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ABSTRACT
of the dissertation
for the degree of Doctor of Philosophy (PhD)

Topic title: «Comprehensive assessment of the rationality of consumption of antibacterial drugs in a temporary hospital in Aktobe before and during the COVID-19 pandemic»

According to the educational program 8D10102 – «Medicine»
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ABSTRACT

Balapasheva A.A. on the topic: «Comprehensive assessment of the rationality of consumption of antibacterial drugs in a dispensary hospital in Aktobe before and during the COVID-19 pandemic» submitted for the degree of Doctor of Philosophy (PhD), specialty 8D10102 – «Medicine»

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The relevance of the study.

Resistance to antibacterial drugs is one of the ten most significant threats to global health according to the classification of the World Health Organization (WHO). Currently, about 700,000 people die every year in the world due to resistance to antibacterial drugs. Experts estimate that by 2050, the number of deaths related to resistance could reach 10 million, of which 2.4 million are in highly developed countries [1, 2]. According to the World Bank's forecast, by 2050, global economic losses caused by antibiotic resistance may amount to 100 trillion US dollars [3].

The coronavirus pandemic (COVID-19), which began in 2019 in Wuhan, China, has spread rapidly around the world and created serious global problems for health systems. One of the significant consequences of the pandemic has been the further aggravation of the problem of resistance to antibacterial drugs. According to WHO, the practice of over-prescribing antibacterial drugs (ABP) to hospitalized COVID-19 patients is widespread. Despite the low prevalence of concomitant and secondary bacterial infections in patients with COVID-19, a significant part of them still received antibacterial treatment [4].

According to systematic studies (Langford BJ., 2023) conducted in a number of countries (based on data from 24 studies), the frequency of prescribing ABP to hospitalized patients with COVID-19 reached 74% «just in case». At the same time, only 15% of patients received antiviral drugs. However, bacterial or fungal infection was confirmed in only 8% of these patients [5]. The most commonly used groups of ABPS were fluoroquinolones, macrolides, cephalosporins, as well as combinations of beta-lactams with beta-lactamase inhibitors [6-8]. According to a study conducted by Davey P. (2017), before the pandemic, 50% of ABP prescriptions in hospital settings are unjustified [9].

In 2015, WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS) to support the strengthening of the evidence base on antibiotic resistance. As indicated in the GLASS 2020 report, WHO calls on countries to switch to surveillance approaches based on systems that include pharmacoepidemiological and clinical-economic data, rather than being limited to laboratory information [10]. This initiative calls on governments to take measures aimed at reducing the spread of antibiotic resistance, minimizing side effects, and reducing treatment costs [11-13].

Kazakhstan, as a part of the global community, follows WHO recommendations. Despite a slight decrease in the consumption of ABPS for systemic use in recent years, the problem of their irrational use remains relevant. The situation is caused by a number of factors, including over-the-counter antibiotics (27.5% of cases of their use occur without a doctor's prescription) and their over-prescription (the share of ABP is 29.9% of all prescribed drugs, which significantly exceeds the WHO recommended level of 20%) [14-16].

During the COVID-19 pandemic in Kazakhstan, there was a significant discrepancy between treatment methods and national diagnostic and treatment protocols. Thus, according to Gazezova S., (2023) 98% of patients received anticoagulants, 95% — ABP, 56% — glucocorticoids and 56% — antiviral drugs [17].

To date, isolated pharmacoepidemiological and clinical-economic studies have been conducted in Kazakhstan to determine the efficacy and safety of the use of ABP at the

population level [18]. No such studies have been conducted in Aktobe region, which is of significant scientific and practical interest, given the continuing threat of other pandemics. Despite the fact that large-scale work has been carried out in recent years to raise awareness among the population and medical professionals, the problem of irrational consumption of ABP remains a serious problem of domestic healthcare.

Based on the above, the goals and objectives of the study were formulated.

Purpose of the study - to assess the rationality of using consumed antibacterial drugs in a temporary hospital in Aktobe before and during the COVID-19 pandemic (2019–2020)

Objectives of the study

1. To conduct a pharmacoepidemiological assessment of the consumption of antibacterial drugs in a dispensary hospital in Aktobe using the ATC/DDD methodology before and during the COVID-19 pandemic (2019-2020);
2. To conduct a clinical and economic assessment of the consumption of antibacterial drugs in a dispensary hospital in Aktobe using ABC/VEN analysis before and during the pandemic COVID-19 (2019-2020);
3. To conduct a comparative assessment of the consumption of antibacterial drugs according to the WHO AWaRe classification in a dispensary hospital in Aktobe before and during the COVID-19 pandemic (2019-2020).

Scientific novelty of the obtained results:

1. For the first time, a retrospective pharmacoepidemiological assessment of the consumption of antibacterial drugs by the ATC/DDD method was conducted for two consecutive years (2019-2020) before and during the COVID-19 pandemic in a dispensary hospital in Aktobe.
2. For the first time, a retrospective clinical and economic assessment of the consumption of antibacterial drugs by ABC/VEN analysis was conducted for two consecutive years (2019-2020) before and during the COVID-19 pandemic in a dispensary hospital in Aktobe.
3. For the first time, an assessment of the consumption of antibacterial drugs according to the WHO AWaRe classification was carried out for two consecutive years (2019-2020) before and during the COVID-19 pandemic in a dispensary hospital in Aktobe.

