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«WEST KAZAKHSTAN MARAT OSPANOV MEDICAL UNIVERSITY»**

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 dispensary hospitals in Aktobe before and during the COVID-19 pandemic»

According to the educational program 8D10102 – «Medicine»

Full name: Balapasheva Aigerim Aldiyarkizy

Completion date: 2021-2024.

Scientific consultants: Candidate of Medical Sciences,
Professor Smagulova G.A.
PhD, Ass. Professor Mussina A.Z.

Foreign scientific consultant: MD, professor Ziganshina L.E.
Patrice Lumumba Peoples' Friendship University of Russia
Russian Federation, Moscow

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ABSTRACT

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

Scientific consultants: PhD, Professor Smagulova G.A.

PhD, Ass. Professor Musina A.Z.

Foreign consultant: MD, Professor Ziganshina L.E.

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 B.J., 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 comparative pharmacoepidemiological assessment of antibacterial drug consumption in provisional hospitals of Aktobe city before and during the COVID-19 pandemic (2019–2020) using the ATC/DDD methodology.

2. To perform a comparative clinical and economic analysis of financial expenditures on antibacterial drugs in provisional hospitals of Aktobe city before and during the COVID-19 pandemic (2019–2020) using the ABC/VEN methodology.

3. To analyze the consumption of antibacterial drugs in provisional hospitals of Aktobe city before and during the COVID-19 pandemic (2019–2020) in accordance with the WHO AWaRe classification and to determine the Rational Use Index (RUI).

Scientific novelty of the obtained results:

1. For the first time, a comprehensive assessment of antibacterial drug consumption in hospitals of Aktobe city before and during the COVID-19 pandemic (2019–2020) was carried out, including a pharmacoepidemiological evaluation based on the ATC/DDD methodology, a clinical and economic analysis using the ABC/VEN system, and an analysis of the antibiotic use structure in accordance with the WHO AWaRe classification.

2. For the first time, the Rational Use Index (RUI) of antibacterial drugs was determined in hospitals of Aktobe city before and during the COVID-19 pandemic (2019–2020) based on the integration of three comprehensive methodological approaches.

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. During the COVID-19 pandemic, a statistically significant increase in the intensity of antibacterial drug consumption was observed in the provisional hospitals of Aktobe city, reflected by a 2.1-fold increase in the DDD/100 bed-days indicator. This indicates an increased frequency of antibiotic prescribing, longer treatment duration, and expansion of the spectrum of antibiotics used. Third-generation cephalosporins, second-generation aminoglycosides, macrolides, and third-generation respiratory fluoroquinolones were predominantly used.

2. During the COVID-19 pandemic, statistically significant changes in the structure of expenditures on antibacterial drugs were identified, characterized by an increased proportion of high-cost medicines in category “A” according to the ABC analysis. At the same time, priority funding for clinically essential antibacterial drugs in category “V” was maintained, reflecting changes in the structure of pharmaceutical provision in hospitals during the pandemic.

3.1. A discrepancy between the structure of antibacterial drug consumption and WHO AWaRe recommendations was identified, characterized by a low proportion of antibiotics in the “Access” group and a significantly higher-than-recommended proportion of “Watch” group antibiotics, indicating the predominant use of antibiotics with a high risk of antimicrobial resistance development.

3.2. In the provisional hospitals of Aktobe city, a statistically significant decrease in the Rational Use Index of antibacterial drugs (RUI-AWaRe) was observed during the COVID-19 pandemic, indicating irrational antibiotic use and confirming the need to implement systematic monitoring and corrective interventions aimed at optimizing antibacterial drug utilization.

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 antibiotictterdi salystyrmaly bagalau", Karaganda, Kazakhstan.

Publications on the topic of the dissertation

7 - 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;

- «Comparative assessment of antibacterial drugs used at the hospital level before and during COVID-19, according to the WHO AWaRe classification». *Frontiers in pharmacology – 2025 Sep 1:16:1642830. doi: 10.3389/fphar.2025.1642830. eCollection 2025.*

