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Chapter 11

Chronic Obstructive Pulmonary Disease (COPD): Clinical and Immunological Effects of Mono-Vaccination Against Influenza Using an Immunoadjuvant Vaccine of a New Class Versus Combined Administration S. pneumoniae, H. influenzae, and Influenza Vaccines

Andrey Dmitrievich Protasov ,
Mikhail Petrovich Kostinov ,
Alexander Victorovich Zhestkov ,
Mikhail L'vovich Shteiner ,
Svetlana Vyacheslavovna Kazharova ,
Yuriy Vladimirovich Tezikov and
Igor Stanislavovich Lipatov

Additional information is available at the end of the chapter

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Abstract

In Russian Federation, 27,300,000–41,200,000 acute upper and lower respiratory infections are reported annually. Patients with chronic obstructive pulmonary disease (COPD) are at higher risk of severe course, complications, and lethal outcomes of influenza. About 30% of COPD exacerbations are due to viral infections, and influenza A and B viruses are among the most common causes. The aim of our study was to assess exacerbation rate, number of courses of antibiotic chemotherapy, pulmonary function, and immunological effects of mono-vaccination with a new immunoadjuvant influenza vaccine vs. combined vaccination against pneumococcal infection, Hemophilus type b infection, and influenza in COPD patients. Both complex vaccination against Streptococcus pneumoniae, Haemophilus influenzae type b, and influenza and mono-vaccination with a new immunoadjuvant influenza vaccine led to statistically significant reduction in the number of COPD exacerbations and of antibiotic chemotherapy courses. Based on the obtained results, widespread implementation of mono-vaccina-

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tion against influenza with a new immunoadjuvant influenza vaccine, as well as complex vaccination against bacterial respiratory infections and influenza can be recommended for COPD patients, as vaccination is beneficial for their functional status, that is, improves forced expiratory volume in 1 s (FEV1) and 6-minute walk test results. In our study, we evaluated immunogenicity of the new influenza immunoadjuvant vaccine administered as mono-vaccine to COPD patients in accordance with Committee for Proprietary Medicinal Products (CPMP) requirements.

Keywords: chronic obstructive pulmonary disease (COPD), vaccination, influenza, clinical effects, immunological effects

1. Introduction

In Russia, 27,300,000–41,200,000 acute upper and lower respiratory infections are reported annually. Patients with chronic obstructive pulmonary disease (COPD) are at higher risk of severe course, complications, and lethal outcomes of influenza. Therefore, influenza prevention in such patients is one of the most urgent tasks.

About 30% of COPD exacerbations are due to viral infections, and influenza A and B viruses are among the most common causes.

The best approach to prophylaxis is provided by vaccination because it combines the advantages of specificity, efficacy, safety, and cost-effectiveness. The GOLD guidelines (Global Initiative for Chronic Obstructive Lung Disease) recommend that influenza vaccination preferentially with split or subunit vaccines must be integrated into treatment strategies for all COPD patients regardless of the disease stage. However, further studies are needed to evaluate the efficacy and immunogenicity of modern adjuvant influenza vaccines [1].

It is not rarely that the risk of COPD exacerbation is associated not directly with the influenza virus as such, but rather with the development of bacterial superinfection, mainly caused by Streptococcus pneumoniae or Haemophilus influenzae type b [2–4].

In the Russian Federation, both inactivated and live vaccines against influenza have been licensed [5]. Antigenic composition of these vaccines is modified annually to adopt current epidemic situation and WHO guidelines. Recently, an innovative new class of immunoadjuvant influenza vaccines has evolved. The use of these vaccines in COPD patients will be outlined below.

According to CPMP criteria (Committee for Proprietary Medicinal Products), a vaccine is considered immunogenic, if at least one of the assessments meets the indicated requirements:

1. Seroconversion rate (at least fourfold increase in anti-hemagglutinin antibody titre): over 40% for individuals aging 18–60 years and over 30% among individuals above 60 years.
2. Seroprotection rate (number of individuals with protective titre of at least 1:40): over 70% for individuals aging 18–60 years and over 60% in individuals above 60 years.

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3. Mean titre increase after vaccination: ≥2.5 in individuals aging 18–60 years and ≥2 in individuals above 60 years.

Vaccination against influenza for COPD patients is included into the National Immunization Calendar of the Russian Federation.

S. pneumoniae, H. influenzae, M. catarrhalis, and influenza virus are the most common causes of COPD infective exacerbations [6]. The standard of care for COPD patients includes vaccination against influenza and pneumococcal infection. Several serotypes of H. influenzae are known, and COPD exacerbation may be caused by each of them, including H. influenzae type b. Vaccine against H. influenzae type b is now available; therefore, it is of interest to evaluate a combined vaccination against S. pneumoniae, H. influenzae, and influenza in COPD patients and the effects of these vaccines on exacerbation rate and pulmonary function tests.