The theoretical significance of the study:

According to the data obtained as a result of scientific research, methodological recommendations "Pharmacoepidemiological and clinical-economic aspects of optimizing antibacterial therapy in COVID-19" have been developed and published, which are used in the educational process of the M. Ospanov West Kazakhstan Medical University (WKMU) at the Department of Pharmacology, Clinical Pharmacology in lectures and practical classes by undergraduate students. Faculty of Medicine, Dentistry, Public Health, Pediatrics, interns, residents specializing in Clinical Pharmacology.

The practical significance of the study:

1. For the first time, the ATC/DDD methodology and the WHO AWaRe classification were introduced on the basis of the GKP at the Aktobe Medical Center in Aktobe, which will help to make informed decisions on the inclusion of antibacterial drugs in the formulary list of the institution and the implementation of the main WHO strategies.

2. Based on the results of clinical and economic research, a master class was held for doctors of various specialties and residents of the ZKMU named after M.Ospanov on the topic «ABC/VEN analysis methodology», which will facilitate the implementation of this methodology in hospitals in Aktobe and will allow rational use of funds for the provision of medicines with antibacterial drugs.

The main provisions submitted for defense:

1. The pandemic of coronavirus infection led to a multiple increase in the consumption of antibacterial drugs in 2020 compared to the figures in 2019 in a dispensary hospital in Aktobe. The established frequency of consumption (DDD per 100 beds) increased from 3 to 600 times for certain types of antibacterial drugs (ceftriaxone $p < 0.05$, azithromycin $p < 0.05$, gentamicin p

<0.05, levofloxacin p <0.05, cefazolin p <0.05, amoxicillin and clavulanic acid p <0.05 and meropenem p <0.05).

2. During the pandemic, increased consumption of antibacterial agents was accompanied by an irrational cost structure according to the Pareto principle. In the total cost structure, the share of the most expensive group "A" increased significantly from 70.5% to 84.9% (p <0.05), while the average cost group "B" decreased from 19.7% to 8.4% (p <0.05). At the same time, the main part of the expenses was directed to antibacterial drugs with proven effectiveness, included in the list of vital and essential medicines "V".

3. In the outpatient hospital of the Aktobe Medical Center, the consumption rates of Access group antibacterial drugs in 2019-2020 were significantly lower than the WHO recommended (60%) 24.8% and 27.6%, respectively. The level of consumption of antibacterial drugs of the Watch group in 2019-2020 exceeded WHO standards (30%) by more than two times (75.2 and 72.4%, respectively). The main goal of the WHO AWaRe classification — shifting the consumption of antibacterial drugs towards a safer Access group — has not been achieved.

Personal contribution of the author

The author conducted a thorough analysis of scientific sources related to the topic of the dissertation. All parts of this research paper, including goals, objectives, research program, statistical data processing, interpretation of the results, conclusions and practical recommendations, were carried out by the author independently. Within the framework of the dissertation, methodological recommendations were developed taking into account the data of their own research, which ensured their practical significance.

Approbation of the work

The main provisions of the dissertations were presented at an expanded meeting of the Scientific Problem Commission of the WKMU named after Marat Ospanov.

The results of the study were reported on:

1. International Scientific and Practical Conference "Science and Youth: New challenges and solutions" on April 22, 2022 Report: "Defining the picture of pharmacoeconomics and pharmacoepidemiology caused by the SARS-COV-2 coronavirus and bacterial pneumonia using the example of Aktobe", Almaty, Kazakhstan.

2. Ramonda. Almanac of scientific works April 30, 2022 Report: "Definition of the picture of pharmacoepidemiology caused by SARS-COV-2 coronavirus and bacterial pneumonia on the example of Aktobe, Kazakhstan", Nis, Serbia.

3. IV Congress of Clinical Pharmacologists of Kazakhstan with international participation on October 03-04, 2024 Report: "COVID-19 dayingi zhane COVID-19 kezenindegi hospital tutynylgan antibioticterdi salystyrmaly bagalau", Karaganda, Kazakhstan.

Publications on the topic of the dissertation

6 scientific publications have been published on the topic of the dissertation, of which:

1 publication is in publications indexed in the Scopus information database, Web of Science, JCR - Q1:

- Pharmacoepidemiological Analysis of Antibacterial Agents Used in a Provisional Hospital in Aktobe, Kazakhstan, in the Context of COVID-19: A Comparison with the Pre-Pandemic Period. Antibiotics 2023, 12(11), 1596 (Cite Score 7.3. IF – 4.8. percentile – 94 %) DOI: 10.3390/antibiotics12111596;

3 publications – in scientific publications recommended by the Committee for Quality Assurance in the Field of Science and Higher Education of the Ministry of Education and Science of the Republic of Kazakhstan (KKSON of the Ministry of Education and Science of the Republic of Kazakhstan):

- Analysis of the expenditure of funds on antibacterial drugs in a dispensary hospital in Aktobe in 2020 during the COVID-19 pandemic using the ABC/VEN method. Pharmacy of Kazakhstan Journal 2022. No. 6. pp. 170-178. DOI: 10.53511/pharmkaz.2022.86.72.028;

- Comprehensive Pharmacoepidemiological and clinical-economic analysis of antibacterial drugs consumed during the pandemic at the hospital level in Aktobe, Kazakhsan. Journal of Clinical Medicine of Kazakhstan 2024. Vol. 21. No. 2. pp. 55-58. DOI: 10.23950/jcmk/14495;

- The impact of the coronavirus pandemic (COVID-19) on antibiotic therapy in hospital settings and control of antimicrobial resistance: a literarture review. Pharmacy of Kazakhstan Journal 2024. No.5. pp.153-158. DOI: 10.53511/pharmkaz.2024.63.30.018;

2 theses are in the collections of International scientific and practical conferences.