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, Kazakhstan. 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 literature 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 terapiyany 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 scientific and technical project "Pharmacoepidemiology of concomitant bacterial infections and antibiotic resistance in patients with COVID-19: the situation in Aktobe region," funded by an internal grant of Marat Ospanov West Kazakhstan Medical University for 2022–2024 (Protocol No. 13/2-18-153-Н/К dated March 3, 2022). The project supervisor was Smagulova G.A. The study object included data obtained from the 1C: Accounting software, section "Movement of medicines in a medical organization," collected from the pharmacy departments of the Republican State Enterprise on the Right of Economic Management "Aktobe Medical Center" and the "Aktobe Regional Clinical Infectious Diseases Hospital" for the period 2019–2020, which enabled the implementation of the three main objectives of the dissertation. Additionally, a retrospective cross-sectional analysis of inpatient medical records of patients aged over 18 years who were treated with a diagnosis of bacterial pneumonia in 2020 in the departments of the "Center of Respiratory Medicine" and "Coronavirus Infection" of the above-mentioned hospitals was conducted. For the cross-sectional study, the general population size was estimated and the required sample size was calculated considering an expected frequency of 50% in the absence of prior data. According to the calculations, the required sample size was 353 patients. Taking into account possible losses, the sample size was increased by 15%, resulting in a final sample of 400 patients, who were divided into two groups ($n_1=200$ and $n_2=200$). In addition, data on patients' sex distribution (number of males and females), mortality rates, and number of bed-days were collected and analyzed from the medical statistics departments of the hospitals.

A comparative analysis of inpatient medical records for 2019 was not performed, as no patients with pneumonia were hospitalized in the Aktobe Regional Clinical Infectious Diseases

Hospital during that period, which excluded the possibility of comparative evaluation of pharmacotherapy and microbiological findings. An expert assessment of the rational use of antibacterial drugs was conducted in accordance with the Order of the Minister of Health of the Republic of Kazakhstan No. ҚР ДСМ-67 dated May 6, 2019, "On approval of the rules for the rational use of medicines," based on adapted indicators of the "Antibiotic Therapy Expert Evaluation Form" for inpatient healthcare organizations. During the study, the modern digital analytical platform AMRcloud (Antimicrobial Resistance Cloud) was used to analyze microbial sensitivity to antibiotics.

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. To conduct a comparative assessment of antibacterial drug consumption using the WHO AWaRe classification and to evaluate antibiotic therapy within the framework of a retrospective cross-sectional study of patients in 2020.

Inclusion criteria: Inclusion criteria: age ≥ 18 years; prescription of at least one systemic antibacterial drug; availability of an inpatient medical record with microbiological examination performed.

Exclusion criteria: Exclusion criteria: patients under 18 years of age (children); incomplete medical records that did not allow assessment of antibiotic therapy; inpatient medical records without microbiological test results.

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 ATC 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 streptogramins, 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:

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: $= B2 * 100 / \text{\$B\$14}$.

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].

Stage 3.1 of the research methods: the Rational Use Index of antibacterial drugs was determined based on the integration of the ATC/DDD, ABC/VEN, and AWaRe methodologies by calculating the integral indicator Rational Use Index (RUI-AWaRe), which represents one of the key scientific novelties of the study. This approach enables a multidimensional assessment of the rationality of antibiotic therapy and provides a tool for systematic monitoring and effective management of antibacterial drug use in healthcare organizations. For this purpose, the Rational Use Index (RUI) was calculated to obtain a comprehensive quantitative assessment of the rational use of antibacterial drugs in the studied hospitals. This indicator provided a comprehensive characterization of antibiotic therapy through the integration of antibiotic burden determined using the ATC/DDD methodology, pharmaco-economic and clinical rationality assessed using ABC/VEN analysis, and the structure of antibiotic consumption according to the WHO AWaRe classification. The RUI was calculated as an integral indicator ranging from 0 to 100 points and included the following components:

- antibiotic burden (ATC/DDD);
- dosage form structure (proportion of orally administered drugs, per os);
- pharmaco-economic cost structure (ABC analysis, proportion of group A drugs);
- clinical rationality of procurement and prescribing (VEN analysis, proportion of category N drugs);
- consumption structure according to the AWaRe classification (proportion of the Access group).

The formula for calculating the RUI-AWaRe was as follows:

$$\text{RUI-AWaRe} = 100 \times (0.30 \times S_{\text{DDD}} + 0.20 \times S_{\text{PO}} + 0.20 \times S_{\text{ABC}} + 0.10 \times S_{\text{VEN}} + 0.20 \times S_{\text{AWaRe}})$$

where:

