HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 8, 2142–2147
http://dx.doi.org/10.1080/21645515.2016.1165373

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

Safety and immunogenicity of a single dose 23-valent pneumococcal polysaccharide vaccine in Russian subjects

Karen Ciprero[a], Kirill A. Zykov[b], Nikolay I. Briko[c], Tulin Shekar[a], Tina M. Sterling[a], Elizaveta Bitieva[d], Jon E. Stek[a], and Luwy Musey[a]

[a]Merck & Co., Inc., Kenilworth, NJ, USA; [b]Moscow State University of Medicine and Dentistry, Moscow, Russian Federation; [c]I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation; [d]Merck Sharp & Dohme (MSD) Pharmaceuticals LLC, Moscow, Russian Federation

ABSTRACT

Pneumococcal infection is a major cause of pneumonia, bacteremia, and meningitis. Incidence of pneumococcal disease (PD) varies worldwide. The 23-valent pneumococcal polysaccharide vaccine (PPV23) displays an acceptable safety profile and has been demonstrated cost-effective in reducing burden of PD.

Methods: Approximately 100 subjects from the Russian Federation who were either 2 to 49 y of age with increased risk for PD or ≥50 years of age were enrolled into the study (NCT01734239) to receive a single dose of PPV23 administered intramuscularly. Each subject was followed for local and systemic adverse events (AEs) for 5 and 14 days, respectively. Serious AEs were collected for 28 d postvaccination. Blood samples were collected immediately prior to vaccination and 28 d postvaccination for the measurement of IgG to serotypes 1, 6B, 14, 19F, and 23F.

Results: High proportion of subjects had ≥2 -fold increase in IgG following receipt of PPV23. Rates were 92.0%, 83.0%, 89.0%, 81%, 84% for serotypes 1, 6B, 14, 19F, and 23F, respectively. Similar rates of responders and increases in the magnitude of immune responses were observed in both age groups (2–49, ≥50). PPV23 was generally safe and well tolerated. Injection site and systemic AEs were reported by 14.7% and 18.6% of study subjects, respectively.

Conclusions: PPV23 is generally safe, well tolerated, and highly immunogenic when given as a single dose to Russian individuals 50 y of age and older, as well as Russian individuals 2 to 49 y of age who are at high risk for PD.

ARTICLE HISTORY
Received 20 August 2015
Revised 25 February 2016
Accepted 8 March 2016

KEYWORDS
immunogenicity; pneumococcal vaccine; pneumococcal polysaccharide vaccine; Russian population; safety

Introduction

Streptococcus pneumoniae is a leading cause of pneumonia, bacteremia without focus, and meningitis, and is associated with significant morbidity and mortality among children and adults worldwide.[1-4] Individuals living in crowded, closed settings (i.e., military camps, shelters, long-term care facilities) and patients with certain chronic conditions are at increased risk of developing pneumococcal infection and severe pneumococcal disease (PD). Children 2 y of age and young adults with sickle cell anemia, Hodgkin disease, congenital or acquired immunodeficiency including Human Immunodeficiency Virus (HIV) infection, diabetes mellitus, nephrotic syndrome, as well as those with functional or anatomic asplenia, are at increased risk of developing invasive pneumococcal disease (IPD) in comparison to healthy individuals without these conditions.[5-10]

The most common PD syndromes include pneumonia (approximately 75%), bacteremia without focus (approximately 20%), and meningitis (approximately 5%). Generally, these syndromes are classified as IPD and pneumococcal pneumonia. The burden of pneumococcal disease in Russian Federation has not been fully analyzed in recent years and available studies have mostly focused on bacterial meningitis as it is the only IPD syndrome that is reportable in Russia. Because of the limited epidemiological studies and often lack of laboratory identification of the microbial agent causing disease, the various forms of invasive and non-invasive pneumococcal disease in the Russian Federation have a low rate of etiological verification. The estimated annual incidence of bacteremic pneumonia and pneumococcal meningitis in children <5 y of age was 100 per 100,000 and 8 per 100,000 population, respectively.[11] There are limited data on serotype distribution for IPD among children and adult subjects in the Russian Federation. The most prevalent serotypes/serogroups associated with IPD in Moscow were 1 (22%), 6 (18%), 19 (16%), 3 (10%) and 23 (6%) while serotypes 14, 6B, and 23 were more prevalent in Vladivostok.[12-14] Although the incidence of pneumococcal meningitis in Russia varies by region (0.15 to 8 per 100,000 population), the overall mortality associated with pneumococcal meningitis in the Russian Federation is ~18%, with case-fatality rates being highest among adults 45 to 64 y (24%) and those 65 y and older (60%).[11,12] A recent study showed that the most frequent serotypes of *S. pneumoniae* associated with pneumococcal meningitis in children up to 18 y in Russia are types 1 (21.2%), 6 (18.2%), 19 (16.2%), and 3 (10.3%), and about 30% of them are resistant to antibiotics (7F, 19F, 23F, 6B).[15] Pneumonia mortality in 2013 in Russia was 26.7 per 100,000 population. It caused