Based on the conducted research, developed and implemented:

- 1 methodological recommendations "Pharmacoepidemiological and clinical-economic aspects of optimizing antibacterial therapy in COVID-19" (UDC 615.281; BBK 52.81; ISBN 978-601-81142-5-0) were approved at the meeting of the Scientific Council of the NAO "West Kazakhstan Medical University named after M. Ospanov" №4 (821) dated 12/26/2024, as well as the Educational and Methodological Association — Project Management Group of the Republican Educational and Methodological Council No. 532 dated May 8, 2025.;

- 2 acts of introducing the results of scientific work into practical healthcare:

- № 38 dated January 22, 2024. "Bacteriyaga karsi preparattardy koldnu tazhiribesin ontaylandyruda DDU pharmacoepidemiologiyalyk ATC/DDD adistemesi" in the State Enterprise at the Aktobe Medical Center;

- № 39 dated January 22, 2024. "Bacteriyaga karsi therapiyany ontayly koldanudy baskaru retide DDU AWaRe zhikteli" in the GKP at the Aktobe Medical Center;

1 act of commercialization:

- № 12 dated July 05, 2023, on clinical and economic research of the dissertation, a master class was held for doctors and residents of the M. Ospanov ZKMU on the topic "ABC/VEN analysis methodology".

MATERIALS AND RESEARCH METHODS:

The dissertation research was carried out within the framework of the funded scientific and technical project of the intramural grant of the ZKMU named after M. Ospanov entitled: "Concomitant bacterial infections and pharmacoepidemiology of antibiotic resistance in patients with COVID-19: the situation in the Aktobe region" for 2022-2024 (Protocol No. 13/2-18-153-n/a dated 03.03.2022), Project Manager — Smagulova G.A.

The object of research on three tasks was the databases of the 1C Accounting System: Accounting program (section "Movement of medicines in the organization") of the pharmacy database of the Aktobe Medical Center dispensary hospital for PCBs for 2019-2020. Additionally, information on the number of treated patients and the number of bed days provided by the Department of Medical Statistics was analyzed.

The study conducted in 2019-2020 covered 23 clinical departments of the Aktobe Medical Center dispensary hospital, including the center for respiratory medicine, the stroke treatment center, surgical, therapeutic, cardiological, endocrinological, neurological, maternity and gynecological departments, reception, traumatology and otorhinolaryngology departments, the center for anesthesiology, intensive care and intensive care, as well as other structural divisions.

Prior to the outbreak of the pandemic, the Aktobe Medical Center dispensary hospital had 400 beds for adult hospitalization. Since March 16, 2020, after the introduction of the state of emergency, in accordance with the order of the Regional Health Department of the Aktobe region of the Republic of Kazakhstan, agreed with the sanitary and epidemiological surveillance authorities, the center began operating under quarantine. During the pandemic, based on Order No. 68о§-5 of April 16, 2020, the institution was converted into a 400-bed dispensary hospital designed exclusively for the treatment of adult patients with suspected COVID-19 and confirmed coronavirus infection.

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Research design: a retrospective, descriptive, cross-sectional study. In accordance with the objectives of the study, the following stages are defined:

- Stage 1. Comparative pharmacoepidemiological study of the consumption of antibacterial drugs using ATC/DDD analysis.
- Stage 2. Comparative clinical and economic study of the consumption of antibacterial drugs using ABC/VEN analysis.
- Stage 3. A comparative study of the assessment of the consumption of antibacterial drugs using the WHO AWaRe classification.

Inclusion criteria: adult department of the dispensary hospital of the GKP Aktobe Medical Center in Aktobe.

Exclusion criteria: children's department of the outpatient hospital of the State Enterprise Aktobe Medical Center in Aktobe; other outpatient medical organizations in Aktobe (State Enterprise Regional Clinical Infectious Diseases Hospital in Aktobe, Aktobe Railway Hospital and Regional Tuberculosis Dispensary.

Stage 1 Research methods:

The ATC/DDD (Anatomical Therapeutic Chemical / Defined Daily Dose) methodology was used to conduct a pharmacoepidemiological study of consumed antibacterial drugs in 2019-2020. This methodology, recommended by the World Health Organization (WHO) as an international standard, is widely used to evaluate the use of medicines. WHO calls it the "gold standard" because it provides a unified approach to data analysis, allows you to compare drug consumption in different regions and countries, as well as track the dynamics of their use over time. The ATC/DDD method helps not only to estimate consumption volumes, but also to identify trends and develop strategies for the rational use of medicinal products [19-21].

In accordance with the ATC/DDD methodology, for all antibacterial drugs consumed in 2019-2020, international nonproprietary names (INN) were identified by their trade names (TN), and the corresponding ATS codes (Anatomical-therapeutic-chemical classification) were assigned in accordance with the State Register of Medicinal Products. The data was obtained using the official website of the National Center for Expertise of Medicines and Medical Devices of the Republic of Kazakhstan (NDDA.KZ) at the following address: http://register.ndda.kz/category/search_prep.

