



## ECONOMIC DAMAGE OF PNEUMOCOCCAL VACCINATION ABSENCE AS A RISK FACTOR FOR COMPLICATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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**The aim** of the article is the evaluation of the economic damage (ED) because of the absence of pneumococcal vaccination as a leading risk factor for the development of community-acquired pneumonia (CAP) and acute exacerbations of a chronic obstructive pulmonary disease (COPD).

**Materials and methods.** The method of attributive statistics was used for the first time to assess the ED of the vaccination absence as an independent risk factor contributing to the development of CAP and COPD exacerbations in the Astrakhan region for the period of 2015–2019. To do this, at the beginning of the study based on the literature data, a relative risk of COPD complications associated with the absence of pneumococcal vaccination was determined. Using it as a risk factor, prevalence rates (a proportion of non-vaccinated patients with COPD), the population attributable risk (PAR) was calculated. Further, the annual economic damage (ED) from the development of CAP and COPD exacerbations was determined. To assess the cost-effectiveness of the COPD complications prevention, vaccination costs of newly registered patients were calculated and the ratio of these costs to the average annual ED was determined.

**Results.** A decrease in the non-vaccinated patients' proportion corresponds to the decrease in the total ED from COPD complications: from 13.16 million rubles to 6.06 million rubles during the observation period. The calculations showed that due to the increase in the vaccinated patients' proportion over a five-year observation period, the ED from the CAP development decreased by 2.1 times, from exacerbations of COPD – by 2.3 times. The vaccination costs of newly diagnosed COPD cases amounted to 0.63 million rubles. Thus, to prevent the annual ED of 3.24 million rubles, the sum for the state to spend, should be 5.2 times as small.

**Conclusion.** A study on the evaluation of the ED due to the risk factor (RF), the pneumococcal vaccination absence, showed that its elimination reduces the risk of acute COPD exacerbations and the development of CAP, as well the ED, as associated with them. Reducing the economic costs of the health care system with significantly lower vaccination costs, makes this preventive measure economically viable.

**Keywords:** chronic obstructive pulmonary disease; community-acquired pneumonia; relative risk; population attributable risk; economic damage; pneumococcal vaccination

**Abbreviations:** COPD – chronic obstructive pulmonary disease; CAP – community-acquired pneumonia; PI – pneumococcal infection; PV – pneumococcal vaccination; RF – risk factor; RR – relative risk; PAR – population attributable risk; PPRF – proportion of individuals in population exposed to RF; ED – economic damage; DCs – direct costs; AR – Astrakhan region; RCTs – randomized clinical trials; CMI – compulsory medical insurance.

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# ЭКОНОМИЧЕСКИЙ УЩЕРБ ОТСУТСТВИЯ ПНЕВМОКОККОВОЙ ВАКЦИНАЦИИ КАК ФАКТОРА РИСКА ОСЛОЖНЕНИЙ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЕГКИХ

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**Цель.** Оценка экономического ущерба (ЭУ) от отсутствия пневмококковой вакцинации, как ведущего фактора риска развития внебольничной пневмонии (ВП) и обострений хронической обструктивной болезни легких (ХОБЛ).

**Материалы и методы.** Методом атрибутивной статистики впервые проведена оценка ЭУ отсутствия вакцинации в качестве самостоятельного фактора риска, способствующего развитию ВП и обострений ХОБЛ в Астраханской области за период 2015–2019 гг. Для этого в начале исследования на основе данных литературных источников был определен относительный риск осложнений ХОБЛ, ассоциированных с отсутствием пневмококковой вакцинации. С помощью него и показателей распространенности фактора риска (доли не вакцинированных пациентов с ХОБЛ) рассчитан популяционный атрибутивный риск. Далее определялся ежегодный ЭУ от развития ВП и обострений ХОБЛ. Для оценки рентабельности профилактики осложнений ХОБЛ рассчитаны затраты на вакцинацию вновь зарегистрированных пациентов и определено соотношение этих затрат к среднему ежегодному ЭУ.

**Результаты.** Снижение доли не вакцинированных пациентов соответствует снижению суммарного ЭУ от осложнений ХОБЛ: с 13,16 млн. рублей до 6,06 млн. рублей за период наблюдения. Расчеты показали, что в связи с увеличением доли вакцинированных пациентов за пятилетний период наблюдения ЭУ, от развития ВП снизился в 2,1 раза, от обострений ХОБЛ в 2,3 раза. Затраты на вакцинацию вновь выявленных случаев ХОБЛ составили 0,63 млн. рублей. Таким образом, для предотвращения ежегодного ЭУ в 3,24 млн рублей государство должно затратить сумму в 5,2 раза меньше.

