



Monte-Carlo simulation of clinical and economic effectiveness of drugs (on example of antibiotics therapy of acute bronchitis with bronchospasm in children)

Olga V. Zhukova¹

¹ *Privolzhsky Research Medical University, 10/1 Minin and Pozharsky Sq., Nizhny Novgorod 603950, Russia*

Corresponding author: *Olga V. Zhukova (ov-zhukova@mail.ru)*

Academic editor: *Oleg Gudyrev* ♦ Received 27 April 2019 ♦ Accepted 20 September 2019 ♦ Published 30 September 2019

Citation: Zhukova OV (2019) Monte-Carlo simulation of clinical and economic effectiveness of drugs (on example of antibiotics therapy of acute bronchitis with bronchospasm in children). *Research Results in Pharmacology* 5(3): 95–100. <https://doi.org/10.3897/rrpharmacology.5.35794>

Abstract

Introduction: The study objective was to determine which antibiotics are optimal in the treatment of children with complicated acute bronchitis with bronchospasm. For that, a Monte-Carlo simulation was conducted.

Materials and methods: The retrospective study was performed on the antibiotic therapy data from 1604 medical records of inpatients from Nizhny Novgorod (Russian Federation) medical centers admitted with acute bronchitis with bronchospasm. The treatment programs involved cephalosporins, inhibitor-protected penicillins, and macrolides. The starter drug was selected empirically considering the possible etiology and sensitivity of the presumed pathogen to the antimicrobial agents. The input data for the model (Monte-Carlo simulation) were the costs of antibiotic therapy and the probability of the clinical outcome (recovery, or the absence of effect). The probabilities of the clinical outcome were described with β -distribution, while the costs distribution was described using gamma-distribution.

Results and discussion: Most positive clinical outcomes were observed with the use of macrolides, which also provided the lowest CER (cost-efficiency ratio), and are, therefore, optimal pharmaco-economically. During the trial, the confidence intervals were evaluated for the clinical efficiency (95% CI of the β -distribution curve). The least interval of probable clinical efficiency for the investigated nosology was found for macrolides, which indicates their high clinical efficiency.

Conclusion: Monte-Carlo method visualizes the results of clinical-economical evaluation of any medical technology in one disease compared to another. That is of value for the clinical pharmacologists and health professionals selecting the drugs for healthcare facilities.

Keywords

acute bronchitis with bronchospasm, antibiotics, beta-lactams, children, clinical and economic effectiveness, macrolides, Monte-Carlo method, simulation.

Introduction

Acute obstructive bronchitis is frequent in children. The repeated (2–3 times or more within one year) episodes of bronchitis with bronchospasm are a recurrent type of obstructive bronchitis. The pathogenesis of recurrent obstructive bronchitis is complex. Infectious factors are of the paramount importance. Bacterially induced inflammation develops through acute respiratory viral infection (ARVI). The bacterial overgrowth contributes to further inflammation, both by damage to the bronchial structure itself and by activation of enzymes in inflammatory cells, resulting in mucociliary clearance impairment. This, in turn, promotes the development of pan-bronchitis and peri-bronchitis and contributes to the development of deforming bronchitis. The antibiotic therapy plays a significant role, not only resolving the symptoms of acute inflammation, but also eradicating the pathogen, eventually decreasing the number of repeated bouts, the inter-exacerbation interval, thus, improving the patients' quality of life. The starter drug is selected empirically, considering the probable etiology and sensitivity of the presumed pathogen to antimicrobials.

One of the major directions when planning and defining the priority therapeutic measures is a clinical and economic analysis of a drug therapy. Using the results of this clinical and financial evaluation can optimize a drug prescription system, prevent the prescription of unnecessary drugs, and also determine the most effective medicines for a specific nosology. Comparative assessment of the quality of two and more methods of prevention, diagnostics, medical and non-medical treatment is the primary method of the clinical and economic analysis.

While an experiment on the real object is often impossible, pharmacoeconomics frequently uses simulation, in particular, Monte-Carlo method (Barton et al. 2004). Monte-Carlo simulation was also used to evaluate the incidence at the population level (Stuebe et al. 2017), to compare the costs and efficiency of empirical treatment including [ceftolozane/tazobactam](#) or [piperacillin/tazobactam](#) in gram-negative hospitalized patients (Kauf et al. 2017). Monte-Carlo simulation is a common name for a group of numerical methods based on obtaining a large number of representations of stochastic (random) process, which is formed in such a way that its probabilistic characteristics match the similar values of the task at hand.

