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CHANGES IN EPIDEMIOLOGICAL INDICATORS DEPENDING ON THE ORGANIZATION OF TUBERCULOSIS TREATMENT

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With the purpose to investigate the impact of improving the effectiveness of tuberculosis treatment through the modernization of outpatient treatment on epidemiological indicators a comparative analysis of treatment effectiveness in 2 groups of patients, consisted of 50 newly diagnosed, drug-sensitive, unilaterally lung-affected, smear-positive, cavitary tuberculosis patients: Group 1 (who received the intensive phase of treatment in hospital and the continuation phase as outpatient care once every 10 days); Group 2 (who received treatment under strict daily supervision in a DOT room). It was found that the treatment success rate in the Group 2 was 98 %, exceeding that of the Group 1 by 18.4 %. Among patients of the Group 2, the rate of decrease in the components of infection allergy (increase in reaction compared to the previous year, conversion, and hyperergy to tuberculin) – was 1.1, 1.8, and 1.8 times higher respectively, compared to the Group 1.

Key words: directly observed therapy, successful treatment, tuberculosis infection, morbidity among children and adolescents, relapse.

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ЗМІНА ЕПІДЕМІОЛОГІЧНИХ ПОКАЗНИКІВ У ЗАЛЕЖНОСТІ ВІД ОРГАНІЗАЦІЇ ЛІКУВАННЯ ТУБЕРКУЛЬОЗУ

З метою вивчення впливу підвищення ефективності лікування туберкульозу шляхом модернізації амбулаторно-поліклінічного лікування на епідеміологічні показники проведено порівняльний аналіз ефективності лікування 2 груп пацієнтів, що включали 50 вперше виявлених хворих на туберкульоз легень з лікарською чутливістю, одностороннім ураженням легень, бактеріовиділенням, кавернозним туберкульозом: 1-а група (отримувала інтенсивну фазу лікування в стаціонарі, фазу продовження – амбулаторно з інтервалом 10 днів); 2-а група (отримувала лікування під суворим щоденним наглядом в умовах DOT-кабінету). Встановлено, що ефективність лікування в 2-й групі склала 98 %, що на 18,4 % перевищує таку в 1-й групі. У хворих 2-ї групи швидкість зниження компонентів інфекційної алергії (підвищення реакції порівняно з попереднім роком, конверсія і гіперергія на туберкулін) – була вищою в 1,1, 1,8 і 1,8 рази відповідно порівняно з 1-ю групою.

Ключові слова: лікування під безпосереднім наглядом, успішне лікування, туберкульозна інфекція, захворюваність дітей та підлітків, рецидив.

The epidemiological situation of tuberculosis (TB) in the world is becoming more tense. The tension is mainly reflected in the increase in the proportion of patients with multidrug-resistant and extensively drug-resistant tuberculosis. The multidrug-resistant and extensively drug-resistant forms of tuberculosis most often occur among relapsed patients. According to WHO data, 9 of the 30 regions with high levels of multidrug-resistant strains are in Europe. Azerbaijan and other former Soviet Union countries [6, 8] belong to these regions. One of the most important anti-epidemic measures against tuberculosis is the effective treatment of registered patients. According to the WHO, the criterion for treatment effectiveness includes patients who have been successfully treated (those who have recovered and those who have completed treatment). According to WHO data, the rate of successful treatment among newly diagnosed patients worldwide is 80–85 %, and among relapsed patients is 70–75 %. In Azerbaijan in 2023, these indicators were 75–80 % and 65–70 %, respectively [5, 10, 13].

In the same year, the proportions of multidrug-resistant and extensively drug-resistant tuberculosis patients among newly diagnosed cases were 11 % and 9 %, respectively, and among relapsed cases were 22.1 % and 13 %, respectively [2, 7, 9]. Analysis shows that over the past 10 years (2011–2020), the relapse rate among relapsed patients was 29.2 %. Among this group of patients, the rate of unsuccessful treatments was 28.9 %. Of the relapses, 68–70 % were bacteriologically confirmed, while the rest were confirmed clinically and radiologically.