**Заключение.** Исследование оценки ЭУ, обусловленного фактором риска – отсутствием пневмококковой вакцинации, показало, что его устранение снижает риск обострений ХОБЛ и развития ВП, а также связанного с ними ЭУ. Сокращение экономических затрат системы здравоохранения при существенно меньших затратах на проведение вакцинации обеспечивает экономическую целесообразность этой профилактической меры.

**Ключевые слова:** хроническая обструктивная болезнь легких; внебольничная пневмония; относительный риск; популяционный атрибутивный риск; экономический ущерб; пневмококковая вакцинация

**Список сокращений:** ХОБЛ – хроническая обструктивная болезнь легких; ВП – внебольничная пневмония; ПИ – пневмококковая инфекция; ПВ – пневмококковая вакцинация; ФР – фактор риска; ОР – относительный риск; ПАР – популяционный атрибутивный риск; П – доля лиц в популяции, которые подвергаются воздействию ФР; ЭУ – экономический ущерб; ПЗ – прямые затраты; АО – Астраханская область; РКИ – рандомизированные клинические исследования; ОМС – обязательное медицинское страхование.

## INTRODUCTION

The diseases that form the mortality structure comprise cardiovascular diseases, type 2 diabetes mellitus, malignant neoplasms, and COPD [1]. According to the WHO, COPD is the third leading cause of death worldwide<sup>1</sup>. Among the diseases spread throughout the world, COPD occupies a leading position in terms of morbidity and mortality, and are accompanied by a growing

socio-economic burden on the healthcare system<sup>2</sup> [2]. Acute exacerbations are an integral part of this disease and cause a rapid progression of the disease against the background of a decrease in the quality of life, which leads to significant economic costs<sup>3</sup> [3–6]. Patients with

<sup>1</sup> World Health Organization (WHO). The top 10 causes of death. Available from: <https://www.who.int/ru/news-room/fact-sheets/detail/the-top-10-causes-of-death>.

<sup>2</sup> Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. 2020, Report. Available from: [https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19\\_WMV.pdf](https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf).

<sup>3</sup> Russian Respiratory Society. Federal clinical guidelines. Chronic obstructive pulmonary disease. Available from: – Режим доступа: <http://spulmo.ru/obrazovatelnye-resursy/federalnye-klinicheskie-rekomendatsii/>.

a severe COPD are at high risk for community-acquired pneumonia (CAP) [7]. The critical role of COPD in increasing rates of pneumococcal pneumonia has been supported by various independent studies. For example, in Europe, the incidence of this pneumonia was 20 times higher in the people with COPD [8, 9].

The official statistics<sup>4</sup> shows that 3.37 million cases of pneumonia are registered every year, one third of them requires hospitalization [10]. Acute exacerbations of COPD and the development of CAP are the main reasons for the patients to seek medical care. *Streptococcus pneumoniae* often acts as an etiological factor in the acute COPD exacerbation. Each subsequent exacerbation is especially severe, accompanied by hospitalization of the patient, associated with a severe prognosis in terms of survival, so the prevention of infectious COPD exacerbations seems critically important [11, 12]. Approximately 80% of the most severe cases of pneumococcal infection (PI) are due to 20 pneumococcal serotypes, most of which are included in modern vaccines for the prevention of PI<sup>5</sup> [13, 14]. In the course of various studies, it has been confirmed that pneumococcal vaccination (PV) of COPD patients, reduces the number of their hospitalizations associated with respiratory viral infections. The results of the studies showed that after vaccination with a pneumococcal conjugated 13-valent vaccine (PCV-13), the ability to eliminate pneumococcus from sputum was 65.6%, and after a year it decreased to 6.3% [13, 15, 16].

Thus, vaccination against *Streptococcus pneumoniae* is one of the most effective measures to prevent pneumonia and reduce the frequency of COPD exacerbations [17]. In the future, vaccination of COPD patients can significantly reduce the budget economic costs for inpatient and outpatient medical care, sick leave payments [18, 19].

The prevention of exacerbations and CAP in COPD patients is an important strategy in this pathology management. To do this, it is necessary to determine the risk factors (RFs) that can be influenced to reduce the development and frequency of exacerbations. Currently, the main risk factors contributing to the development of severe COPD exacerbations, are traditionally identified as smoking, occupational hazards, the air pollution, an excessive alcohol consumption, respiratory infections, as well as their combinations [20, 21]. An important trend is the evaluation of the economic damage caused by the impact of various risk factors. Thus, McKensy & Company experts showed that in the world, the economic damage from smoking and obesity is comparable to the damage from all wars, terrorism and armed conflicts [22].

