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Pharmacoeconomic Modelling in an Assessment of Acute Respiratory Disease Treatment Under Etiological Uncertainty

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ABSTRACT

The rising of medical innovative treatment costs, combined with limited resources, have resulted in an explosion in the number of pharmacoeconomic assessments currently being conducted. In parallel with the escalating prices of novel pharmacological entities, pharmacoeconomic assessments have become increasingly relevant in decision-making. The aim of this study was to provide a theoretical justification and develop the scientific and methodological underpinnings of the efficacy of pharmacotherapy of viral infections using a mix of pharmacoeconomic analysis and mathematical modelling methodologies. The general concept of modelling was based on patient recovery or death using various pharmacotherapy technologies in the presence and absence of a viral infection, as well as using speed of recovery as a favourable prognostic sign and criterion for the effectiveness of the applied pharmacotherapy technology. Two alternative approaches were compared on the basis of decision trees, with the derivation of a universal criterion for the cost-effectiveness of introducing an additional treatment. The practical implementation of the proposed model was shown using the example of inclusion of the drug vitaglutam as an additional antiviral pharmacotherapy for patients with community-acquired pneumonia. Modelling of the normalisation of clinical and laboratory parameters combined and the duration of hospitalisation showed that the cost-effectiveness of additional pharmacotherapy for community-acquired pneumonia of viral-bacterial etiology could be reduced by an average of 29 %, based on the dynamics of normalisation of clinical and laboratory parameters compared with days of hospitalisation. This indicates that resource savings can be made by introducing this method to analyse the effectiveness of pharmacotherapy.

Keywords: Cost-effectiveness; mathematical modeling; pharmacoeconomic; pneumonia; viral infection

INTRODUCTION

In the 21st century, the burden of infectious diseases of viral etiology has been significantly reduced thanks to numerous efforts to develop and implement various healthcare technologies. Until recently, it was believed that infectious diseases, including those of viral etiology, will gradually disappear in modern society, primarily thanks to the development of new technologies for the production of vaccines and pharmaceuticals. However, infectious diseases still threaten the health of society today and are the second largest cause of death in the world (Michaud, 2009). Respiratory viruses are among the main pathogens of acute non-hospital infections of the lower respiratory tract. Their role in the emergence and development of human infectious diseases is continuing to grow steadily (Pavia, 2011). Today, a significant number of causative agents of acute respiratory viral infections mainly belong to nine different groups of viruses: influenza, parainfluenza, adenovirus, respiratory syncytial (RS) virus, picornavirus, coronavirus, reovirus, enterovirus and the herpes virus (Charlton et al, 2018). The most significant respiratory viruses are the influenza virus, coronavirus and rhinovirus, which cause about a third of all cases of pneumonia in adults (Johnstone et al, 2008; Macfarlane et al, 2001). Modern molecular and biological methods of etiological diagnosis and the high propensity of viruses to mutate have led to the discovery of a number of new previously unknown pathogenic viruses for humans, including metapneumovirus, polyomaviruses Ki and WU, four types of bocaviruses and coronaviruses NL63, HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2, but most of them are capable of causing severe infectious diseases that often result in DEATH (Ruuskanen et al, 2011; Drysdale et al, 2012; Viasus et al, 2012; Ramsey and Kumar, 2013; Walsh et al, 2013; Jain et al, 2015; Prina et al, 2015; Salata et al, 2019).

The diverse range of effects of viruses affecting the human body, the significant spread of viral infections, their complex course and severe complications mean that there is an urgent need to develop methods to combat them. One such means that is effective at combating infectious diseases of viral etiology is etiotropic pharmacotherapy, the aim of which is to suppress various stages of virus reproduction in the cells. The appearance of new viral pathogens of human infectious diseases, such as bocaviruses, is stimulating the development of an increasing number of new drugs with antiviral action (Potaczek et al, 2016). The introduction of such drugs into the scheme of pharmaceutical care for patients with viral diseases is accompanied by issues concerning the evaluation of their effectiveness compared with existing drugs based on randomised clinical trials. The search for highly effective, safe and relatively inexpensive pharmacotherapy technologies using etiotropic drugs based on pharmacoeconomic principles remains relevant and will potentially reduce the burden on state and regional budgets (Soloviov et al, 2020).

In practice, a choice usually needs to be made between various pharmacotherapy technologies aimed at both the normalisation of individual clinical and laboratory indicators of an infectious disease and its possible etiological cause. If an antiviral pharmaceutical drug is included in the scheme of pharmacotherapy of infectious diseases, which can be caused by the formation of pathogens of a viral nature, pharmacoeconomic criteria for its effectiveness need to be developed. Furthermore, a decision can be made to analyse retrospective clinical laboratory and pharmacotherapeutic data, determine pharmacoeconomic criteria based on the relationship between various clinical and laboratory signs of an infectious disease, and to select the pharmacotherapy technology to give the expected outcome (Soloviov et al, 2020; Weintraub, 2008).