Thus, the conducted analysis shows that relapses predominate among patients who have completed tuberculosis treatment. Tuberculosis management remains a key priority for public health systems worldwide. The primary objective of therapy is the complete elimination of Mycobacterium tuberculosis infection. A wide range of clinical guidelines has been issued to regulate TB treatment; however, their scope and methodological quality differ considerably [3, 4]. This variability can create challenges for healthcare providers when determining the most appropriate therapeutic approach for individuals affected by TB. In recent WHO documentation, priority is given to the outpatient treatment model [6, 8, 9].

From this perspective, improving the organization of treatment remains a pressing issue.

The purpose of the study was to investigate the impact of modernizing outpatient tuberculosis treatment on epidemiological indicators.

Materials and methods. The study was conducted by the Scientific Research Institute of Lung Diseases (Baku, Azerbaijan) during 2021–2023. In total, 100 newly diagnosed active tuberculosis patients with preserved sensitivity to first-line specific drugs were involved in the study.

The treatment effectiveness of two groups of pulmonary tuberculosis patients, each consisting of 50 newly diagnosed active tuberculosis patients with preserved sensitivity to first-line specific drugs, was analyzed. All patients had the destruction phase and were excreting Mycobacterium tuberculosis. The first group (Group 1) consisted of patients who received the intensive phase of treatment in a hospital setting and the continuation phase in an outpatient setting with medication administration every 10 days. The second group (Group 2) consisted of patients who received both phases of treatment in a DOT (Directly Observed Therapy) outpatient cabinet, with daily strict supervision and administration of specific drugs.

In Group 1, there were 31 male and 19 female patients.

Among males, the 19–29 age group dominated, while among females, the 30–39 age group was predominant. Among Group 1, 12 % had focal tuberculosis at the cavitary stage, and 88 % had infiltrative tuberculosis at the cavitary stage. In this group, 56 % (28 patients) exhibited massive MTB excretion, and 44 % (22 patients) exhibited partial excretion.

Regarding the extent of specific lung lesions, single-segment involvement was observed in 18 male and 7 female patients. Their age and gender distribution matched that of Group 1 (19–29 years, 27 males, 23 females, with 19–29 years predominant among males and 30–39 years among females). In Group 2, focal tuberculosis with single-segment involvement was observed in 14 % (7 patients), and infiltrative tuberculosis involving two or more segments was observed in 86 % (43 patients). Massive MTB excretion was observed in 60 % (30 patients), while partial excretion was seen in 40 % (20 patients).

The study was conducted in accordance with ethical principles and bioethical standards consistent with current international requirements for clinical and clinical-epidemiological research involving human participants (World Medical Association Declaration of Helsinki (as amended), the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS), and the standards of Good Clinical Practice (GCP)). Informed consent was obtained from all patients in both groups. All study participants (or their legal representatives) were informed about the objectives, design, potential risks, and expected benefits of the study. Written informed consent was obtained from all participants before inclusion in the study. The confidentiality of personal data was ensured throughout the research, and data processing and analysis were conducted using anonymized datasets. Participants who were temporarily or permanently legally incapacitated were included solely with the written informed consent of their legal representatives, in strict accordance with applicable legislation and ethical standards. The terms of treatment were specified in the consent, and patients were thoroughly informed.

Inclusion criteria: age 19–79 years; presence of unilateral lung involvement, confirmed by radiological imaging (radiography, computed tomography); microbiologically confirmed pulmonary tuberculosis with MTB excretion (positive sputum smear microscopy, PCR or culture); presence of cavitary lung lesions, confirmed by radiological imaging; newly diagnosed or recurrent active pulmonary tuberculosis in the infiltrative and/or cavitary phase; informed consent to participate in the study.