In adult COPD patients, the pioneer studies evaluating the therapeutic effect of PPV23 were performed in 2004. Elimination of S. pneumoniae from the sputum was observed in 52.9% cases, that is, at a lower rate compared to children. Other findings include increased levels of IgG against S. pneumoniae serotypes 3, 6B, 9N, 23F; decreased total IgE, and increased Wright's phagocytic index [7].

Immunization of COPD patients with PPV23 contributed to a 2.2-fold decrease in exacerbation rate by 18 months; at 12 months post vaccination, the duration of acute episodes decreased 1.8-fold compared to the control group [8].

Though disputable, the preliminary results regarding therapeutic effects of vaccination against respiratory infections were thus obtained. The common controversy is whether it is possible to improve the respiratory function tests in COPD patients through vaccination.

Study aim—to assess exacerbation rate, number of courses of antibiotic chemotherapy, pulmonary function, and immunological effects of mono-vaccination with a new immunoadjuvant influenza vaccine vs. combined vaccination against pneumococcal infection, Haemophilus type b infection, and influenza in COPD patients.

2. Material and methods

The study enrolled 170 patients with grade 1, 2, 3, 4 COPD (age 30–80 years) who had signed informed consent according to the study protocol approved by the ethics committee of the Samara State Medical University (Russian Federation) and Research Institute of Pulmonology (Moscow, Russian Federation). The diagnosis was determined according to GOLD guidelines (2012) [9].

Patients were divided into four groups. Group I enrolled 50 patients with COPD who continued to receive basic therapy for the main disease and were vaccinated with commercially available vaccines against pneumococcal infection (Pneumo 23, France), H. influenzae type b infection (Hiberix, Belgium), and influenza (new immunoadjuvant vaccine Grippol® plus,

Russian Federation). Vaccines were administered once intramuscularly into various parts of the body. Two patients from Group I did not complete the study per protocol (one patient died after a traffic accident, and one patient died from sudden massive pulmonary embolism). Therefore, the data from these patients were not included into final analysis, and it was based on 48 patients of Group I.

Group II (control for patients who received complex vaccination against pneumococcal infection, Haemophilus type b infection, and influenza) consisted of 80 patients with COPD of similar grade, who were not vaccinated and received only basic therapy.

Group III consisted of 20 COPD patients vaccinated against influenza with a new immunoadjuvant vaccine. Group IV (control for patients who received mono-vaccination against influenza with a new immunoadjuvant vaccine) enrolled 20 unvaccinated COPD patients. Groups II and IV were composed of patients who categorically rejected any vaccination, despite the information provided. Nevertheless, these patients gave their consent to participate in the study. All study patients were followed up for 1 year and subjected to function and immunological tests at baseline and at 12 months.

The use of two control groups was associated with enrollment of patients in two various study centers. Each study center enrolled subjects either to Group I (group of complex vaccination and control group) or to Group III (group of mono-vaccination against influenza and control group). Another reason for the use of two control groups was the probability that baseline characteristics of the patients in Group 1 and Group 3 will not be well balanced, and their comparison with the total control group will be incorrect. Our study is not a direct comparison between the groups of complex vaccination and mono-vaccination. We just compare each of these groups with its own control.

All study patients underwent a history taking (identification of risk factors for COPD, complaints for cough, sputum discharge, dyspnea of any grade worsened by physical exercise). To verify the diagnosis of COPD, all patients were subjected to pulmonary function tests and broncholytic test with 400 μg of salbutamol according to the standard techniques [8]. The study enrolled patients with Tiffeneau index forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) below 70%.

Inclusion criteria:

- Men and women above 30 years of age.
- Patients with mild/moderate/severe/extremely severe COPD.
- Patient's informed consent.

Exclusion criteria:

- Age below 30 years.
- Vaccination against pneumococcal infection within the previous 3 years.
- Previous vaccination against H. influenzae type b infection.

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- Acute infectious diseases and tuberculosis.
- Active phase of chronic virus hepatitis.
- Mental disorders.
- Renal or hepatic failure.
- Malignancies.
- Exacerbation of chronic diseases.
- Hypersensitivity to vaccine components.
- Severe complications of previous vaccination.
- Pregnancy.
- Autoimmune disorders.

Patients were followed up by general practice physicians, pulmonologists, or allergologists-immunologists in the outpatient context or in hospitals, if hospitalization was required. In cases of COPD exacerbation, if necessary, patients were hospitalized to departments of pulmonology.