- $S_{\text{DDD}} = \min(1; \text{DDD}_{\text{ref}} / \text{DDD}_{\text{fact}})$ — an indicator based on the ratio of the actual antibiotic consumption level (DDD_{fact}) to the reference level (DDD_{ref}), with a maximum value limited to 1;
- $S_{\text{PO}} = \min(1; \text{PO}_{\text{fact}} / \text{PO}_{\text{ref}})$ — an indicator reflecting the ratio of the actual proportion of orally administered antibiotics (PO_{fact}) to the reference proportion (PO_{ref}), with a maximum value limited to 1;
- $S_{\text{ABC}} = 1 - (\text{A}_{\text{share}} - \text{A}_{\text{ref}}) / (1 - \text{A}_{\text{ref}})$ — an indicator based on the actual proportion of group A drugs (A_{share}) according to the ABC analysis, normalized to the reference value (A_{ref}) and limited to the range from 0 to 1;
- $S_{\text{VEN}} = 1 - \text{N}_{\text{share}}$ — an indicator inversely proportional to the proportion of category N drugs (N_{share}), which have low clinical significance, according to the VEN analysis;
- $S_{\text{AWaRe}} = \min(1; \text{Access}_{\text{share}} / 60)$ — an indicator reflecting the ratio of the actual proportion of Access group antibiotics ($\text{Access}_{\text{share}}$) to the WHO-recommended reference level of 60%, with a maximum value limited to 1.

Methods of statistical data processing:

All statistical procedures were performed using IBM SPSS Statistics software, version 22 (SPSS Inc., Chicago, Illinois, USA). Graphs, charts, and data visualization were created using GraphPad Prism, version 9.5.1 (GraphPad Software, San Diego, California, USA), ensuring high-quality presentation of analytical results. The analysis was conducted in several stages according to the study objectives and types of variables. For data obtained using the ATC/DDD methodology, ABC/VEN analysis, and the AWaRe classification, descriptive statistical methods were applied, including calculation of absolute values, frequencies, and relative proportions (%), with 95% confidence intervals (CI) determined where appropriate. The dataset included the following variable types: categorical variables (ABC groups, VEN categories, and AWaRe categories) and quantitative variables (antibacterial drug consumption expressed as DDD/100 bed-days and financial expenditures in tenge). To assess differences in the proportions of categorical variables between 2019 and 2020 (for example, proportions of Access/Watch/Reserve groups and ABC/VEN categories), the Pearson chi-square (χ^2) test was used when expected frequencies exceeded 5, along with the Z-test for comparison of proportions. These methods were selected due to the categorical nature of the data and the need to compare distributions between independent samples. To evaluate differences in antibacterial consumption expressed as DDD/100 bed-days between the years, the Z-test for comparison of two proportions was applied. This approach allowed the assessment of the statistical significance of differences between the pre-pandemic and pandemic periods. Calculations were performed using an online statistical tool and additionally verified using the `scipy.stats` and `statsmodels` modules of the Python programming language in the Visual Studio Code environment, ensuring transparency and reproducibility of the analysis. For all statistical tests, the level of statistical significance was set at $p < 0.05$. Where necessary, the robustness of the results was additionally evaluated, taking into account potential systematic errors.

RESEARCH RESULTS

During the study, demographic indicators of the inpatient departments of the Aktobe Medical Center and the Regional Clinical Infectious Diseases Hospital for 2019–2020 were analyzed. At the Aktobe Medical Center, 15,986 patients received inpatient treatment in 2019, of whom 1,535 were diagnosed with pneumonia. In 2020, the total number of hospitalized patients decreased to 11,682; however, the number of pneumonia cases increased to 2,737. The proportion of male patients slightly changed from 31.0% to 30.7%, while the proportion of female patients increased from 69.0% to 69.3%. The mean age of patients increased from 58.3 ± 6.8 years to 62.6 ± 11.2 years. At the Regional Clinical Infectious Diseases Hospital, 5,506 patients received treatment in 2019, with pneumonia registered in 12 cases. In 2020, the total number of patients was 4,951; however, the number of pneumonia cases sharply increased to 1,502. The proportion of male patients decreased from 53.9% to 52.2%, while the proportion of female patients increased from 46.1% to 47.8%. The mean age of patients also increased from 58.3 ± 6.8 years to 62.6 ± 11.2 years.

Results 1- research objectives:

In 2019–2020, a pharmacoepidemiological analysis of antibacterial drug (ABD) consumption was conducted in two large provisional hospitals in the city of Aktobe using the ATC/DDD methodology. At the Aktobe Medical Center, the proportion of ABDs was 10.3% (95% CI: 6.5–14.1%) in 2019 and 11.3% (95% CI: 6.1–14.3%) in 2020. At the Regional Clinical Infectious Diseases Hospital, this indicator was 9.6% (95% CI: 5.4–13.8%) and 9.5% (95% CI: 5.6–13.4%), respectively. During the COVID-19 pandemic, a significant increase in the level of ABD consumption was observed. Thus, the DDD/100 bed-days indicator at the Aktobe Medical Center increased from 26.189 to 53.786, and at the Regional Clinical Infectious Diseases Hospital from 49.922 to 105.684, representing a 2.1-fold increase. At the same time, a decrease in the proportion of oral dosage forms was noted (from 47.9% to 41.2% and from 35.4% to 26.7%, respectively), along with an increase in the proportion of parenteral forms (from 52.1% to 58.8% and from 45.8% to 64.2%).