CONTACT Luwy Musey luwy_musey@merck.com Merck & Co., Inc. 2000 Galloping Hill Rd. UG3CD-28 Kenilworth, NJ 07033, USA.

51.7% of all deaths due to respiratory diseases.[15] Pneumonia accounts for approximately 3% of all deaths in children <5 y of age in the Russian Federation.[16-17] Annual incidence of pneumococcal pneumonia in Russian children up to 15 y is 490 per 100,000 population while incidence in children 1 month to 4 y of age was estimated at 1,060 per 100,000 population.[13] In Russia among 500,000 annual cases of pneumonia, *S. pneumoniae* is a causative agent in 76% and 90% of cases in adults and children <5 y, respectively.[13] Other studies demonstrated, that in different Russian regions pneumococcal etiology of pneumonia was confirmed in 10.6–25.9% of hospitalized adult patients.[18] The annual incidence of community acquired pneumonia (CAP) was evaluated in new Russian Army recruits confined in training centers, a group with higher (5-fold) incidence of pneumococcal disease than the general adult population in Russia; the annual incidence of CAP in military camps was 4.2% and reached 20% during outbreaks.[19] Among Russian individuals, the most common serotypes/serogroups associated with CAP were 14 (21.9%), 6B (17.1%), and 23 (17.1%). In one study among armed forces personnel during a 2-year survey of serotypes/serogroups associated with pneumococcal pneumonia in healthy young adults, serotypes 1, 14, 23, 18C and 19F were more prevalent during the first year and serotypes 23, 9, 14, 15, 19F and 6B were more commonly identified during the second year.[14] In Russia, vaccination against pneumococcal infection was included in the National Immunization Schedule in 2014.

PNEUMOVAX™ 23 (PPV23; Merck & Co., Inc., Kenilworth, NJ) is a polyvalent pneumococcal polysaccharide (PnPs) vaccine comprised of 23 of the most important serotypes causing disease in adults and children (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F). The vaccine was first approved in the US in 1983 and is currently licensed in >75 countries worldwide. To date, more than 220 million doses of PPV23 have been distributed worldwide. Effectiveness against IPD in the population for which PPV23 is recommended in the United States has generally ranged from 56 to 81%; estimates are considerably lower in immunocompromised individuals, although a decline has been observed over time following vaccination, especially in the elderly.[20] Effectiveness of PPV23 against all pneumococcal pneumonia varies between studies possibly due to differences in study design, case definition of the clinical endpoint used in the trial, and characteristics of the population evaluated (outpatient, nursing home residents, or high-risk individuals with comorbidities).[21-27] The current study (NCT01734239) evaluated the safety and immunogenicity of PPV23 in Russian adults 50 y of age and older, as well as in individuals 2 to 49 y of age with increased risk for PD.

Results

Participant accounting and demographics

There were 50 subjects randomized to Group 1 (≥50 years) and 52 subjects randomized to Group 2 (2 to 49 years) (Table 1). There were slightly more males (63.7%) than females (36.3%) enrolled. All 102 subjects were vaccinated. No subjects discontinued from the study due to a clinical adverse experience (AE). Two subjects incurred protocol deviations (blood sample collected outside the visit window), and were excluded from immunogenicity analysis. All subjects were included in the safety analysis.

Table 1. Demographics (All subjects as treated population).