The Monte-Carlo method reproduces and studies the behavior of all the components of the system under study (Briggs et al. 2007).

The study was aimed to determine the clinically and economically optimal antibiotics for the treatment of acute bronchitis complicated with bronchospasm in children using Monte-Carlo simulation.

Materials and methods

The analysis included retrospective evaluation of 2 519 physicians' prescriptions from the case histories from 2008 to 2014 in three medical centers of Nizhny Novgorod (Russian Federation). The patients were from 0 to 18 years old. To 31.0% (n=781) of the patients, no antibiotics were prescribed. Also, the study excluded case histories of the patients in whom the antibiotic therapy had caused side effects in the form of allergic reactions (5.3%, n=134). No cases of dysbiosis were noted, as the antibiotic therapy was administered along with probiotics. The study population included only the case histories from 1604 patients who had been receiving the antibiotic therapy.

In this study, the number of boys with acute bronchitis with bronchospasm exceeded the number of girls by 1.5 times. The narrower airways, an increased tonus of smooth muscles of the bronchial tree and a higher level of IgE (immunoglobulin E) explain an increased risk of developing acute bronchitis with bronchospasm in boys relative to girls.

The highest number of cases of complicated bronchitis with bronchospasm was observed in children under six years old. The patient distribution by age was: 1) 0–1 y/o – 663 (41.3%); 2) 1–3 y/o – 550 (34.3%); 3) 3–6 y/o – 312 (19.5%); 4) > 6 y/o – 79 (4.93%). That predominance can be explained by an immature immune system of the children, and by their susceptibility to colds often complicated by bronchitis (which can further lead to bronchial obstruction).

The start drug was chosen empirically, considering the probable etiology and sensitivity of the presumed pathogen to antimicrobials (Table 1). The antibiotics in acute bronchitis in children were prescribed for the following reasons: severe intoxication, fever lasting more than three days, the presence of an obstructive syndrome, clinical signs of bronchitis, an early age of the patient, and a

Table 1. Dosage regimen and treatment duration for the used antibiotics.

Medication (INN (International Nonproprietary Name))	Average dosage, mg (IU)	Frequency and route of administration	Average treatment duration, days	
Cephalosporins	Cefotaxime	600 (610±4.42)	Twice daily, im	8.5
	Ceftriaxone	625 (626.25±3.96)	Once daily, im	8.5
	Cefuroxime	180 (182±1.47)	Twice daily, im	8.5
	Cefazolin	900 (896.12±1.71)	Three times daily, im	8.5
Inhibitor-protected penicillins	Amoxicillin/clavulanate	270 (271.58±1.38)	Twice daily, oral intake	7
Macrolides	Azithromycin	250	Once daily, orally	4
	Clarithromycin	250	Twice daily, orally	7
	Spiramycin	375 (374.71±4.75) thsd. IU	Twice daily, orally	9
	Midecamycin	350 (350±3.84)	Twice daily, orally	10

prolonged course of the disease. The concurrent diseases (otitis, sinusitis, tonsillitis) were observed in 32.6% (2008), 27.5% (2009), 32.3% (2010), 30.7% (2011), 29.8% (2012), 29.2% (2013), and 31.2% (2014) of the cases. The number of children with recurrent bronchial obstruction was 40.7%. Currently, the most common antibacterials to treat bronchitis were three groups of antibiotics, so-called "gold standard drugs": penicillins (**amoxicillin**, inhibitor-protected penicillins), II–III generation cephalosporins, and macrolides.

The cost of an antibiotic treatment course was calculated by multiplying the average dosage of the drug (mg) by administration frequency, by the average treatment duration (days), and by the price of 1 mg of the antibiotic (US\$).

The average duration of cephalosporines therapy was 8.5 (8.51±1.41) days, of inhibitor-protected penicillin (**amoxicillin/clavulanate**) – 7 days, and of macrolides, it varied from 3–5 days for **azithromycin** to 10 days for **midecamycin**. With ineffective antibiotic treatment, the treatment duration could be increased to 10–13.5 days. In this case, after a course of antibiotic therapy, the disease symptoms persisted in 35.7% of the cases. In 37.1% of these patients, another course of antibacterial drugs of a different class (sequential antibiotic therapy) was prescribed. The following changes were made: cephalosporin/macrolide (76.5%), inhibitor-protected penicillin/macrolide (15.0%), and cephalosporin/inhibitor-protected penicillin (8%). The sequential antibiotic therapy conducted to the favorable clinical outcomes in 100% of the cases.