Among ABD groups, the highest level of consumption was observed for third-generation cephalosporins (Aktobe Medical Center: from 12.028 to 26.43 DDD; Regional Clinical Infectious Diseases Hospital: from 5.073 to 11.219 DDD; $p < 0.001$). A statistically significant increase was also identified in the consumption of fluoroquinolones (Aktobe Medical Center: from 1.129 to 3.658 DDD; Regional Clinical Infectious Diseases Hospital: from 11.483 to 17.085 DDD; $p < 0.001$), carbapenems (from 2.365 to 9.575 DDD; $p < 0.001$), aminoglycosides (from 11.658 to 17.389 DDD; $p = 0.007$), azalides (from 4.444 to 7.138 DDD; $p < 0.001$), and glycopeptides (from 1.888 to 4.195 DDD; $p < 0.001$). Among individual drugs, an increase in the consumption of levofloxacin from 0.978 to 3.386 DDD/100 bed-days ($p < 0.05$), ceftriaxone from 3.592 to 11.219, gentamicin from 8.495 to 11.987, and amikacin from 3.163 to 5.402 was identified (in all cases $p < 0.001$). Thus, during the COVID-19 pandemic period, more than a twofold increase in antibacterial drug consumption was observed in both hospitals, accompanied by a substantial expansion in the use of broad-spectrum antibiotics.

Results 2- research objectives:

In 2019, the total expenditure on medicines at the Aktobe Medical Center amounted to 221,354,368 tenge, of which 34,699,440 tenge was spent on antibacterial drugs (ABDs), corresponding to a share of 15.70% (95% CI: 15.5–15.7%). In 2020, total expenditures increased to 226,738,775 tenge, while spending on ABDs reached 39,331,114 tenge, or 17.30% (95% CI: 17.1–17.4%), indicating a statistically significant increase ($p < 0.05$). According to the ABC analysis, the proportion of group A drugs increased significantly from 70.5% to 84.9% ($p < 0.05$), whereas the proportion of group B drugs decreased from 19.7% to 8.4%, and group C drugs from 9.8% to 6.7%. At the Regional Clinical Infectious Diseases Hospital, expenditures on ABDs in 2019 amounted to 3,872,536 tenge, or 16.15% (95% CI: 11.03–21.27%), and increased to 11,204,006 tenge in 2020, with their share reaching 17.20% (95% CI: 12.22–22.18%); however, this increase did not reach statistical significance ($p = 0.306$). At the same time, the ABC analysis demonstrated a statistically significant increase in the proportion of group A drugs in the expenditure structure from 77.54% to 79.19% ($p = 0.041$), along with a decrease in the proportion of group B drugs from 17.83% to 17.31% and group C drugs from 4.64% to 3.5%. According to the VEN analysis, in both hospitals the majority of financial resources were allocated to category V drugs, which have high clinical importance, whereas the proportion of category N drugs did not exceed 0.14%. Thus, during the COVID-19 pandemic, an increase in financial expenditures on antibacterial drugs was observed, accompanied by a statistically significant shift in their structure toward the high-cost group A, reflecting the increased burden on the hospital pharmaceutical supply system.

Results 3- research objectives:

According to the WHO AWaRe classification, at the Aktobe Medical Center the proportion of antibacterial drugs (ABDs) in the Access category was 24.8% (95% CI: 7.3–40.7%) in 2019 and 27.6% (95% CI: 11.3–43.9%) in 2020. At the same time, the proportion of Watch category drugs was 75.2% (95% CI: 59.3–92.7%) and 72.4% (95% CI: 56.1–88.7%), respectively. These indicators significantly deviated from WHO recommendations: the proportion of Watch category drugs substantially exceeded the recommended level of 30% ($p < 0.05$), whereas the proportion of Access category drugs did not reach the recommended level of $\geq 60\%$ ($p < 0.05$). At the Regional Clinical Infectious Diseases Hospital, the proportion of Access category drugs was 42.1% (95% CI: 21.3–62.9%) in 2019 and 42.9% (95% CI: 20.6–65.2%) in 2020, which was also below the WHO-recommended level of 60%. The proportion of Watch category drugs was 57.9% (95% CI: 35.8–80.0%) and 57.1% (95% CI: 35.9–78.3%), respectively, significantly exceeding the recommended level of 30%. In both hospitals, Reserve category antibacterial drugs were not used during 2019–2020. Thus, during the study period, a mismatch between the structure of antibacterial drug consumption and WHO recommendations was identified in both hospitals, characterized by the predominance of Watch category drugs, the use of which is associated with an increased risk of antimicrobial resistance development.