Today the global incidence of community-acquired pneumonia (CAP) among adults remains a significant public health concern. The incidence rate varies by region but is generally estimated to be between 5 to 10 cases per 1,000 adult population annually, with higher rates observed in regions with lower vaccination coverage and greater prevalence of risk factors such as smoking and chronic diseases. For instance, in North America, the incidence rate is approximately 6 per 1,000 adults per year, while in Europe, it ranges from 5 to 11 per 1,000 adults annually. In regions with lower healthcare access, such as parts of Africa and Asia, the incidence rates can exceed 10 cases per 1,000 adults annually. (Ochoa-Gondar et al, 2023; Anderson and Feldman 2023; World Health Organization, 2023).

This pathology is characterised by high morbidity with a tendency for further growth, including among young people, as well as an increase in the frequency of a protracted course of the disease, long-term loss of working capacity, an increase in the number of severe forms and the threat of developing complications. According to

modern concepts, bacterial pathogens are the leading and most frequent cause of CAP. Meanwhile, the results of numerous microbiological studies conducted in recent years convincingly indicate that viruses are the second leading cause of CAP (Gao et al, 2013; Musher and Thorner, 2014; Wunderink and Waterer, 2014).

Usually, the pharmacotherapy of CAP requires strict adherence to approved national guidelines, especially if antimicrobial chemotherapy drugs are prescribed empirically. At the same time, certain clinical situations and individual characteristics of patients necessitate the use of alternative technologies and approaches to pharmacotherapy. Moreover, in connection with the deepening of knowledge on the epidemiology of respiratory infections, the introduction into practice of highly effective express methods of identification of the causative agents of CAP, antiviral therapy, which can reduce the severity of the course of the disease and minimise the risk of development, is currently being used successfully in the complex therapy of complications with respiratory diseases. This is confirmed by global and domestic experience of using antiviral drugs both with a direct mechanism of action (agents that suppress various stages of virus reproduction) and an indirect one (through optimisation of the immune response).

Despite significant advancements in pharmacoeconomic modeling and research on the cost-effectiveness of antiviral therapy, substantial gaps remain, particularly in addressing diseases with broad etiologies, such as CAP. Current pharmacoeconomic models often narrowly focus on a single clinical endpoint, such as disease duration or total treatment costs, and frequently fail to account for the complexity and multifaceted nature of the disease (Kostic et al, 2024; Zhao et al, 2022). Moreover, traditional criteria for evaluating the effectiveness of pharmacotherapy, such as the duration of hospitalisation, may not accurately reflect the patient's actual condition and overlook key aspects of recovery: the rate of clinical improvement, normalisation of laboratory parameters, and the probability of achieving favorable outcomes in the context of viral-bacterial coinfections. The emergence of new drugs that could be integrated into existing treatment regimens further underscores the inadequacy of current decision-making frameworks. There is a pressing need for pharmacoeconomic models that not only reflect real-world scenarios but also take into account the variability in the prevalence of viral and bacterial pathogens. By addressing these gaps, the present study lays the groundwork for more informed decision-making to optimise healthcare resource utilisation and pharmacotherapy planning, particularly for diseases with broad etiological spectrum.

Thus, the aim of the study was to provide a theoretical justification and develop the scientific and methodological foundations of the effectiveness of pharmacotherapy for viral infections where the causative agent is unclear, based on a combination of methods of pharmacoeconomic analysis and mathematical modelling on the example of CAP treatment.

MATERIALS AND METHODS

Information about the frequency of detection of viral infection among patients and the effectiveness and cost of each pharmacotherapy technology is important in the evaluation of alternative pharmacotherapy technologies. The main source of data on the cost of diagnostic and therapeutic procedures is price lists of leading medical and preventive institutions at the time of the analysis (Berger et al, 2003).

The development of a model to assess the economic efficiency of the technology of pharmacotherapy of an infectious disease with a wide etiological spectrum was based on classical pharmacoeconomic methods. Figure S1 shows an algorithm for modelling the economic efficiency of the researched technology of pharmacotherapy of an infectious disease of a possible viral etiology using retrospective data.

The algorithm allows patients to be grouped according to certain demographic, clinical-laboratory or pharmacotherapeutic parameters, followed by determination of the effectiveness of the studied technology of pharmacotherapy both in general and by the presence of a viral pathogen as a possible factor in its effectiveness.

This study built on existing work on decision theory in medicine, as described in Felder et al. (2011). At the same time, attempts were made to revise significantly and simplify existing models so that they can be understood by practising healthcare experts. Thus, this study focused on acute respiratory viral diseases, with the implication that treatment outcomes are presented by alternatives in terms of total costs rather than utility.

It was proposed that a pharmacoeconomic model would be applied for each homogenous group of patients based on defined characteristics. The general concept for this is based on recovery or death, using various pharmacotherapy technologies in the presence and absence of a viral infection, as well as on the speed of recovery as a favourable prognostic sign and criterion of the effectiveness of the applied technology of pharmacotherapy (Figure S2).

Pharmacoeconomic analysis of the effectiveness of antiviral therapy can also be carried out, taking into account the fact that an effective technology of pharmacotherapy should contribute to the normalisation of clinical and laboratory indicators. In order to conduct a pharmacoeconomic analysis by minimising the costs of clinical and laboratory indicators (whether by body temperature or by the nature of sputum etc.), the results of the study of the dynamics of the normalisation of these indicators were used, with the speed of normalisation as a favourable prognostic sign and a criterion for the effectiveness of the applied pharmacotherapy technology (Figure S2).