The efficiency of an antibiotic therapy was evaluated by the rate of positive clinical outcomes, using the initially prescribed drug without adding any other ethiotropic drugs. Positive clinical outcomes, such as "recovery" or "significant improvement", were registered by a physician in each case history. The clinical outcome was considered positive in cases of body temperature normalization, elimination of intoxication, elimination of bronchial obstruction, and normalization of humoral activity.

When using Monte-Carlo method for the cost-effectiveness analysis, a mathematical model was created for each treatment method to evaluate. Using this model, the cost-effectiveness ratio was calculated for each of the treatment methods under comparison. This analysis was performed in three stages:

- constructing a mathematical relationship between the data sought for and the variable parameters, such as the cost of medical resources, the probability of the clinical outcome, etc.;
- estimating types of mathematical distributions to describe the distribution of particular variable parameters;
- Monte-Carlo simulation itself.

The input data for the model included the costs of an antibiotics therapy, as well as the probabilities of clinical outcomes for different methods of treatment. There were two possible clinical outcomes of the antibiotics therapy:

1) positive clinical effect (recovery), or 2) adverse clinical effect. It was assumed that all the experimental data were as a set of random numbers that are subject to certain statistical distributions. To calculate the probability of a clinical outcome, beta-distribution was used, and to describe costs, a gamma-distribution was used. Beta-distribution is typically used when describing probabilities for the binomial data (ill or healthy). In the probability theory and statistics, beta-distribution is used as a two-parameter family of absolutely continuous distributions. It is limited to the interval from 0 to 1 and is characterized by two parameters, α and β . Parameters of beta-distribution are calculated on the basis of the existing experimental data. Considering the sample of n events (the patients who used the drug studied), and taking the number of successful uses as r (the number of positive clinical outcomes when using the examined antibiotic), then the parameters α and β are defined as $\alpha = r$, $\beta = n - r$. Thus, beta-distribution fits the objectives of the study.

As noted above, the costs are usually described by using gamma-distribution. In the probability theory, it is considered as a two-parameter family of absolutely continuous distributions.

This choice was based on the assumption that the gamma-distribution is defined and is continuous in the range from 0 to infinity, which is more appropriate to describe costs.

Based on beta- and gamma-distributions with the parameters set for each antibiotic, samples were generated, containing 1000 random uses each. Then the cost-effectiveness ratio was calculated in each sample.

Results and discussion

In the analyzed period, two groups of antibiotics: β -lactams (cephalosporins, protected penicillins), and macrolides were used for treatment of acute bronchitis with bronchospasm. The injections of cephalosporins were prescribed most often (57.8%).

From the cephalosporins, **cefotaxime** (56.9%), **ceftriaxone** (23.0%), **cefuroxime** (13.8%), and **cefazolin** (6.3%) were mostly used. **Cefazolin** was excluded from the further analysis due to the low frequency of its prescription (to fewer than 100 patients) and, therefore, the impossibility to evaluate its clinical and economic component.

Of the protected penicillins group, the only drug used was **amoxicillin/clavulanic** (16.3%). Macrolides were prescribed in 25.9% of the cases. Of the macrolides, **azithromycin** (65.6%), **clarithromycin** (9.5%), **spiramycin** (18.9%), and **midecamycin** (6%) were mainly used.

The antimicrobial therapy of acute bronchitis with bronchospasm was most efficient ("recovery") when using macrolides. The clinical outcomes "significant improvement" and "recovery" after using cephalosporins and protected penicillins were observed when there were co-morbidities, such as otitis, sinusitis, and tonsillitis, which are often accompanied by fever and intoxication.

Low efficiency of cephalosporins and protected penicillins in the treatment of acute bronchitis with bronchospasm

Table 2. Frequency of positive clinical outcomes*, costs, cost-effectiveness ratio for a course of antibiotic therapy of acute bronchitis with bronchospasm.