Exclusion criteria: age <19 and >79 years; bilateral lung involvement, confirmed by radiological imaging; absence of MTB excretion (MTB-negative tuberculosis); absence of cavitary lesions on imaging, extrapulmonary tuberculosis without pulmonary involvement; severe concomitant diseases in the stage of decompensation (cardiovascular, renal, hepatic, or other conditions) that could affect study outcomes, immunodeficiency states, including HIV infection in the AIDS stage, if not specifically addressed by the study protocol.

All patients preserved sensitivity to specific anti-tuberculosis drugs.

Tuberculosis treatment was carried out in accordance with the protocol approved in the Republic of Azerbaijan [1]. Tuberculosis treatment consists of intensive (2 months) and maintenance or continuation (4 months) phases, with a combination of several drugs, including Isoniazid (4–6 mg/kg); Rifampicin (8–12 mg/kg); Ethambutol (15–25 mg/kg); Pyrazinamide (20–30 mg/kg) for at least 6 months. The protocol covers diagnosis, drug susceptibility, individual approach, and management of complications.

Intensive phase: A 4-drug regimen (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) to rapidly reduce the number of bacteria and eliminate the infection.

Continuation phase: A 2-drug regimen (usually Isoniazid and Rifampicin) to kill any bacteria remaining in healthy cells.

To manage adverse reactions during treatment, specific approaches such as drug substitution and transition to individualized treatment regimens were employed. Similar indicators were observed among Group 2 of patients. This group received specific drugs daily under strict supervision.

To achieve the goal, the following objectives have been set: **t**o analyze the results of treatment effectiveness according to WHO criteria at the end of the treatment course in patients who received the intensive phase of treatment in a hospital setting and the continuation phase every 10 days in an outpatient setting; to analyze the effectiveness of treatment according to WHO criteria in patients who received specific drugs under strict daily supervision during both phases of treatment; to conduct a comparative analysis of changes in epidemiological indicators such as the rate of cessation of MTB (Mycobacterium tuberculosis) excretion, closure of cavitary lesions, the extensive level of morbidity among children and adolescents, the proportion of infection with infectious allergy forms, and the proportion of relapse cases, which are considered the main components of successful treatment outcomes in both patient groups.

At the beginning of treatment, bacteriological examination was conducted using the molecular-genetic Genexpert MBT/Rif method. If MTB excretion continued at the end of the intensive phase, molecular-genetic testing was repeated to assess rifampicin resistance. During treatment, samples for solid culture were sent to the National Reference Laboratory (NRL) at the end of the first and second months of the intensive phase.

A repeat culture test was performed in the fifth month of treatment. If the culture remained positive for two months, drug sensitivity testing was carried out. Radiological examinations (mainly chest X-rays) were performed at the beginning of treatment, at the end of the intensive phase, and at the end of the treatment course. Biochemical tests (determination of total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, alpha-amylase, creatinine concentration, urea, glucose, bilirubin and its fractions, electrolytes (potassium)) were conducted at the beginning of treatment, at the end of the intensive phase, and, if necessary, during the continuation phase.

To evaluate treatment effectiveness, an analysis was conducted according to WHO criteria:

– Cure – patients with MTB excretion whose excretion ceased during treatment and who had negative bacteriological results in the last month of treatment and the month before it;

– Treatment completion – patients who completed the treatment course but whose bacteriological results were either unknown or not conducted during the last month of treatment or the month before;

– Successful treatment – the total number of cured patients and those who completed treatment combined (optimal level 95–97 %);

– Unsuccessful treatment – patients who still had positive bacteriological results at the end of treatment or in the preceding month (optimal level 3–5 %);

– Conversion – two consecutive negative simple microscopy or culture results obtained at least 30 days apart;

– Reversion – in patients without conversion, two consecutive positive culture results obtained at least 30 days after the initial results;

– Extensive level of morbidity among child and adolescent contacts – the ratio of new cases among contacts to the total number of child and adolescent contacts, expressed as a percentage;

– Infection – determined by the level of infectious allergy using immunodiagnostics such as the Mantoux 2TE test or Diaskintest.