If there is a lack of information about the available viral pathogen, the question arises of the choice of a rational pharmacotherapy of an infectious disease, the algorithm of which depends on the possible results: total costs in the absence (C_n) and presence (C_v) of the viral pathogen of interest (1):

$$EC_A = p \cdot D_v^A \cdot \overline{C} + (1-p) \cdot D_n^A \cdot \overline{C} = [p \cdot D_v^A + (1-p) \cdot D_n^A] \cdot \overline{C}, \quad \textbf{(1)}$$

where:
D is the length of stay in the hospital/duration of the infectious disease/duration of normalisation of clinical and laboratory parameters depending on the chosen technology of pharmacotherapy A; v is the presence of a viral pathogen; n is the absence of a viral pathogen; $\overline{C}$ is the average cost of one day of basic therapy.

In both cases, the expected costs ($EC^A(p)$) when choosing a certain pharmacotherapy technology (pharmacotherapy A) are determined on the basis of the tree of alternatives.

Additional costs C_T when the researched pharmaceutical drug is included in the pharmacotherapy scheme should be balanced by achieving a level of effectiveness, which is expressed in the reduction of hospitalisation days, taking into account the average costs $\overline{C}$ for one day of basic therapy during hospitalisation (2):

$$EC_B = p \cdot D_v^B \cdot \overline{C} + (1-p) \cdot D_n^B \cdot \overline{C} + C_\text{T} = [p \cdot D_v^B + (1-p) \cdot D_n^B] \cdot \overline{C} + C_\text{T} \quad \textbf{(2)}$$

where:
D is the length of stay in the hospital/duration of the infectious disease/duration of the normalisation of clinical and laboratory indicators, depending on the selected technology of pharmacotherapy B; n is the presence of a viral pathogen; v is absence of a viral pathogen; $\overline{C}$ is average costs of one day of basic therapy; C_T is the cost of additional antiviral therapy (in the case of alternative technology of pharmacotherapy B).

Then the expected costs($EC^B(p)$) when choosing an alternative technology of pharmacotherapy B can be determined as a weighted value for two cases (absence or presence of viral infection), taking into account the corresponding probabilities of their occurrence (Figure S3).

In this case, the expected number of days of hospitalisation for both technologies of pharmacotherapy is (3, 4):

$$D_A = [p \cdot D_v^A + (1-p) \cdot D_n^A]; \quad \textbf{(3)}$$
$$D_B = [p \cdot D_v^B + (1-p) \cdot D_n^B]. \quad \textbf{(4)}$$

The next step was to determine the criteria for the comparative selection of each of the pharmacotherapeutic options. A simple transformation of the cost decision-making rule allows universal pharmacoeconomic criteria to be obtained that determine the rationality of implementing a new pharmacotherapy technology. These criteria are equivalent to standard rules from the point of view of pharmacoeconomics, but have the advantage that they unambiguously determine the possibility of making a decision only in the cost plane. Using this approach, some of the problems that usually arise when determining the cost-effectiveness ratio can be avoided. The technology of pharmacotherapy B implies a clear advantage over the technology of pharmacotherapy A if the expected costs of the technology of pharmacotherapy B are lower than the corresponding expected costs when technology of pharmacotherapy A is used (5, 6):

$$EC_B < EC_A; \quad \textbf{(5)}$$
$$D_B \cdot \overline{C} + C_\text{T} < D_A \cdot \overline{C}. \quad \textbf{(6)}$$

From expression (6), it is possible to derive a universal pharmacoeconomic criterion for the inclusion of an antiviral drug in the scheme of pharmacotherapy of an infectious disease. It will be appropriate if the ratio of the costs of additional

pharmacotherapy and the average costs of one day of basic therapy are less than the difference in the expected number of days of hospitalisation when using the technology of pharmacotherapy *A* and *B* respectively (marginal relative costs) (7):

$$\frac{C_T}{\overline{C}} < p \cdot [D_v^A - D_n^A - D_v^B + D_n^B] + [D_n^A - D_n^B] \quad \textbf{(7)}$$

A comparison of pharmacotherapy technologies *A* and *B* requires a comparison of their costs, which depend on the value of the prevalence of viral infection *p.* In the absence of viral infection (*p = 0)*, the technology of pharmacotherapy with lower costs is desirable. In another extreme case, if a viral infection is always present (*p = 1)*, the rational choice is the technology of pharmacotherapy with lower costs. Therefore, there may be an intermediate indicator of the prevalence of viral infection, for which any choice of pharmacotherapy for a given level of marginal relative costs will give the same expected result. The marginal level of prevalence of viral infection is the level of prevalence at which any choice of pharmacotherapy leads to the same expected costs.