The analysis of ED of various COPD RFs is widely reported in the world [1, 18, 23, 24]. A detailed monitoring of foreign and domestic studies of this problem showed that the absence of vaccination as an independent risk factor contributing to the development of CAP and COPD exacerbations, had had not been previously considered.

**THE AIM** of the article is the evaluation of the economic damage (ED) from the risk factors (RFs) represented by the absence of pneumococcal vaccination in COPD patients.

## MATERIALS AND METHODS

### Calculation of population attributable risk (PAR)

According to the literature database, at the first stage of the study, the relative risk (RR) of developing COPD exacerbations and the incidence of CAP associated with the absence of PV as a risk factor was determined. To do this, the available databases (Cochrane Library, PubMed, Russian scientific electronic library eLIBRARY) were searched for the studies on the PV effectiveness in preventing the development of exacerbations and CAP in COPD patients for the period from 2016 to 2021. The search queries were performed in Russian and English and included “pneumococcal vaccination in COPD patients”, “effectiveness of pneumococcal vaccination in patients with COPD”.

Initially, 100 literature sources were identified. Then they were selected according to the type and content of publications (Fig. 1). The identical publications found in different databases, the works that are not original studies, were excluded. The publications that did not evaluate the effectiveness of vaccination in COPD patients or were devoted to the study of the effectiveness of pneumococcal polysaccharide 23-valent vaccine (PPV-23) alone, were not subjected to the review, either. In addition, the studies evaluating the effects of vaccination in COPD patients with comorbid pathology were excluded.

As a result, 10 studies were selected [16, 17, 25–32], from which in 2017, the Cochrane systematic review by Walters J.A. et al. [25] was chosen out as the gold standard for high-quality, reliable information in evidence-based medicine and healthcare. This review included the results of 12 randomized controlled trials (RCTs) and 2,171 COPD patients. The average age of the participants was 66 years, 67% of them were men. All participants had a COPD diagnosis from moderate to heavy severity level. Compared to the controls, the vaccinated group had a lower likelihood of developing CAP (the relative risk (RR) 0.62, 95% confidence interval (CI) from 0.43 to 0.89; six studies, n = 1372; the level of evidence – medium). The number of patients requiring treatment to obtain an additional favorable outcome (NNTB) (avoiding one episode of CAP) was 19 (95% CI from 13 to 52). Vaccination significantly

<sup>4</sup> European Respiratory Society. European Lung White Book. Lausanne, Switzerland: ERS / European Respiratory Society. Available from: [https://www.erswhitebook.org/files/public/Chapters/13\\_COPD.pdf](https://www.erswhitebook.org/files/public/Chapters/13_COPD.pdf)

<sup>5</sup> Zverev V.V., Kostin M.P., Magarshak O.O., et al. Rukovodstvo po klinicheskoy immunologii v respiratornoj medicene [Guidelines for Clinical Immunology in Respiratory Medicine]. Suppl. 2nd ed. Moscow: MDB, 2018. – 304 p. Russian

reduced the chance of a COPD exacerbation (OR 0.60, 95% CI from 0.39 to 0.93; four studies,  $n = 446$ ; the level of evidence: moderate). The NNTB for preventing an acute exacerbation in the patient was 8 (95% CI 5 to 58).

Further, in accordance with the data obtained, RR was calculated separately for the development of acute exacerbations and CAPs in non-vaccinated (1) and vaccinated (2) patients according to the formula:

$$RR = \frac{\left[ \frac{a}{(a+b)} \right]}{\left[ \frac{c}{(c+d)} \right]}, \quad (1)$$

$$RR = \frac{\left[ \frac{c}{(c+d)} \right]}{\left[ \frac{a}{(a+b)} \right]}, \quad (2)$$

where: RR is a relative risk; a is the number of exacerbations (CAPs) in non-vaccinated patients; b denotes the absence of exacerbations (CAPs) in non-vaccinated patients; c is the number of exacerbations (CAPs) in vaccinated patients; d denotes the absence of exacerbations (CAPs) in vaccinated patients.

By calculating the RR, it is possible to show the association strength between the influencing risk factor and the outcome, e. i., how many times the probability of exacerbations and the development of CAPs caused by the lack of vaccination in COPD patients, increases. If the development of exacerbations of COPD and CAPs is higher in the non-vaccinated group, then the RR will be higher than 1, if lower, then the RR will be lower than 1; if the probability in the two groups is the same, then their ratio will be equal to 1<sup>6</sup>.

The PAR population attributable risk (PAR) was calculated based on the FR and RR prevalence rates.