The integral Rational Use Index (RUI-AWaRe), calculated based on the integration of ATC/DDD, ABC/VEN, and AWaRe methodologies, demonstrated a decrease in the rational use of antibiotics in both hospitals. At the Aktobe Medical Center, the RUI-AWaRe value decreased from 88.26 in 2019 to 68.90 in 2020 (−19.36 points; $p < 0.05$), against the background of an increase in antibiotic consumption from 26.189 to 53.786 DDD/100 bed-days. According to the ABC analysis, the proportion of group A drugs increased from 70.50% to 84.90%, whereas the proportion of Access category drugs according to the AWaRe classification increased only slightly from 24.8% to 27.6%, remaining below the recommended level of $\geq 60\%$, while maintaining a high proportion of Watch category drugs (75.2% and 72.4%). At the Regional Clinical Infectious Diseases Hospital, the RUI-AWaRe indicator decreased from 94.03 to 73.54 (−20.49 points; $p < 0.05$), alongside an increase in antibiotic consumption from 49.922 to 105.684 DDD/100 bed-days. The proportion of group A drugs increased from 77.54% to 79.19%, while the proportion of Access category drugs changed only slightly, from 42.1% to 42.9%, remaining below the recommended level of $\geq 60\%$, with a persistently high proportion of Watch category drugs. Thus, during the COVID-19 pandemic, in both hospitals, a more than twofold increase in antibiotic consumption intensity, increased use of expensive and broad-spectrum antibiotics, and non-compliance of the consumption structure with WHO recommendations were accompanied by a statistically significant decrease in the RUI-AWaRe index, indicating a deterioration in the rational use of antibiotic therapy.

CONCLUSIONS:

1. During the COVID-19 pandemic, particularly in 2020, a significant increase in the intensity of antibacterial drug (ABD) consumption was observed. The DDD/100 bed-days indicator increased from 26.189 to 53.786 at the Aktobe Medical Center and from 49.922 to 105.684 at the Regional Clinical Infectious Diseases Hospital, representing approximately a 2.1-fold increase in both hospitals. This indicates an increased frequency of antibiotic prescribing, possible prolongation of treatment courses, and an expansion in the spectrum of antibiotics used. The consumption structure was characterized by the predominance of third-generation cephalosporins, second-generation aminoglycosides, macrolides, and third-generation respiratory fluoroquinolones ($p < 0.05$).

2. During the COVID-19 pandemic, the ABC/VEN analysis revealed changes in the expenditure structure. The proportion of group A drugs increased significantly from 70.5% to 84.9% ($p < 0.05$) at the Aktobe Medical Center and from 77.54% to 79.19% ($p < 0.05$) at the Regional Clinical Infectious Diseases Hospital, indicating an increased share of high-cost drugs in the overall consumption. At the same time, it was established that the majority of expenditures were attributed to category V (Vital) antibacterial drugs, which represent essential medicines with proven clinical effectiveness.

3.1. In the provisional hospitals of Aktobe in 2019–2020, the proportion of Access group antibacterial drugs was below the WHO-recommended target level (60%), accounting for 24.8–27.6% at the Aktobe Medical Center and 42.1–42.9% at the Regional Clinical Infectious Diseases Hospital. At the same time, the proportion of Watch group drugs exceeded the recommended threshold level (30%) by more than twofold, reaching 75.2–72.4% and 57.9–57.1%, respectively. This indicates the predominant use of antibiotics associated with a high risk of antimicrobial resistance development. The increase in the proportion of Access group drugs was minimal and did not compensate for the persistent imbalance in the antibacterial drug consumption structure.

3.2. At the Aktobe Medical Center, the decrease in the Rational Use Index (RUI-AWaRe) from 88.26 to 68.90 (by 19.36 points), and at the Regional Clinical Infectious Diseases Hospital from 94.03 to 73.54 (by 20.49 points), was associated with a deterioration in the balance between rational and irrational antibacterial drug use. The statistically significant decrease in this

indicator ($p < 0.001$) reliably confirms the deterioration in antibiotic use practices during the study period.

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 terapiyany 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, pharmacoconomics, infectious diseases.