Thus, the value of the prevalence of viral infection *p*, at which pharmacotherapy *B* will cease to dominate over pharmacotherapy *A,* is found by equating expected costs (8):

$$[p \cdot D_v^B + (1-p) \cdot D_n^B] \cdot \overline{C} + C_T < [p \cdot D_v^A + (1-p) \cdot D_n^A] \cdot \overline{C} \quad \textbf{(8)}$$

Solving this inequality makes it possible to determine the level of prevalence of viral infection *p* as a decision-making criterion for the pharmacotherapy of an infectious disease with a wide etiological spectrum for a known cost ratio $\frac{C_T}{\overline{C}}$ (9):

$$p > \frac{1}{D_v^A - D_n^A - D_v^B + D_n^B} \cdot \frac{C_T}{\overline{C}} - \frac{D_n^A - D_n^B}{D_v^A - D_n^A - D_v^B + D_n^B}. \quad \textbf{(9)}$$

Clinical and diagnostic modelling of the effectiveness of technologies of pharmacotherapy of infectious diseases of uncertain etiology

A decrease in expected costs indicates the economic efficiency of the studied pharmacotherapy technology compared with the basic one. At the same time, these costs depend on numerous parameters, such as the probability of recovery, variation in costs, the prevalence of viral infection etc. Presenting the results of a pharmacoeconomic study on a cost plane provides an opportunity to understand the relative influence of different parameters (sensitivity, specificity and spread of viral disease) in terms of their contribution to the uncertainty of the results of the pharmacoeconomic analysis. This implies the possibility of incorrect decision-making and therefore lost benefits.

Probabilistic methods of pharmacoeconomic analysis have recently been introduced that can be used for a more detailed assessment of pharmacotherapy technologies, with the likelihood that the technology being studied is less costly and more effective than another. The purpose of probabilistic modelling is to reflect the impact of uncertainty in the input parameters of the pharmacoeconomic model when estimating costs on the outcome of decision-making (Bebu et al, 2016).

The proposed measure of economic efficiency is called the probability of profitability, which is the probability that the investigated pharmacotherapeutic technology will be less expensive than others. From a practical point of view, additional costs C_T can be considered as the maximum permissible impact on the budget. The motivation for determining the cost-effectiveness probability is that it represents the proportion of patients for whom the investigated pharmacotherapy technology is less costly than other technologies. Data on pharmacotherapy costs are observational in nature and usually involve problems that require simulation and subsequent analysis. Probabilistic decision rules are fully equivalent to standard pharmacoeconomic analysis approaches but, when applied to Monte Carlo simulations based on retrospective clinical and laboratory data, they have the advantage of allowing for the exploration of uncertainty in stochastic cost analysis (Neuman et al, 2011; Grefenstette et al, 2013; Huang et al, 2014).

The results of choosing each pharmacotherapeutic alternative (Figure S3) are determined from the retrospective data of patients, which are the terms of hospitalisation or normalisation of individual clinical and laboratory indicators (Figure S4).

Such data are central to the research process based on a simple model with two states: disease (*S)* and recovery (or death depending on the purpose of the study) (*H)*, which are used to determine the probabilities of recovery based on days of hospitalisation (*D)* or normalisation of clinical laboratory indicators (*N)*.

The proposed model predicts a change in the proportion of patients (*S)* with a certain clinical or laboratory indicator over time (dynamics of normalisation), and therefore allows the distribution of terms of hospitalisation or normalisation of the set of clinical and laboratory indicators (*X)* to be determined (10):

$$X = \{X_1, X_2, \dots, X_n\}. \quad \textbf{(10)}$$

In addition, each clinical and laboratory indicator X_i at any moment in time can acquire only two universal values: normal (*N)* or non-normal (*NN)* (11):

$$X \in \{N, NN\}. \quad \textbf{(11)}$$

This requires the establishment of an additional rule, according to which the totality of all clinical and laboratory indicators is defined as the norm as a whole, for example, only if all indicators are normal and one indicator is not normal etc.

The distributions of recovery times and normalisation of clinical and laboratory indicators determined on the basis of retrospective data allow simulation modelling of the dynamics of recovery or normalisation of indicators followed by a pharmacoeconomic study in an artificial standardised cohort of patients. Computer modelling allows the distribution of days of hospitalisation to be determined when using a certain technology of pharmacotherapy in standardised conditions D_H. Similarly, the average number of days of normalisation of clinical and laboratory indicators D_N is determined, and the relative difference of these values ΔD allows an analysis of how efficiently health care resources are used (12):

$$\Delta D = \frac{D_H - D_N}{D_N} \cdot 100\%. \quad \textbf{(12)}$$

The value of $\Delta D > 100$ % indicates the level of excessive use of healthcare resources to achieve the recovery of patients in the study group.

Pharmacoeconomic modelling of pharmacotherapy technologies using the example of treatment of patients with community-acquired pneumonia (CAP)

The new antiviral drug vitaglutam fully meets the main requirements for an antiviral drug (trade name Ingavirin, J05AX according to ATC classification), the active component of which, imidazolyl ethanamide pentanedioic acid, is a low-molecular compound, an analogue of natural peptidoamine, isolated from the nervous tissue of the sea mollusc *Aplysia californica*. In some experimental studies, the inhibitory effect of vitaglutam on the reproduction of influenza A and B viruses, parainfluenza, adenoviruses and viruses that cause respiratory syncytial infection has been shown. In addition, the influence of this drug on indicators of non-specific immune response has been established.