To determine the ATC code for all antibacterial drugs for systemic use, the code "J01" was used in accordance with the ATC classification. Category "J" refers to anti-infective drugs for systemic use and includes drugs used to treat infections caused by bacteria or other microorganisms. This category includes: J01A-tetracyclines, J01B – amphenicols, J01C – beta-lactam antibacterial drugs, penicillins, J01D – other beta-lactam antibacterial drugs, J01E –

sulfonamides and trimethoprim, J01F – macrolides, lincosomides and streptogramines, J01G – aminoglycoside antibacterial drugs, J01M – quinolone antibacterial drugs , J01R – combinations antibacterial drugs, J01X – other antibacterial agents).

After determining the PBX code for each of the used antibacterial drugs, the amount of DDD (a certain daily dose) per 100 bed days is calculated. According to the WHO definition, DDD is the established average daily maintenance dose of a medicinal product used for the main indication in an adult with a body weight of 70 kg. For this purpose, the doses of all ABPS consumed in 2019-2020 were determined. (vials, tablets, ampoules, etc.) as well as the total number of bed days, DDD (average daily doses) and ATC/DDD index in grams. The values of the ATC/DDD index in grams were obtained from the website of the WHO Collaborating Center for Drug Statistics Methodology, which is updated every 2 years: (https://atcddd.fhi.no/atc_ddd_index/?code=J&showdescription=yes).

The extracted data was entered into a Microsoft Office Excel template developed in accordance with the guidelines of the Global Surveillance System for Antibiotic Resistance and Use (GLASS) for national surveillance systems monitoring drug consumption in hospitals. The template was presented at the educational and practical seminar "Supervision of the consumption of antibacterial drugs in hospitals in Kazakhstan", organized by the Ministry of Health of the Republic of Kazakhstan at the special invitation of WHO (Regional Office for Europe) in Astana (November 22, 2022). The WHO template for calculation allowed to determine the daily doses (DDD) per 100 bed-days for each antibacterial drug with the code "J01". The calculations were performed according to the methodology using the following formula:

$$\frac{DDDs}{total\ bed-day}\text{x}100$$

Where:

DDDs - the number of average daily doses for adults

DDD – the average daily dose for adults

Result: number of DDD/100 bed days

Stage 2 research methods:

To conduct a clinical and economic study of consumed antibacterial drugs in 2019-2020, the ABC/VEN methodology was used. ABC analysis (Pareto-WHO analysis) is a method for estimating the structure of drug supply costs. It allows you to determine the most expensive areas of drug spending [22]. To conduct an ABC analysis, all prescribed antibacterial drugs are ranked by cost into three groups:

- Group "A" is the most expensive - 10-20% of INN items, which account for 70-80% of the budget;
- Group "B" is less expensive - 10-20% of INN items, the cost of which is 15-20% of the budget;
- Group "C" is the least expensive - 60-80% of INN items, which account for 5-10% of the budget.

VEN – analysis allows you to evaluate the rationality of spending financial resources. VEN analysis should be performed in conjunction with ABC analysis. To do this, all ABPS are divided into three categories:

- Category "V" - (vital) - drugs necessary to save lives, dangerous but serious diseases;
- Categories "E" - (essential/necessary) - Drugs that are effective in the treatment of less dangerous but serious diseases;
- Categories "N" - (non-essential/unimportant) - Drugs for the treatment of "mild" diseases; DRUGS with questionable effectiveness; expensive [23].

For the ABC/VEN analysis, the amounts of expenses of all drugs, including ABPS, consumed in 2019-2020 were determined. Based on the data obtained, a database was created in

Microsoft Office Excel. In the first column, INN were entered in accordance with the State Register of Medicines, available on the official website of the National Center for Expertise of Medicines and Medical Devices of the Republic of Kazakhstan (NDDA.KZ). Then the PBX code for all medicines was indicated in the next column. The database was obtained from the website: http://register.ndda.kz/category/search_prep .

After receiving the necessary data, the following steps were completed to carry out:

Stage 1. Sorting by INN: for further analysis, it was necessary to identify these groups, united by a common INN, which was performed automatically in an Excel spreadsheet by alphabetically sorting INN. To do this, the INN column was highlighted, then the "Data" tab was selected in the Excel menu. The "Sort" function was selected in the submenu that appeared. When this function was selected, a window opened in which the sorting parameters were set: in the "Sort by" window, a column with an INN was selected. After clicking the "OK" button, all the INN were grouped with each other.

Stage 2. Cost calculation: at this stage, the amount of financial costs (in tenge) for all medicines for the analyzed period was indicated for each INN.

Stage 3. Cost share calculation: At this stage, the cost structure of all medicines was analyzed. Data on the costs of each drug was collected and their share in the total cost was calculated. For this purpose, the ratio of the cost of individual drugs to the total cost, expressed as a percentage, was determined. The share of costs for each drug was calculated using the following formula: = B2 * 100 / B14.

Stage 4. Cumulative percentage calculation: next, the cumulative percentage of costs for all medicines was calculated. The cumulative percentage was calculated by adding the share of drug costs to the total cost of more expensive drugs. The cumulative percentage was calculated by sequentially adding the share of the cost of the current drug to the sum of the percentages of all previous, more expensive drugs. The cumulative percentage is calculated using the formula: =D2+C3.

Stage 5. ABC analysis: at this stage, each drug was assigned a corresponding group A, B, C. Until the total percentage of costs reached 80%, the drugs were classified as group "A" (the most expensive). Further, until 95% was reached, the drugs were classified as group "B" (average cost). After reaching 95%, the drugs were assigned to group "C" (low-cost group).

Stage 6. VEN analysis: At this stage, the analysis was carried out taking into account the clinical rationality of all the antibacterial drugs used. All drugs were divided into three categories according to the classification of the VEN analysis: Vital, Essential and Non-essential.