– An increase compared to the previous year in the results of tuberculin testing (optimal levels: 10–15 % for overall increase, 0.8–1 % for virage, 1.3–1.5 % for hyperergy) is accepted.

– Alternatively, based on positive tuberculin results, optimal levels are accepted as 5–10 % for overall increase, 0.5 % for virage, and 1.0 % for hyperergy.

– Relapse – patients who had previously completed treatment successfully but are currently diagnosed again with active tuberculosis based on bacteriological, clinical, and radiological findings (optimal level 1–2 %);

– Closure of cavitary lesions – closure of cavitary lesions confirmed by radiological and tomographic methods by the end of the treatment course.

– Cavitary lesions are considered reservoirs of infection and a significant cause of relapse.

These indicators are considered the main epidemiological aspects of the scientific study and the primary targets of treatment outcomes. The accuracy coefficient for the obtained results was determined using Student's t-test.

Results of the study and their discussion. Among the patients in the first group, by the end of the second month of treatment, sputum smear conversion (TDM cessation) was observed in 12 % (6 patients) (optimal target: 100 %). By the third month of treatment, conversion occurred in 40 % (20 patients). Similarly, conversion rates were 24 % (12 patients) in the fourth month, 4 % (2 patients) in the fifth month, and 20 % (10 patients) in the sixth month. In some patients who had previously achieved sputum smear conversion, reappearance of TDM was recorded, resulting in an unsuccessful treatment rate of 20 %. These patients were mainly those who interrupted or violated the treatment regimen.

The closure of cavitary lesions was also analyzed during the treatment course in the first group. No cavitary closure was observed during the intensive phase. By the third month, cavitary closure was achieved in 12 % (6 patients); by the fourth month, in 16 % (8 patients); by the fifth month, in 20 % (10 patients); and by the sixth month, in 8 % (4 patients). In other words, in 44 % of cases, cavitary lesions remained open by the end of the treatment course.

Thus, the overall treatment success rate in the first group was 80 %, and the failure rate was 20 %.

A corresponding analysis was conducted for the second group of patients. By the end of the second month of treatment, sputum smear conversion occurred in 76 % (38 patients), and by the third month, conversion was achieved in 100 % of patients. By the sixth month, one patient had an unsuccessful treatment outcome, accounting for 2 % of all patients. A similar analysis was conducted regarding the closure of cavitary lesions by month. It was observed that by the end of the second month, closure occurred in 8 % of patients; by the third month, in 24 %; and by the end of the first half of the treatment course (after three months), in 32 % of patients. By the sixth month, cavitary lesions remained open in 12 % of cases. In other words, while the non-closure rate was 44 % in the first group, it was 3.7 times lower in the second group. Table 1 presents the treatment outcomes for both patient groups.

Table 1

Treatment outcomes at the end of the therapy course in patients of Group 1 and Group 2

Group of patients	The result of the treatment			
	Successful treatment		Unsuccessful treatment	
	abs.n	%	abs.n	%
Group 1 (n=50)	40	80	10	20
Group 2 (n=50)	49	98	1	2

The successful treatment rate in the second group was 18.4 % higher than in the first group, while the failure rate was 10 times lower (P≤0.01). The WHO prioritizes outpatient treatment models. However, the significant risk associated with this model is the increased likelihood of transmission and disease development among contacts. In the study, 94 child and adolescent contacts were monitored in the first group and 80 in the second. The incidence of new TB cases and the level of “hyperergic” reactions to tuberculin among these contacts were investigated. It was found that, during the observation year, the incidence rate of TB among child and adolescent contacts in the first group was 3.2 %, and the rate of “hyperergic” reactions to tuberculin was 9.6 %. In comparison, the corresponding indicators in the second group were 2.5 % and 12.3 %, respectively. Additionally, the extent of TB infection among contacts – measured by rates of tuberculin test conversion, increases in tuberculin test results compared to the previous year, virage, and hyperergy – along with the incidence of new TB cases, was reassessed one and two years after the initial observation. These results are presented in Table 2.