	PPV23 (N = 102)	
	n	(%)
Gender		
Male	65	(63.7)
Female	37	(36.3)
Age (years)		
2 to 6	12	(11.8)
7 to 13	9	(8.8)
14 to 17	4	(3.9)
18 to 49	27	(26.5)
≥50	50	(49.0)
Mean (SD)	40.4 (23.1)	
Median	49	
Range	2 to 79	
Race		
White	101	(99.0)
Other	1	(1.0)

N = Number of subjects randomized in the vaccination group.
n = Number of subjects in each category.

Immunogenicity

Baseline IgG geometric mean concentrations (GMCs) varied between serotypes and were generally low for all 5 serotypes (1, 6B, 14, 19F, and 23F) evaluated in the study. Across the 5 tested serotypes, IgG GMCs consistently increased from prevaccination to postvaccination, and similar increases in magnitude of the immune responses were also observed in both age groups (Table 2). Percentages of subjects with ≥2-fold increase in serotype-specific IgG GMC from prevaccination to postvaccination were ≥79.2% and ≥76.9 for subjects ≥50 years of age and 2–49 y of age, respectively (Table 3).

Safety

A total of 25/102 (24.5%) subjects reported one or more AEs following vaccination, including 15/102 (14.7%) who reported at least one injection-site AE, and 19/102 (18.6%) who reported at least one systemic AE (Table 4). One subject experienced a fever of 37.8°C (axillary). The majority of the adverse experiences were transient and mild to moderate in intensity. No subjects reported a serious AE or were discontinued from the study due to an AE.

Discussion

In the present study, we have demonstrated that PPV23 displays an acceptable safety profile and is highly immunogenic when given as a single dose in Russian subjects. The safety profile was comparable to that demonstrated in previous studies as the majority of adverse events were those solicited in these trials, namely injection site reactions (pain/tenderness, erythema, and swelling) as well as headache and fatigue.[28-31] Although vaccine-induced immune responses evaluated in the study only focused on IgG GMCs to a subset of 5 serotypes causing most

Table 2. Serotype-specific IgG GMCs at prevaccination and 28 d postvaccination.

Serotype	Timing to Vaccination	IgG GMC	95% CI[†]
	Group 1 (≥50 y of age; N = 48)		
1	Prevaccination	0.2	(0.2, 0.3)
	Postvaccination	2.5	(1.7, 3.8)
6B	Prevaccination	0.6	(0.5, 0.8)
	Postvaccination	5.3	(3.4, 8.5)
14	Prevaccination	3.6	(2.5, 5.1)
	Postvaccination	32.7	(22.7, 47.3)
19F	Prevaccination	1.5	(1.1, 2.1)
	Postvaccination	9.9	(7.0, 14.1)
23F	Prevaccination	1.1	(0.7, 1.5)
	Postvaccination	8.1	(5.3, 12.4)
	Group 2 (2 to 49 y of age; N = 52)		
1	Prevaccination	0.2	(0.2, 0.3)
	Postvaccination	4.1	(3.0, 5.4)
6B	Prevaccination	0.5	(0.4, 0.8)
	Postvaccination	2.7	(1.8, 3.9)
14	Prevaccination	1.3	(0.8, 2.0)
	Postvaccination	13.2	(8.7, 20.1)
19F	Prevaccination	1.5	(1.1, 2.2)
	Postvaccination	12.6	(9.0, 17.8)
23F	Prevaccination	0.6	(0.4, 1.0)
	Postvaccination	5.3	(3.6, 7.7)

[†]Based on the natural-log transformed serotype-specific antibody concentrations and back transformed values, and the t-distribution.
N = number of subjects with measurement.
CI = confidence interval