When conducting the VEN analysis, a formal approach based on trustworthy regulatory documents was used, such as the Republican Pharmaceutical Formulary (KNF), the official source of the Republic of Kazakhstan providing standardized information on medicines (www.knf.kz); WHO List of Essential Medicines — official documents regulating standards of therapy and use of medicines adopted leading WHO organizations (iris.who.int/bitstream/handle/10665/371090/WHO-MHP-HPS-EML-2); The British National Formulary (BNF) is an international guideline for the use of medicines. Available on the website of the UK National Institute of Health and Care Quality (https://www.nice.org.uk/bnf-uk-only).

When conducting a formal approach to VEN analysis, all antibacterial drugs were divided into two main categories: Categories "V" - (vital) — include drugs listed in the Republican Form, diagnostic and treatment protocols, as well as in the list of drugs included in the guaranteed volume of free medical care of the Ministry of Health of the Republic of Kazakhstan (GOBMP) from 08/01/2023. These drugs have a high priority and provide key therapeutic effects; Categories "N" - (non-essential/unimportant) — cover drugs that are not included in the above regulatory documents. They are of lesser importance and can be acquired only after meeting the needs for drugs of category "V"; after determining the proportion of antibacterial drugs from the total volume of medicines consumed in 2019-2020, a separate ABC/VEN analysis was conducted for antibacterial drugs.

Stage 3 research methods:

To assess the rationality of the use of antibacterial drugs consumed in 2019-2020, the AWaRe classification recommended by WHO "AWaRe classification of antibiotics for evaluation and monitoring of use, 2021" was used. available on the website https://www.who.int/publications/i/item/2021-aware-classification . The AWaRe classification was developed by WHO within the framework of the concept of essential medicines "Essential Medicines List". Its main goals are to curb the growth of resistance to antibacterial drugs, as well as to increase the safety and effectiveness of their use. WHO sets a goal that by 2023 at least 60% of all antibacterial drugs prescribed at the inpatient level belong to the "Access" category, no more than 30% to the "Watch" category, and 10% to the "Reserve" category [24-26].

In preparation for this study, training was conducted on the advanced training course "AWaRe methodology in the practice of antibiotics", organized by the NAO "Astana Medical University" (Astana, 2024). All consumed antibacterial drugs (2019-2020) were classified in accordance with the principles of AWaRe recommended by WHO.

A color coding system similar to the traffic light system was used for various categories.:

- **Access – green:** This group includes antibacterial drugs that have activity against a wide range of frequently detected susceptible pathogens and at the same time demonstrate a lower potential for resistance than antibacterial drugs of other groups.

- **Watch – yellow:** This group includes antibacterial drugs with a higher potential for resistance, as well as most of the top-priority drugs among those critically important for human medicine that are at a relatively high risk of developing bacterial resistance. Antibacterial drugs in the "Watch" group should be prioritized as key objectives of management and monitoring programs.

- **Reserve – Red:** This group includes antibacterial drugs that should be reserved for the treatment of confirmed or suspected infections caused by multidrug-resistant microorganisms. Antibacterial drugs in the reserve group should be considered as "last resort" options that should be available, but their use should be adapted to very specific patients and conditions when all alternatives have failed or are not suitable [27].

Methods of statistical data processing:

All statistical procedures were performed using IBM SPSS Statistics software version 22 (SPSS Inc., Chicago, IL, USA). GraphPad Prism version 9.5.1 (GraphPad Software, San Diego, California, USA) was used to build graphs, diagrams and visualize the results, which ensured high-quality presentation of analytical data. The analysis was carried out in several stages, depending on the goals and types of variables: descriptive statistics were used to analyze ATC/DDD, ABC/VEN data and the AWaRe classification: calculation of absolute values, frequencies, specific weights (%), as well as 95% confidence intervals (CI), if necessary. The data structure included categorical variables (classification groups of drugs, VEN-categories, AWaRe-categories) and quantitative indicators (volume of consumption in DDD/100 bed-days, costs in tenge). To assess the differences between 2019 and 2020. According to the fractional distribution of categorical variables (for example, the proportion of drugs in the Access/Watch/Reserve groups, ABC/VEN categories), the Pearson chi-square criterion (for expected frequencies >5) and the Z-criterion were used to compare the proportions. The choice of these tests is determined by the categorical nature of the data and the comparison of independent samples according to the distribution of features.

The analysis of consumption rates in DDD/100 bed-days between the years was carried out using a Z-test to compare the two proportions, which allowed us to determine statistically significant differences between the relative values in the pre- and post-pandemic periods. Calculations were performed using specialized online tools (https://tiburon-research.ru/free-tools/z-test-calculator), as well as using the Python programming language (scipy.stats and

statsmodels modules) in the Visual Studio Code environment, which ensured transparency and reproducibility of the analysis. The level of statistical significance in all tests was assumed to be $p<0.05$. If necessary, the sustainability of the results was checked, taking into account potential sources of systematic errors (for example, incompleteness of data, possible distortion in the aggregation of procurement information). Thus, the choice of statistical methods corresponded to both the type of variables (categorical and quantitative) and the structure of the data under study, and the use of visual and software analysis tools made it possible to ensure the validity and visibility of the presented results.