INN (International Nonproprietary Name)	Frequency of positive clinical outcomes	Cost of the course, US\$	CER (cost-effectiveness/efficacy ratio)
Cefotaxime	0.584±0.066	4.54±3.42	7.78
Ceftriaxone	0.546	4.51	8.26
Cefuroxime	0.512	12.82	25.04
Amoxicillin/clavulanate	0.561±0.043	1.66±0.04	2.96
Azithromycin	0.966±0.014	3.52±1.74	3.64
Clarithromycin	0.956±0.011	6.43±4.82	6.73
Spiramycin	0.920	3.35	3.64
Midecamycin	0.850	1.23	1.45

Note: * – presented as a unit fraction

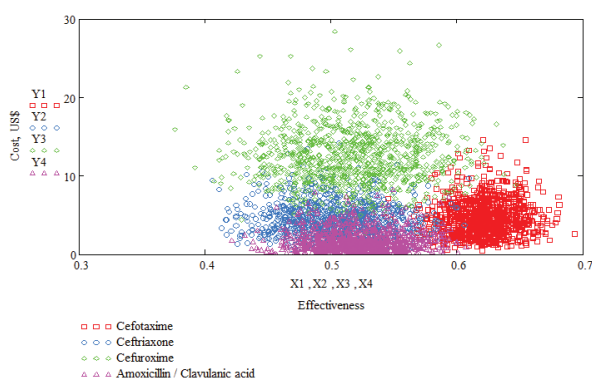


Figure 1. The results of Monte-Carlo cost-effectiveness simulation of the treatment of acute bronchitis with bronchospasm in children with β -lactam antibiotics.

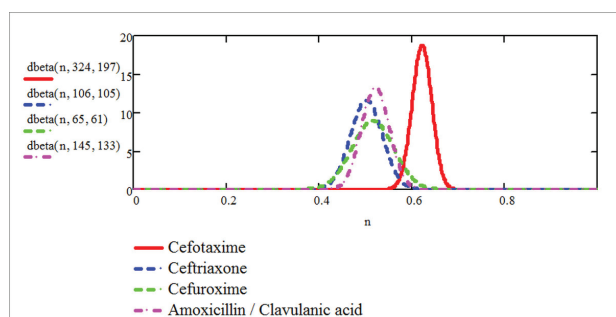


Figure 2. Beta-distribution of clinical outcomes for β -lactam antibiotics used in the treatment of acute bronchitis with bronchospasm in children.

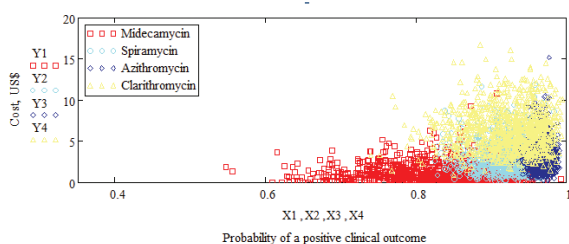


Figure 3. Simulation results of Monte-Carlo cost-effectiveness analysis for macrolide antibiotics used in the treatment of acute bronchitis with bronchospasm in children.

without any co-morbidities can indicate an allergic, atypical bacterial, or viral nature of acute bronchitis with bronchospasm (Table 2).

During the study, the models for β -lactam antibiotics (protected penicillins and cephalosporins) were constructed (Fig. 1).

Figure 1 shows that the **cefuroxime** course is the most expensive. The least expensive is the course of **amoxicillin/clavulanic acid**. The most effective are the courses of **cefotaxime**, with the probability of a positive clinical outcome when using this drug being much higher in comparison with the other drugs.

To compare the clinical efficacy of β -lactam antibiotics, the curves of beta-distributions of the effectiveness of the studied antibiotics were constructed (Fig. 2).

If the curve is narrow and sharply peaked, the measurement results (in this case, the probability of a positive clinical outcome) are highly reproducible. When the curve is broad and shallow, the reproducibility of the drug effect is low. The simulation showed that clinically and economically, the most efficient of the β -lactam antibiotics is **cefotaxime**, despite the fact that its CER=7.78, which is 2.65 times higher than that for **amoxicillin/clavulanic acid** (CER=2.93).

During the next phase of the study, the clinical and economic effectiveness of the macrolides widely used in the treatment of acute bronchitis with bronchospasm in the hospitalized children was simulated.

The models of costs and efficacy distribution were constructed for macrolides (Fig. 3).

The **azithromycin** groups have the greatest clinical efficacy (Fig. 3). **Midecamycin** has the lowest CER among macrolides, with a wide scatter of possible clinical efficacy. The most expensive of macrolides is a **clarithromycin** course. At the same time, it has a wider scatter of distribution points. **Azithromycin** groups have the highest clinical efficacy, with the narrowest scatter of distribution points.

To compare the clinical efficacy, the curves of beta-distribution of the effectiveness of the antibiotics analyzed were plotted (Fig. 4).

The **azithromycin** beta-distribution curve is narrow, sharply peaked and shifted to the right, indicating the high clinical efficacy of the antibiotic for the treatment of the disease studied, which proves the feasibility of using **azithromycin**.