pneumococcal disease in Russia, PPV23 has been shown to elicit both IgG and OPA antibodies to all 23 serotypes included in the vaccine.[28-31] In addition, a previous study has demonstrated a good correlation between IgG and OPA responses following vaccination with PPV23.[32] Although the concentration of anti-capsular antibody required to protect against pneumococcal infection caused by any specific capsular type has not been established in adults, a ≥2-fold increase in antibody level following vaccination was associated with efficacy in clinical trials of polyvalent pneumococcal polysaccharide vaccines.[28,33] In our study, more than 75% of Russian subjects in both age cohorts (≥50 y of age and 2–49 y of age) had ≥2-fold increase in serotype-specific antibodies following vaccination with a single dose of PPV23. Such a finding implies that vaccine effectiveness among Russians is likely to be comparable to that observed in many countries worldwide. Further evidence for the likely effectiveness of PPV23 in Russian individuals is supported by the significant reduction in incidence of outpatient (not hospitalized) pneumonia in Russian military servicemen who received a single dose of a similar 23-valent pneumococcal polysaccharide vaccine (Pneumo 23™, Sanofi-Pasteur, Lyon, France). Military recruits in Russia have higher (5-fold) incidence of pneumonia than the general adult population and vaccine effectiveness was ~74.2% in that population; moreover, co-administration with influenza vaccine during the same influenza season increased vaccine effectiveness to ~78.5%.[34] Some limitations of our study include the small sample size in the study overall but also within each age cohort. In addition, only IgG antibodies were measured for 5 out of 23 vaccine serotypes. Moreover, the clinical benefits of the observed increases in antibody levels following vaccination with PPV23 cannot be clearly established, as thresholds of serotype-specific antibody concentrations that correlate with prevention of pneumococcal disease in adults have not been established. Lastly, the long-term clinical effectiveness of the single-dose vaccine was not evaluated.

Table 3. Proportion of Subjects with ≥2 -fold Increase in IgG Antibody Concentration for Serotypes 1, 6B, 14, 19F, and 23F (Per-Protocol Immunogenicity Population).

	PPV23 (N = 100) Proportion of Subjects with ≥2-Fold Increase		
Serotype	n	%	95% CI[†];
	Group 1 (≥50 years; N = 48)		
1	42	87.5	(74.8, 98.3)
6B	43	89.6	(77.3, 96.5)
14	43	89.6	(77.3, 96.5)
19F	38	79.2	(65.0, 89.5)
23F	42	87.5	(74.8, 95.3)
	Group 2 (2 to 49 years; N = 52)		
1	50	96.2	(86.8, 99.5)
6B	40	76.9	(63.2, 87.5)
14	46	88.5	(76.6, 95.6)
19F	43	82.7	(69.7, 91.8)
23F	42	80.8	(67.5, 90.4)

[†]Based on the 2-sided exact CI method for a single binomial proportion.
[‡]N = Total number of subjects with evaluable serology at Prevaccination and Postvaccination.
[§]n = Total number of subjects with IgG ≥2-fold increase.
CI = confidence interval

Table 4. Summary of Subjects with Adverse Experiences Following Vaccination.

	n	(%)	95% CI
Subjects with follow-up	102		
With one or more AE	25	(24.5)	(16.5, 34.0)
Injection-site AEs[†]	15	(14.7)	(8.5, 23.1)
Systemic AEs	19	(18.6)	(11.6, 27.6)
With vaccine-related AEs[†]	21	(20.6)	(13.2, 29.7)
Injection-site AEs	14	(13.7)	(7.7, 22.0)
Erythema	13	(12.7)	
Pain	1	(1.0)	
Swelling	1	(1.0)	
Systemic AEs	12	(11.8)	(6.2, 19.7)
With serious AEs	0	0.0	(0.0, 3.5)
Serious vaccine-related AEs	0	0.0	(0.0, 3.5)
Who died	0	0.0	(0.0, 3.5)
Discontinued due to AE	0	0.0	(0.0, 3.5)
Discontinued due to vaccine-related AE	0	0.0	(0.0, 3.5)

AE = Adverse experience
n = Number of subjects in each category
[†]Determined by the investigator to be possibly, probably, or definitely related to the vaccine
The same subject may appear in different categories, but counted only once in each category

Conclusion

PPV23 is generally safe, well tolerated, and highly immunogenic when given as a single dose to Russian individuals 50 y of age and older, as well as Russian individuals 2 to 49 y of age who are at high risk for PD.