This indicator reflects the additional incidence in the population associated with risk factors. In addition, with the help of PAR, it is possible to determine the proportion of morbidity in the population associated with this risk factor, i.e., the additional proportion of a population risk. The PAR depends on the degree the risk factors are widespread in the given population:

$$PAR = \frac{P_{nv}(RR - 1)}{P_{nv}(RR - 1) + 1},$$

where:  $P_{nv}$  is the proportion of non-vaccinated individuals in the population (exposed to risk factors); RR is the relative risk of developing a disease under the influence of the FR under consideration [33, 34].

To determine the proportion of the people exposed

to the FR is the lack of vaccination (UV), the number of the non-vaccinated patients was calculated relative to the total number of the people suffering from the COPD registered in the Astrakhan region (AR), for the period from 2015 to 2019:

$$P_{nv} = \frac{N_1}{N},$$

where:  $N_1$  is the number of non-vaccinated patients with COPD;  $N$  is the total number of patients with COPD.

The total number of COPD patients was taken from the state statistical observation form No.12 "Information on the number of diseases registered in patients living in the medical organization service area" in the Astrakhan region (AR) for the period from 2015 to 2019. The number of vaccinated patients was determined by adding the number of pneumococcal vaccinations (PVs) for each year with the indicator of the previous year, based on the data provided upon the request by medical institutions of the city and region. The number of non-vaccinated patients per year was determined by diminution the sum of those vaccinated from the total number of the COPD patients during the same period.

#### Calculation of government economic damage in disease management of patients with exacerbations of COPD and CAPs, due to RF

At the second stage of the study, the government economic damage was calculated in the management of patients with exacerbations of COPD and CAPs, due to RFs. The calculation was carried out according to the formula:

$$ED_{RF} = PAR_{RF} \times DCs,$$

where:  $ED_{RF}$  is the economic damage from the risk factor;  $PAR_{RF}$  denotes the population attributable risk for each analyzed disease associated with RF; DCs are direct costs of treating COPD.

Direct costs were calculated in the earlier study "Evaluating Socioeconomic Burden of COPD over a Five-Year Period – Regional Aspect" [35].

Subsequently, the ED of COPD and CAPs exacerbations were summed up.

Then, to determine  $PAR_{RF}$  for new non-vaccinated COPD patients for the period of 2015-2019, the average number of newly diagnosed patients were calculated.

Using the data obtained, the ED for CAPs was calculated for the first detected cases of the COPD exposed to RF. The calculation was carried out according to the formula:

$$ED_{rf} = PAR_{rf} \times DCs_{av},$$

where:  $ED_{rf}$  is an economic damage from the risk factor;  $PAR_{rf}$  is the population attributable risk for each analyzed disease associated with RF;  $DCs_{av}$  denotes the average direct costs of COPD treatment from 2015 to 2019.

<sup>6</sup> Zhukova OV. Application of attributive statistics methods in pharmaceutical and biomedical research (contingency tables). Privolzhsky Research Medical University. – Kazan: Buk Limited Liability Company, 2020. – 76 p. Russian

**Table 1 – Contingency table for RR calculating of COPD exacerbations development**

Risk factor	One exacerbation episode within a period of 6 months to 1 year	Absence of exacerbations
Absence of vaccination	608(a)	392(b)
Vaccination	482(c)	518(d)

Note: a – the number of CAPs in non-vaccinated patients, b – the absence of CAPs in non-vaccinated patients, c – the number of CAPs in vaccinated patients; d – the absence of CAPs in vaccinated patients.

**Table 2 – Contingency table for RR calculating of CAP development**

Risk factor	One CAP episode within a period of 6 to 36 months	Absence of CAP
Absence of vaccination	148(a)	852(b)
Vaccination	93(c)	907(d)

Note: a – the number of CAPs in non-vaccinated patients, b – the absence of CAPs in non-vaccinated patients, c – the number of CAPs in vaccinated patients; d – the absence of CAPs in vaccinated patients.

**Table 3 – Information necessary for PAR CAPs calculation, COPD exacerbations and their results**

Indicators	Period					On average
	2015	2016	2017	2018	2019	
Number of COPD persons	2 869	2788	2721	2913	3.180	2.894
COPD incidence (CAP first detected cases)	445	226	266	310	496	369
Annually vaccinated	333	138	559	617	940	–
Total number of vaccinated	333	471	1030	1.647	2.587	–
Non-vaccinated	2 536	2317	1691	1.266	593	369
Proportion of non-vaccinated ( $P_{nv}$ )	0.88	0.83	0.62	0.43	0.19	0.13
PAR CAP	0.34	0.33	0.27	0.20	0.10	0.07
PAR exacerbations of COPD	0.19	0.18	0.14	0.10	0.05	0.03