Patients meeting inclusion/exclusion criteria were divided into four groups. Groups II and IV enrolled patients who categorically rejected any vaccination. Other patients were first recruited to Group I to undergo complex vaccination and then to Group III to be vaccinated against influenza using a new immunoadjuvant vaccine. Sample size was determined by the number of vaccines.

All patients received basic bronchodilatory and anti-inflammatory therapies in accordance with the disease severity and GOLD guidelines (2012). At baseline, groups were well balanced for age, gender, disease severity, and scope of basic therapy, which remained unchanged throughout the study period. Vaccination was performed at remission in the outpatient context, follow-up period lasted for 12 months after vaccination.

PPV23 vaccine is a polyvalent pneumococcal vaccine manufactured by Sanofi aventis (France). It contains purified capsule S. pneumoniae polysaccharides of 23 serotypes. One dose of vaccine is 0.5 ml.

Hiberix is a conjugated vaccine to prevent infections caused by H. influenzae type b (GlaxoSmithKline Biologicals s.a., Belgium). One dose contains 10 μg of purified capsule polysaccharide isolated from str. H. influenzae type b conjugated with 30 μg of tetanus toxoid.

Grippol plus vaccine (NPO Petrovax Pharm, Russia) is a trivalent polymeric subunit immunoadjuvant vaccine (Petrovax, Russia) containing protective antigens isolated from purified influenza type A and B viruses grown in chicken embryos. One immunization dose (0.5 ml) contains at least 5 μg of hemagglutinin of epidemiologically relevant influenza subtype A (H1N1 and H3N2) and type B viruses, and polyoxidonium immunoadjuvant 500 μg in sodium phosphate buffer. Vaccine is free of preservatives.

Clinical efficacy of vaccination was assessed by the number of COPD exacerbations during the year before vaccination and after vaccination. COPD exacerbation was defined as increased dyspnea, cough, and sputum volume requiring medical advice and modification of current therapy documented by primary medical records.

Ventilation function was investigated using a Spiro S-100 spirometer (Russian Federation). The following parameters were measured: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and a calculated ratio of these two parameters (FEV1%/FVC), that is, modified Tiffeneau test. Exercise tolerance was assessed using the 6-minute walk test (6MWT) according to the standard protocol.

The levels of IgG antibodies against influenza virus strains were measured using standard HAI assay (hemagglutination inhibition assay) in accordance with the manufacturer's instructions to the kit.

The results were studied statistically using StatPlus 2009 Professional 5.8.4. Measures of central tendency and dispersion were chosen depending on the data distribution type. Continuous variables corresponding to normal distribution are presented as means (SD); variables differing from normal distribution as medians (interquartile distance). Categorical variables are presented as proportions (%) and absolute values.

The choice of statistical test depends on the data distribution type and evaluation of dispersion equality. The hypothesis of data distribution normality was tested (Shapiro-Wilks test). In cases of normal distribution of data in each sample, dispersion is to be compared between two distributions (Levene's test). If both criteria are met, Student's t test is selected, if no, its non-parametric alternative is used (Mann-Whitney test). The same is applicable to paired tests for comparisons of changing variables (pairwise Student's t test or Wilcoxon test for paired comparisons). Comparative analysis of categorical variables was performed using exact two-sided Fisher's test. Differences were statistically significant at $p < 0.05$ [10].

Prospective study design allows calculating the following statistics:

- Number of patients with exacerbations per year before and after vaccination.
- Absolute risk (AR) of exacerbation per year before and after vaccination.
- Relative risk (RR) of exacerbation per year before and after vaccination.
- Reduction of absolute risk (RAR) of exacerbation after vaccination.
- Reduction of relative risk (RRR) of exacerbation after vaccination.
- Chance of exacerbation.
- Odds ratio (OR) for exacerbation after vaccination compared to no vaccination.
- Number of patients needed to treat to prevent one additional bad outcome (NNTp).

About 95% CI of the difference of absolute risks (AR): the results are statistically significant, if 95% CI will not contain 0.

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About 95% CI of the relative risk (RR): the results are statistically significant, if 95% CI will not contain 1.

About 95% CI for the odds ratio (OR): the results are statistically significant, if 95% CI will not contain 1.

3. Results and discussion

3.1. Clinical effects of vaccination in COPD patients

The clinical effects of vaccination (exacerbation rate) in COPD patients are characterized by groups in **Table 1**.