Methods

Study design

From June 2013 to October 2013, this open-label, multicenter clinical trial was conducted across 7 sites in Russia (3 in St. Petersburg, 2 in Moscow, 1 in Smolensk, and 1 in

Saratov). This study evaluated the immunogenicity, safety, and tolerability of PPV23 in healthy Russian subjects. Subjects were enrolled into one of 2 groups: subjects ≥50 years of age (Group 1); subjects between 2 and 49 y of age at increased risk for PD (Group 2). Because this was an open-label, single-arm estimation study, no statistical hypothesis testing was performed and no statistical assumptions or Type I/Type II errors were used. Randomization numbers were computer-generated and assigned sequentially as subjects were enrolled in the study. The sample size was based on the following assumptions: 1) an approximate 2% to 3% overall dropout and protocol violation rate; and 2) the underlying response rate based on recent studies conducted with PPV23, the expected serotype-specific IgG GMCs measured following vaccination, and the percentage of subjects with at least a 2-fold rise between pre- and postvaccination for serotypes 1, 6B, 14, 19F, and 23F. Serum samples were collected prior to vaccination (baseline) and 28 d postvaccination. All subjects were followed for safety, including injection site, systemic, and serious AEs for 5 days, 14 days, and 28 days, respectively. For this study, serotypes 1, 6B, 14, 19F, and 23F were selected for antibody testing because they represent the serotypes associated with the most cases of IPD in Russia.

Study objectives

The study objectives were to describe the (1) safety and tolerability and (2) immunogenicity profile of PPV23.

Study population

Russian subjects 2 to 49 y of age with an increased risk of PD or ≥50 years of age, and no prior vaccination with any pneumococcal polysaccharide or conjugate vaccine were eligible for the study. Risk factors for pneumococcal disease were determined through clinical screening and participant's medical history prior to enrollment into the study. Subjects were excluded if they had known or suspected immune dysfunction; received a live vaccine within 3 months or an inactivated vaccine within 28 d of enrollment; participated in another interventional study within 2 months of enrollment or at any time during the study; received blood products or immunoglobulin within 6 months of enrollment; were pregnant or nursing; had a history of pneumococcal disease; received antibiotic therapy within 7 d of any vaccination; or had a known hypersensitivity to any of the vaccine components. The study was conducted in accordance with principles of Good Clinical Practice, approved by the Ethical Review Committee of each participating site, and written informed consent was obtained from each subject prior to study entry.

Vaccine description

PPV23 (lots 0927AA and 1919AA) is a sterile, liquid vaccine consisting of a mixture of purified capsular polysaccharides from *S. pneumoniae* types (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F). PNEUMOVAX^{TM}23 is a clear, colorless solution. Each 0.5-mL dose of vaccine contains 25 μg of each polysaccharide type in isotonic saline solution containing 0.25% phenol as a preservative. The vaccine was used directly as supplied. No dilution or reconstitution was necessary.

Immunogenicity and safety measurements

Immunogenicity

Serotype-specific pneumococcal IgG antibodies were quantitated by a validated sandwich-type enzyme-linked immunosorbent assay (ELISA), using adsorption with pneumococcal cell wall polysaccharide (CPs) and non-vaccine heterologous capsular polysaccharides (types 25 and 72) to reduce cross-reacting antibody.[35] The standard curve was prepared from the international anti-pneumococcal calibrator serum, 89SF (Center for Biologics Evaluation and Research, US Food & Drug Administration). The serotype-specific IgG GMC for each serum sample was calculated by comparing the optical density to that of the reference standard. No formal immunogenicity hypothesis was tested in this study. Baseline and postvaccination serotype-specific IgG GMCs as well as the proportion of subjects with ≥2-fold rises in IgG antibody concentrations from baseline were estimated for antibody responses to pneumococcal serotypes 1, 6B, 14, 19F, and 23F as measured by ELISA.

Safety

No formal safety hypothesis was tested in this study, but all subjects were followed for safety. All systemic AEs occurring within 14 d postvaccination were summarized. Body temperatures and solicited injection-site AEs (redness, swelling, pain/tenderness) were recorded Day 1 through Day 5 on a standardized Vaccination Report Card (VRC). No serious AEs were reported during the 28-day study follow-up period. All AEs were assessed by the investigator as mild (awareness of sign or symptom, but easily tolerated), moderate (discomfort enough to cause interference with usual activity), or severe (incapacitating with inability to work or do usual activity).