**Table 4 – Economic damage to regional healthcare system due to RF – absence of vaccination**

Indicators	Period				
	2015	2016	2017	2018	2019
Direct COPD costs, mln rubles	24.83	28.14	29.6	32.94	40.39
ED due to CAPs, mln rubles	8.44	9.29	7.99	6.59	4.04
ED exacerbations of COPD, mln rubles	4.72	5.07	4.14	3.29	2.02
ED due to CAP + COPD exacerbations, mln rubles	13.16	14.35	12.14	9.88	6.06

**Table 5 – Sensitivity analysis of the obtained results**

Changes in initial parameters	Indicators										
	25%	20%	15%	10%	5%	Basic variant	5%	10%	15%	20%	25%
Change in vaccine price, rubles	1275	1360	1445	1530	1615	1700	1.785	1.870	1,955	2040	2125
Change in the number of people	277	295	314	332	351	369	387	406	424	443	461
Change in vaccination costs, mln rubles	0.47	0.50	0.53	0.56	0.60	0.63	0.66	0.69	0.70	0.75	0.78
Change in economic damage, mln rubles	2,43	2.59	2,75	2.92	3,08	3.24	3.40	3.56	3,73	3.89	4.05

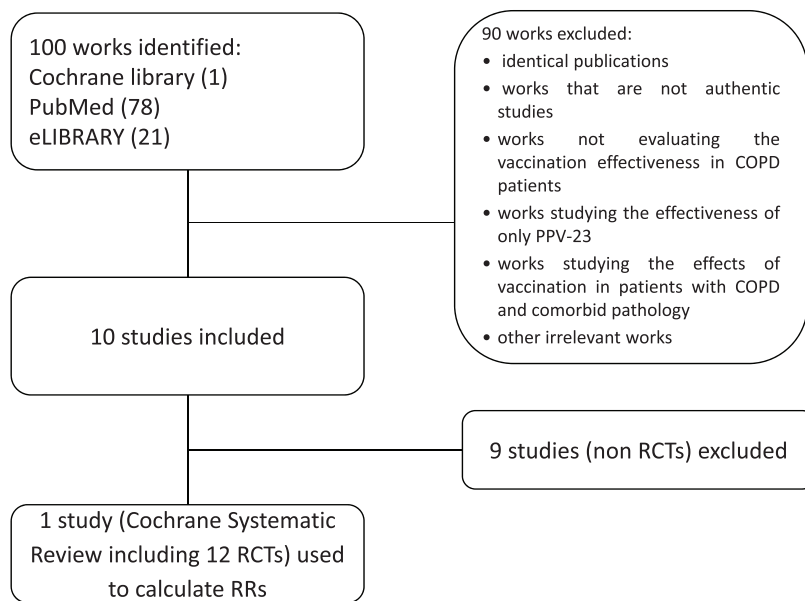


Figure 1 – Research selection methodology

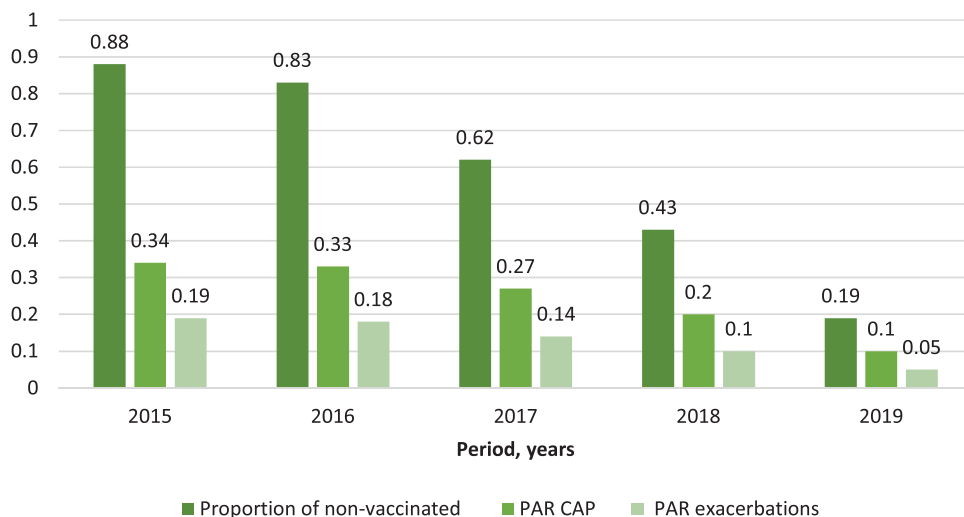


Figure 2 – Proportion ratio of non-vaccinated COPD patients related to PAR CAPs and COPD exacerbations