Parameter (formula)	Before vaccination				After vaccination			
	Group I Complex (n=48)	Group II Control I (n=80)	Group III Mono (n=20)	Group IV Control II (n=20)	Group I Complex (n=48)	Group II Control I (n=80)	Group III Mono (n=20)	Group IV Control II (n=20)
Number of COPD exacerbations over 12 months	2 [1,75; 3]	2 [1; 3]	2 [2; 3]	2 [1; 3]	0 [0; 1]***	2 [1; 3]	1 [0; 2]*	2 [1; 3]
Number of patients with exacerbations	44	67	16	17	18	71	10	18
Chance of exacerbation (no. patients with exacerbations /no. patients without exacerbations)	44/4 = 11	67/13 = 5.2	16/4 = 4	17/3 = 5.7	18/30 = 0.6	71/9 = 7.9	10/10 = 1	18/2 = 9
AP (no. patients with exacerbations /no. patients at risk of exacerbation)	44/48 = 0.92 = 92%	67/80 = 0.84 = 84%	16/20 = 0.8 = 80%	17/20 = 0.85 = 85%	18/48 = 0,38 = 38%	71/80 = 0.89 = 89%	10/20 = 0.5 = 50%	18/20 = 0.9 = 90%
OR (AR after vaccination/ AR without vaccination), 95% CI	**Flu+PPV23+ HIB (n=48)**		**Control I (n=80)**		**Flu (n=20)**		**Control II (n=20)**	
	0.38/0.92 = 0.41 = 41% (0.16; 1.08)		0.89/0.84 = 1.06 = 106% (0.49; 2.29)		0.5/0.8 = 0.63 = 63% (0.23; 1.69)		0.9/0.85 = 1.06 = 106% (0.19; 5.7)	
RAR (AR after vaccinations – AR without vaccination), 95% CI	0.38 – 0.92 = - 0.54 = - 54% (-1.53; 0.45)		0.89 – 0.84 = 0.05 = 5% (-0.76; 0.86)		0.5 – 0.8 = - 0.3 = - 30% (-1.29; 0.69)		0.9 – 0.85 = 0.05 = 5% (-1.63; 1.73)	
RRR (AR difference /AR without vaccination)	(92% - 38%)/92% = 0.59 = 59%		(84% - 89%)/84% = - 0.06 = -6%		(80% - 50%)/80% = 0.38 = 38%		(85% - 90%)/85% = - 0.06 = - 6%	
OR (chance with vaccination / chance without vaccination), 95% CI	0.6/11 = 0.05 = 5% (0.02; 0.17)#		7.9/5.2 = 1.52 = 152% (0.61; 3.78)		1/4 = 0.25 = 25% (0.06; 1.02)		9/5.7 = 1.58 = 158% (0.23; 10.8)	
NNTp (1/RAR)	1/0.54 = **1.9**		-		1/0.3 = **3.3**		-	

Notes: continuous variables are presented as medians and interquartile distances.
* p<0.05 vs. before vaccination in a given group (exact Fisher's test).
*** p<0.001 vs. before vaccination in a given group (exact Fisher's test).
# p<0.05.
Abbreviations: AR – absolute risk, RR – relative risk, RAR – reduction of absolute risk, RRR – reduction of relative risk, OR – odds ratio, NNTp – number of patients needed to treat to prevent unfavorable outcome.

Table 1. Number of exacerbations (calculated statistics) in COPD patients per year before and after vaccination.

Both complex and mono-vaccination resulted in a statistically significant reduction of the number of COPD exacerbations. The risk of COPD exacerbation was reduced by 54% after complex vaccination vs. 30% after mono-vaccination ($p > 0.05$ for all comparisons).