Statistical analysis

Immunogenicity

IgG GMC was calculated by taking the natural-log transformation of the antibody titer, computing the arithmetic mean, and back-transforming. The 95% confidence intervals (CIs) for the GMCs were based on the natural-log transformed serotype-specific antibody concentrations and the t-distribution. For the proportion of subjects with ≥2-fold increase in IgG antibody concentration from prevaccination to postvaccination for serotypes 1, 6B, 14, 19F, and 23F, the one-sample 2-sided 95% CIs for each serotype were computed using the exact CI method for a single binomial proportion.[36] The primary immunogenicity analyses were based on the PP population. The PP population excluded subjects with important protocol violations that may have affected the results of the primary immunogenicity endpoints.

Safety

The analysis of safety results followed a tiered approach. Clinical adverse experiences through Day 14 postvaccination, including the day of vaccination, were summarized. Point estimates were provided for all safety parameters. All reported clinical adverse experiences were tabulated for the follow-up period through Day 28 postvaccination. The All Subjects as Treated Population (ASaT) was used for the analysis of safety data in this study. The ASaT population consisted of all enrolled subjects who received one dose of vaccine.

Sponsor's role

This study was funded by Merck & Co., Inc. (sponsor). In conjunction with the external investigators, this study was designed, executed, and analyzed by the sponsor and outsource partner. Although the sponsor formally reviewed a penultimate draft, the opinions expressed are those of the authors and may not necessarily reflect those of the sponsor. All co-authors approved the final version of the manuscript.

Disclosure of potential conflicts of interest

Ciprero K, Shekar T, Sterling TM, Bitieva E, Stek JE, and Musey L were employees of Merck & Co., Inc. (sponsor), and may hold stock and/or stock options in the company. Zykov KA and Briko NI received funding from the study sponsor as study site investigators.

Acknowledgments

The authors would like to thank all the subjects who participated in this study and PNEUMOVAX® 23 Protocol 018 Study Group: BM Goloshchekin (St. Petersburg), SM Harit (St. Petersburg), RM Kozlov (Smolensk), VB Popova (St. Petersburg), AA Shuldyakov (Saratov), AI Sinopainkov (Moskow), KA Zykov (Moskow).

Funding

Funding for this research was provided by Merck & Co., Inc. Kenilworth. NJ.

Author contributions

Sterling, Stek: analysis and interpretation of data, and preparation of manuscript. Ciprero, Shekar, Musey: study concept and design, analysis and interpretation of data, and preparation of manuscript. Zykov, Briko, and Bitieva: conduct of the trial, preparation of manuscript.

References

[1] Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, Reingold A, Thomas A, Schaffner W, Craig AS, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 2010; 201(1):32-41; PMID:19947881; http://dx.doi.org/10.1086/648593

[2] Robinson KA, Baughman W, Rothrock G, Barrett NL, Pass M, Lexau C, Damaske B, Stefonek K, Barnes B, Patterson J, et al. Epidemiology of invasive streptococcus pneumoniae infections in the United States, 1995–1998: opportunities for prevention in the conjugate vaccine era. JAMA 2001; 285(13):1729-35; PMID:11277827; http://dx.doi.org/10.1001/jama.285.13.1729

[3] Weycker D, Strutton D, Edelsberg J, Sato R, Jackson LA. Clinical and economic burden of pneumococcal disease in older US adults. Vaccine 2010; 28(31):4955-60; PMID:20576535; http://dx.doi.org/10.1016/j.vaccine.2010.05.030

[4] O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria- Knoll M, McCall N, Lee E, Mulholland K, Levine OS, Cherian T, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet 2009; 374(9693):893-902; PMID:19748398; http://dx.doi.org/10.1016/S0140-6736(09)61204-6

[5] Fedson DS, Musher DM. Pneumococcal vaccine. In: Plotkin SA, Mortimer EA, Jr., eds. Vaccines 2 ed. Philadelphia: W.B. Saunders Company, 1994:517-64.

[6] Kyaw MH, Rose CE, Jr., Fry AM, Singleton JA, Moore Z, Zell ER, Whitney CG. Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis 2005; 192(3):377-86; PMID:15995950; http://dx.doi.org/10.1086/431521

[7] Vila-Corcoles A, Aguirre-Chavarria C, Ochoa-Gondar O, de Diego C, Rodriguez-Blanco T, Gomez F, Raga X, Barnes L, Magarolas R, Esteban L. Influence of chronic illnesses and underlying risk conditions on the incidence of pneumococcal pneumonia in older adults. Infection 2015; 43:699-706; PMID:26037386.