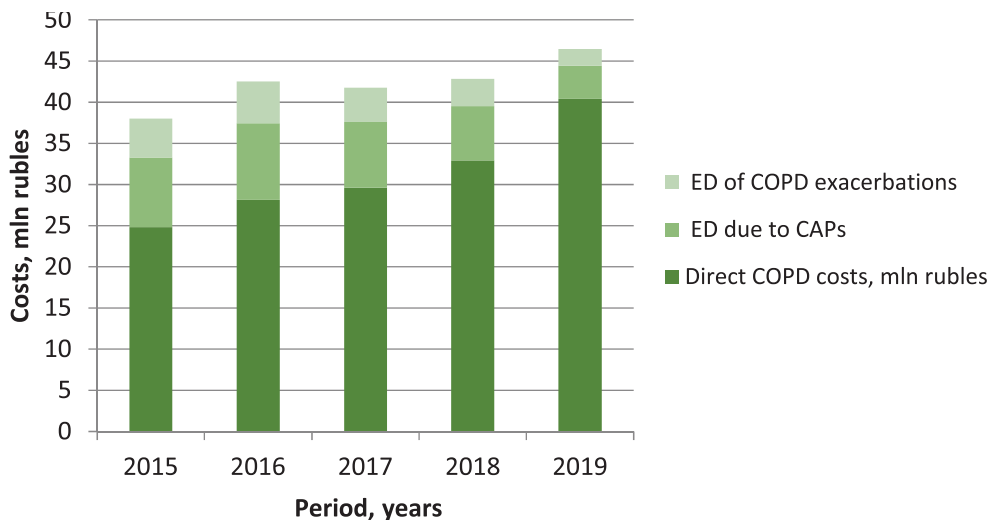


Figure 3 – Correlation of direct COPD and ED costs from exacerbations and CAPs

### Determining economic benefit of pneumococcal vaccination of newly diagnosed COPD cases

At the third stage of the study, the calculation of the pneumococcal vaccine prophylaxis cost was carried out for the CAPs patients with the first diagnosed COPD. The calculation was carried out according to the formula [36]:

$$\text{Cost}_{\text{vp}} = \text{Cost}_{\text{vac}} \times N,$$

where: is the cost of vaccine prophylaxis;  $\text{Cost}_{\text{vac}}$  is the cost of a medicinal product (vaccine); N is the number of patients to be vaccinated.

The cost of the vaccine was taken into account based on the results of competitive tendering for the purchase of pneumococcal vaccines held by the regional Ministry of Health. The cost of PKV-13 "Prevenar 13" remained unchanged for the entire study period and corresponded to 1700 rubles<sup>7</sup>.

Next, the ratio of pneumococcal vaccination cost for patients with CAPs of the first detected COPD and the average possible annual ED from the occurrence of COPD and CAPs exacerbations were calculated.

### Sensitivity analysis of the study results

The study result was a sensitivity analysis of the results obtained in order to determine their resistance to changes in the initial parameters. To do this, a one-way sensitivity analysis was performed with a variation in the price of pneumococcal vaccine and the number of patients by sequentially increasing them by 25% with a 5% step.

The work with the data and their statistical processing was carried out using MS Excel 10.0 (Microsoft Office 2010, USA). For these data processing, the method of population attributive statistics was used; RR, PAR.

### RESULTS

Based on the systematic review data, contingency tables were compiled to calculate the OR (Tables 1, 2).

In accordance with the study program, the RRs for the development of COPD exacerbations in vaccinated and non-vaccinated PV patients were calculated and analyzed.

$$\begin{aligned} \text{RRs of non-vaccinated} &= \\ &= [608/(608+392)]/[482/(482+518)]=1.26 \\ \text{RRs of vaccinated} &= \\ &= [482/(482+518)]/[608/(608+392)]=0.79 \end{aligned}$$

The RR for COPD exacerbations in non-vaccinated COPD patients based on the results of a systematic review was 1.26 versus 0.79 in the vaccinated patients.

The relative risk is the ratio of the exacerbation of COPD risk in the individuals exposed to the risk factor (of the non-vaccinated) relative to a comparison group (the vaccinated).

The next step was to calculate the RR for the CAP development in vaccinated and non-vaccinated PV patients with COPD.

$$\begin{aligned} \text{RRs of non-vaccinated} &= \\ &= [148/(148+852)]/[93/(93+907)]=1.59 \\ \text{RRs of vaccinated} &= \\ &= [93/(93+907)]/[148/(148+852)]=0.62 \end{aligned}$$

Accordingly, the RRs for developing CAPs in the non-vaccinated COPD patients was 1.59 versus 0.62 in the vaccinated patients.