Parameter (formula)	Before vaccination				After vaccination			
	Group I Complex (n=48)	Group II Control I (n=80)	Group III Mono (n=20)	Group IV. Control II (n=20)	Group I Complex (n=48)	Group II Control I (n=80)	Group III Mono (n=20)	Group IV Control II (n=20)
Number of courses of antibiotic chemotherapy (ABC) over 12 months	2 [1; 3]	2 [1; 3]	2 [2; 3]	2 [1; 3]	0 [0; 1]***	2 [1; 3]	0 [0; 1]*	2 [1; 3]
Number of patients treated with ABC	41	62	17	15	15	63	11	18
Chance of ABC (no. patients treated with ABC/no. patients not treated with ABC)	41/7 = 5.9	62/18 = 3.4	17/3 = 5.7	15/5 = 3	15/33 = 0.5	63/17 = 3.7	11/9 = 1.2	18/2 = 9
AR (no. patients treated with ABC/no. patients not treated with ABC)	41/48 = 0.85 = 85%	62/80 = 0.78 = 78%	17/20 = 0.85 = 85%	15/20 = 0.75 = 75%	15/48 = 0.31 = 31%	63/80 = 0.79 = 79%	11/20 = 0.55 = 55%	18/20 = 0.9 = 90%
RR (AR with vaccination – AR without vaccination), 95% CI	**Combined (n=48)**		**Control I (n=80)**		**Mono (n=20)**		**Control II (n=20)**	
	0.31/0.85 = 0.36 = 36% (0.18; 0.73)#		0.79/0.78 = 1.01 = 101% (0.56; 1.82)		0.55/0.85 = 0.65 = 65% (0.21; 2.06)		0.9/0.75 = 1.2 = 120% (0.26; 5.48)	
RAR (AR with vaccination – AR without vaccination), 95% CI	0.31 – 0.85 = - 0.54 = - 54% (-1.25; 0.17)		0.79 – 0.78 = 0.01 = 1% (-0.58; 0.6)		0.55 – 0.85 = - 0.3 = - 30% (-1.45; 0.85)		0.9 – 0.75 = 0.15 = 15% (-1.37; 1.67)	
RRR (difference AR/AR without vaccination)	(85% - 31%)/85% = 0.64 = 64%		(78% - 79%)/78% = - 0.01 = -1%		(85% - 55%)/85% = 0.35 = 35%		(75% - 90%)/75% = - 0.2 = - 20%	
OR (chance with vaccination/chance without vaccination), 95% CI	0.5/5.9 = 0.08 = 8% (0.03; 0.22)#		3.7/3.4 = 1.09 = 109% (0.49; 2.41)		1.2/5.7 = 0.21 = 21% (0.05; 0.96)#		9/3 = 3 = 300% (0.49; 18.03)	
NNTp (1/RAR)	1/0.54 = **1.9**		-		1/0.3 = **3.3**		-	

Notes: continuous variables are presented as medians and interquartile distances.
* - p<0.05 vs. baseline value in a given group (exact Fisher's test).
*** - p<0.001 vs. baseline value in a given group (exact Fisher's test).
# - p<0.05.
Abbreviations: AR – absolute risk, RR – relative risk, RAR – reduction of absolute risk, RRR – reduction of relative risk, OR – odds ratio, NNTp – number of patients needed to treat to prevent unfavorable outcome.

Table 2. Number of courses of antibiotic chemotherapy (calculated statistics) in COPD patients per year before and after vaccination in the groups considered.

As compared to unvaccinated patients, complex vaccination reduced the risk of COPD exacerbation by 59 vs. 38% reduction after mono-vaccination vs. increase by 6% in unvaccinated patients.

In the group of complex vaccination against pneumococcal, Haemophilus type b infection, and influenza, the chance of COPD exacerbation was 5% of that in unvaccinated patients ($p < 0.05$). In the group of mono-vaccination, the chance of COPD exacerbation was 25% of that without vaccination ($p > 0.05$).

Table 2 presents characteristics of the clinical effect of vaccination (i.e., number of courses of antibiotic chemotherapy) in different groups of COPD patients.

Both complex and mono-vaccination led to statistically significant reduction in the number of antibacterial chemotherapy courses.

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The risk of antibiotic chemotherapy was reduced by 54% in the group of complex vaccination against pneumococcal, Hemophilus type b infection, and influenza vs. 30% in the group of mono-vaccination ($p > 0.05$ for all comparisons).

As compared to no vaccination, complex vaccination reduced the risk of antibiotic chemotherapy in patients with COPD by 64%, whereas mono-vaccination reduced it by 35%.

In the group of complex vaccination against pneumococcal, Hemophilus type b infection, and influenza, the chance of antibiotic chemotherapy was 8% of that in unvaccinated patients ($p < 0.05$). In the group of mono-vaccination, the chance of antibiotic chemotherapy was 21% of that in unvaccinated ($p < 0.05$).

3.2. The effect of vaccination on the pulmonary function tests in COPD patients

In COPD patients from Groups I and II, FVC changes did not undergo any statistically significant changes over 12 months (**Table 3**). In Group I (patients vaccinated against pneumococcal, Hemophilus type b infection, and influenza), forced expiratory volume in 1 s (FEV1) increased to 57.4% (2.0%) at 12 months vs. 53.9% (2.7%) at baseline ($p < 0.05$). In unvaccinated patients (Group II), these parameters remained unchanged: 54.1% (1.9%) at baseline vs. 50.4% (2.8%) at 12 months ($p > 0.05$), indicating that the rate of FEV1 decrease was lower in vaccinated COPD patients (Group I). Detailed characteristics of FEV1 changes in Groups I and II depending on the disease severity are given in **Table 4**, and **Table 5** outlines the same for Tiffeneau index.