RESEARCH RESULTS

In 2019, 15,986 patients were treated at the outpatient hospital of the Aktobe Medical Center, 1,535 of them with pneumonia. Men accounted for 31.0% (95% CI: 30.3–31.7%), women — 69.0% (95% CI: 68.3–69.7%). In 2020, 11,682 patients with confirmed COVID-19 were hospitalized, 2,737 were diagnosed with pneumonia. The decrease in hospital admissions (by 27%) is due to the suspension of planned care. Men — 30.7% (95% CI: 29.8–31.5%), women — 69.3% (95% CI: 68.5–70.2%). The average age increased from 58.3 ± 6.8 years (2019) to 62.6 ± 11.2 years (2020). The number of beds is 400 in both years. Mortality increased from 1.64% to 7.25% ($p < 0.041$), which is associated with the severe course of COVID-19, respiratory and multiple organ failure, lack of resources and a change in the structure of hospitalizations.

Results 2- research objectives::

The results of the analysis of the consumption of antibacterial drugs in the outpatient hospital of the Aktobe Medical Center (Aktobe) for 2019-2020, performed using the ATC/DDD methodology, showed that in 2019, 25 antibacterial drugs were used out of 242 names of medicines (10.3%; 95% CI: 6.5–14.1%), and in 2020 — 28 out of 248 (11.3%; 95% CI: 6.1–14.3%). The consumption rate of antibacterial drugs for systemic use (DDD/100 bed-days) increased twofold: from 26,189 in 2019 to 53,786 in 2020.

At the same time, there was a decrease in the proportion of oral forms from 47.9% to 41.2% and an increase in the proportion of parenteral forms from 52.3% to 58.8%. In both years, the leading position was occupied by cephalosporins of the third generation (J01D), the consumption of which increased from 12,028 to 26,430 DDD ($p < 0.05$). This was followed by: other antibacterial drugs (J01X): increase from 5,414 to 6,906 DDD; first generation cephalosporins (J01D): from 0.147 to 4,204 DDD ($p < 0.05$); fluoroquinolones (J01M): from 1,129 to 3,658 DDD; azalides (J01F): from 0.024 to 3.476 DDD ($p < 0.05$); carbapenems (J01DH): from 0.783 to 2,541 DDD; Aminoglycosides (J01G): from 0.672 to 2.189 DDD; combined penicillins (J01CR): from 0.536 to 2.026 DDD ($p < 0.05$); macrolides (J01F): from 0.244 to 1.322 DDD; fourth generation cephalosporins (J01D): from 0.499 to 0.553 DDD. The greatest increase in consumption was demonstrated by ceftriaxone: from 5,568 to 19,043 DDD/100 bed-days ($p < 0.05$). The use of cefazolin also increased significantly, from 0.147 to 4.204 DDD/100 bed days ($p < 0.05$).

There was a general increase in the consumption of antibacterial drugs in 2020 compared to 2019. Thus, the level of use of ceftazidime (third generation cephalosporins) increased from 0.459 to 1.275 DDD/100 bed-days, but this increase was not statistically significant ($p = 0.686$). The most pronounced increase in consumption was demonstrated by azithromycin (azalides, J01F) — from 0.024 to 3.476 DDD/100 bed-days ($p < 0.05$). A similar trend was observed for levofloxacin (fluoroquinolones, J01M), the consumption of which increased from 0.978 to 3.386 DDD/100 bed-days ($p < 0.05$). Ciprofloxacin also showed an increase from 1,789 to 2,872 DDD/100 bed-days, but without statistical significance ($p=0.632$). Moxifloxacin and ofloxacin showed a moderate increase, from 0.003 to 0.023 DDD/100 bed-days ($p = 0.993$) and from 0.148 to 0.246 ($p = 0.897$), respectively. The change in cefuroxime

intake was minimal, from 0.688 to 0.718 DDD/100 bed days (p = 0.989). Ertapenem and erythromycin showed a more pronounced increase, from 0.364 to 0.980 DDD/100 bed days (p = 0.768) and from 0.178 to 0.979 (p = 0.765), respectively. A significant increase was recorded in gentamicin (aminoglycosides, J01G) — from 0.003 to 1.811 DDD/100 bed-days (p < 0.05), as well as in amoxicillin with clavulanic acid (penicillins, J01C), the consumption of which increased more than fourfold — from 0.363 to 2.026 DDD/100 bed-days (p < 0.05). Meropenem (carbapenems, J01D) also showed an increase from 0.364 to 1.479 DDD/100 bed days (p < 0.05), while doripenem showed a less pronounced increase from 0.043 to 0.079 (p = 0.897).

The consumption of metronidazole (J01X) increased from 5,414 to 6,906 DDD/100 bed-days (p = 0.756), indicating its stable use. At the same time, vancomycin showed a decrease from 0.210 to 0.077 DDD/100 bed days (p = 0.957), while lincomycin showed a slight increase from 0.278 to 0.302 (p = 0.998). The combination of imipenem with cilastatin demonstrated a decrease in consumption from 0.012 to 0.003 DDD/100 bed-days (p = 0.923). In contrast, clarithromycin showed an increase from 0.021 to 0.343 DDD/100 bed—days (p=0.879), which may indicate an expansion of its use in a pandemic.A number of drugs were not used in 2019, but were prescribed in 2020. Thus, the consumption of amoxicillin was 0.018 DDD/100 bed-days (p = 0.963), and piperacillin was 0.165 DDD/100 bed—days (p = 0.845).