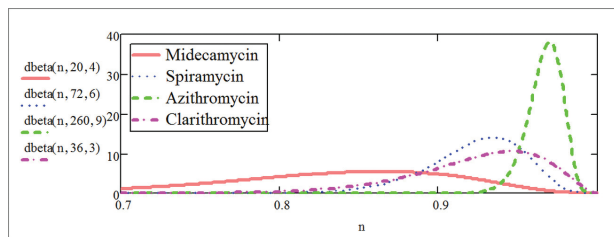


Figure 4. Beta-distribution of outcomes for the macrolides antibiotics, used in the treatment of acute bronchitis with bronchospasm in children.

However, the values obtained through the simulation can vary with different samples of patients. Therefore, at the next stage of the study, it was identified how significant those changes were, and what were the minimum ranges covering the exact actual value of the desired frequencies, i.e., a minimum interval that contained the real value of the sought for clinical efficacy with a probability of 95%, which is known in statistics as the 95% confidence interval (95%CI). In practice, the 95% confidence interval means that 95% of the potential samples of the drug use for the studied disease will provide the values of clinical efficacy that fall within the resulting intervals, with only 5% of values lying outside. For this purpose, the area under the curve of beta-distribution of clinical outcomes for β -lactam antibiotics used in the treatment of acute bronchitis with bronchospasm in children was found, with 2.5% of the area being cut on the right and on the left. The corresponding x values were considered the minimum (min (95%)) and the maximum (max (95%)) confidential clinical efficacy (Table 3).

The Table shows that **cefotaxime** is the best β -lactam, with the 95% confidence interval of clinical efficacy from 0.585 to 0.655.

The most optimal of macrolides are azithromycines (0.947–0.982), providing the smallest interval of probable clinical efficacy for the disease studied.

Conclusion

As the result of the study, it was found that the most effective antibiotics from the clinical and economic points of view in the hospital environment to treat children with acute bronchitis with bronchospasm are **cefotaxime** from the beta-lactam group and **azithromycin** from the macrolide group. Also, the study showed that it was preferable to use macrolide group antibiotics for treatment of acute bronchitis with bronchospasm. Antibiotics are widely used in the pediatric population to treat respiratory diseases, though viruses often act as etiologic agents (Tief et al. 2016). In this study, the antibiotic therapy was evaluated in bronchitis complicated with secondary bacterial infection. Antibiotics use for such conditions corresponds with the results from other researchers (McCallum et al. 2017). The first-choice medications for the treatment of moderate and severe episodes of bronchitis are protec-

Table 3. Probable clinical efficiency of antibiotics used in the treatment of acute bronchitis with bronchospasm in inpatient children.

INN (International Nonproprietary Name)	Min (95%)	Max (95%)
Cefotaxime	0.585	0.655
Ceftriaxone	0.446	0.559
Cefuroxime	0.429	0.602
Amoxicillin/Clavulanic acid	0.472	0.571
Azithromycin	0.947	0.982
Clarithromycin	0.843	0.978
Spiramycin	0.855	0.992
Midecamycin	0.664	0.950

ted beta-lactams and macrolides (Lopardo et al. 2013). Macrolides demonstrated the high efficiency in various respiratory diseases, especially chronic ones (Spagnolo et al. 2013). Laopaiboon M., Panpanich R., Swa Mya K. published the results of a search for and analysis of randomized clinical trials comparing **azithromycin** with **amoxicillin** or **amoxicillin/clavulanic acid** in patients with clinically defined acute bronchitis, pneumonia, and chronic bronchitis exacerbation. In patients with suspected acute bacterial bronchitis, **azithromycin** was found to be more effective, regarding a lower probability of treatment failure and adverse effects compared to **amoxicillin** or **amoxicillin/clavulanic acid** (Laopaiboon et al. 2015). The specific feature of macrolides is their efficiency against atypical pathogens. Bezerra P.G. Britto MC, Correia JB, et al. detected viruses and atypical bacteria in all the severity degrees and clinical manifestations of respiratory infections, but *Mycoplasma pneumoniae* (along with respiratory syncytial virus) were associated with a more severe course of bronchiolitis and pneumonia (Bezerra et al. 2011). Another study was conducted to investigate a role of atypical pathogens in the development of asthma in children with acute and recurrent obstructive bronchitis with bronchospasm, which found the presence of antibodies to atypical pathogens in 32.2% of the patients (n=756) (Zhukova et al. 2017). This data confirms the usefulness of macrolides in the treatment of bronchitis complicated with bronchospasm. The Monte-Carlo method visualizes the results of a clinical-economical evaluation of any medical technology in one disease compared to another. That is of value for the clinical pharmacologists and health professionals selecting the drugs for healthcare facilities.