COPD grade	At baseline		At 12 months	
	Abs., ml	%	Abs., ml	%
1 (n = 3/n = 24)	3611 (466)	100.7 (3)	3724 (489)	104 (0.4)
	3608 (206)	97.8 (3.2)	3572 (176)	95.6 (2.9)
2 (n = 23/n = 25)	2943 (180)	78.9 (3.3)	2867 (169)	79.3 (3.3)
	2936 (173)	77.9 (4.1)	2918 (167)	76.9 (3.5)
3 (n = 18/n = 25)	2301 (129)	55.2 (2.8)	2173 (208)	53.3 (3.5)
	2311 (128)	55.2 (2.7)	2086 (96.2)	51.2 (2.6)
4 (n = 4/n = 6)	1854 (116)	46.6 (5.6)	2158 (119)&	55.8 (3.8)&
	1845 (129)	45.2 (5.1)	1778 (106)	43.3 (2.2)
Total (n = 48/n = 80)	2653 (119)	68.7 (2.9)	2602 (131)	68.3 (2.9)
	2648 (122)	67.9 (2.5)	2562 (131)	64.8 (2.2)

Data are presented as means (standard deviation).
Group I patients in the numerator, Group II patients in the denominator.
& $p < 0.05$—differences between Groups I and II (Student's test).

Table 3. FVC changes in COPD patients from Groups I and II over 12 months.

COPD grade	At baseline		At 12 months	
	Abs., ml	%	Abs., ml	%
1 (n = 3/n = 24)	2412 (236)	86.7 (1.6)	2597 (337)	90.5 (1.1)&&
	2399 (205)	85.8 (2.0)	2384 (136)	85.4 (1.2)
2 (n = 23/n = 25)	1954 (112)	66.1 (2.1)	1985 (109)	69.9 (2.6)&
	1959 (110)	66.4 (2.7)	1916 (102)	62.9 (1.4)
3 (n = 18/n = 25)	1274 (65.1)	39.1 (1.4)	1314 (101)	42.0 (2.2)
	1280 (69.3)	40.0 (1.3)	1204 (76.3)	37.2 (1.6)
4 (n = 4/n = 6)	876 (106.5)	26.9 (1.4)	951 (106.5)	28.6 (2.7)
	883 (115.5)	27.9 (1.2)	826 (97.2)	25.9 (1.0)
Total (n = 48/n = 80)	1638 (86.6)	53.9 (2.7)	1685 (95.4)	57.4 (2.0)&
	1642 (92.5)	54.1 (1.9)	1574 (94.4)	50.4 (2.8)

Data are presented as means (standard deviation).
Group I patients in the numerator, Group II patients in the denominator.
& $p < 0.05$; && $p < 0.01$—differences between Groups I and II (Student's test).

Table 4. FEV1 changes in COPD patients from Groups I and II over 12 months.

COPD grade	At baseline	At 12 months
	%	%
1 (n = 3/n = 24)	67.27 (1.95)	69.8 (0.1)
	66.34 (2.18)	68.4 (0.89)
2 (n = 23/n = 25)	67.14 (2.04)	69.9 (2.29)&
	66.85 (1.95)	64.24 (1.58)
3 (n = 18/n = 25)	56.68 (2.59)	62.39 (2.61)
	55.43 (2.12)	58.4 (2.53)
4 (n = 4/n = 6)	47.85 (6.69)	44.2 (4.95)
	47.38 (5.12)	45.84 (2.53)
Total (n = 48/n = 80)	61.62 (1.73)	64.93 (1.94)&
	60.98 (1.85)	59.13 (2.15)

Data are presented as means (standard deviation).
Group I patients in the numerator, Group II patients in the denominator.
& $p < 0.05$—differences between Groups I and II (Student's test).

Table 5. Tiffeneau index changes in COPD patients from Groups I and II over 12 months.

One year post vaccination, vaccinated COPD patients (Group I) showed 6MWT results that were 75.2% (2.8%) of the desired values vs. 60.4% (2.3%) in Group II patients ($p < 0.001$). Detail

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characteristics of the dynamics of the 6-minute walk test depending on the disease severity are given in **Table 6**.

