologist and ophthalmologist). In subjects with positive results of nontreponemal tests, clinical and serological control can be completed if the following conditions are met: full specific and adjuvant treatment has been performed; clinical and serological follow-up has been performed for 5 years; normal indicators of the cerebrospinal fluid before deregistration; no signs of cardiovascular syphilis during ultrasound examination of the heart and aorta; no specific clinical pathology according to specialists' consultations (neurologist, ophthalmologist, otorhinolaryngologist, therapist/pediatrician). Subjects with late forms of syphilis, in whom the results of nontreponemal tests after the treatment often remain positive, remain under follow-up for at least 5 years, and to complete the clinical and serological control, they undergo examination of the cerebrospinal fluid, Echo-CG, blood biochemistry test (liver enzymes, bilirubin, creatinine, lipid spectrum) and other tests as indicated. After the treatment of neurosyphilis, subjects must have their cerebrospinal fluid examined once every 6–12 months for 5 years. The decision to discontinue clinical and serological monitoring for these subjects after 5 years or to extend it shall be made on an individual basis after the above examinations have been performed.

Conclusion

Over the past decades, the dermatovenerological services of the Russian Federation and the Republic of Uzbekistan have been actively developing and improving, which allowed effective monitoring of syphilis incidence and maintenance of epidemiologic well-being in both countries.

In 2023, the incidence rate of syphilis in the Russian Federation was 2-fold higher than in the Republic of Uzbekistan, while in 1997, during the period of the most unfavorable socioeconomic conditions in the countries, the difference between the indicators was 5.9 times. During the study it was possible to establish a significant redistribution of clinical forms of syphilis in the disease structure.

In Russia, there was a trend toward an increase in late and other unspecified forms of syphilis, including neurosyphilis and syphilis of the cardiovascular system, predominantly among the population over 40 years of age, which may indicate both untimely diagnosis and treatment of the disease and an imperfect prevention system. In addition, due to the absence of criminal and administrative responsibility of syphilis patients for evading treatment in the country, one cannot exclude refusal from therapy or subject's voluntary desire to independently complete the course of treatment not received in full, which may also lead to late forms of the disease. In the Russian Federation, a combination of a nontreponemal quantitative test and at least two treponemal tests (TPHA and/or $ELISA_{IgM+IgG}$, and/or $FTAP_{abs/200}$, and/or $IB_{IgM+IgG}$, and/or TPHT, and/or CLIA) is used to detect late and unspecified forms of syphilis.

In contrast, in the Republic of Uzbekistan, there was an increase in the incidence of early latent syphilis, which was also more frequently reported among the population over 40 years of age. Taking into account that the use of qualifying tests for prophylactic examination of the population for syphilis in the country is regulated by local health authorities, taking into account the specific local conditions and economic opportunities, screening can start with both treponemal and nontreponemal reactions. Simultaneous performance of two specific tests is used to diagnose latent and late syphilis, depending on the level of the medical institution. In district institutions, ICA or TPHA with RMP or RPR are used; in municipal institutions, ICA or TPHA or ELISA with RMP or RPR are used; in regional specialized institutions, FTAP + ELISA, or FTAP + TPHA, or FTAP + ICA, or ICA + TPHA, or ELISA + TPHA, or other combinations with RMP or RPR are used; in the republican specialized institutions, FTAP + ELISA, or FTAP + TPHT, or FTAP + TPHA, or FTAP + ICA, or FTAP + IB, or ICA + TPHA, or ELISA + TPHA, or other combinations with RMP or CSR or RPR are used. The detection of both early syphilis and other clinical forms of the disease in citizens from Uzbekistan who underwent medical assessment in the Russian Federation with three serological reactions may indicate both possible problems with diagnosis, missing difficult-to-recognize late forms of syphilis, and the limited number of serological tests used to confirm the diagnosis in the Republic of Uzbekistan. In 2023, the proportion of foreign citizens, migrants from Uzbekistan, in the total structure of syphilis incidence in the Russian Federation was 11.1 %, where all clinical forms of the disease were represented. In the same year, only early syphilis was reported in 99.9 % of cases in Uzbekistan. The lack of detection of late forms of syphilis in Uzbekistan in the setting of their active detection in Russia emphasizes the need for further study of this situation.

It should also be noted that the strengths of drug products, especially penicillin antibiotics, for the treatment of various forms of syphilis in the Republic of Uzbekistan are lower than in the Russian Federation. It is known that insufficient concentration of an antimicrobial and a short course of treatment of early syphilis can lead to undertreated cases that progress to latent late forms.

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чие или отсутствие у иностранного гражданина или лица без гражданства инфекционных заболеваний, представляющих опасность для окружающих, и заболевания, вызываемого вирусом иммунодефицита человека (ВИЧ-инфекции), формы бланка и срока действия медицинского заключения об отсутствии факта употребления наркотических средств или психотропных веществ без назначения врача либо новых потенциально опасных психоактивных веществ, а также формы, описания бланка и срока действия медицинского заключения о наличии (отсутствии) инфекционных заболеваний, представляющих опасность для окружающих». [Order of the Ministry of Health of the Russian Federation of November, 19 2021 No. 1079n "On Approval of the Procedure for medical examination, including chemical and toxicological studies of the presence in the body of a foreign citizen or stateless person of narcotic drugs or psychotropic substances or new potentially dangerous psychoactive substances and their metabolites, for the presence or absence in a foreign citizen or stateless person of infectious diseases that pose a danger to others, and a disease caused by a virus". (In Russ.)]

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Information about the authors

***Elena Yu. Novoselova** — Head of the Group of the Scientific and Organizational Department; address: 3 bldg 6 Korolenko street, 107076 Moscow, Russia]; ORCID: https://orcid.org/0000-0003-1907-2592; eLibrary SPIN: 6955-5842; e-mail: novoselova@cnikvi.ru
Margarita R. Rakhmatulina — MD, Dr. Sci. (Med.), Professor; ORCID: https://orcid.org/0000-0003-3039-7769; eLibrary SPIN: 6222-8684; e-mail: rahmatulina@cnikvi.ru
Delya F. Porsokhonova — MD, Dr. Sci. (Med.), Senior Researcher; ORCID: https://orcid.org/0000-0003-1566-5964; e-mail: delya.porsokhonova@mail.ru
Avaz Sh. Inoyatov — MD, Dr. Sci. (Med.), Senior Researcher; ORCID: https://orcid.org/0000-0002-5098-5034; e-mail: avaz_inoyatov@yahoo.com

Информация об авторах

***Новоселова Елена Юрьевна** — руководитель группы научно-организационного отдела; адрес: Россия, 107076, Москва, ул. Короленко, д. 3, стр. 6; ORCID: https://orcid.org/0000-0003-1907-2592; eLibrary SPIN: 6955-5842; e-mail: novoselova@cnikvi.ru
Рахматулина Маргарита Рафиковна — д.м.н., профессор; ORCID: https://orcid.org/0000-0003-3039-7769; eLibrary SPIN: 6222-8684; e-mail: rahmatulina@cnikvi.ru
Порсохонова Дэля Фозиловна — д.м.н., старший научный сотрудник; ORCID: https://orcid.org/0000-0003-1566-5964; e-mail: delya.porsokhonova@mail.ru;
Иноятов Аваз Шавкатович — д.м.н., старший научный сотрудник; ORCID: https://orcid.org/0000-0002-5098-5034; e-mail: avaz_inoyatov@yahoo.com

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