One of the promising areas of development in clinical pulmonology, which ensures the high efficiency of antibacterial and antiviral pharmacotherapy schemes, is the use of analytical methods. These methods are based on the assessment of information from traditional clinical and laboratory-instrumental indicators, for which it is necessary to have a retrospective database of clinical and laboratory parameters and applied pharmacotherapy schemes patients with CAP. To fill such a database with information, an appropriate algorithm is used (Figure 1).

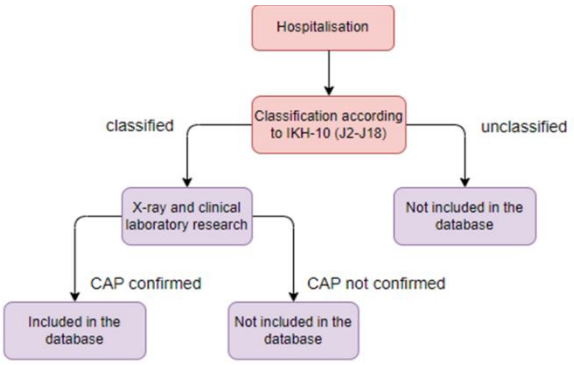

Figure 1. Algorithm for filling the database of retrospective data patients with CAP

Such an algorithm requires homogeneity of data, taking into account inclusion-exclusion criteria when using them. It is assumed that information enters the database only for patients in whom CAP is clearly classified according to International Classification of Diseases -10 and confirmed by radiological and clinical laboratory studies. Furthermore, the economic assessments include an essential component termed 'perspective', which indicates the point of view taken when determining which sorts of expenses and health benefits to include in the study (Stahl, 2008). In this research, retrospective data in the database belong to three groups of parameters determined at certain time intervals: parameters

characterising the patient's clinical and laboratory profile, etiological agents of CAP etc., and parameters of pharmacotherapy such as the use of antibiotics (AB) and antiviral drugs, as well as their administration modes. The result of pharmacotherapy is the duration of hospitalisation or normalisation of clinical and laboratory indicators (Table I).

As a basis for the pharmacoeconomic analysis of the effectiveness of pharmacotherapy of CAP with the inclusion of vitaglutam, retrospective data of 114 patients with viral/bacterial CAP of moderate course, in whom the disease began with SARS and after four to seven days was complicated by pneumonia, were provided by the department of non-specific lung diseases of the National Institute of Phthisiology and Pulmonology named after F. G. Yanovsky as part of the scientific cooperation. The peculiarity of this contingent was that it was homogeneous in terms of gender (100 % were men). In the studied sample, patients were divided by age group: 18-30, 31-60 and over 60 years old. The sample of patients was homogeneous in terms of location and the timing of the onset of the disease.

The object of the study during the pharmacoeconomic evaluation of the provision of pharmaceutical care to patients with CAP was the medical records of the inpatient patient. The records were selected in chronological order, based on the date of the request for medical help indicated in the log of registration of requests for medical help and/or statistical cards of the registration of requests. The clinical and laboratory studies conducted and the results of the treatment, which were judged on the basis of the dynamics of symptoms, were recorded. The clinical effectiveness of CAP pharmacotherapy was evaluated according to the achievement of clinical stabilisation within 24-72 hours of the start of pharmacotherapy by the regression of clinical manifestations and laboratory abnormalities.

Patients were randomly divided into two subgroups depending on the technology of empiric antimicrobial chemotherapy. In the first main subgroup (48 patients), antibiotics were combined with an antiviral drug, and in the second, the control group (66 patients), only antibacterial therapy was used. Both subgroups received antibiotic therapy in the same way: approximately half of the patients in each subgroup received protected aminopenicillin (intravenously) and the others received third-generation cephalosporin (intravenously or intramuscularly). Each of these antibiotics was combined with an oral macrolide. After stabilisation of the process (after three to four days), antibiotic therapy was replaced by oral administration of protected aminopenicillin or second-generation cephalosporin.

In addition to antibacterial therapy from the first day of treatment, patients in the first subgroup were prescribed vitaglutam at a dose of 90 mg once a day, regardless of food intake, for five to seven days. Both subgroups were comparable in terms of all significant indicators of the study, such as the age of the patients, clinical and radiological data, results of laboratory tests, and the timing of the occurrence of CAP.

Bacteriological and virological studies based on the PCR method were simultaneously performed for patients in both groups. The result of the research was the identification of viral pathogens in 62.5 % of patients, which indicated the importance of viral etiology in the outcome of the CAP disease (Figure 2).

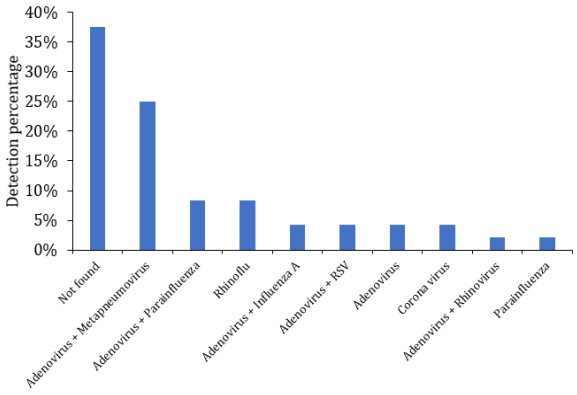

Figure 2. Etiological spectrum of viral pathogens in patients with CAP.