COPD grade	At baseline		At 12 months	
	Abs., m	%	Abs., m	%
1 (n = 3/n = 24)	440 (49.0)	86.1 (8.6)	450 (54.5)	92.8 (4.3)
	434 (52.8)	84.7 (9.1)	429 (41.2)	83.5 (4.2)
2 (n = 23/n = 25)	355 (13.1)	71.8 (2.4)	401 (15.8)*,&&&	81.2 (3.1)*, &&&
	351 (10.2)	70.9 (2.6)	324 (8.7)#	64.1 (1.2)#
3 (n = 18/n = 25)	314 (21.1)	64.0 (3.8)	338 (26.4)	69.7 (4.3)&
	319 (20.3)	64.1 (3.6)	296 (17.1)	59.4 (1.7)
4 (n = 4/n = 6)	230 (45.2)	47.4 (13)	266 (37.3)	54 (12.3)
	235 (40.3)	48.6 (10.3)	213 (10.5)	44.2 (2.3)
Total (n = 48/n = 80)	335 (12.6)	67.8 (2.4)	369 (14.5)&&&	75.2 (2.8)*, &&&
	332 (18.4)	66.3 (2.6)	305 (10.5)	60.4 (2.3)

Data are presented as means (standard deviation).
Group I patients in the numerator, Group II patients in the denominator.
* $p < 0.05$ vs. baseline values in Group I (Student's test).
# $p < 0.05$ vs. baseline values in Group II (Student's test).
& $p < 0.05$; &&& $p < 0.001$—differences between Groups I and II (Student's test).

Table 6. Dynamics of 6MWT in COPD patients from Groups I and II over 12 months.

Detailed characteristics of spirometry data in COPD patients from Groups III and IV are presented in **Table 7**.

Parameter		Vaccinated against influenza (Group III, n = 20)		Unvaccinated (Group IV, n = 20)	
		At baseline	At 12 months	At baseline	At 12 months
FVC	Abs.	1.62 (0.18)	1.71 (0.13)	2.05 (0.12)	1.88 (0.16)
	%	37.69 (3.61)	42 (2.74)	47.06 (2.9)	41.94 (3.05)
FEV1	Abs.	1.13 (0.13)	1.17 (0.08)	1.48 (0.1)	1.38 (0.11)
	%	33.65 (3.43)	35.76 (2.16)	42.25 (2.76)	40.83 (3.46)
FEV1/FVC	%	52.7 (3.42)	46.46 (3.2)&	55.8 (2.18)	57.9 (2.66)

Data are presented as means (standard deviation).
& $p < 0.05$—differences between Groups III and IV at 12 months (Student's test).

Table 7. Spirometry values in COPD patients vaccinated against influenza (Group III) and in unvaccinated control patients (Group IV).

The analysis of the 6-minute walk test results showed a trend to distance increase by 13 m (+3.7%) 1 year after mono-vaccination ($p > 0.05$, Student's test).

Thus, the study demonstrated statistically significant increase in FEV1 [57.4% (2.0%)] at 12 months after complex vaccination when compared to unvaccinated COPD patients [50.4% (2.8%)]. This FEV1 increase was 3.5%, that is, not statistically significant vs. baseline value, although the positive trend was observed.

The group of mono-vaccination against influenza also demonstrated the positive trend of FEV1 increase, but the increase was only 2.11%, which is less than 3.5% in the group of complex vaccination.

In the group of complex vaccination, patients demonstrated significantly improved 6MWT results at 12 months vs. baseline distance. In Group I, the increase was 7.4% (+34 m), that is, statistically significant ($p < 0.05$). In patients vaccinated against influenza, 6MWT increase approached trend levels of significance.

3.3. Immunological effect of vaccination in patients with COPD

Previously, we have reported the dynamics of specific antibodies against influenza virus in COPD patients after complex vaccination against S. pneumoniae, H. influenzae type b, and influenza [11].

Combined vaccination against pneumococcal, H. influenzae type b and influenza is accompanied by production of antibodies to these infections, which persist during 1 year (observation period), regardless of disease severity. In patients with stage 4 COPD, the level of antibodies to influenza virus (strains A/H1N1, A/H3N2 and B) in post-vaccination period was lower than in patients with stages 1, 2, and 3. Probably, these patients should be vaccinated against influenza twice. Despite the fact that patients with COPD had lower levels of post-vaccination antibodies than control, they demonstrated apparent clinical effect throughout 12 months, which was recorded as reduction of both exacerbation number and the need in antibacterial medications. Combined vaccination against bacterial and viral infections contributes to the achievement of antibody levels leading to the development of significant clinical effect in patients with COPD.

Table 8 demonstrates lists immunogenicity parameter of the new immunoadjuvant vaccine against influenza after mono vaccination of COPD patients.

No statistically significant differences in immunogenicity were found between COPD patients and healthy participants vaccinated only against influenza, the latter, however, demonstrated a trend toward higher immune response to vaccination.

In the comparative analysis of COPD patients, in whom antibodies to all three influenza virus strains were detected at arbitrarily protective titres (≥1:40) at 6 months after vaccination, and patients, in whom, despite vaccination, antibody titres were <1:40, COPD patients at risk of low response to vaccination were identified. These patients had a long history of COPD with frequent respiratory infections and COPD exacerbations requiring hospitalization and systemic glucocorticosteroids or antibiotic chemotherapy.