Results 2- research objectives:

The results of an analysis of the consumption of antibacterial drugs in the outpatient hospital of the Aktobe Medical Center for 2019-2020, performed using ABC/VEN analysis, showed an increase in the cost of antibacterial drugs. In 2019, of the 242 items of medicines purchased for a total amount of 221.4 million tenge, antibacterial drugs accounted for 34,699,440 million tenge (15.7% (95% CI: 15.5% – 15.7%). In 2020, the number of items increased to 248, and total expenses increased to 226.7 million tenge. At the same time, the share of antibacterial drugs increased to 39,331,114 tenge 17.30% (95% CI: 17.1% – 17.4%), which represents a statistically significant increase and is likely related to the COVID-19 pandemic.

The results of the ABC analysis showed that in 2019, 7 antibacterial drugs were included in the most expensive category "A" according to international nonproprietary names (INN): meropenem, ertapenem, cefepime, ceftriaxone, metronidazole, cefotaxime and cefazolin. Their purchase accounted for 70.5% (95% CI: 61.5–79.4%) of the total cost of all antibacterial agents. In 2020, Group A expanded to 9 drugs: meropenem, ceftriaxone, cefepime, amoxicillin/clavulanic acid, ertapenem, metronidazole, clarithromycin, cefotaxime and levofloxacin. The share of these drugs in the total cost of antibiotics increased to 84.9% (95% CI: 77.9–91.9%), indicating an increased concentration of costs on a limited number of expensive drugs.

The average cost group "B" according to INN in 2019 included 7 antibacterial drugs: ciprofloxacin, ofloxacin, doripenem, clarithromycin, amoxicillin/clavulanic acid, levofloxacin and cefuroxime. These drugs accounted for 19.7% (95% CI: 11.9–27.5%) of the total cost of all antibacterial agents. In 2020, the composition of group B was reduced to 4 drugs: cefazolin, ciprofloxacin, azithromycin and gentamicin. The share of these drugs decreased to 8.4% (95% CI: 2.9–13.8%) of the total cost of antibacterial agents. At the same time, drugs such as clarithromycin, amoxicillin/clavulanic acid and levofloxacin, which were in group B in 2019, were moved to Group A in 2020.

In 2019, 11 antibacterial drugs were included in the low—cost group "C" by international nonproprietary names (INN), the share of which was 9.8% (95% CI: 4.0% - 15.6%) of the total cost of all antibacterial drugs. This group includes the following drugs: azithromycin, amikacin, vancomycin, imipenem-cilastatin, ampicillin, ceftazidime, moxifloxacin, gentamicin, benzylpenicillin, lincomycin and erythromycin. In 2020, the composition of Group C increased to 15 drugs, but their combined share in costs decreased to 6.7% (95% CI: 1.8% — 11.6%). The following drugs were included in this group: cefuroxime, vancomycin, amikacin, imipenem-

cilastatin, ampicillin, ceftazidime, moxifloxacin, doripenem, benzylpenicillin, lincomycin, ofloxacin, amoxicillin, thiamphenicol glycinate and piperacillin.

Table 1. Results of the analysis of the distribution of costs for antibacterial drugs according to the Pareto principle

ABC Group	2019		2020		The Pareto principle	
	Names of ABP	Expenses	Names of ABP	Expenses	Names of drugs	Expenses
A	7 (28,0%)	70,5%	9 (32,1%)	84,9%	10–20 %	70–80 %
B	7 (28,0%)	19,7%	4 (14,3%)	8,4%	10–20 %	15–20 %
C	11 (44,0%)	9,8%	15 (53,6%)	6,7%	60–80 %	5–10 %

In 2019, group A included 7 names of antibacterial drugs (28%), which accounted for 70.5% of total expenses. In 2020, the number of drugs in this group increased to 9 (32.1%), and their share in costs increased to 84.9% ($p < 0.05$).

Group "B" in 2019 included 7 items (28%), their share in costs was 19.7%. However, in 2020, the number of drugs in this group decreased to 4 (14.3%), and their share in costs decreased to 8.4% ($p < 0.05$).

In the "C" group in 2019, there were 11 items (44%), which accounted for 9.8% of expenses. In 2020, the number of drugs in this group increased to 15 (53.6%), but their share in costs decreased to 6.7%. Thus, in 2020, expenses became more concentrated: the share of expenses for group "A" increased from 70.5% to 84.9%, while it decreased for groups "B" and "C". This redistribution deviates from the 80/20 Pareto rule, according to which 20% of items account for 80% of expenses.

The results of the VEN analysis showed that the costs of all antibacterial drugs used in 2019 and 2020 were reasonable. The main part of the expenses in both years fell on group "V" — drugs with proven effectiveness included in the list of "Vital and important medicines" according to the Kazakhstan National Pharmaceutical Formulary (KNF).

Results 3- research objectives:

The results of the analysis of the consumption of antibacterial drugs in the outpatient hospital of the Aktobe Medical Center for 2019-2020, performed using the WHO AWaRe classification, showed that in 2019, the "Access" category, which includes the main antibacterial drugs widely available for the treatment of common infections and used as first-line drugs, 6 names were included: ampicillin sodium salt, amoxicillin/clavulanic acid, amikacin, benzylpenicillin, gentamicin and metronidazole. Their total share was 24.8% (95% CI: 7.3% — 40.7%) of the total volume of antibacterial drugs consumed. In 2020, the number of drugs in the "Access" category increased to 8 due to the inclusion of amoxicillin and thiamphenicol glycinate acetylcysteinate. At the same time, their share in the total consumption of antibacterial drugs increased to 27.6% (95% CI: 11.3% — 43.9%).