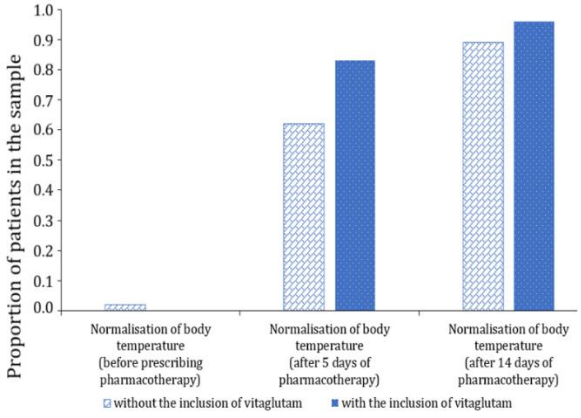

Figure 3. Dynamics of normalisation of body temperature in patients with CAP.

Table I**.** Indicators that are taken into account in the pharmacoeconomic analysis a patient with CAP

Indicators	**Gradation**
Status parameters	
Age group	1) 18-30 years 2) 31-60 years 3) >60 years
Associated diseases	1) yes 2) no
Body temperature	1) <37 °C 2) 37-38 °C 3) >38 °C
Character of sputum	1) none 2) mucous 3) mucopurulent 4) purulent
Localisation of CAP	1) none 2) unilateral 3) bilateral
Prevalence of the process	1) none 2) partial 3) segmental 4) polysegmental 5) lobar
X-ray dynamics	1) complete resorption 2) partial 3) no dynamics 4) negative dynamics
Level of leukocytes	$\times 10^9$ ml^{-1}
General condition of the patient	1) satisfactory 2) moderate 3) severe
Viral agent	1) Adenovirus + Metapneumovirus 2) Adenovirus + Parainfluenza 3) Adenovirus + Metapneumovirus 4) Rhinovirus 5) Adenovirus + Influenza A 6) Adenovirus + Respiratory Syncytial Virus (RSV) 7) Adenovirus 8) Coronavirus 9) Adenovirus + Rhinovirus 10) Parainfluenza 11) Unknown
Bacterial agent	1) *St. aureus* 2) *Str. viridans* 3) *Str. pneumoniae* 4) *St. saprophyticus* 5) *St. pyogenes* 6) *Candida albicans* 7) Unknown

Continuation of Table I**.** Indicators that are taken into account in the pharmacoeconomic analysis a patient with CAP

Indicators		Gradation
Parameters of pharmacotherapy		
Empirical AB treatment	1)	Cefotaxime
	2)	Azithromycin
	3)	Azithromycin
	4)	Levofloxacin
	5)	Gatifloxacin
	6)	Meropenem
	7)	Ceftriaxone
	8)	Amoxicillin
	9)	Azithromycin
	10)	Penicillin
	11)	Amikacin
	12)	Azithromycin
	13)	Cefuroxime
	14)	Ciprofloxacin
	15)	Cefoperazone/Sulbactam
	16)	Sulbactam
	17)	Levofloxacin
	18)	Cefazolin
	19)	Amoxicillin/Clavulanic acid
Antiviral treatment	1)	Imidazolyl ethanamide pentanedioic acid (vitaglutam)
	2)	None
The result of pharmacotherapy		
Number of days of hospitalization	Days	

One of the criteria for the effectiveness of the applied chemotherapy regimens in the subgroups was the period of normalisation of body temperature from the day of hospitalisation (Figure 3).

This was 1.8 days in the main group and 4.8 days in the control group. Positive clinical changes were also accompanied by an improvement in clinical blood analysis indicators. After the therapy, the number of leukocytes in the blood decreased in both patient subgroups: in the first subgroup to 5.1×10^9 / l and in the second to 6.2×10^9 / l. The dynamics of ESR was equally significant. After treatment, this indicator decreased in patients in both subgroups: in the first to 5.4 mm/h and in the second to 7.1 mm/h. X-ray examination showed the complete disappearance of infiltrative changes in the lungs in patients: 94.0 % of the first subgroup and 87.5 % of the second subgroup. Analysis of the dynamics of the results of clinical laboratory and radiological studies shows that the pharmacotherapy contributed to the achievement of positive results in all cases. At the same time, the time in which positive results were achieved differed significantly between the groups: 14.6 days in the main group and 16.8 days in the control group. As a result of antiviral pharmacotherapy, the dynamics of sputum secretion in the lungs was less intense, and its character changed more rapidly from mucous-purulent to mucous and disappearing in general (Figure 4).