Table 2

Frequency of the occurrence of infectious allergic forms of infection and new cases of illness among children and adolescents in Group 1 and Group 2

Forms of infectious allergy and the extensive level of new illness cases	Group 1		Group 2	
	One year after the observation (%)	Two years after the observation (%)	One year after the observation (%)	Two years after the observation (%)
Increase in results compared to the previous year	22	20.8	26.4	19
Curve	3.7	2.8	2.9	1.6
Hyperergy	6.1	5.6	4.4	3.2
Extensive level of new illness cases	2.4	1.4	-	-

Thus, it is evident that among patients in the first group, the indicators characterizing infection – namely, "an increase in tuberculin results compared to the previous year, “conversion (virage)”, and “hyperergic reactions” – were observed one year after monitoring at rates of 22 %, 3.7 %, and 6.1 %, respectively, and two years after monitoring at rates of 20.8 %, 2.8 %, and 5.6 %, respectively. Additionally, the incidence rate of new TB cases was 2.4 % one year after monitoring and 1.4 % two years after monitoring. In other words, there was a 5.4 % increase in “tuberculin result elevation”, a 24.3 % increase in “virage”, and an 8.2 % increase in “hyperergic reactions”, while new TB cases decreased by 41.7 % over the two-year period. A similar analysis among the contacts of the second group patients showed that one year after monitoring, the rates of “tuberculin result elevation”, “virage”, and “hyperergic reactions” were 26.4 %, 2.9 %, and 4.4 %, respectively. After two years, these indicators had decreased by 28.0 %, 44.8 %, and 27.3 %, respectively (P≤0.05). Importantly, no new TB cases were recorded among the contacts of the second group. Comparative analysis demonstrated that the infection indicators –

reflecting tuberculin-based infectious allergy responses – decreased more rapidly among contacts of the second group compared to the first group, and no new disease cases were observed among them.

The analysis also investigated relapse events occurring two years after treatment. Relapse was defined as the recurrence of TDM (tubercle bacilli) excretion among successfully treated patients. Specifically, among the first group, 3 out of 28 patients (10.7 %) whose cavities had closed at the end of treatment, and 12 out of 22 patients (54.5 %) whose cavities had not closed, experienced relapse. Overall, relapse occurred in 37.5 % (15 patients) of successfully treated individuals in the first group. A similar analysis in the second group revealed that relapse occurred in only one patient (2.3 %) out of 43 whose cavities had closed and in two patients (33.3 %) out of six whose cavities had not closed.

Thus, overall, relapse was observed in 6.1 % (3 patients**)** of successfully treated individuals in the second group. Compared to the first group, relapse among the second group was 4.4 times lower for patients with closed cavities and 1.6 times lower for those with unclosed cavities. In conclusion, strict daily supervised treatment at DOTS (Directly Observed Treatment Short-course) centers led to significantly higher rates of successful treatment outcomes, reduced infection among contacts, decreased new disease cases among contacts, and lower relapse rates compared to patients who received only partially supervised outpatient care (with medication provided every ten days after hospitalization during the intensive phase). Daily sanitary-educational talks conducted with patients under strict supervision significantly improved adherence to infection control measures and prophylactic interventions. As a result, contact transmission and new cases of disease among contacts sharply decreased.

In their research, Zimmer AJ, and colleagues (2021), reported both quantitative and qualitative outcomes from an international community-based survey exploring the difficulties of implementing facility-based DOT during the COVID-19 pandemic, as well as possible alternatives. The findings revealed that barriers such as limited access to transportation, fear of contracting COVID-19, stigma arising from overlapping clinical symptoms, and punitive actions for violating quarantine regulations significantly hindered tuberculosis patients' ability to access care at health facilities, particularly in resource-limited settings. Suggested alternatives included expanding community-based DOT, providing home delivery of medications, adopting multi-month dispensing, and implementing video-supported DOT approaches. The authors emphasize the importance of rethinking TB program delivery models and underline that any reforms should be developed in close collaboration with individuals affected by TB and TB survivors to ensure a genuinely people-centered framework of care [14]. In our study, the impact of the COVID-19 pandemic was not assessed; however, we also obtained positive results of DOT therapy.