Vaccine strains	Seroconversion, % (N ≥ 40%)		Seroprotection, % (N ≥ 70%)		Mean geometric antibody titre (N ≥ 40)		
	6 months	12 months	6 months	12 months	At baseline	6 months	12 months
A/H1N1/ Brisbane/ 59/07	60 ± 16	40 ± 16	58 ± 14	67 ± 14	20 (log_2 4.32 ± 0.36)	30.64 (log_2 4.94 ± 0.38)	33.64^p(log_2 5.07 ± 0.28)
A/H3N2/ Uruguay/ 716/2007	70 ± 15	50 ± 16	75 ± 13	83.3 ± 11	24.75 (log_2 4.63 ± 0.63)	71.91 (log_2 6.17 ± 0.62)	59.93 (log_2 5.91 ± 0.38)
B/Florida/ 4/2006	30 [15; 45]	10 [1; 20]	100 ± 0	100 ± 0	46.94 (log_2 5.55 ± 0.30)	84.38 (log_2 6.4 ± 0.33)	59.9 (log_2 5.91 ± 0.38)

Marked values meet CPMP requirements.

Table 8. Immunogenicity parameters of the new immunoadjuvant vaccine against influenza after mono-vaccination of COPD patients (n = 15).

4. Conclusions

During post-vaccination period, treating physicians and patients as well focus their attention on the main disease course. The clinical course of the disease may be characterized by number of COPD exacerbations and the need for antibiotic chemotherapy. Both complex vaccination against S. pneumoniae, H. influenzae type b, and influenza and mono-vaccination with a new immunoadjuvant influenza vaccine led to statistically significant reduction in the number of COPD exacerbations and of antibiotic chemotherapy courses.

Our study had some limitations, that is, its pilot character, absence of randomization and blinding, and small sample size. As follows from the study results, complex vaccination of COPD patients against bacterial and viral respiratory infections have more expressed beneficial effects on their functional status when compared to mono-vaccination against influenza. Further well-designed multicenter clinical studies devoid of these limitations are needed to refine the hypothesis. Nevertheless, based on the obtained results, widespread implementation of mono-vaccination against influenza with a new immunoadjuvant influenza vaccine, as well as complex vaccination against bacterial respiratory infections and influenza can be recommended for COPD patients, as vaccination is beneficial for their functional status, that is, improves FEV1 and 6-minute walk test results.

Mono-vaccination of COPD patients using immunoadjuvant vaccines of a new class as well as combined vaccination against S. pneumoniae, H. influenzae, and influenza is associated with protective antibody titres. In our study, we evaluated immunogenicity of the new influenza immunoadjuvant vaccine administered as mono-vaccine to COPD patients in accordance with CPMP requirements. Immune response to vaccine strains of influenza virus was more intense and durable in initially seropositive patients compared to seronegative.

Combined vaccination against pneumococcal, H. influenzae type b and influenza is accompanied by production of antibodies to these infections. In patients with stage 4, COPD the level of antibodies to influenza virus (strains A/H1N1, A/H3N2 and B) in post-vaccination period was lower than in patients with stages 1, 2, and 3. Probably, these patients should be vaccinated against influenza twice. Combined vaccination against bacterial and viral infections contributes to the achievement of antibody levels leading to the development of significant clinical effect in patients with COPD.

Influenza prophylaxis in COPD patients implies annual influenza vaccination of all individuals having no contraindications regardless of the disease severity. Influenza vaccine prophylaxis must be included into patient's care plan and into the list of recommendations given by a pulmonologist at an outpatient visit or at discharge from hospital. If possible, simultaneous vaccination against S. pneumoniae, H. influenzae type b, and influenza is recommended as early as possible before the season of respiratory infections starts. Combined vaccination against respiratory infections has more significant effects on clinical characteristics and functional status of COPD patients and promotes production of specific antibodies not only against vaccine strains of influenza virus but also against S. pneumoniae and H. influenzae antigens contained in the corresponding vaccines.

Author details

Andrey Dmitrievich Protasov[1,2*], Mikhail Petrovich Kostinov[1,2],
Alexander Victorovich Zhestkov[1,2], Mikhail L'vovich Shteiner[1,2],
Svetlana Vyacheslavovna Kazharova[1,2], Yuriy Vladimirovich Tezikov[1,2] and
Igor Stanislavovich Lipatov[1,2]

*Address all correspondence to: crosss82@mail.ru

1 Samara State Medical University, Samara, Russian Federation

2 Mechnikov Research Institute of Vaccines and Sera, Moscow, Russian Federation

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