[8] Torres A, Blasi F, Dartois N, Akova M. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. Thorax 2105; 70:984-9; PMID:26219979.

[9] Harboe ZB, Larsen MV, Ladelund S, Kronborg G, Konradsen HB, Gerstoft J, Larsen CS, Pedersen C, Pedersen G, Obel N, et al. Incidence and risk factors of invasive pneumococcal disease in HIV-infected and non-HIV-infected individuals before and after the introduction of combination antiretroviral therapy: Persistent high risk among HIV-infected injecting drug users. Clin Infect Dis 2014; 59:1168-76; PMID:25038114; http://dx.doi.org/10.1093/cid/ciu558

[10] Fletcher MA, Balmer P, Bonnet E, Dartois N. PCVs in individuals at increased risk of pneumococcal disease: a literature review. Expert Rev Vaccines 2015; 14:975-1030; PMID:26083459; http://dx.doi.org/10.1586/14760584.2015.1037743

[11] Tatochenko V, Sidorenko S, Namazova-Baranova L, Mayanskiy N, Kulichenko T, Baranov A, Lobzin Y, Kharit S, Kozlov R, Andreeva I, et al. Streptococcus pneumoniae serotype distribution in children in the Russian Federation before the introduction of pneumococcal conjugate vaccines into the National Immunization Program. Expert Rev Vaccines 2014; 13:257-64; PMID:24350587; http://dx.doi.org/10.1586/14760584.2013.871205

[12] Beloshickij GV, Koroleva IS, Koshkina NI. (Pneumococcal meningitis in the Russian Federation). Epidemiology and Vaccinoprophylaxis. 2009; 45(2):21-6 (translated Russian).

[13] Baranov AA, Briko NY, Namazova-Baranova LS, Chuchalin AG, Tatochenko VK, et al. (Vaccinal prevention of infection caused by streptococcus pneumoniae. Federal Clinical recommendations) 2015; (4):6-9; Available from: http://www.pediatr-russia.ru/sites/default/files/file/kr_pnev.pdf (translated Russian).

[14] Turkutukov VB, Martinova AV. (Serotype description and pathogenic evidence of pneumococcus strains and pathogenic organisms bringing on community-acquired pneumonia at young people in closed groups). Pacific Med J 2004; 3:49-51 (translated Russian).

[15] Briko NI. The burden of pneumococcal infections and the directions of improving epidemiological surveillance in Russia. Epidemiol Infectious Diseases 2013; 6:4-937.

[16] Koroleva IS, Kharit SM, Ruleva AA, Perova AL, Sidorenko SV. (Pneumococcal infection in Russia: epidemiological situation). Pediatric Pharmacology 2010; 7(4):12-8 (translated Russian).

[17] World Health Organization. Country specific and global health estimates: Russian Federation, 2009.

[18] Bilichenko TN, Argunova AN, Antonova OA, et al. Pneumococcal pneumonia frequency in therapeutic adult inpatients at three Russian Regions. Pulmonology 2013; 4:29-36.

[19] Guchev IA, Yu VL, Sinopalnikov A, Klochkov OL, Kozlov RS, Stratchounski LS. Management of nonsevere pneumonia in military trainees with the urinary antigen test for streptococcus pneumoniae: an

innovative approach to targeted therapy. CID 2005; 40(11):1608-16; http://dx.doi.org/10.1086/429919

[20] Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, Adair RK, Clemens JD, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med 1991; 325 (21):1453-60; PMID:1944423; http://dx.doi.org/10.1056/NEJM199111213252101

[21] Vila-Corcoles A, Salsench E, Rodriguez-Blanco T, Ochoa-Gondar O, de Diego C, Valdivieso A, Hospital I, Gomez-Bertomeu F, Raga X. Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in middle-aged and older adults: a matched case-control study. Vaccine 2009; 27(10):1504-10; PMID:19171174; http://dx.doi.org/10.1016/j.vaccine.2009.01.013

[22] Murayama T, Taguchi O, Niederman MS, Morser J, Kobayashi H, Kobayashi T, et al. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. BMJ 2010; 340:1-7.