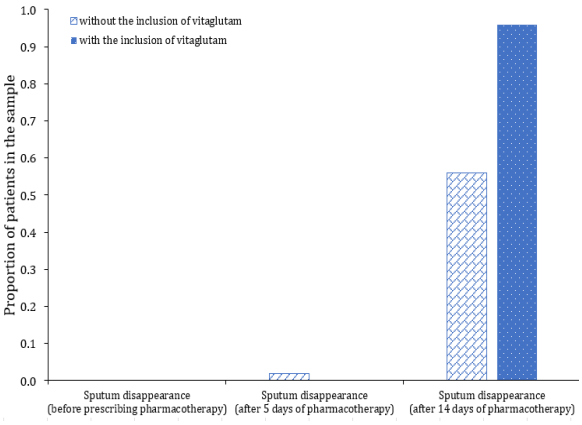

Figure 4. Dynamics of sputum disappearance in patients with CAP.

The pharmacoeconomic analysis of the effectiveness of antiviral therapy of CAP involved grouping patients and determining their distribution according to three gradations of clinical and laboratory indicators, such as the nature of sputum, body temperature, the number of leukocytes in the blood and ESR at certain points in time (before treatment, after eight days and after 14 days from the start of treatment). The next stage was to construct a model of the dynamics of these clinical and laboratory indicators for patients who received different schemes of pharmacotherapy. According to the results of the study, the criterion for the effectiveness of antiviral therapy was the rate of normalisation of body temperature, which was higher in patients who took vitaglutam, especially in the first five to seven days of the disease.

Positive clinical changes in the group of patients receiving additional antiviral pharmacotherapy were also accompanied by an improvement in clinical blood analysis indicators, namely a decrease in ESR and the number of leukocytes in the blood (Figure 5). As for other indicators, there was a significant difference in the speed at which positive results of therapy were achieved in the first eight days of the disease.

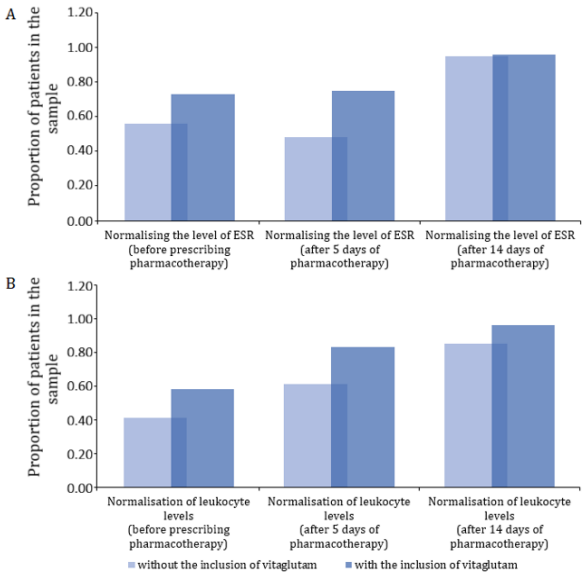

Figure 5. Dynamics of normalisation of: A- ESR level in patients with CAP, B - the level of leukocytes in patients with CAP.

The achievement of positive results of pharmacotherapy using vitaglutam was also determined by the duration of hospitalisation in both studied groups. Thus, for the group of patients where vitaglutam was used in their pharmacotherapy, the distribution of hospitalisation days shifted downwards, indicating its effectiveness compared with the use of basic pharmacotherapy only. The distributions of normalisation of individual clinical and laboratory indicators obtained in both studied groups allowed modelling of the dynamics of the general normalisation of the clinical and laboratory profile of patients with CAP with and without the use of vitaglutam, and a comparison of the results obtained with the dynamics of patient discharge (Figure S5). It was determined that the costs of pharmacotherapy of CAP of viral/bacterial etiology could be reduced by 24 %, based on the curves of the dynamics of normalisation of clinical and laboratory indicators, compared with the days of hospitalisation for patients who were not prescribed vitaglutam, and by 34 % for patients who were prescribed vitaglutam. This indicates a significant saving of resources.

The simulation results showed that the cost effectiveness of additional pharmacotherapy of CAPs of viral and bacterial etiology can be reduced by an average of 29 %, based on the dynamics of normalisation of clinical and laboratory indicators compared with days of hospitalisation, which indicates that resources can be saved by implementing such a method to analyse the effectiveness of pharmacotherapy.

The additional sensitivity analysis, considering the variation in both the days of hospitalisation and the days of normalisation of clinical and laboratory indicators across all comparison groups, demonstrated that, for any variation in marginal relative cost, the effectiveness rate — the probability of the cost-effectiveness of including an additional antiviral drug — will always be higher when focusing on the terms of normalisation of clinical and laboratory indicators in pharmacoeconomic analysis (Figure S6).

Therefore, the basis of the pharmacotherapy of patients with CAP should be antibacterial therapy, which is always empirical and differentiated depending on the severity of the course of the disease, the presence of concomitant pathology, and previous use of antibacterial agents for three months before the onset of the disease. The rationality of antiviral therapy of CAP was evaluated according to the following criteria: the feasibility of prescribing an antiviral drug taking into account clinical and laboratory data, and the availability of data from the results of clinical and laboratory research on the

identification of viral pathogens. The analysis of the dynamics of clinical and laboratory indicators, such as the nature of sputum, body temperature, the number of leukocytes in the blood and ESR according to retrospective data of patients, showed that in patients with viral-bacterial CAP, the additional use of vitaglutam in empiric graded antibiotic therapy allows a reliable reduction in the time taken to achieve the clinical and laboratory results of pharmacotherapy, especially in the first days of the disease.