The obtained values may change when calculations are carried out on a different sample, for this it is necessary to determine how significant these changes can be. To confirm the results of RRs for both groups of patients, the confidence interval (CI) was calculated. In COPD exacerbations (95% CI), the CI of RRs was 1.163–1.368. For the RR of the CAP development, (95% CI) is 1.247–2.031, which confirms the statistical significance of the results.

Thus, the RR calculation performed shows that non-vaccinated COPD patients are 1.26 and 1.59 times more likely to develop exacerbations or CAPs, respectively.

The results of the RRs obtained from the data on the COPD patients taken in the systematic review, allowed us to create a computational model with which we can evaluate the RRs in the regional population.

In order to evaluate risks in the population, it is necessary to know how often the members of the population under consideration are exposed to risk factors. This study was based on the data of the COPD incidence registered in patients living in the service area of the Astrakhan region medical organizations. We

PAR CAPs and COPD exacerbations were calculated for the period of 2015–2019: The results are presented in Table 3.

Thus, over the study period, with a decrease in the proportion of non-vaccinated PV COPD patients, the population risk of developing CAPs and exacerbating COPD decreases, which is reflected in Fig. 2.

Having PAR indicators for the study period, the costs of the regional healthcare system for the treatment of CAPs and COPD exacerbations in the form of ED were estimated.

As for the compulsory medical insurance (CMI) of the AR healthcare system for the period of 2015–2019, its structure of direct costs included direct medical costs for hospitalization, outpatient treatment, calls for ambulances and emergency medical care. For the research purposes, direct cost estimates (Table 4) from a previous study assessing the economic burden of COPD in the AO, were extrapolated [35].

Having received all the necessary data, the ED from the RF were calculated in accordance with the study program. The results are presented in Table 4.

The calculations showed that, due to a decrease in the proportion of non-vaccinated patients over a five-year follow-up period, the ED from the RF due to CAPs

<sup>7</sup> Procurement contract card of the Ministry of Health JSC No. 2301506815919000378. Available from: <https://zakupki.gov.ru/epz/contract/contractCard/document-info.html?reestrNumbr=2301506815919000378>.

decreased by 2.1 times, from COPD exacerbations by 2.3 times (Fig. 3).

Considering that new cases of COPD are detected every year, these patients can be considered as a risk group for exacerbations and CAPs due to the absence of PV. The mean value of the non-vaccinated newly diagnosed patients with PV makes it possible to calculate the mean annual ED from the occurrence of COPD and CAP exacerbations. In this regard, a number of CAPs of new COPD cases during the study period were analyzed. For the period of 2015-2019, the average number of newly diagnosed patients was 369 cases  $\pm$  124 (from 245 to 493). The median number of COPD patients over the same period was 2894. Then the percentage of non-vaccinated patients was calculated relative to the median of the total number of COPD patients during the study period, which made 0.13 or 13%. PAR CAP and exacerbations of COPD were determined as 0.07 (7%) and 0.03 (3%), respectively. The average DCs for COPD was calculated as the average value for 5 years under study, which amounted to 31.18  $\pm$  4.4 million rubles. Based on the results obtained, the ED was determined equal to 2.22 million rubles from CAPs and 1.02 million rubles from COPD exacerbations. In total, this damage amounted to 3.24 million rubles. Next, we calculated the vaccination cost of newly diagnosed COPD cases, which amounted to 627,300 rubles (from 416,500 to 838,100 rubles). Thus, in order to prevent an annual economic loss of 3.24 million rubles, the government must spend the sum 5.2 times less.

The sensitivity analysis demonstrated the stability of the obtained results to changes in the initial parameters. If the vaccination cost is increased by 25% (both due to an increase in the price of the vaccine and due to the number of the vaccinated), then the indicators will not go beyond the indicators of the economic damage caused by the absence of vaccination (Table 5).

## DISCUSSION

The COPD incidence among the adult population of the Russian Federation shows a steady increase, thus reflecting global trends. The increase in the incidence rate for 2007–2017 amounted to 16.5%<sup>8</sup>. As the results of the SUPPORT<sup>9</sup> study showed, in Russia, there are more than 50% of patients with frequent exacerbations. A high risk of exacerbations and the CAP development in COPD patients determine the importance of preventing complications of this disease. Risk factors make a significant contribution to the COPD progression and severity, so the study of risk factors plays an important role in the effective allocation of resources