[23] Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, Gomez-Bertomeu F, Figuerola-Massana E, Raga-Luria X, Hospital-Guardiola I. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged 60 years: 3 years of follow-up in the CAMPAMIS study. Clin Infect Dis 2014; 58:909-17; PMID:24532544; http://dx.doi.org/10.1093/cid/ciu002

[24] Örtqvist A, Hedlund J, Burman LA, Elbel E, Höfer M, Leinonen M, Lindblad I, Sundelöf B, Kalin M. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish Pneumococcal Vaccination Study Group. Lancet 1998; 351(9100):399-403.

[25] Jackson LA, Neuzil KM, Yu O, Benson P, Barlow WE, Adams AL, Hanson CA, Mahoney LD, Shay DK, Thompson WW, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. N Engl J Med 2003; 348(18):1747-55; PMID:12724480; http://dx.doi.org/10.1056/NEJMoa022678

[26] Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ 2009; 180(1):48-58; PMID:19124790; http://dx.doi.org/10.1503/cmaj.080734

[27] Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults (review), 2008.

[28] Robbins JB, Austrian R, Lee CJ, Rastogi SC, Schiffman G, Henrichsen J, Mäkelä PH, Broome CV, Facklam RR, Tiesjema RH, et al. Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. J Infect Dis 1983; 148:1136-59; PMID:6361173; http://dx.doi.org/10.1093/infdis/148.6.1136

[29] Artz AS, Ershler WB, Longo DL. Pneumococcal vaccination and revaccination of older adults. Clin Microbiol Rev 2003; 16:308-318; PMID:12692100; http://dx.doi.org/10.1128/CMR.16.2.308-318.2003

[30] Mair S, Fiquet A, Meghlaoui G, Thomas S, Ledesma E. Immunogenicity and safety of PNEUMOVAX II manufactured by a new process in older adults. Hum Vaccin 2009; 5:608-13; PMID:19617717; http://dx.doi.org/10.4161/hv.9228

[31] Musher DM, Manoff SB, McFetridge RD, Liss C, Marchese RD, Raab J, Rueda AM, Walker ML, Hoover PA. Antibody persistence ten years after first and second doses of 23-valent pneumococcal polysaccharide vaccine, and immunogenicity and safety of second and third doses in older adults. Human Vaccin 2011; 7:919-28; http://dx.doi.org/10.4161/hv.7.9.15996

[32] Manoff SB, Liss C, Caulfield MJ, Marchese RD, Silber J, Boslego J, Romero-Steiner S, Rajam G, Glass NE, Whitney CG, et al. Revaccination with a 23-valent pneumococcal polysaccharide vaccine induces elevated and persistent functional antibody responses in adults $\geq$65 years. J Infect Dis 2010; 201: 525-33; PMID:20088694; http://dx.doi.org/10.1086/651131

[33] Smit P, Oberholzer D, Hayden-Smith S, Koornhof HJ, Hilleman MR. Protective efficacy of pneumococcal polysaccharide vaccines. JAMA 1977; 238(24):2613-6; PMID:21973; http://dx.doi.org/10.1001/jama.1977.03280250039019

[34] Zhogolev SD, Ogarkov PI, Mel'nichenko PI. (The prophylaxis of nonhospital pneumonia using 23-valent pneumococcus vaccine in the military collectives). Voen Med Zh 2004; 325(12):35-43, 96 (translated Russian); PMID:15690855.

[35] Marchese RD, Jain NT, Antonello J, Mallette L, Butterfield-Gerson KL, Raab J, Burke P, Schulman C, Adgate H, Sikkema DJ, et al. Enzyme-linked immunosorbent assay for measuring antibodies to pneumococcal polysaccharides for the PNEUMOVAX 23 vaccine: Assay operating characteristics and correlation to the WHO International Assay. Clin Vaccine Immunol 2006; 13:905-12; PMID:16893991; http://dx.doi.org/10.1128/CVI.00014-06

[36] Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934; 26(4):404-13; http://dx.doi.org/10.1093/biomet/26.4.404