Several studies have examined various therapeutic methods in patients with tuberculosis [11, 12, 14].

Thus, the evaluation of wirelessly observed therapy (WOT) in patients with active Mycobacterium tuberculosis complex was conducted by Browne SH, et al (2019), using an ingestible sensor–enabled fixed-dose formulation of isoniazid 150 mg/rifampin 300 mg. A total of 77 individuals with drug-susceptible tuberculosis, who were in the continuation phase and receiving the standard daily regimen of isoniazid 300 mg plus rifampin 600 mg, participated in the study with IS-Rifamate. The findings indicated that, in terms of diagnostic accuracy, WOT performed on par with DOT. However, WOT demonstrated clear advantages over DOT in verifying consistent daily adherence to anti-tuberculosis medication throughout the continuation phase and was strongly favored by patients. The authors highlight that WOT should be further evaluated in high-incidence settings, as it has the potential to significantly strengthen tuberculosis control programs in low- and middle-income countries [5].

In the meta-analysis conducted by Huda MH, et al (2024), in was established that a wide range of technology-driven strategies has been developed with the aim of enhancing adherence to therapy and improving treatment outcomes. Nevertheless, evidence regarding which specific approach is the most effective remains insufficient. In this study, we assessed the impact of digital interventions on medication adherence, treatment completion, and overall success rates among individuals with tuberculosis. To achieve this, we performed a meta-analysis of randomized controlled trials, systematically reviewing publications indexed in six major databases – PubMed, ScienceDirect, Cochrane, JSTOR, Embase, and Scopus – covering the period from 2018 through April 2023. The analysis demonstrated that interventions such as medication event reminder monitors (MERM), SMS reminders, video consultations, and video-observed therapy (VOT) significantly improve adherence and completion of treatment among tuberculosis patients. These findings suggest that digital health technologies hold considerable promise for optimizing patient care and improving outcomes in TB management [11]. We used and evaluated the other method – DOT, and did not assess the interventions mentioned above, so it will be the subject of our further work.

The study has several limitations. The relatively small sample size may reduce statistical power and limit the generalizability of the findings. The single-center design may restrict applicability to other

clinical settings. In addition, the strict inclusion criteria limit extrapolation of the results to other forms of tuberculosis. Long-term outcomes, including relapse rates, were not evaluated, and potential confounding factors were not fully controlled.

Conclusion

1. Among patients treated daily under strict supervision at the DOTS center, the rates of successful treatment and cavity closure within the first three months of therapy were 98 % and 32 %, respectively. In comparison, for patients who underwent the intensive phase of treatment in hospital and received outpatient therapy every ten days during the continuation phase, these rates were 80 % and 12 %, respectively.

2. Among the child and adolescent contacts of patients treated under strict supervision at the DOTS center, the decline rates of tuberculin-based infectious allergy indicators – "increase in tuberculin results compared to the previous year", "conversion (virage)", and "hyperergic reactions" – two years after observation were 1.1, 1.8, and 1.8 times faster, respectively, compared to the corresponding rates among contacts of patients treated with hospital-based intensive therapy followed by outpatient care every 10 days.

3. No new tuberculosis cases were recorded among the child and adolescent contacts of patients treated under strict supervision at the DOTS center during the second year of observation, whereas among contacts of patients treated with hospital and ten-day outpatient regimens, the extensive rate of new cases was 1.4 % two years after treatment.

4. Among patients successfully treated under strict supervision at the DOTS center, the rate of relapse- defined by renewed TDM (tubercle bacilli) excretion two years after treatment – was 6.1 %, whereas this rate was 37.5 % among patients treated with a hospital-based and ten-day outpatient regimen. In other words, relapse occurred 6.1 times less frequently among patients treated under strict supervision.

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