DISCUSSION

For most diseases caused by a viral infection, the development of pharmaceuticals is complicated due to the high rate of evolution of the viral pathogen. Permanent genetic mutations affect the effectiveness of pharmacotherapy technologies in combating viral infections. Therefore, understanding and analysing molecular- biological changes in the structure of the pathogen, the modes of virus transmission and the dynamics of the course of the disease are extremely important in the development of pharmacoeconomically-justified technologies for the pharmacotherapy of infectious diseases of viral etiology.

Pharmacoeconomic analysis is widely used in a number of countries where there are relevant guidelines regulating the issue of the feasibility of including drugs in lists for the provision of the population, the development of formularies and treatment guidelines, and price setting for pharmaceutical drugs (Schumock et al, 2003; Perez et al, 2009; Chisholm-Burns et al, 2010; Shafie and Hassali, 2010; Mi et al, 2020).

In the modern era of "evidence-based medicine", which can be defined as "the conscientious, clear and reasonable use of the best clinical results in decision-making", predictive models have become actively used in the diagnosis and pharmacotherapy of viral infections. Clinical prognostic models can be an evidence base for shared decision-making as they provide estimates of individual probabilities and the risks and benefits of an intervention. They combine a number of characteristics (e.g. patient-related, viral disease specificity and the pharmacotherapy applied) to predict diagnostic or pharmacotherapeutic effects.

To date, there is a complete lack of reliable criteria for evaluating the effectiveness of pharmacotherapy that could be used to analyse the effectiveness of pharmacotherapy technologies for viral infections and they are usually chosen arbitrarily. To assess the technologies of pharmacotherapy of acute diseases, it is recommended that a set of indicators of clinical effectiveness (duration of clinical manifestations of a viral disease, hospitalisation, normalisation of clinical and laboratory indicators etc.) be used with a limited observation interval. Each of the indicators gives a one-sided view of effectiveness and does not exhaust the full range of pathophysiological changes occurring in the human body.

The main finding of the study is development of the new complex approach of clinical efficiency treatment evaluation based on a set of clinical and laboratory indicators that fully characterise all human processes of adaptation of the body during the course of the disease, comprehensively reflect the state of the organism and take into account the uncertainty of the course of the disease and the results of pharmacotherapy. It is possible to compare the results of pharmacoeconomic evaluation, based both on the duration of hospitalisation of patients and of normalisation of certain clinical and laboratory indicators, followed by a determination of the level of excessive use of healthcare resources.

While this study provides valuable insights into the pharmacoeconomic evaluation of antiviral drug inclusion into pharmacotherapy of CAP, it has several limitations. Firstly, the study focused exclusively on male patients with moderate viral-bacterial CAP. While this ensured consistency in the data, it limits the generalisability of the findings to broader, more diverse populations, including women, children, and patients with severe CAP or other comorbidities. Then the use of retrospective clinical and laboratory data, while practical for initial modeling, may introduce biases related to data collection and variability in diagnostic and treatment practices across institutions. The study evaluated the cost-effectiveness of vitaglutam as the sole antiviral treatment. Although the results indicate its potential benefits, additional studies are required to compare vitaglutam with other antiviral agents to validate its relative effectiveness. The analysis primarily focused on short-term clinical and economic outcomes, such as hospital stay duration and normalisation of laboratory parameters. Longer-term impacts, such as recurrence rates, quality of life, and healthcare costs post-discharge, were not evaluated. While the proposed decision-tree model effectively integrates clinical and economic factors, it does not account for all real-world complexities, such as

indirect costs (e.g., lost productivity) or variations in healthcare resource allocation between regions. The model assumes a clear differentiation between viral and bacterial contributions to CAP etiology. However, real-world diagnostic uncertainty may impact the effectiveness of antiviral therapies and challenge the applicability of the model in settings with limited diagnostic capabilities. Future studies should address these limitations by incorporating prospective data, diverse patient populations, comparisons with alternative antiviral treatment, and evaluations of long-term clinical and economic outcomes. These improvements will enhance the robustness and applicability of the findings to real-world healthcare settings.

CONCLUSION

A model of the economic efficiency of inclusion of an antiviral drug in the complex pharmacotherapy of infectious diseases with a wide etiological spectrum, including viral etiology, based on the "minimisation of costs" method, was developed. The implementation of the proposed modelling method was shown using indicators of effectiveness, period of normalisation of clinical and laboratory indicators such as body temperature, the presence of sputum, the level of ESR and the level of leukocytes, and the period of hospitalisation using the example of vitaglutam as an additional antiviral pharmacotherapy in patients with CAP. Modelling of the economic efficiency of the inclusion of vitaglutam as an additional antiviral pharmacotherapy in patients with CAP after normalisation of both the set of clinical and laboratory indicators and the duration of hospitalisation showed that the costs of additional pharmacotherapy for CAP of viral and bacterial etiology can be reduced by 29 % on average if based on the dynamics of the normalisation of clinical and laboratory indicators compared with the days of hospitalisation. The results of this study indicate that this method to analyse the effectiveness of pharmacotherapy can save resources.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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