Conflict of interests

I declare that I have no conflict of interest.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

This study described in the article did not involve any human and animal subjects.

References

- Barton P, Bryan S, Robinson S (2004) Modelling in the economic evaluation of health care: selecting the appropriate approach. *Journal of Health Services Research and Policy* 9(2): 110–118. <https://doi.org/10.1258/135581904322987535> [PubMed]
- Stuebe AM, Jegier BJ, Schwarz EB, Green BD, Reinhold AG, Colaizy TT, Bogen DL, Schaefer AJ, Jegier JT, Green NS, Bartick MC (2017) An online calculator to estimate the impact of changes in breastfeeding rates on population health and costs. *Breastfeeding Medicine* 12(10): 645–658. <https://doi.org/10.1089/bfm.2017.0083> [PubMed]
- Kauf TL, Prabhu VS, Medic, Borse RH, Miller B, Gaultney J, Sen SS, Basu A (2017) Cost-effectiveness of ceftolozane/tazobactam compared with piperacillin/tazobactam as empiric therapy based on the in-vitro surveillance of bacterial isolates in the United States for the treatment of complicated urinary tract infections. *BMC Infectious Diseases* 17(1): 314. <https://doi.org/10.1186/s12879-017-2408-7> [PubMed] [PMC]
- Briggs A, Claxton K, Sculpher M (2007) *Decision Modelling for Health Economic Evaluation*. Oxford University Press, Oxford, 236 pp.
- Tief F, Hoppe C, Seeber L, Obermeier P, Chen X, Karsch K, Mühlhans S, Adamou E, Conrad T, Beresniak A, Schweiger B, Adam T, Rath B (2016) An inception cohort study assessing the role of pneumococcal and other bacterial pathogens in children with influenza and ILI and a clinical decision model for stringent antibiotic use. *Antiviral Therapy* 21(5): 413–424. <https://doi.org/10.3851/IMP3034> [PubMed]
- McCallum GB, Plumb EJ, Morris PS, Chang AB (2017) Antibiotics for persistent cough or wheeze following acute bronchiolitis in children. *Cochrane Database of Systematic Reviews* 8: CD009834. <https://doi.org/10.1002/14651858.CD009834.pub3>
- Lopardo G, Pensotti C, Scapellato P, Caberlotto O, Calmaggi A, Clara L, Klein M, Levy Hara G, López Furst MJ, Mykietiuik A, Pryluka D, Rial MJ, Vujacich C, Yahni D (2013) Inter-society consensus for the management of respiratory infections: acute bronchitis and chronic obstructive pulmonary disease. *Medicina* 73(2): 163–173. [PubMed]
- Spagnolo P, Fabbri LM, Bush A (2013) Long-term macrolide treatment for chronic respiratory disease. *The European Respiratory Journal* 42(1): 239–251. <https://doi.org/10.1183/09031936.00136712> [PubMed]
- Laopaiboon M, Panpanich R, Swa Mya K (2015) Azithromycin for acute lower respiratory tract infections. *The Cochrane Database of Systematic Reviews* 8(3): CD001954. <https://doi.org/10.1002/14651858.CD001954.pub4> [PubMed]
- Bezerra PGM, Britto MCA, Correia JB, Duarte MdCMB, Fonceca AM, Rose K, Hopkins MJ, Cuevas LE, McNamara PS (2011) Viral and atypical bacterial detection in acute respiratory infection in children under five years. *PLoS ONE* 6(4): e18928. <https://doi.org/10.1371/journal.pone.0018928> [PubMed] [PMC]
- Zhukova OV, Konyshkina TM, Kononova SV (2017) Role of “atypical” microorganisms on the formation of bronchial asthma in children with acute and recurrent obstructive bronchitis. *Asian Journal of Pharmaceutical and Clinical Research* 10(4): 239–242. <https://doi.org/10.22159/ajpcr.2017.v10i4.16656>

Author contributions

- **Olga V. Zhukova**, PhD, Assistant Professor, Department of Management and Economics of Pharmacy and Pharmaceutical Technology, e-mail: ov-zhukova@mail.ru, ORCID 0000-0002-6454-1346.