for the prevention and treatment of COPD by health authorities. In COPD studies, a significant attention is paid to risk factors such as smoking, an excessive alcohol consumption, a low physical activity, etc. [1]. Thus, the greatest contribution to the morbidity and mortality from COPD is made by smoking (9.6%), arterial hypertension (24%), an excessive alcohol consumption (9%), a low physical activity (16%) [1]. These works are carried out both in domestic and foreign studies [37, 38]. So, in the studies by Zhukova O.V. et al., the effect of smoking on the COPD exacerbation is shown [37]. In another paper by this author, an attempt to link the risk of developing CAP in patients with COPD with the use of inhaled glucocorticosteroids has been made. Against the background of cardiovascular diseases, a trend towards an increase in the development of CAP in COPD patients has also been shown [23]. The likelihood of COPD occurring against the background of the exposure to occupational hazards such as gas fumes and dust, was demonstrated in the meta-analysis conducted by scientists from the Russian Federation, Kazakhstan and Azerbaijan [20]. In the work by Khalid F. et al. [39], in Latin Americans under the age of 50 years (7,565 people), the risk factors for early COPD were determined as asthma (PAR – 26.5%), smoking (21.4%), chronic sinusitis (6.7%). The aim of the study by Shulmin A.V. et al. was the costs research related with tobacco-associated diseases, including COPD [24].

According to the data on the PV effectiveness of the Chelyabinsk "City Pulmonological Center", obtained for 2012–2015, vaccination provided a sevenfold decrease in the number of hospitalizations keeping up to the results and 3 years afterwards of follow-up in comparison with the control group [31]. Pneumococci often act as an etiological factor of exacerbations and development of pneumonia in the patients suffering from COPD, which is of interest in studying the absence of PV as an independent RF. When conducting an information search in the available databases (Cochrane Library, PubMed, e-LIBRARY), it was notified that there were no studies in which the absence of PV was considered as RF complications of COPD.

In accordance with the developed research program, based on the data of a systematic review using the method of attributive statistics, the RR of COPD complications was calculated to determine the proportion of individuals in the regional population associated with the studied RF for the period of 2015–2019. During the five-year follow-up period, there was a decrease in PAR: with CAP from 34 to 10%, and with COPD exacerbations from 19 to 5%. In the process of calculating PAR, there was a positive tendency to reduce the population risk of COPD complications against the background of an increase in the number of vaccinated patients. The decrease in the proportion of non-vaccinated patients corresponds to a decrease in the total economic damage from COPD

<sup>8</sup> Chronic obstructive pulmonary disease as a socially significant disease. XXVIII National Congress on Respiratory Diseases; Moscow, October 17, 2018. – P. 54–60. Available from: <https://umedp.ru/upload/iblock/73b/GSK.pdf>. Russian

<sup>9</sup> The 28<sup>th</sup> National Congress on Respiratory Diseases: a time for innovations. Pulmonologiya. 2018;28(5):632–634. Available from: <https://umedp.ru/upload/iblock/73b/GSK.pdf>. Russian



complications: from 13.16 million rubles to 6.06 million rubles during the follow-up period. To assess the cost-effectiveness of COPD complications prevention, the ratio of the average number of non-vaccinated newly diagnosed patients to the average annual economic damage was calculated. The calculation of the average PV costs showed that the costs necessary to prevent the RF action will be 5.2 times less than the possible annual ED. The results of the study indicate that pneumococcal vaccination is an effective method in reducing healthcare costs associated with the treatment of COPD complications.

### Study limitations

When analyzing the contribution of risk factors to the development of COPD complications, the literature data were used to determine the RR for CAP and COPD exacerbations, which could affect the accuracy of the PAR calculation.

### CONCLUSION

CAP was the first study to assess ED using an attributive statistics methodology, in which the absence of PV acted as RF. The results obtained suggest that pneumococcal vaccination significantly reduces the risk of COPD exacerbations and the CAP development. Reducing the risks of COPD complications leads to a marked reduction in the economic costs of the health care system, with significantly lower costs for vaccination, which, in turn, makes this preventive measure economically viable. The determination of the population risk makes it possible to provide people with important information about the potential impact of prevention programs and interventions on the health system and will be extremely useful to health decision makers. In addition to traditional financial aspects, investments in population-based preventive measures have an important social value, since a decrease in the burden of various diseases leads to an increase in well-being, motivation and harmonization of patients' private lives.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHORS' CONTRIBUTION

Ekaterina A. Orlova – material collection, text writing and editing; Inna P. Dorfman – study design, data collection and editing; Adela R. Umerova – text writing and editing; Bela I. Kantemirova – data search, editing; Mikhail A. Orlov – text writing and editing; Musalitdin A. Abdullaev – compiling drawings and bibliographic lists. All the authors made a significant contribution to the search and analytical work and preparation of the article, read and approved the final version before the publication.

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