In 2019, the "Watch" category included 19 drugs, including azithromycin, vancomycin, doripenem, clarithromycin, levofloxacin, lincomycin, meropenem, moxifloxacin, ofloxacin, prepenem, cefotaxime, ceftriaxone, cefepime, cefazolin, ciprofloxacin, cefuroxime, ceftazidime, ertapenem and Erythromycin. The share of consumption of these drugs was 75.2% (95% CI: 59.3% — 92.7%) of the total volume of consumed antibacterial drugs. In 2020, piperacillin was added to the "Watch" category, which increased the total number of drugs to 20. The share of "Watch" drugs in 2020 was 72.4% (95% CI: 56.1% — 88.7%) of the total volume of antibacterial drugs consumed.

The "Reserve" category includes antibacterial drugs that should be used exclusively for the treatment of severe infections caused by multidrug-resistant microorganisms. These drugs are

intended for cases where standard treatment regimens are ineffective. In 2019 and 2020, the "Reserve" drugs registered in the Republic of Kazakhstan, such as ceftazidime/avibactam, colistin, polymyxin B and linezolid, were not used in the outpatient hospital of the Aktobe Medical Center. The remaining drugs recommended by WHO for the "Reserve" category are not registered in Kazakhstan. In general, antibacterial drugs of the "Watch" category significantly exceeded the WHO recommended level of 30% ($p < 0.05$) and accounted for the bulk of consumption. At the same time, the proportion of Access group drugs did not reach the WHO recommended level of 60% ($p < 0.05$), which may indicate a shift in preferences towards drugs with a higher risk of developing resistance.

An analysis of the consumption of antibacterial drugs for 2019-2020 using the classifications AWaRe, ABC, VEN and the analysis of membership in the WHO OLS list showed that in 2019 the proportion of drugs included in this list was 64.0% (95% CI: 45.2–82.8%), and in 2020 decreased to 60.7% (95% DI: 42.6–78.8%). As a result, the proportion of drugs not included in the WHO OLS list increased from 36.0% (95% CI: 17.2–54.8%) in 2019 to 39.3% (95% CI: 21.2–57.4%) in 2020. Among the drugs not included in the WHO OLS list, levofloxacin, cefepime and ertapenem became the most expensive group ("A") in 2020, accounting for 20.4% of the total consumption of antibacterial drugs. All antibacterial drugs consumed in 2019 and 2020 fully complied with the clinical protocols used in the healthcare system of the Republic of Kazakhstan. This correspondence indicates that the prescribed antibacterial therapy was carried out in accordance with national standards, and the choice of medicines was based on the principles of evidence-based medicine.

CONCLUSIONS:

1. It was found that in the context of the COVID-19 pandemic in 2020, the consumption of antibacterial drugs in a dispensary hospital in Aktobe increased many times compared to 2019: for individual drugs (ceftriaxone, azithromycin, gentamicin, levofloxacin, cefazolin, amoxicillin/clavulanate, meropenem), the increase in the frequency of consumption (DDD per 100 beds) was from 3 to 600 times ($p<0.05$).

2. It was revealed that the increase in the consumption of antibacterial drugs during the pandemic was accompanied by an irrational cost structure based on the Pareto principle: the share of the cost group "A" increased from 70.5% to 84.9% ($p<0.05$), while group "B" decreased from 19.7% to 8.4% ($p<0.05$), At the same time, the main part of the expenses fell on drugs from the list of vital and essential medicines of group "V".

3. It was found that the structure of consumption of antibacterial drugs according to the WHO AWaRe classification in 2019-2020 in a dispensary hospital in Aktobe did not meet international recommendations: the share of the Access group was 24.8% and 27.6% (with a recommended level of ≥60%), while the share of the Watch group exceeded the permissible limit (30%) by more than It doubled — 75.2% and 72.4%, respectively, which indicates insufficient implementation of the strategy of a rational approach to antibacterial therapy.

PRACTICAL RECOMMENDATIONS:

1. The results of the study make it possible to develop and implement local protocols for the rational use of antibacterial drugs in hospitals, based on the principles of the WHO AWaRe classification, with an emphasis on increasing the proportion of Access group drugs to the recommended 60% and reducing the proportion of the Watch group to 30%.

2. It is recommended to regularly monitor and analyze the consumption pattern of antibacterial drugs using DDD and ABC/VEN analysis indicators to identify irrational spending of funds.

3. It is recommended to continue conducting educational trainings for doctors and pharmacists on the rational use of antibiotics, with special attention to compliance with clinical protocols for the prevention of antibacterial resistance.

The results of the survey have been implemented in practical healthcare. There are acts of implementation:

- № 38 dated January 22, 2024. "Bacteriyaga karsi preparattardy koldnu tazhiribesin ontaylandyruda DDU pharmacoepidemiologiyalyk ATC/DDD adistemesi" in the State Enterprise at the Aktobe Medical Center;

- № 39 dated January 22, 2024. "Bacteriyaga karsi therapiyany ontayly koldanudy baskaru retide DDU AWaRe zhikteli" in the GKP at the Aktobe Medical Center;

The methodological recommendation "Pharmacoepidemiological and clinical-economic aspects of optimizing antibacterial therapy in COVID-19" has been published (UDC:615.281. BBK:52.81. ISBN 978-601-81142-5-0). Approved at the meeting of the UMO RUMS No. 532 dated May 8, 2025.

Possible fields of application: clinical pharmacology, pharmacoepidemiology, pharmacoeconomics, infectious diseases.